Tumor Biol. (2015) 36:9457–9463
DOI 10.1007/s13277-015-3707-5

RESEARCH ARTICLE

Single nucleotide polymorphisms (SNPs) of *hOGG1* and *XRCC1* DNA repair genes and the risk of ovarian cancer in Polish women

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Received: 11 May 2015 / Accepted: 22 June 2015 / Published online: 30 June 2015

Abstract The aim of this study was to determine single nucleotide polymorphisms in *hOGG1* (Ser326Cys (rs13181)) and *XRCC1* (Arg194Trp (rs1799782)) genes, respectively, and to identify the correlation between them and the overall risk, grading and staging of ovarian cancer in Polish women. Our study comprised 720 patients diagnosed with ovarian cancer and 720 healthy controls. The genotype analysis of *hOGG1* and *XRCC1* polymorphisms was performed using polymerase chain reaction (PCR)-based restriction fragment length polymorphism (PCR-RFLP). Odds ratios (OR) and 95 % confidence intervals (CI) for each genotype and allele were calculated. Results revealed an association between *hOGG1* Ser326Cys polymorphism and the incidence of ovarian cancer. Variant Cys allele of *hOGG1* increased the overall cancer risk (OR 2.89; 95 % CI 2.47–3.38; $p<.0001$). Moreover, ovarian cancer grading remained in a relationship with both analysed polymorphisms; G1 tumours presented increased frequencies of *hOGG1* Cys/Cys homozygotes (OR 18.33; 95 % CI 9.38–35.81; $p<.0001$) and *XRCC1* Trp/Trp homozygotes (OR 20.50; 95 % CI 10.17–41.32; $p<.0001$). Furthermore, G1 ovarian cancers displayed an overrepresentation of Cys and Trp allele. In conclusion, *hOGG1* Ser326Cys and *XRCC1* Arg194Trp polymorphisms may be regarded as risk factors of ovarian cancer.

Keywords Ovarian cancer · hOGG1 · XRCC1 · Polymorphism

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Introduction

Low cancer detection rates in their initial stages in Poland result in much higher cancer mortality than in Western Europe or the USA [1, 2]. This phenomenon seems to be a matter of great concern principally because current medicine provides effective management strategies for almost every type of cancer as long as it is diagnosed early [2].

We observed that the diagnosis of ovarian cancer in Poland is set mostly in its advanced stage, largely due to the fact that both patient and physician often ignore the first—predominantly non-characteristic—symptoms and signs. Although much research efforts have been lately focused on ovarian cancer, still no effective screening algorithms have been identified, and therefore, there is a clear need to find such ones, also including new risk factors.

Investigation of variability in DNA repair genes may provide new possibilities for risk evaluation in cancer, as well as its prophylactics and therapy [3–5]. For example, polymorphisms in DNA repair genes are to some extent related to various types of cancer [6]. However, the exact function of these polymorphic variants still remains unclear.

The repair process usually encompasses two stages: the excision of lesion and the repair synthesis. This is how repair

system acts via base-excision repair (BER), nucleotide excision repair (NER) and mismatch repair (MMR). Totally converse is the repair system activity by direct lesion reversal, in which there is merely a single-stage process with maintained integrity of the DNA phosphodiester chain and the system of recombination repair (HR).

The repair by BER enables removal of a number of serious DNA lesions, including the oxidated and N-alkylated nitrogenous bases (e.g. thymine glycol, 8-oxoguanine, 7-methylguanine, 3-methyladenine), uracil and apurin/pyrimidin (AP) sites [7, 8].

Uterine body cancer formation may be associated with endometrial exposure to exogenous and endogenous oestrogens [9]. The oestrogens may bring about oxidative DNA defects, which are eliminated by the BER mechanism [10, 11].

The *hOGG1* and *XRCC1* genes encode a protein which participates in DNA repair via BER [10, 12]. According to current literature, single nucleotide polymorphisms in these two BER genes are correlated with various cancers [13–25].

In the presented literature data, the association between *XRCC1* and *hOGG1* polymorphisms and risk of ovarian cancer, aggressiveness of the tumour, patient prognosis and therapeutic consequences is also widely discussed [26–32]. Unfortunately, the results of research concerning the associations between *XRCC1* and *hOGG1* polymorphisms with either pathological ovarian tumour features or cancer risk have been contradictory, and no firm conclusions can be drawn from them [26–32]. Therefore, more research is needed to better understand the possible biological mechanisms of development and the role of both polymorphisms in this rare, neoplastic transformation process.

The aim of this study was to determine single nucleotide polymorphisms in these two BER genes (single nucleotide polymorphisms (SNPs): Ser326Cys (rs13181) and Arg194Trp (rs1799782), respectively) and to identify the correlation between them and the overall risk, grading and staging of ovarian cancer in Polish women.

Materials and methods

Patients

Seven hundred twenty patients with histologically proven diagnosis of ovarian cancer were included in the study. Patient's characteristics are presented in Table 1. Formalin-fixed paraffin-embedded (FFPE) tumour tissue specimens were obtained from women with ovarian cancer who were treated in the Department of Surgical Gynaecology and Gynaecologic Oncology, Institute of Polish Mothers Memorial Hospital, between 1998 and 2013. The age of patients ranged from 38 to 82 years (mean age 54.2±10.11 years). Ovarian cancer cases are categorized by stage, which indicates how far the cancer has spread, and by grade which describes how active the cancer is. All diagnosed tumours were staged according to the criteria of the International Federation of Gynaecology and Obstetrics (FIGO) [33]. Histological typing and grading were done according to the WHO classification [34]. In addition, normal ovarian tissue was obtained from women undergoing laparoscopy for non-malignant conditions. 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 from normal ovarian tissue (n=720) served as

Table 1 The characteristic summary of ovarian cancer patients[a]

Characteristics	Number of cases (%)
Histology of tumour	
Serous	196 (27.2)
Mucinous	68 (9.4)
Endometrioid	169 (23.5)
Clear cell	71 (9.9)
Undifferentiated	151 (21.0)
Other	65 (9.0)
Number of pregnancy	
1	292 (41 %)
2–3	248 (34 %)
>4	180 (25 %)
Ascites	
Present	298 (41 %)
Absent	422 (59 %)
Use of hormone replacement therapy—HRT	
Yes	438 (61 %)
No	282 (39 %)
Grading	
G1	270 (38 %)
G2	430 (60 %)
G3	20 (2 %)
Staging	
I	290 (40 %)
II	400 (56 %)
III	30 (4 %)
Size of tumour	
>5 cm	270 (38 %)
<5 cm	450 (62 %)
Tumour wall infiltration/injury	
Present	274 (38 %)
Absent	446 (62 %)
Menarche	
<12 years old	390 (54 %)
>12 years old	330 (46 %)

Italics designate a subgroup of investigated patients

[a] n=720

control (age range 39–83, mean age 51.41±18.21 years). The test group comprised not related individuals without chronic diseases and with no history of ovarian or any other tumours. The Local Ethical Committee approved the study, and each patient gave a written consent for participation in the study (approval number 240/04, 05.02.2004).

DNA isolation

DNA was extracted from the material, using a commercially available QIAamp DNA FFPE Tissue Kit (Qiagen GmbH, Hilden, Germany), according to the manufacturer's instruction.

Determination of hOGG1 genotype

Polymorphism Ser326Cys of *hOGG1* gene was determined by polymerase chain reaction (PCR)-based restriction fragment length polymorphism (PCR-RFLP), using the following primers 5′-GGAAGGTGCTTGGGGAAT-3′ and 5′-ACTG TCACTAGTCTCACCAG-3′. The 25-μL PCR mixture contained about 100 ng of DNA, 12.5 pmol of each primer, 0.2 mmol/L of deoxynucleotide triphosphates (dNTPs), 2 mmol/L of $MgCl_2$ and 1 U of Taq DNA polymerase. PCR products were electrophoresed in a 2 % agarose gel and visualised by ethidium bromide staining. Only one 100-bp fragment was seen in subjects with the Cys/Cys genotype. In subjects with the Ser/Cys genotype, two bands of 100 and 200 bp were seen, whereas in those subjects homozygous for the Ser variant (Ser/Ser), only one 200-bp PCR fragment is seen. All PCR were carried out in a DNA Thermal Cycler (GeneAmp PCR System 2400; Perkin-Elmer, Norwalk, CT, USA). After an initial denaturation at 95 °C for 5 min, 35 cycles of amplification with denaturation at 95 °C for 30 s, annealing at 56 °C for 30 s and extension at 72 ° C for 30 s were performed, followed by a final extension step of 7 min at 72 ° C. The PCR product was digested overnight with 1 U of *Sat*I (Fermentas, Vilnius, Lithuania) at 37 °C.

Determination of XRCC1 genotype

Polymorphism Arg194Trp of *XRCC1* gene was determined by PCR-RFLP, using the following primers forward 5′-GCCCGTCCCAGGTA-3′ and reverse 5′-AGCCCCAAGA CCCTTTCACT-3′. The PCR was carried out in a PTC-100 TM (MJ Research, INC, Waltham, MA, USA) thermal cycler. PCR amplification was performed in the final volume of 25 μl of reaction mixture, which contained 100 ng of genomic DNA, 0.2 μmol of each primer (ARK Scientific GmbH Biosystems, Darmstadt, Germany), 2.5 mM of $MgCl_2$, 1 mM of dNTPs and 1 unit of Taq Polymerase (Qiagen GmbH, Hilden, Germany). PCR cycle conditions were the following: 95 °C for 30 s, 62 °C for 30 s and 72 °C for 40 s, repeated in 35 cycles. After digestion with *Pvu*II (New England Biolabs, Ipswich, MA, USA) for 4 h at 37 °C, the samples were run on 2 % agarose gel and visualised by ethidium bromide staining. The cleavage of the *XRCC1* fragment with *Pvu*II (New England Biolabs, Ipswich, MA, USA) produced bands of 292/174/21, 313/292/174/21 and 313/174 bp corresponding to the Arg/Arg, Arg/Trp and Trp/Trp genotypes, respectively.

Statistical analysis

The allelic frequencies were estimated by gene counting, and the genotypes were scored. The observed numbers of each *hOGG1* and *XRCC1* genotype were compared with those expected for a population in Hardy–Weinberg equilibrium (HWE) by using the Chi-square test. Genotype frequencies in the study cases and the controls were compared by the Chi-square test. Genotype specific risks were estimated as odds ratios (OR) with associated 95 % intervals (CI) by unconditional logistic regression. Statistical comparisons were performed using Fisher's exact test. p values <0.05 were considered statistically significant. All statistical analyses were performed using the STATISTICA 6.0 software (Statsoft, Tulsa, OK, USA).

Results

Table 2 shows the distribution of genotypes and the frequency of alleles of *hOGG1* gene polymorphisms in patients and controls. A weak association was observed between ovarian cancer occurrence and Cys/Cys and Ser/Cys genotypes with a stronger correlation for Cys/Cys than Ser/Cys heterozygotes. Variant Cys allele of *hOGG1* increased the overall cancer risk ($p<0.05$).

No statistically significant differences between patients and controls were observed in genotype frequencies of *XRCC1* Arg194Trp polymorphism (Table 3). Within controls, the genotype distribution did not differ significantly ($p>0.05$) from those expected by the Hardy–Weinberg equilibrium (HWE). The observed genotype frequencies of *XRCC1* Arg194Trp SNP in patients were in agreement with HWE ($p>0.05$), but the observed genotype frequencies of *hOGG1* Ser326Cys polymorphism departed from Hardy–Weinberg equilibrium ($p<0.05$).

Moreover, histological grading was related to *hOGG1* Ser326Cys and the *XRCC1* Arg194Trp polymorphisms. Grading was assessed in all cases ($n=720$), with a distribution as follows: G1—270 cases, G2—430 cases and G3—20 cases. Grades 2 and 3 were accounted together for statistical analysis (Table 4). A correlation was observed between the *hOGG1* Ser326Cys and *XRCC1* Arg194Trp genotype distribution and cancer progression assessed by ovarian cancer

Table 2 Distribution of Lys/Lys, Lys/Gln and Gln/Gln genotypes and frequencies of the Ser and Cys alleles of *hOGG1* gene in patients with ovarian cancer and control

	Patients (n=720)		Controls (n=720)			
hOGG1-Ser326Cys	Number	Percent	Number	Percent	OR (95 % CI)[a]	p[b]
Ser/Ser	160	22	196	27	1.00 Ref	
Ser/Cys	160	22	340	47	0.57 (0.43–0.76)	0.0002
Cys/Cys	400	56	184	26	2.66 (2.02–3.49)	<.0001
Ser	480	33	732	51	1.00 Ref	
Cys	960	67	506	49	2.89 (2.47–3.38)	<.0001

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

[b] Chi-square

grading (p<0.05). G1 patients displayed a statistically significant (p<0.05) increased frequency of Cys/Cys (OR 18.33; 95 % CI 9.38–35.81; p<.0001) and Trp/Trp homozygotes (OR 20.50; 95 % CI 10.17–41.32; p<.0001). Furthermore, G1 ovarian cancer patients had a general overrepresentation of Cys (89 %) and Trp (89 %) alleles (p<0.05).

However, the results did not reveal any association between *hOGG1* and *XRCC1* polymorphisms and cancer staging (p>0.05). Nor did our outcomes demonstrate any statistically significant correlation (p>0.05) between *hOGG1* and *XRCC1* polymorphisms and the risk factors for ovarian cancer, such as number of pregnancies, tumour size, age, menarche and previous history of ovarian cancer. Our data did not demonstrate any statistically significant correlation between *hOGG1* and *XRCC1* polymorphisms and the risk factors for cancer recurrence or survival, such as ascites and tumour wall infiltration (p>0.05).

Discussion

Protein defects that directly impair DNA repair mechanisms and their control are strongly associated with an increased risk of malignancies [35]. The genes encoding DNA lesion repair systems play a key role in maintaining the genome integrity and controlling the repair of mutation-affected DNA [36]. Without such ones, DNA would continue to accumulate errors which would shortly result in cell's inability of further survival [37]. Proper DNA repair mechanisms ensure genomic integrity and are crucial in its protection against effects of carcinogenic factors [38]. Polymorphisms of repair genes may influence the performance of the repair process and thus influence the individual susceptibility to cancer [39].

There are more than 130 DNA repair genes identified, among which numerous single nucleotide polymorphisms (SNP) are already discovered. In order to define the role they play in cancer risk, it is necessary to define the functional significance these genetic variants have. Investigation of variability in DNA repair genes may therefore provide new possibilities for risk evaluation in cancer, as well as its prophylactics and therapy.

This study was an attempt to determine whether SNPs in BER pathway (*hOGG1*-Ser326Cys, *XRCC1*-Arg194Trp) are associated with the risk of ovarian cancer in Polish women.

The *hOGG1*-Ser326Cys and *XRCC1*-Arg194Trp polymorphisms may influence the performance of the process, by which defects of genetic material are removed, thus influencing the individual susceptibility to formation of neoplastic disease [40–43].

Common variants within *hOGG1*, including Ser326Cys polymorphism, have been identified as potential cancer susceptibility loci in recent studies, although association results are controversial [44–48].

Table 3 Distribution of Arg/Arg, Arg/Trp and Trp/Trp genotypes and frequencies of the Arg and Trp alleles of *XRCC1* gene in patients with ovarian cancer and control

	Patients (n=720)		Controls (n=720)			
XRCC1-Arg194Trp	Number	Percent	Number	Percent	OR (95 % CI)[a]	p[b]
Arg/Arg	180	25	190	26	1.00 Ref	
Arg/Trp	360	50	334	46	1.13 (0.88–1.46)	0.348
Trp/Trp	180	25	196	28	0.96 (0.72–1.29)	0.887
Arg	720	50	714	49	1.00 Ref	
Trp	720	50	726	51	0.98 (0.84–1.13)	0.862

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

[b] Chi-square

Table 4 Dependence of *hOGG1* and *XRCC1* gene polymorphism genotypes and allele frequency on tumour grade in patients with ovarian cancer[a]

	Ovarian cancer patients			
Grade[b]	G1 (n=270)	G2 + G3 (n=450)	OR (95 % CI)[c]	p[d]
hOGG1-Ser326Cys	Number (%)	Number (%)		
Ser/Ser	10 (4)	150 (33)	1.00 Ref	
Ser/Cys	40 (15)	120 (27)	5.00 (2.40–10.41)	<.0001
Cys/Cys	220 (81)	180 (40)	18.33 (9.38–35.81)	<.0001
Ser	60 (11)	420 (47)	1.00 Ref	
Cys	480 (89)	480 (53)	7.00 (5.19–9.43)	<.0001
XRCC1-Arg194Trp				
Arg/Arg	9 (3.3)	151 (34)	1.00 Ref	
Arg/Trp	41 (15.2)	119 (26)	5.78 (2.70–12.36)	<.0001
Trp/Trp	220 (81.5)	180 (40)	20.50 (10.17–41.32)	<.0001
Arg	59 (11)	421 (47)	1.00 Ref	
Trp	481 (89)	479 (53)	7.16 (5.30–9.67)	<.0001

[a] n=720

[b] According to FIGO criteria

[c] Crude odds ratio (OR) and 95 % CI=confidence interval at 95 %

[d] Chi-square

In the current study, a PCR method was used to analyse 720 ovarian cancer patients for the *hOGG1*-Ser326Cys polymorphism. We demonstrated that *hOGG1*-Cys/Cys genotype was associated with an increased risk of ovarian cancer. Our analysis revealed that allele Cys of the investigated polymorphism in women with ovarian cancer is significantly more frequent, and allele Ser is significantly less frequent than in lean controls. Additionally, a correlation between the abovementioned polymorphisms and ovarian cancer grading was discovered. The frequencies of genotypes Cys/Cys in hOGG1 were significantly high in the patients with grade 1 but not in the patients with grades 2 and 3.

The observed genotype frequencies of *hOGG1* polymorphism in the patients were not in agreement with Hardy–Weinberg equilibrium. It is caused by a very high prevalence of *hOGG1* Cys/Cys genotype in the examined Polish population.

The latest literature reports indicate a role of the Ser326Cys polymorphism of *hOGG1* gene for the development of sporadic epithelial ovarian cancer (EOC). Chen et al. evaluated the Ser326Cys (c.977C>G) polymorphism in 420 patients with EOC and in a group of 840 controls. They demonstrated that the c.977G/G genotype was more frequently observed in Chinese patients with type II EOC than in patients with type I EOC [26].

This is not consistent with our study results which clearly indicate that *hOGG1*-Ser326Cys genotype is associated with grading 1 (G1) Polish patients. Our study was performed on an ethnically homogenous population, which may improve our knowledge, regarding to what an extent the genotype-phenotype relationship variations are population-related. We supposed that ethnicity may be significantly associated with ovarian cancer risk and the genotype of *hOGG1* gene.

The second studied polymorphism of *XRCC1* gene, namely Arg194Trp, was associated with the occurrence of ovarian cancer. In our study, a correlation was observed between the genotypes of *XRCC1* Arg194Trp polymorphism and ovarian cancer grading: Trp allele was more frequent in G1 tumours than in remaining grades (2 and 3) analysed together.

The performed studies not only contribute to a better understanding of the molecular base of ovarian cancer but also present with some clinical implications as well. According to our data, Ser326Cys and Arg194Trp polymorphism may serve as one of the genetic markers responsible for screening low-risk asymptomatic women. A cumulative assessment of the polymorphisms provides a chance to identify a group of patients with low risk of the abovementioned cancer type, what may become extremely useful in clinical practice, namely in an individual assessment of the risk in asymptomatic carriers. The results of studies on the polymorphisms of the analysed DNA repair genes may contribute in the diagnostics and prophylactics of neoplasm, mainly by a potential algorithm project, taking into account the risk assessment of their incidence. The results will be used to improve earlier diagnostics of ovarian cancer and, eventually, to extend the survival of patients.

In literature, several of researches suggest that polymorphisms of *XRCC1* gene may contribute to ovary carcinogenesis. However, the reported results have rather been inconsistent [27–30].

In Poland, only one report has so far been published on this issue, describing a study of the *XRCC1* polymorphisms in a

group of 146 ovarian cancer patients. The obtained results suggest no relationship between ovarian cancer and the abovementioned polymorphisms of *XRCC1* gene in the population of the Polish women [27].

Kim et al. examined the role of single nucleotide polymorphism (SNP) in *XRCC1* repair gene and the risk of ovarian cancer. In the reported study, Arg194Trp and Arg399Gln gene polymorphisms, of *XRCC1* gene, were associated with survival of ovarian cancer with chemotherapy [49]. Similarly, Khrunin et al., while analysing the *XRCC1* polymorphisms, provided evidence for the Arg194Trp and Arg399Gln genotypes to be most closely associated with survival of ovarian cancer with chemotherapy, observed in the Russian population [50]. Other experimental studies conducted in Chinese reported the association of *XRCC1*-Arg194Trp and *XRCC1*-Arg399Gln gene polymorphisms with survival of ovarian cancer treated by adjuvant chemotherapy [31–33].

Our results suggest an important role of *hOGG1*-Ser326Cys and of *XRCC1*-Arg194Trp gene polymorphisms in ovarian cancer pathophysiology and aetiology. Our chief research achievement has been an indication which genes, participating in the main DNA defect repair pathways, and which SNPs of the genes may participate in formation of ovarian cancer and which genes, which participate in DNA repairs, do not exert any effect on the abovementioned neoplastic transformation processes. These "positive" and "negative" markers of neoplasia may play a certain role in defining the risk factors for ovarian carcinoma. Further research on SNP in ovarian cancer is warranted to obtain more conclusive outcomes.

Conflicts of interest None

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
2. Abdulrahman Jr GO, Rahman GA. Epidemiology of breast cancer in Europe and Africa. J Cancer Epidemiol. 2012;2012:915610.
3. Limp-Foster M, Kelley MR. DNA repair and gene therapy: implications for translational uses. Environ Mol Mutagen. 2000;35:71–81.
4. Dietlein F, Thelen L, Reinhardt HC. Cancer-specific defects in DNA repair pathways as targets for personalized therapeutic approaches. Trends Genet. 2014;30:326–39.
5. Marin JJ, Briz O, Monte MJ, Blazquez AG, Macias RI. Genetic variants in genes involved in mechanisms of chemoresistance to anticancer drugs. Curr Cancer Drug Targets. 2012;12:402–38.
6. Au WW, Salama SA, Sierra-Torres CH. Functional characterization of polymorphisms in DNA repair genes using cytogenetic challenge assays. Environ Health Perspect. 2003;111:1843–50.
7. Wilson DM, Bohr VA. The mechanics of base excision repair, and its relationship to aging and disease. DNA Repair (Amst). 2007;6:544–59.
8. Almeida KH, Sobol RW. A unified view of base excision repair: lesion-dependent protein complexes regulated by post-translational modification. DNA Repair (Amst). 2007;6:695–711.
9. Martucci CP, Fishman J. P450 enzymes of estrogen metabolism. Pharmacol Ther. 1993;57:237–57.
10. Yu Z, Chen J, Ford BN, Brackley ME, Glickman BW. Human DNA repair systems: an overview. Environ Mol Mutagen. 1999;33:3–20.
11. Cooke MS, Evans MD, Dizdaroglu M, Lunec J. Oxidative DNA damage: mechanisms, mutation, and disease. FASEB J. 2003;17:1195–214.
12. Wood RD, Mitchell M, Sgouros J, Lindahl T. Human DNA repair genes. Science. 2001;291:1284–8.
13. Patel AV, Calle EE, Pavluck AL, Feigelson HS, Thun MJ, Rodriguez C. A prospective study of XRCC1 (X-ray crosscomplementing group 1) polymorphisms and breast cancer risk. Breast Cancer Res. 2005;7:1168–73.
14. Kohno T, Kunitoh H, Toyama K, Yamamoto S, Kuchiba A, Saito D, et al. Association of the OGG1-Ser326Cys polymorphism with lung adenocarcinoma risk. Cancer Sci. 2006;97:724–8.
15. Poplawski T, Arabski M, Kozirowska D, Blasinska-Morawiec M, Morawiec Z, Morawiec-Bajda A, et al. DNA damage and repair in gastric cancer—a correlation with the hOGG1 and RAD51 genes polymorphisms. Mutat Res. 2006;601:83–91.
16. De Ruyck K, Szaumkessel M, De Rudder I, Dehoorne A, Vral A, Claes K, et al. Polymorphisms in base-excision repair and nucleotide-excision repair genes in relation to lung cancer risk. Mutat Res. 2007;631:101–10.
17. Pachouri SS, Sobti RC, Kaur P, Singh J. Contrasting impact of DNA repair gene XRCC1 polymorphisms Arg399Gln and Arg194Trp on the risk of lung cancer in the north-Indian population. DNA Cell Biol. 2007;26:186–91.
18. Yin J, Vogel U, Ma Y, Qi R, Sun Z, Wang H. The DNA repair gene XRCC1 and genetic susceptibility of lung cancer in a northeastern Chinese population. Lung Cancer. 2007;56:153–60.
19. Hatt L, Loft S, Risom L, Møller P, Sørensen M, Raaschou-Nielsen O, et al. OGG1 expression and OGG1 Ser326Cys polymorphism and risk of lung cancer in a prospective study. Mutat Res. 2008;639:45–54.
20. Ming-Shiean H, Yu JC, Wang HW, Chen ST, Hsiung CN, Ding SL, et al. Synergistic effects of polymorphisms in DNA repair genes and endogenous estrogen exposure on female breast cancer risk. Ann Surg Oncol. 2010;17:760–71.
21. Bewick MA, Lafrenie RM, Conlon MS. Nucleotide excision repair polymorphisms and survival outcome for patients with metastatic breast cancer. J Cancer Res Clin Oncol. 2011;137:543–50.
22. Zhu S, Zhang H, Tang Y, Wang J. Polymorphisms in XPD and hOGG1 and prostate cancer risk: a meta-analysis. Urol Int. 2012;89:233–40.
23. Xue X, Yin Z, Lu Y, Zhang H, Yan Y, Zhao Y, et al. The joint effect of hOGG1, APE1, and ADPRT polymorphisms and cooking oil fumes on the risk of lung adenocarcinoma in Chinese nonsmoking females. PLoS One. 2013;8, e71157.
24. Wang W, Dang S, Li Y, Sun M, Jia X, Wang R, et al. hOGG1 Ser326Cys polymorphism and risk of hepatocellular carcinoma among East Asians: a meta-analysis. PLoS One. 2013;8, e60178.
25. Mao Y, Xu X, Lin Y, Chen H, Wu J, Hu Z, et al. Quantitative assessment of the associations between XRCC1 polymorphisms and bladder cancer risk. World J Surg Oncol. 2013;11:58.
26. Chen X, Liu X, Wang J, Guo W, Sun C, Cai Z, et al. Functional polymorphisms of the hOGG1 gene confer risk to type 2 epithelial ovarian cancer in Chinese. Int J Gynecol Cancer. 2011;21:1407–13.
27. Jakubowska A, Gronwald J, Menkiszak J, Górski B, Huzarski T, Byrski T, et al. BRCA1-associated breast and ovarian cancer risks in Poland: no association with commonly studied polymorphisms. Breast Cancer Res Treat. 2010;119:201–11.

28. Siddiqui-Jain A, Bliesath J, Macalino D, Omori M, Huser N, Streiner N, et al. CK2 inhibitor CX-4945 suppresses DNA repair response triggered by DNA-targeted anticancer drugs and augments efficacy: mechanistic rationale for drug combination therapy. Mol Cancer Ther. 2012;11:994–1005.
29. Kang S, Sun HY, Zhou RM, Wang N, Hu P, Li Y. DNA repair gene associated with clinical outcome of epithelial ovarian cancer treated with platinum-based chemotherapy. Asian Pac J Cancer Prev. 2013;14:941–6.
30. Miao J, Zhang X, Tang QL, Wang XY, Kai L. Prediction value of XRCC 1 gene polymorphism on the survival of ovarian cancer treated by adjuvant chemotherapy. Asian Pac J Cancer Prev. 2012;13:5007–10.
31. Li K, Li W. Association between polymorphisms of XRCC1 and ADPRT genes and ovarian cancer survival with platinum-based chemotherapy in Chinese population. Mol Cell Biochem. 2013;372:27–33.
32. Cheng CX, Xue M, Li K, Li WS. Predictive value of XRCC1 and XRCC3 gene polymorphisms for risk of ovarian cancer death after chemotherapy. Asian Pac J Cancer Prev. 2012;13:2541–5.
33. Pecorelli S, Benedet JL, Creasman WT, Shepherd JH. FIGO staging of gynecologic cancer. 1994–1997 FIGO Committee on Gynecologic Oncology. International Federation of Gynecology and Obstetrics. Int J Gynaecol Obstet. 1999;65:243–9.
34. Scully R. Histological typing of ovarian tumours. Berlin: Springer; 1999.
35. Hakem R. DNA-damage repair; the good, the bad, and the ugly. EMBO J. 2008;27:589–605.
36. Clancy S. DNA damage & repair: mechanisms for maintaining DNA integrity. Nat Educ. 2008;1:103.
37. Brown TA. Chapter 14. In: Department of Biomolecular Sciences, UMIST, editor. Genomes. 2nd ed. Manchester: Oxford Wiley-Liss; 2002.
38. Rastogi RP, Richa, Kumar A, Tyagi MB, Sinha RP. Molecular mechanisms of ultraviolet radiation-induced DNA damage and repair. J Nucleic Acids. 2010;2010:592980.
39. Frank SA. Genetic predisposition to cancer—insights from population genetics. Nat Rev Genet. 2004;5:764–72.
40. Abdel-Rahman SZ, El-Zein RA. The 399Gln polymorphism in the DNA repair gene XRCC1 modulates the genotoxic response induced in human lymphocytes by the tobacco-specific nitrosamine NNK. Cancer Lett. 2000;159:63–71.
41. Wang Y, Spitz MR, Zhu Y, Dong Q, Shete S, Wu X. From genotype to phenotype: correlating XRCC1 polymorphisms with mutagen sensitivity. DNA Repair. 2003;2:901–8.
42. Vodicka P, Stetina R, Polakova V, Tulupova E, Naccarati A, Vodickova L, et al. Association of DNA repair polymorphisms with DNA repair functional outcomes in healthy human subjects. Carcinogenesis. 2007;28:657–64.
43. Silva SN, Moita R, Azevedo AP, Gouveia R, Manita I, Pina JE, et al. Menopausal age and XRCC1 gene polymorphisms: role in breast cancer risk. Cancer Detect Prev. 2007;31:303–9.
44. Tsai CW, Tsai MH, Tsou YA, Shih LC, Tseng HC, Chang WS, et al. The joint effect of smoking and hOGG1 genotype on oral cancer in Taiwan. Anticancer Res. 2012;32:3799–803.
45. Ji C, Liu Z, Chen H, Guo H, Liu C. An association between hOGG1 Ser326Cys polymorphism and the risk of bladder cancer in non-smokers: a meta-analysis. BMC Cancer. 2012;12:335.
46. Wang W, Wang M, Chen Y, Zhang Z, Wang S, Xu M, et al. The hOGG1 Ser326Cys polymorphism contributes to cancer susceptibility: evidence from 83 case–control studies. Mutagenesis. 2012;27:329–36.
47. Zhang M, Mo R. Association of hOGG1 Ser326Cys polymorphism with colorectal cancer risk: an updated meta-analysis including 5235 cases and 8438 controls. Tumour Biol. 2014;35:12627–33.
48. Yin ZB, Hua RX, Li JH, Sun C, Zhu JH, Su X, et al. Smoking and hOGG1 Ser326Cys polymorphism contribute to lung cancer risk: evidence from a meta-analysis. Tumour Biol. 2014;35:1609–18.
49. Kim HS, Kim MK, Chung HH, Kim JW, Park NH, Song YS, et al. Genetic polymorphisms affecting clinical outcomes in epithelial ovarian cancer patients treated with taxanes and platinum compounds: a Korean population-based study. Gynecol Oncol. 2009;113:264–9.
50. Khrunin AV, Moisseev A, Gorbunova V, Limborska S. Genetic polymorphisms and the efficacy and toxicity of cisplatin-based chemotherapy in ovarian cancer patients. Pharmacogenomics J. 2010;10:54–61.