Online journal ISSN - 1676-5680
GMR Genetics and Molecular Research
EVOLUTION AND TECHNOLOGY

DNA repair genes in endometriosis

R. Attar[1], C. Cacina[2], S. Sozen[2], E. Attar[3] and B. Agachan[2]

[1]Department of Obstetrics and Gynecology,
Yeditepe University Hospital, Istanbul, Turkey
[2]Department of Molecular Medicine, Istanbul University,
Institute for Experimental Medicine, Istanbul, Turkey
[3]Department of Obstetrics and Gynecology,
Division of Reproductive Endocrinology and Infertility,
Istanbul University, Istanbul Medical School, Istanbul, Turkey

Corresponding author: B. Agachan
E-mail: agachanb@yahoo.com

Genet. Mol. Res. 9 (2): 629-636 (2010)
Received January 4, 2010
Accepted February 5, 2010
Published April 6, 2010
DOI 10.4238/vol9-2gmr779

ABSTRACT. Several polymorphisms in the DNA repair gene are thought to have significant effects on cancer risk. We investigated the association of polymorphisms in the DNA repair genes XRCC1 Arg399Gln, XRCC3 Thr241Met, XPD Lys751Gln, XPG Asp1104His, APE1 Asp148Glu, and HOGG1 Ser326Cys with endometriosis risk. Genotypes were determined by PCR-RFLP assays in 52 patients with endometriosis and 101 age-matched healthy controls. Although there were no significant ($P > 0.05$) differences in the frequencies of genotypes or alleles of APE1, XRCC1, XPD, XPG, and HOGG1 genes between patients and controls, the frequency of the XRCC3 Thr/Thr genotype was significantly greater in endometriosis patients compared with controls ($P = 0.005$). XRCC3 Thr/Met genotypes ($P = 0.022$), and the Met allele ($P = 0.005$) seem to have a protective role against endometriosis. The distributions of genotypes and alleles of the genes APE1, XRCC1, XRCC3, XPD, XPG, and HOGG1 were not significantly associated with the different stages of endometriosis ($P > 0.05$). We conclude that the XRCC3 Thr/Thr genotype is associated with endometriosis in Turkish women.

Key words: DNA repair; XRCC3 Thr/Thr; Endometriosis; Polymorphism

INTRODUCTION

Endometriosis is a common, benign, estrogen-dependent, chronic gynecological disorder associated with pelvic pain and infertility. It is characterized by the presence of uterine endometrial tissue outside the uterine cavity (Giudice and Kao, 2004). Although multiple theories exist regarding the etiology of endometriosis, the exact etiology and pathogenesis remain uncertain. Recently, several lines of genetic-association studies have revealed associations between the development of endometriosis and certain genetic polymorphisms. However, the genes that play a role in susceptibility to the development and progression of endometriosis are still unknown (Hsieh et al., 2005; Luisi et al., 2006).

Oxidative stress has been proposed as a potential factor involved in the pathophysiology of endometriosis (Lambrinoudaki et al., 2009). Several studies indicate that antioxidant defenses may be altered in endometriosis, as suggested by aberrant expression of endometrial antioxidant enzymes and lower levels of the antioxidant vitamin E in peritoneal fluid (Van Langendonckt et al., 2002; Lambrinoudaki et al., 2009). Excess reactive oxygen species may induce oxidative DNA damage, DNA strand breaks, base modifications, and chromosomal aberrations (Marnett, 2000). For repair of oxidative DNA damage, human cells are supported by five DNA repair systems: direct reversal, mismatch repair, double-strand break repair, base excision repair (BER), and nucleotide excision repair (NER) (Wood et al., 2001). Nearly all oxidatively induced DNA lesions, as well as single-strand breaks, are repaired via the BER pathway in organisms ranging from *Escherichia coli* to mammals (Krokan et al., 2000; Hazra et al., 2007). The human oxoguanine glycosylase 1 (hOGG1), APE1 and X-ray repair cross-complementing 1 (XRCC1) genes are key genes in the BER pathway (Wood et al., 2001). Human 8-oxoguanine glycosylase 1 (hOGG1) encoded by the hOGG1 gene can directly remove 8-hydroxy-2-deoxyguanine from damaged DNA as a part of the BER pathway (Kohno et al., 1998; Yamane et al., 2004). XRCC1 is a multidomain protein that repairs single-strand breaks in DNA (Kubota et al., 1996; Masson et al., 1998). APE1 is the rate-limiting enzyme in the BER pathway. The gene encoding APE1 is located on chromosome 14q11.2-q12 and encodes a 317-amino acid protein (Ramana et al., 1998). The XRCC3 protein functions in the homologous DNA double-strand break repair pathway and directly interacts with and stabilizes Rad51 (Bishop et al., 1998). NER is the major pathway in humans for the removal of cyclopyrimidine dimers and 6-4 photoproducts produced by ultraviolet (UV) light and a wide variety of bulky lesions formed by chemical agents (Friedberg et al., 1995). The NER pathway consists of 30 proteins involved in DNA damage recognition, incision, DNA ligation, and resynthesis (Costa et al., 2003). The NER pathway consists of several genes termed xeroderma pigmentosum (XP) or excision repair cross complementing (ERCC) where XPA, ERCC1, ERCC2/XPD, ERCC4/XPF, and ERCC5/XPG are central (Hanawalt et al., 2003).

Endometriosis displays some features of metaplasia and tumorigenesis, and it can be suggested that some genetic variants of DNA repair genes may contribute to the pathogenesis of endometriosis. For this reason, we investigated the association between polymorphisms in different DNA repair pathway genes, namely XRCC1 Arg399Gln, XRCC3 Thr241Met, XPD Lys751Gln, XPG Asp1104His, APE1 Asp148Glu, HOGG1 Ser326Cys, and endometriosis risk.

MATERIAL AND METHODS

Subjects

One hundred and fifty-three women of reproductive age undergoing laparoscopy for unexplained infertility, pelvic pain, ultrasonographically identified adnexal mass, or tubal ligation at the Obstetrics and Gynecology Department of I.U. Istanbul Medical School were included in the study. One hundred and one women (mean age 38.43 ± 7.23 years) who did not have endometriosis served as the control group. The endometriosis group (mean age 35.20 ± 9.04 years) consisted of 52 women: 9 at stage I, 4 at stage II, 16 at stage III, and 23 at stage IV. Diagnosis of endometriosis was made on the basis of laparoscopic findings. The revised American Fertility Society staging system was used for staging (Anonymous, 1997). All participants signed an informed consent form before enrollment and Institutional Ethics Committee approval was obtained for the study.

Polymorphism analysis

Blood samples from all study participants were collected in EDTA-containing tubes. Genomic DNA was extracted from peripheral whole blood according to the salting-out technique (Miller et al., 1988). The genotypes were determined by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method and primers, annealing temperature, length of amplified fragments, restriction pattern, and restriction enzymes used are listed in Table 1 (Sturgis et al., 1999; Hu et al., 2002; Le Marchand et al., 2002; Mort et al., 2003; Yeh et al., 2005). PCR was done using 50 ng genomic DNA in a 25-µL reaction mixture containing 20 mM Tris-HCl, 50 mM KCl, 20 mM $MgCl_2$, 0.3 mM each dNTP, 0.3 mM each primer and 0.2 U Taq DNA polymerase. The temperature conditions for PCR were established as denaturation at 94°C for 30 s, annealing for 30 s, elongation at 72°C for 30 s and final extension at 72°C for 5 min. The amplified fragments were digested with appropriate restriction endonucleases and analyzed. The digested PCR products were resolved on 3% agarose gels containing ethidium bromide and visualized under UV light. Each gel was read by two researchers independently. If there was disagreement, genotyping was repeated.

Table 1. Primer sequences, conditions for amplification, restriction pattern, and restriction enzymes used.

Polymorphisms	Primers (forward and reverse)	Annealing temperature (°C)	PCR product	Restriction enzyme	Restriction pattern (bp)
APE Asp148Glu	5'-CTGTTTCATTTCTATAGGCTA-3' 5'-AGGAACTTGCGAAAGGCTTC-3'	52°C	164 bp	FspBI (*Mae*I)	Asp/Asp: 164 bp Asp/Glu: 164 bp, 144 bp, 20 bp Glu/Glu: 144 bp, 20 bp
XRCC1 Arg399Gln	5'-GCCAGGGCCCCTCCTTCAA-3' 5'-TACCCTCAGACCCACGAGT-3'	61°C	485 bp	*Pvu*II	Arg/Arg: 485 bp Arg/Gln: 485 bp, 399 bp, 194 bp Gln/Gln: 399 bp, 194 bp
XRCC3 Thr241Met	5'-GGTCGAGTGACAGTCCAAAC-3' 5'-TGCAACGGCTGAGGGTCTT-3'	59°C	456 bp	Hsp92 (*Nla*III)	Thr/Thr: 456 bp Thr/Met: 456 bp, 315 bp, 141 bp Met/Met: 315 bp, 141 bp
XPD Lys751Gln	5'-CCTCTCCCTTTCCTCTGTTC-3' 5'-CAGGTGAGGGGGGACATCT-3'	52°C	734 bp	*Pst*I	Lys/Lys: 734 bp Lys/Gln: 734 bp, 646 bp, 88 bp Gln/ Gln: 646 bp, 88 bp
XPG Asp1104His	5'-GACCTGCCTCTCAGAATCATC-3' 5'-CCTCGCACGTCTTAGTTTCC-3'	62°C	271 bp	*Nla*III	GG: 271 bp GC: 271 bp, 227 bp, 44 bp CC: 227 bp, 44 bp
HOGG1 Ser326Cys	5'-ACTGTCACTAGTCTCACCAG-3' 5'-GGAAGGTGCTTGGGGAAT-3'	60°C	200 bp	*Fnu*4HI	Ser/Ser: 200 bp Ser/Cys: 100 bp, 200 bp Cys/Cys: 100 bp

Statistical analyses

Statistical analyses were performed with SPSS for Windows (version 11.5; SPSS Inc., Chicago, IL, USA). The chi-square test was used to differentiate the genotype and allele frequencies between groups. The Fisher exact test was used if the number in any cell of the 2 x 2 contingency table was <5. Relative risk at 95% confidence intervals (CI) was calculated as the odds ratio (OR). Statistical significance was set at $P < 0.05$.

RESULTS

Table 2 summarizes the distributions of genotypes and alleles of *APE1*, *XRCC1*, *XRCC3*, *XPD*, *XPG*, and *HOGG1* genes in patients with endometriosis and controls. The distributions of the genotypes and alleles of the study groups were in Hardy-Weinberg equilibrium. We did not find any significant differences for *APE1*, *XRCC1*, *XPD*, *XPG*, and *HOGG1* genotype and allele frequencies in patients with endometriosis and controls. The distribution of XRCC3 genotypes in patients was significantly different from that of controls (P = 0.018). XRCC3 Thr/Thr genotype was significantly increased in endometriosis patients compared with the control group (P = 0.005;

Table 2. Distribution of APE1, XRCC1, XRCC3, XPD, XPG, and HOGG1 genotype frequencies in patients with endometriosis and control groups.

Polymorphism	Controls (N = 101)	%	Endometriosis (N = 52)	%	P
APE Asp148Glu					
Asp/Asp	58	57.4%	27	51.9%	
Asp/Glu	31	30.7%	21	40.4%	
Glu/Glu	12	11.9%	4	7.7%	0.42
Asp/Glu+Asp/Asp	89	88.1%	48	92.3%	0.42
Asp/Glu+Glu/Glu	43	42.6%	25	48.1%	0.51
XRCC1 Arg399Gln					
Arg/Arg	86	85.1%	40	76.9%	
Arg/Gln	15	14.9%	12	23.1%	
Gln/Gln	0	0%	0	0%	0.20
Arg/Gln+Arg/Arg	101	100%	52	100%	0
Arg/Gln+Gln/Gln	15	14.9%	12	23.1%	0.20
XRCC3 Thr241Met					
Thr/Thr	24	23.8%	24	46.2%	
Thr/Met	66	65.3%	24	46.2%	
Met/Met	11	10.9%	4	7.7%	0.018
Thr/Met+Thr/Thr	90	89.1%	48	92.3%	0.52
Thr/Met+Met/Met	77	76.2%	28	53.8%	0.005
XPD Lys751Gln					
Lys/Lys	39	38.6%	19	36.5%	
Lys/Gln	50	49.5%	28	53.8%	
Gln/Gln	12	11.9%	5	9.6%	0.85
Lys/Gln+Lys/Lys	89	88.1%	47	90.4%	0.67
Lys/Gln+Gln/Gln	62	61.4%	33	63.5%	0.80
XPG Asp1104His					
Asp/Asp	62	61.4%	34	65.4%	
Asp/His	33	32.7%	13	25.0%	
His/His	6	5.9%	5	9.6%	0.49
Asp/His+Asp/Asp	95	94.1%	47	90.4%	0.40
Asp/His+His/His	39	38.6%	18	34.6%	0.62
HOGG1 Ser326Cys					
Ser/Ser	70	69.3%	35	67.3%	
Ser/Cys	27	26.7%	15	28.8%	
Cys/Cys	4	4%	2	3.8%	0.96
Ser/Cys+Ser/Ser	97	96.0%	50	96.2%	0.97
Ser/Cys+Cys/Cys	31	30.7%	17	32.7%	0.80

χ^2 = 7.99; OR = 2.75; 95%CI = 1.34-5.60). We also found that there are protective role of XRCC3 Thr/Met genotypes (P = 0.022; χ^2 = 5.22; OR = 0.45; 95%CI = 0.23-0.89) and Met allele (P = 0.005; χ^2 = 7.99; OR = 0.36; 95%CI = 0.17-0.74) against endometriosis.

In order to evaluate whether DNA repair gene polymorphisms were associated with the severity of endometriosis or not, participants were categorized into two groups according to r-AFS classification: early stage (stage I + II) and late stage (stage III + IV) (Table 3). We did not find any association between the distributions of genotypes or alleles in *APE1*, *XRCC1*, *XRCC3*, *XPD*, *XPG*, and *HOGG1* and the stage of endometriosis (P > 0.05).

Table 3. The distribution of APE1, XRCC1, XRCC3, XPD, XPG, and HOGG1 genotypes according to the stage of endometriosis.

Polymorphisms	Early stage (N = 13)	%	Late stage (N = 39)	%	P
APE Asp148Glu					
Asp/Asp	8	61.5%	19	48.7%	
Asp/Glu	5	38.5%	16	41.0%	
Glu/Glu	0	0%	4	10.3%	0.43
XRCC1 Arg399Gln					
Arg/Arg	10	76.9%	30	76.9%	
Arg/Gln	3	23.1%	9	23.1%	
Gln/Gln	0	0%	0	0%	1.0
XRCC3 Thr241Met					
Thr/Thr	6	46.2%	18	46.2%	
Thr/Met	7	53.8%	17	43.6%	
Met/Met	0	0%	4	10.3%	0.45
XPD Lys751Gln					
Lys/Lys	2	15.4%	17	43.6%	
Lys/Gln	10	76.9%	18	46.2%	
Gln/Gln	1	7.7%	4	10.3%	0.14
XPG Asp1104His					
Asp/Asp	7	53.8%	27	69.2%	
Asp/His	5	38.5%	8	20.5%	
His/His	1	7.7%	4	10.3%	0.43
HOGG1 Ser326Cys					
Ser/Ser	9	69.2%	26	66.7%	
Ser/Cys	3	23.1%	12	30.8%	
Cys/Cys	1	7.7%	1	2.6%	0.64

DISCUSSION

Endometriosis is increasingly recognized as a complex trait, the development of which is influenced by interactions between multiple genes and environmental factors (Zondervan et al., 2001). In the present study, we determined whether polymorphisms in the DNA repair pathway (*XRCC1* Arg399Gln, *XRCC3* Thr241Met, *XPD* Lys751Gln, *XPG* Asp1104His, *APE1* Asp148Glu, *HOGG1* Ser326Cys) are associated with the risk of endometriosis. Although the XRCC3 Thr/Thr genotype was associated with the risk of endometriosis, the XRCC3 Thr/Met genotypes and Met allele appear to have a protective role against endometriosis. On the other hand, we could not find any statistically significant difference in the distribution of genotypes between the control and the endometriosis groups, except with regard to the XRCC3 polymorphism. To the best of our knowledge, this is the first study showing the association between the XRCC3 gene and endometriosis.

Although most studies have suggested that the *XRCC3* 241Met variant is a risk factor for different kinds of diseases, in our study, the XRCC3 Thr/Thr genotype was associated with the risk of endometriosis. There are conflicting results with respect to almost all

studies related to polymorphisms. These differences may be attributable to some factors such as ethnic differences and sample size. Variant allele frequencies ranged from 5 to 45%, so there are significant differences in the prevalence of the XRCC3-241 polymorphism between different ethnic groups. Prevalence of Met/Met homozygosity was 4.6% in African Americans, 0.2% in Asians, and 12.4% in Caucasians (Manuguerra et al., 2006). The frequency of these genotypes in our population matches that in Caucasians.

Several studies have examined the association between the *XRCC3* Thr241Met polymorphism and risk of cancer (Matullo et al., 2001; Butkiewicz et al. 2001; Kuschel et al., 2002). For example, *XRCC3* 241Met was reportedly associated with an increased risk of melanoma (Winsey et al., 2000; Tomescu et al., 2001), bladder cancer (Matullo et al., 2001; Narter et al., 2009) and breast cancer (Kuschel et al., 2002). On the other hand, other studies found that the *XRCC3* 241Met variant was not associated with risk of lung cancer and cervical cancer (Butkiewicz et al., 2001; He et al., 2008). The protein product of the XRCC3 gene participates in DNA double-strand break/recombinational repair. This protein is a member of a family of Rad-51-related proteins that participate in homologous recombination to maintain chromosome stability and repair DNA damage (Tebbs et al., 1995). The protein product of XRCC3 may be altered depeding on the genotype. As mentioned above, the XRCC3 Thr/Thr genotype was associated with endometriosis risk, but XRCC3 Thr/Met genotypes and Met allele seem to protect against endometriosis. Subjects with XRCC3 Thr/Thr may be susceptible to DNA damage, because the activity of product of Thr/Thr genotypes may be lower than that of the other genotypes of the same gene, which has an effect on chromosome stability and repair DNA damage (Tebbs et al., 1995). It is hard to decide whether oxidative stress is a cause or result of mutation or polymorphism, which is correlated with diseases such as endometriosis. The development of endometriosis is estrogen-dependent. Estrogens and their metabolites play a role in tumor initiation via direct damage to DNA by the formation of bulky DNA adducts (Zhu and Conney, 1998). Also, estrogens and their metabolites can undergo redox cycling, producing reactive oxygen species, which may cause oxidative stress, lipid peroxidation (Wang and Liehr, 1995) and DNA damage (Zhu and Conney, 1998; Cavalieri et al., 2000).

In conclusion, women with the XRCC3 Thr/Thr genotype may be susceptible to the development of endometriosis. In contrast, the XRCC3 Thr/Met genotype or Met allele seem to be protective against the risk of endometriosis.

The present study reports a novel finding, as to date there are no reliable markers for diagnosing endometriosis. However, our study has some limitations. The major limitation of our study is the small sample size. Our results should encourage investigators to conduct a multicenter study involving women of other ethnicities and nationalities to confirm the results obtained here. In such a study, it could be determined if the XRCC3 Thr/Met genotype and the Met allele do in fact have a protective effect against endometriosis.

REFERENCES

Anonymous (1997). Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil. Steril.* 67: 817-821.

Bishop DK, Ear U, Bhattacharyya A, Calderone C, et al. (1998). Xrcc3 is required for assembly of Rad51 complexes *in vivo*. *J. Biol. Chem.* 273: 21482-21488.

Butkiewicz D, Rusin M, Enewold L, Shields PG, et al. (2001). Genetic polymorphisms in DNA repair genes and risk of lung cancer. *Carcinogenesis* 22: 593-597.

Cavalieri E, Frenkel K, Liehr JG, Rogan E, et al. (2000). Estrogens as endogenous genotoxic agents - DNA adducts and mutations. *J. Natl. Cancer Inst. Monogr.* 27: 75-93.

Costa RM, Chigancas V, Galhardo RS, Carvalho H, et al. (2003). The eukaryotic nucleotide excision repair pathway. *Biochimie* 85: 1083-1099.

Friedberg EC, Walker GC and Siede W (1995). DNA Repair and Mutagenesis. Vol. 17. ASM Press, Washington.

Giudice LC and Kao LC (2004). Endometriosis. *Lancet* 364: 1789-1799.

Hanawalt PC, Ford JM and Lloyd DR (2003). Functional characterization of global genomic DNA repair and its implications for cancer. *Mutat. Res.* 544: 107-114.

Hazra TK, Das A, Das S, Choudhury S, et al. (2007). Oxidative DNA damage repair in mammalian cells: a new perspective. *DNA Repair* 6: 470-480.

He X, Ye F, Zhang J, Cheng Q, et al. (2008). Susceptibility of XRCC3, XPD, and XPG genetic variants to cervical carcinoma. *Pathobiology* 75: 356-363.

Hsieh YY, Chang CC, Tsai FJ, Peng CT, et al. (2005). Polymorphism for transforming growth factor beta 1-509 (TGF-B1-509): association with endometriosis. *Biochem. Genet.* 43: 203-210.

Hu JJ, Mohrenweiser HW, Bell DA, Leadon SA, et al. (2002). Symposium overview: genetic polymorphisms in DNA repair and cancer risk. *Toxicol. Appl. Pharmacol.* 185: 64-73.

Kohno T, Shinmura K, Tosaka M, Tani M, et al. (1998). Genetic polymorphisms and alternative splicing of the hOGG1 gene, that is involved in the repair of 8-hydroxyguanine in damaged DNA. *Oncogene* 16: 3219-3225.

Krokan HE, Nilsen H, Skorpen F, Otterlei M, et al. (2000). Base excision repair of DNA in mammalian cells. *FEBS Lett.* 476: 73-77.

Kubota Y, Nash RA, Klungland A, Schar P, et al. (1996). Reconstitution of DNA base excision-repair with purified human proteins: interaction between DNA polymerase beta and the XRCC1 protein. *EMBO J.* 15: 6662-6670.

Kuschel B, Auranen A, McBride S, Novik KL, et al. (2002). Variants in DNA double-strand break repair genes and breast cancer susceptibility. *Hum. Mol. Genet.* 11: 1399-1407.

Lambrinoudaki IV, Augoulea A, Christodoulakos GE, Economou EV, et al. (2009). Measurable serum markers of oxidative stress response in women with endometriosis. *Fertil. Steril.* 91: 46-50.

Le Marchand L, Donlon T, Lum-Jones A, Seifried A, et al. (2002). Association of the hOGG1 Ser326Cys polymorphism with lung cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 11: 409-412.

Luisi S, Galleri L, Marini F, Ambrosini G, et al. (2006). Estrogen receptor gene polymorphisms are associated with recurrence of endometriosis. *Fertil. Steril.* 85: 764-766.

Manuguerra M, Saletta F, Karagas MR, Berwick M, et al. (2006). XRCC3 and XPD/ERCC2 single nucleotide polymorphisms and the risk of cancer: a HuGE review. *Am. J. Epidemiol.* 164: 297-302.

Marnett LJ (2000). Oxyradicals and DNA damage. *Carcinogenesis* 21: 361-370.

Masson M, Niedergang C, Schreiber V, Muller S, et al. (1998). XRCC1 is specifically associated with poly (ADP-ribose) polymerase and negatively regulates its activity following DNA damage. *Mol. Cell Biol.* 18: 3563-3571.

Matullo G, Palli D, Peluso M, Guarrera S, et al. (2001). XRCC1, XRCC3, XPD gene polymorphisms, smoking and (32) P-DNA adducts in a sample of healthy subjects. *Carcinogenesis* 22: 1437-1445.

Miller SA, Dykes DD and Polesky HF (1988). A simple salting out procedure for extracting DNA from human nucleated cells. *Nucleic Acids Res.* 16: 1215.

Mort R, Mo L, McEwan C and Melton DW (2003). Lack of involvement of nucleotide excision repair gene polymorphisms in colorectal cancer. *Br. J. Cancer* 89: 333-337.

Narter KF, Ergen A, Agachan B, Gormus U, et al. (2009). Bladder cancer and polymorphisms of DNA repair genes (XRCC1, XRCC3, XPD, XPG, APE1, hOGG1). *Anticancer Res.* 29: 1389-1393.

Ramana CV, Boldogh I, Izumi T and Mitra S (1998). Activation of apurinic/apyrimidinic endonuclease in human cells by reactive oxygen species and its correlation with their adaptive response to genotoxicity of free radicals. *Proc. Natl. Acad. Sci. U. S. A.* 95: 5061-5066.

Sturgis EM, Castillo EJ, Li L, Zheng R, et al. (1999). Polymorphisms of DNA repair gene XRCC1 in squamous cell carcinoma of the head and neck. *Carcinogenesis* 20: 2125-2129.

Tebbs RS, Zhao Y, Tucker JD, Scheerer JB, et al. (1995). Correction of chromosomal instability and sensitivity to diverse mutagens by a cloned cDNA of the XRCC3 DNA repair gene. *Proc. Natl. Acad. Sci. U. S. A.* 92: 6354-6358.

Tomescu D, Kavanagh G, Ha T, Campbell H, et al. (2001). Nucleotide excision repair gene XPD polymorphisms and genetic predisposition to melanoma. *Carcinogenesis* 22: 403-408.

Van Langendonckt A, Casanas-Roux F and Donnez J (2002). Oxidative stress and peritoneal endometriosis. *Fertil. Steril.* 77: 861-870.

Wang MY and Liehr JG (1995). Induction by estrogens of lipid peroxidation and lipid peroxide-derived malonaldehyde-

DNA adducts in male Syrian hamsters: role of lipid peroxidation in estrogen-induced kidney carcinogenesis. *Carcinogenesis* 16: 1941-1945.

Winsey SL, Haldar NA, Marsh HP, Bunce M, et al. (2000). A variant within the DNA repair gene XRCC3 is associated with the development of melanoma skin cancer. *Cancer Res.* 60: 5612-5616.

Wood RD, Mitchell M, Sgouros J and Lindahl T (2001). Human DNA repair genes. *Science* 291: 1284-1289.

Yamane A, Kohno T, Ito K, Sunaga N, et al. (2004). Differential ability of polymorphic OGG1 proteins to suppress mutagenesis induced by 8-hydroxyguanine in human cell *in vivo*. *Carcinogenesis* 25: 1689-1694.

Yeh CC, Sung FC, Tang R, Chang-Chieh CR, et al. (2005). Polymorphisms of the XRCC1, XRCC3 & XPD genes, and colorectal cancer risk: a case-control study in Taiwan. *BMC Cancer* 5: 12.

Zhu BT and Conney AH (1998). Functional role of estrogen metabolism in target cells: review and perspectives. *Carcinogenesis* 19: 1-27.

Zondervan KT, Cardon LR and Kennedy SH (2001). The genetic basis of endometriosis. *Curr. Opin. Obstet. Gynecol.* 13: 309-314.