GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Pharmacogenetics of DNA repair gene polymorphisms in non-small-cell lung carcinoma patients on platinum-based chemotherapy

L. Zhang[1], W. Ma[1], Y. Li[1], J. Wu[2] and G.Y. Shi[2]

[1]Department of General Thoracic Surgery,
Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China
[2]Department of Medical Oncology,
The Third Affiliated Hospital of Harbin Medical University, Harbin,
Heilongjiang, China

Corresponding author: W. Ma
E-mail: xiandongli67@126.com

Genet. Mol. Res. 13 (1): 228-236 (2014)
Received June 10, 2013
Accepted October 16, 2013
Published January 14, 2014
DOI http://dx.doi.org/10.4238/2014.January.14.2

ABSTRACT. Individual differences in chemosensitivity and clinical outcome of non-small-cell lung carcinoma (NSCLC) patients can be influenced by host-inherited factors. We investigated the impact of *XRCC1 Arg194Trp*, *XRCC1 Arg280His*, *XRCC1 Arg399Gln*, *XPD Arg156Arg*, *XPD Asp312Asn*, *XPD Asp711Asp*, and *XPD Lys751Gln* gene polymorphisms on treatment efficacy in 375 NSCLC patients on platinum-based chemotherapy. We also examined progression-free survival and overall survival. The gene polymorphisms were analyzed by duplex PCR. The patients with *XRCC1 399A/A* had a significantly better response to chemotherapy. Individuals with *XPD 711 Asp* and *XPD 312 Asn* alleles responded poorly to chemotherapy when compared with the wide-type genotype. The adjusted hazard ratio

(HR) in the Cox regression model was calculated. The *XRCC1 399A/A* polymorphism was associated with better progression free survival and overall survival of NSCLC patients (HR=0.61 and 0.55). On the other hand, the *XPD 711 Asp* allele was associated with poorer progression free survival and overall survival compared to the C/C genotype, with HRs of 1.89 and 1.90. The *XPD 312 Asn* allele was found to be associated with non-significantly reduced survival of NSCLC patients (HR = 1.73). In conclusion, we found the polymorphisms of *XRCC1* and *XPD* to be related to the efficacy of platinum-based chemotherapy in NSCLC patients. This information should aid in therapeutic decisions for individualized therapy in NSCLC cases.

Key words: *XRCC1*; *XPD*; Non-small cell lung cancer; Chemotherapy

INTRODUCTION

Lung cancer is one of the most frequently diagnosed cancers worldwide, and it is reported to be the main cause of death from cancer worldwide, with 1.38 million deaths from this kind of cancer each year (IARC, 2008). Non-small cell lung cancer (NSCLC) is the major histological type of lung cancer, of which approximately more than 65% have a 5-year survival rate of 15% and are diagnosed in the later stages due to the asymptomatic nature of early disease and lack of effective screening modalities (William et al., 2009).

Advanced NSCLC patients show poor prognosis and have few effective treatment options, and it is reported that the five-year survival rate is less than 15% (Jemal et al., 2002). Since curative surgery is not a better treatment for NSCLC, chemotherapy has become the main treatment measure for advanced NSCLC patients. The first-line chemotherapy regimen is platinum-based with cisplatin or carboplatin (Azzoli et al., 2010). The clinical factors, such as patient's age, disease stage, and histological types are the main determinants of prognosis of NSCLC (Azzoli et al., 2010). However, NSCLC patients with similar clinical characteristics always show variability in outcomes, which has suggested that the genetic factors may have an impact on treatment efficacy in NSCLC patients. Thus, it is necessary to indentify the genetic markers for optimally individualized therapy.

The efficiency of DNA damage repair systems is considered to be one of the most important mechanisms affecting interindividual differences in the clinical outcome of patients treated with chemotherapy. The activity of platinum agents is mediated through the process of DNA adducts, which may inhibit DNA replication. A previous study indicated that NSCLC patients with better survival are associated with high expression of cisplatin DNA adducts (van de Vaart et al., 2010). Additionally, cisplatin adducts are mainly removed by the of nucleotide excision repair (NER) pathway, and patients with NER-deficient cells have been found to be hypersensitive to cisplatin treatment (Wu et al., 2005).

Xeroderma pigmentosum group D (*XPD*) encodes an ATP-dependent helicase, and this protein mediates DNA unwinding during NER activity (Spitz et al., 2001). Previous experimental studies have suggested that the overexpression of *XPD* would induce reduced sensitivity to cisplatin (Spitz et al., 2001). Previous epidemiologic studies have indicated that *XPD Asp312Asn* and *XPD Lys751Gln* polymorphisms are correlated with risk outcome of

several cancers, such as prostate cancer, esophageal cancer and NSCLC (Duan et al., 2012; Mi et al., 2012; Provencio et al., 2012; Zhang et al., 2012). However, few studies have explored the association of polymorphisms of *XPD Arg156Arg* and *XPD Asp711Asp* with the clinical outcomes of NSCLC patients.

X-ray repair cross-complementing protein 1 (XRCC1) is reported to function in DNA repair through the BER pathway (Lunn et al., 1999). It is also reported that enhanced DNA repair capacity is another critical mechanism of resistance to platinum-based chemotherapy, which induces the removal of cisplatin-DNA adducts, and *XRCC1 399Gln* allele is related to decreased risk of various cancers (Bianchino et al., 2011; Tahara et al., 2011; Zhou et al., 2011; Mittal et al., 2012). However, the prognostic importance of the *XRCC1* and *XPD* polymorphisms remains inconclusive.

We investigated the potential association of *XRCC1 Arg194Trp*, *XRCC1 Arg399Gln*, *XPD Arg156Arg*, *XPD Asp312Asn*, *XPD Asp711Asp*, and *XPD Lys751Gln* gene polymorphisms with response and clinical outcome among NSCLC patients who were treated with platinum-based chemotherapy, and thus to evaluate the predictive role of these biomarkers in the outcomes of these patients.

MATERIAL AND METHODS

Subjects

A prospective study was performed in 375 cases consecutively selected from the Shandong provincial hospital affiliated to Shandong University between January 2003 and November 2006. All hospital patients with newly diagnosed primary NSCLC were asked to participate within one month after diagnosis, and all cases were histopathologically confirmed. The inclusion criteria were ECOG performance score no greater than 2, good kidney, liver and heart function and no other chronic diseases. Patients who had a history of cancer, or an already cured cancer, previous chemotherapy, radiotherapy or surgery were excluded.

All patients involved in our study were treated with platinum-based chemotherapy as the first line. The first regimens of platinum-based chemotherapy were navelbine (25 mg/m^2) and carboplatin (AUC 5) on the first day of treatment, and cisplatin (75 mg/m^2) on the eighth day. A regimen of every three weeks for a maximum of six cycles was used for all patients. The second regimen was docetaxel (75 mg/m^2) and cisplatin (75 mg/m^2) on the first day, and these drugs were used every three weeks for a maximum of six cycles. The third regimen was Taxol (175 mg/m^2) with cisplatin (75 mg/m^2) or carboplatin (AUC 5) on the first day, and these agents were used every three weeks for a maximum of six cycles. The treatment would be stopped when disease progression and/or unacceptable toxicity presented. When patients presented with significant 3/4 non-hematology and hematology toxicity, the dosage of treatment regimens would be decreased by 25%.

The clinical characteristics included age, gender, smoking, and drinking status and tumor histology from medical records. Cigarette smoking status was divided into smokers with a history of <40 pack-years and smokers with ≥40 pack-years. All patients were followed up every two months by telephone and until January 2011.

Our study was approved by the ethics committee of the Shandong provincial hospital affiliated to Shandong University, and all patients signed a consent form.

DNA collection and genotyping

Genomic DNA was extracted from venous blood by using a Qiagen Blood kit (Qiagen, Chastworth, CA). The SNPs of *XRCC1 Arg194Trp*, *XRCC1 Arg399Gln*, *XPD Arg156Arg*, *XPD Asp312Asn*, *XPD Asp711Asp* and *XPD Lys751Gln* were assessed by using Sequenom MassARRAY platform with a 384-well plate format (Sequenom, San Diego, CA). The Sequenom Assay Design 3.1 software was used for designing probes and primers for polymerase chain reaction (PCR) amplification. PCR amplification was conducted in a reaction mixture of 20 μL containing 50 ng genomic DNA, 200 μM dNTPs and 2.5 U Taq DNA polymerase, as well as 200 μM primers. The reaction conditions for PCR used in our study were initial denaturation at 94°C for 10 min, followed by 35 cycles of amplification at 95°C for 30 s, annealing at 64°C for 30 s, and extension at 72°C for 45 s. The cycles were followed by a final extension at 72°C for 8 min. To ensure the reliability of the results, 10% of DNA samples were randomly selected for DNA sequencing. Finally, genotype concordance of the selected samples was 100%.

Statistical analysis

The difference between the categorical variables was analyzed by the Pearson χ^2 test, and the continuous variables were assessed by the Student *t*-test. The patients were divided into responders who showed complete response (CR) or partial response (PR) and non-responders who showed stable disease (SD) or progressive disease. Odds ratios (OR) and 95% confidence interval (CI) were used to assess the impact of six gene polymorphisms on the efficacy of chemotherapy among NSCLC patients. Overall survival (OS) was regarded as the primary end point, and it was calculated as the time from diagnosis to death. Progression-free survival (PFS) was used as the secondary outcome, which was calculated from diagnosis to the time of progression, death or last follow-up. The log-rank test was used to compare the PFS or OS of different genotypes. Cox proportional hazards model was used to estimate the adjusted hazard ratios (HR) with 95%CI of *XRCC1 Arg194Trp*, *XRCC1 Arg399Gln*, *XPD Arg156Arg*, *XPD Asp312Asn*, *XPD Asp711Asp*, and *XPD Lys751Gln* for NSCLC after adjusting for gender, age, histological stage, TMN stage and smoking status. Major homozygotes served as a reference group, and variant homozygotes and small limited number of homozygous variant genotypes of the *XPD Arg156Arg*, *XPD Asp312Asn*, *XPD Asp711Asp*, and *XPD Lys751Gln* polymorphisms were combined in a dominant model for analysis. Statistical significance of all the tests was defined as two-sided with $P < 0.05$.

RESULTS

Patients' characteristics are presented in Table 1. The mean age of the patients included was 60.9 ± 9.3 years, and 249 were males. Among the subjects, 27 (7.1%) had stage IIIA, 114 (30.5%) stage IIIB and 234 (62.4%) stage IV. In terms of histological type, more than 63% of the enrolled patients had adenocarcinoma. The distribution of the *XRCC1 Arg194Trp*, *XRCC1 Arg399Gln*, *XPD Arg156Arg*, *XPD Asp312Asn*, *XPD Asp711Asp* and *XPD Lys751Gln* genotypes are shown in Table 2. The Pearson χ^2 test showed that those with *XRCC1 399 A/A* had significantly better response to chemotherapy. Similarly, individuals with *XPD 312 Asn* allele

and *XPD 711 Asp* allele had poor response to chemotherapy when compared with wide-type genotype, and significant ORs for them were found (OR = 0.67 and OR = 0.52, respectively). The association of PFS and OS with *XRCC1* and *XPD* gene polymorphisms is shown in Table 3. The overall median PFS and OS were 8.86 (3.92-15.26) and 25.15 (14.05-28.76) months, respectively. There was a significant difference in PFS with respect to the *XPD Asp711Asp* genotype, and the *XPD 711 Asp* allele showed a significant association with shorter PFS and OS by the log-rank test (Table 3). We found significantly longer OS only for individuals with the XRCC1 399A/A genotype, and shorter OS for XPD 312 Asn allele.

Table 1. Characteristics of NSCLC patients.

Patient characteristics	N = 375	%
Age (means ± SD, year)	60.9 ± 9.3	
<60	72	19.1
60-75	241	64.3
>75	62	16.6
Gender		
Male	249	66.3
Female	126	33.7
Histology		
Adenocarcinoma	239	63.6
Squamous-cell carcinoma	105	28.2
Other	31	8.2
TMN stage		
IIIA	27	7.1
IIIB	114	30.5
IV	234	62.4
Smoking status		
<40 pack/year	185	49.2
≥40 pack/year	190	50.8

Table 2. XRCC1 and XPD polymorphisms and response to non-small-cell lung carcinoma.

Genotypes	Responders		Non-responders		P value	OR (95%CI)[1]
	N = 127	%	N = 248	%		
XRCC1 Arg194Trp						
C/C	60	47.48	118	47.5		-
C/T	44	34.32	90	36.1		1.06 (0.65-1.71)
T/T	23	18.2	41	16.4		1.18 (0.63-2.23)
C/T+ T/T	67	52.52	130.2	52.5	0.78	1.10 (0.72-1.71)
XRCC1 Arg399Gln	0					
G/G	49	38.6	125	50.5		-
G/A	54	42.5	94	37.8		1.45 (0.92-2.41)
A/A	24	18.9	29	11.7		1.97 (1.05-3.84)
G/A+ A/A	78	61	123	50	<0.05	1.69 (1.12-2.64)
XPD Arg156Arg	0		0			
C/C	53	42.1	102	41.2		-
C/A+A/A	74	57.9	146	58.8	0.66	0.91 (0.65-1.50)
XPD Asp312Asn						
C/C	88	69.4	158	63.7		-
C/T+T/T	39	30.6	90	36.3	0.08	0.67 (0.36-0.97)
XPD Asp711Asp						
C/C	102	80.2	177	71.3		-
C/T+T/T	25	19.8	71	28.7	<0.05	0.52 (0.37-0.96)
XPD Lys751Gln						
C/C	107	84.5	194	78.3		-
C/G+G/G	20	15.5	54	21.7	0.17	0.61 (0.34-1.18)

[1]Adjusted for gender, age, histological stage, TMN stage, and smoking status.

Table 3. Association between XRCC1 and XPD gene polymorphisms and survival of non-small-cell lung carcinoma.

Polymorphisms	Patients (N = 375)	%	Progression-free survival			Overall survival		
			Median survival (months, 95%CI)	Log-rank P	HR (95%CI)[1]	Median survival (months, 95%CI)	Log-rank P	HR (95%CI)[1]
XRCC1 Arg194Trp								
C/C	180	47.9	8.6 (3.4-14.2)		-	23.4 (14.2-28.5)		-
C/T	138	36.8	8.7 (3.8-15.1)		0.89 (0.54-1.60)	25.3 (14.4-29.4)		0.79 (0.55-1.67)
T/T	57	15.3	9.4 (4.2-16.4)		0.83 (0.42-1.43)	26.6 (14.9-28.8)		0.83 (0.51-1.62)
C/T+T/T	195	52.1	8.8 (4.3-16.3)	0.51	0.85 (0.57-1.59)	25.9 (13.8-29.1)	0.41	0.81 (0.56-1.66)
XRCC1 Arg399Gln								
G/G	181	48.2	7.8 (3.2-13.6)		-	22.3 (13.5-27.2)		-
G/A	146	38.9	8.5 (3.2-14.2)		0.79 (0.52-1.58)	23.7 (14.3-27.4)		0.74 (0.48-1.53)
A/A	48	12.9	10.9 (5.4-18.6)		0.51 (0.23-0.96)	27.5 (15.8-32.3)		0.48 (0.25-0.86)
G/A+A/A	194	51.8	10.4 (5.1-18.3)	0.16	0.61 (0.31-1.22)	25.6 (15.2-28.2)	<0.05	0.55 (0.23-0.94)
XPD Arg156Arg								
C/C	163	43.5	9.0 (3.2-14.2)		-	25.8 (14.8-28.2)		-
C/A+A/A	212	56.5	8.6 (3.4-15.1)	0.44	1.24 (0.76-1.91)	24.4 (14.3-29.1)	0.71	1.28 (0.76-1.66)
XPD Asp312Asn	0							
C/C	254	67.8	10.4 (4.6-18.1)		-	28.3 (17.4-31.2)		-
C/T+T/T	121	32.2	8.7 (3.6-14.2)	0.23	1.29 (0.67-1.93)	24.1 (13.2-25.8)	0.07	1.73 (0.97 -2.92)
XPD Asp711Asp	0							
C/C	278	74.1	10.8 (4.7-18.1)		-	28.9 (15.9-30.8)		-
C/T+T/T	97	25.9	7.7 (3.0-14.3)	<0.05	1.89 (1.08-3.03)	23.8 (12.4-26.6)	<0.05	1.90 (1.17-3.22)
XPD Lys751Gln	0							
C/C	299	79.8	9.9 (4.1-15.4)		-	26.8 (16.2-28.5)		-
C/G+G/G	76	20.2	8.6 (3.3-14.5)	0.62	1.34 (0.75-1.82)	24.9 (14.4-28.1)	0.28	1.41 (0.85-1.85)

[1]Adjusted for gender, age, histological stage, TMN stage, and smoking status. HR = hazard ratio.

Cox regression mode showed that polymorphisms in XRCC1 Arg399Gln and XPD Asp711Asp had an impact on the OS of NSCLC patients. We found that individuals with the XRCC1 A/A genotype had lower risk of death from NSCLC, and the HR (95%CI) was 0.55 (0.23-0.94). Conversely, individuals with the XPD 711 Asp allele had 1.89- and 1.90-fold risk of PFS and death relative to the C/C genotype, respectively. We found a borderline non-significant reduced overall survival in those with the XPD 312Asn allele genotype, with HR (95%CI) of 1.73 (0.97-2.92). These significances remained after adjusting for potential risk factors, including sex, age, histological and TMN stage, as well as smoking status in Cox regression mode. However, we did not observe a significant effect of polymorphisms in XRCC1 Arg194Trp, XPD Arg156Arg, XPD Asp312Asn and XPD Lys751Gln on the PFS and OS of NSCLC.

DISCUSSION

Platinum-based chemotherapy is regarded as the first-line treatment for NSCLC, and growing evidence shows that inherent factors have a role in modifying drug response and toxicity in NSCLC patients by metabolism, signaling, DNA-repair and cellular response pathways (Ada et al., 2010; Butkiewicz et al., 2012). In our study, we showed that polymorphisms in XRCC1 Arg399Gln, XPD Asp312Asn and XPD Asp711Asp could influence response to chemotherapy among NSCLC patients, and thus these genes could be associated with the efficacy of platinum-based (cisplatin and carboplatin) chemotherapy for patients with NSCLC. Furthermore, those carrying the XPD 312 Asn allele and XPD 711 Asp allele were found to have decreased survival time when compared with corresponding wide-type homozygous genotypes. In contrast, XRCC1 399 Gln allele was found to be correlated with longer PFS and OS.

XPD is reported to be involved in the efficacy of cisplatin and carboplatin resistance for several cancers, but the results are inconsistent (Wei et al., 2011; Yin et al., 2011). A recent meta-analysis which included 17 studies (2097 cancer patients) examined the predictive value of XPD Lys751Gln and XPD Asp312Asn polymorphisms for clinical outcome of NSCLC (Yin et al., 2011), and this meta-analysis indicated that polymorphisms in XPD Lys751Gln and XPD Asp312Asn were not associated with the objective response of platinum-based chemotherapy, and would not have effect on the PFS and OS of patients with NSCLC (Yin et al., 2011). Another meta-analysis with 12 studies indicated that XPD751G/G and XPD 312T/T had a 1.33- and 1.02-fold risk from death for NSCLC patients when compared with the wide-type homozygous genotypes, respectively (Wei et al., 2011), which suggested that the XPD would not be a predictive marker for platinum-based chemotherapy. However, our study suggested that the XPD Asp312Asn and XPD Asp711Asp polymorphisms could influence response to chemotherapy and the clinical outcomes of NSCLC patients. Previous experimental studies suggested that XPD Lys751Gln substitutions may induce conformational changes of this protein (Monaco et al., 2009) and decrease the risk of chromatid aberration and suboptimal DNA repair, and thus improve efficient DNA repair capacity and poor effect of cytotoxic chemotherapy.

It is well known that XRCC1 has a prominent function in the pathway of efficiently repairing DNA damage induced by ionizing radiation and other kind of DNA alkylating agents as well as oxidative stress produce, that means the capacity of repairing the damaged cancer cell would also be changed by the polymorphisms of XRCC1, and the cytotoxic effects of chemotherapy would be altered (Zhou et al., 2011). In previous studies, XRCC1 Arg399Gln polymorphisms were reported to be associated with resistance to chemotherapy among sev-

eral human cancers (Bianchino et al., 2011; Tahara et al., 2011; Zhou et al., 2011; Mittal et al., 2012). In our study, we found that XRCC1 Arg399Gln was associated with response to a platinum-based regimen, and that XRCC1 399 A/A correlated with better survival of NSCLC patients. Previous clinical studies have indicated that the XRCC1 399Gln allele could have an impact on the prognosis of NSCLC patients treated with chemotherapy and radiotherapy (Yoon et al., 2005; Xu et al., 2011; Liao et al., 2012), and that this gene may play a role in the repair of cigarette smoking-induced DNA damage (Casse et al., 2003). Our results are inconsistent with previous studies.

Limitations in our study should be considered, including single-center design of this study, lack of data on other DNA repair genes and relatively small sample size. The single-center design study may induce selection bias, making it difficult to extrapolate the results. We did not explore the role of all the DNA repair genes in the clinical outcome of NSCLC, and other DNA repair genes may have an interaction effect on the XRCC1 and XPD genes. Furthermore, due to the relatively small sample size, there may be lack of statistical power to find the role of XPD Asp312Asn in the response to chemotherapy. Therefore, further multi-center prospective and large sample size studies are strongly needed.

In conclusion, our results provide evidence for the predictive role of polymorphisms in XRCC1 Arg399Gln and XPD Asp711Asp in the prognosis of NSCLC patients with platinum-based chemotherapy, which suggests that the status of gene polymorphism could be taken as a prognostic marker for NSCLC patients receiving platinum-based chemotherapy. Our finding could provide information for therapeutic decisions for individualized therapy in NSCLC.

REFERENCES

Ada AO, Kunak C, Hancer F, Bilgen S, et al. (2010). CYP and GST polymorphisms and survival in advanced non-small cell lung cancer patients. *Neoplasma* 57: 512-521.

Azzoli CG, Baker S Jr, Temin S, Pao W, et al. (2010). American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. *Zhongguo Fei Ai Za Zhi* 13: 171-189.

Bianchino G, Cittadini A, Grieco V, Traficante A, et al. (2011). Polymorphisms of the CYP1A1, CYP2E1 and XRCC1 genes and cancer risk in a Southern Italian population: a case-control study. *Anticancer Res.* 31: 1359-1365.

Butkiewicz D, Drosik A, Suwinski R, Krzesniak M, et al. (2012). Influence of DNA repair gene polymorphisms on prognosis in inoperable non-small cell lung cancer patients treated with radiotherapy and platinum-based chemotherapy. *Int. J. Cancer* 131: E1100-E1108.

Casse C, Hu YC and Ahrendt SA (2003). The XRCC1 codon 399 Gln allele is associated with adenine to guanine p53 mutations in non-small cell lung cancer. *Mutat. Res.* 528: 19-27.

Duan XL, Gong H, Zeng XT, Ni XB, et al. (2012). Association between XPD Asp312Asn polymorphism and esophageal cancer susceptibility: a meta-analysis. *Asian Pac. J. Cancer Prev.* 13: 3299-3303.

International Agency for Research on Cancer - IARC (2008). Lung Cancer Incidence, Mortality and Prevalence Worldwide in 2008. Avaliable at [http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=900].

Jemal A, Thomas A, Murray T and Thun M (2002). Cancer statistics, 2002. *CA Cancer J. Clin.* 52: 23-47.

Liao WY, Shih JY, Chang GC, Cheng YK, et al. (2012). Genetic polymorphism of XRCC1 Arg399Gln is associated with survival in non-small-cell lung cancer patients treated with gemcitabine/platinum. *J. Thorac. Oncol.* 7: 973-981.

Lunn RM, Langlois RG, Hsieh LL, Thompson CL, et al. (1999). XRCC1 polymorphisms: effects on aflatoxin B1-DNA adducts and glycophorin A variant frequency. *Cancer Res.* 59: 2557-2561.

Mi Y, Zhang L, Feng N, Wu S, et al. (2012). Impact of two common xeroderma pigmentosum group D (XPD) gene polymorphisms on risk of prostate cancer. *PLoS One* 7: e44756.

Mittal RD, Gangwar R, Mandal RK, Srivastava P, et al. (2012). Gene variants of XRCC4 and XRCC3 and their association with risk for urothelial bladder cancer. *Mol. Biol. Rep.* 39: 1667-1675.

Monaco R, Rosal R, Dolan MA, Pincus MR, et al. (2009). Conformational effects of a common codon 751 polymorphism on the C-terminal domain of the xeroderma pigmentosum D protein. *J. Carcinog.* 8: 12.

Provencio M, Camps C, Cobo M, De las Peñas R, et al. (2012). Prospective assessment of XRCC3, XPD and Aurora kinase A single-nucleotide polymorphisms in advanced lung cancer. *Cancer Chemother. Pharmacol.* 70: 883-890.

Spitz MR, Wu X, Wang Y, Wang LE, et al. (2001). Modulation of nucleotide excision repair capacity by XPD polymorphisms in lung cancer patients. *Cancer Res.* 61: 1354-1357.

Tahara T, Shibata T, Nakamura M, Yamashita H, et al. (2011). Effect of genetic polymorphisms related to DNA repair and the xenobiotic pathway on the prognosis and survival of gastric cancer patients. *Anticancer Res.* 31: 705-710.

van de Vaart PJ, Belderbos J, de Jong D, Sneeuw KC, et al. (2000). DNA-adduct levels as a predictor of outcome for NSCLC patients receiving daily cisplatin and radiotherapy. *Int. J. Cancer* 89: 160-166.

Wei SZ, Zhan P, Shi MQ, Shi Y, et al. (2011). Predictive value of ERCC1 and XPD polymorphism in patients with advanced non-small cell lung cancer receiving platinum-based chemotherapy: a systematic review and meta-analysis. *Med. Oncol.* 28: 315-321.

William WN, Jr., Lin HY, Lee JJ, Lippman SM, et al. (2009). Revisiting stage IIIB and IV non-small cell lung cancer: analysis of the surveillance, epidemiology, and end results data. *Chest* 136: 701-709.

Wu Q, Christensen LA, Legerski RJ and Vasquez KM (2005). Mismatch repair participates in error-free processing of DNA interstrand crosslinks in human cells. *EMBO Rep.* 6: 551-557.

Xu C, Wang X, Zhang Y and Li L (2011). Effect of the XRCC1 and XRCC3 genetic polymorphisms on the efficacy of platinum-based chemotherapy in patients with advanced non-small cell lung cancer. *Zhongguo Fei Ai Za Zhi* 14: 912-917.

Yin M, Yan J, Voutsina A, Tibaldi C, et al. (2011). No evidence of an association of ERCC1 and ERCC2 polymorphisms with clinical outcomes of platinum-based chemotherapies in non-small cell lung cancer: a meta-analysis. *Lung Cancer* 72: 370-377.

Yoon SM, Hong YC, Park HJ, Lee JE, et al. (2005). The polymorphism and haplotypes of XRCC1 and survival of non-small-cell lung cancer after radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* 63: 885-891.

Zhang ZY, Tian X, Wu R, Liang Y, et al. (2012). Predictive role of ERCC1 and XPD genetic polymorphisms in survival of Chinese non-small cell lung cancer patients receiving chemotherapy. *Asian Pac. J. Cancer Prev.* 13: 2583-2586.

Zhou F, Yu Z, Jiang T, Lv H, et al. (2011). Genetic polymorphisms of GSTP1 and XRCC1: prediction of clinical outcome of platinum-based chemotherapy in advanced non-small cell lung cancer (NSCLC) patients. *Swiss. Med. Wkly.* 141: w13275.