Int J Clin Exp Pathol 2015;8(9):11579-11586
www.ijcep.com /ISSN:1936-2625/IJCEP0013592

Original Article

Association of single nucleotide polymorphisms of DNA repair genes in NER pathway and susceptibility to pancreatic cancer

Fuli Zhao[1], Yuhong Shang[2], Chen Zeng[1], Dongdong Gao[1], Ke Li[3]

[1]The First Department of Tumor Internal Medicine, Zhumadian Central Hospital, Zhumadian 463000, China; [2]Department of Tumor, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China; [3]Department of Hepatobiliary Surgery, Henan Provincial People's Hospital, Zhengzhou 450003, China

Received July 28, 2015; Accepted August 28, 2015; Epub September 1, 2015; Published September 15, 2015

Abstract: In our study, we conducted a case-control study to investigate the association of ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, XPA, XPC and DDB2 gene polymorphisms in the risk of pancreatic cancer. Between May 2012 and May 2014, a total of 246 patients with who were newly diagnosed with histopathologically confirmed primary pancreatic cancer and 246 controls were selected into our study. Genotyping of ERCC1 rs3212986 and rs11615, ERCC2 rs13181, ERCC3 rs4150441, ERCC4 rs6498486, ERCC5 rs873601, XPA rs2808668, XPC rs2228000, XPC rs2228001 and DDB2 rs2029298 were analyzed using polymerase chain reaction (PCR) coupled with restriction fragment length polymorphism (RFLP). By conditional logistic regression analysis, individuals carrying with TT genotype of ERCC1 rs3212986 and GG genotype of ERCC2 rs13181 were associated with increased risk of pancreatic cancer when compared with wide-type genotype, and the adjusted ORs (95% CI) were 2.40 (1.29-4.52) and 2.27 (1.26-4.15), respectively. We found that individuals carrying with GT+TT genotype of ERCC1 rs3212986 and TG+GG genotype of ERCC2 rs1318 gene polymorphisms were correlated with higher risk of pancreatic cancer in smokers when compared with non-smokers, and the adjusted ORs (95% CI) were 1.89 (1.05-3.40) and 1.88 (1.06-3.34), respectively. In conclusion, our study suggests that ERCC1 rs3212986 and ERCC2 rs1318 gene polymorphisms contribute to the development of pancreatic cancer, especially in smokers.

Keywords: DNA repair genes, polymorphism, pancreatic cancer

Introduction

Pancreatic cancer is one of the most fatal malignant tumors worldwide, and this cancer has the highest fatality rates and the fourth-highest mortality rate among both men and women [1, 2]. It is estimated that there are 65,727 new cases with pancreatic cancer and 63,662 deaths due to this cancer in China [3]. It is reported that the pancreatic cancer is gradually increasing, and less than 5% patients live 5 years after diagnosis although the advanced in detection and treatment for pancreatic cancer [1]. It is well known that the development of pancreatic cancer is involved in complex and multifactorial process, and this cancer is caused by many environmental factors, such as alcohol drinking, tobacco smoking, overall weight, diabetes mellitus and family history of pancreatic cancers in the first relatives [4, 5]. However, not all the individuals who expose to the risk factors would develop pancreatic cancer, which suggests that genetic factors may contribute to the development of this cancer.

Efficient DNA repair plays an important role in preventing the propagation of errors and maintaining genomic stability. There are about 130 genes and several molecular pathways in the repairing of the DNA damages, including nucleotide excision repair (NER), base-excision repair (BER), homologous recombination, and non-homologous end joining [6]. NER pathway is an important DNA repair process involved in maintaining genome integrity, such as damage recognition, damage demarcation and unwinding, damage incision and new strand ligation [7]. ERCC1, ERCC4 and ERCC5 are three important

Table 1. Demographic characteristics of patients with pancreatic cancer and control subjects

Variables	Patients	%	Controls	%	χ^2-test	*P* value
Age, years						
≤55	102	41.46	104	42.28		
>55	144	58.54	142	57.72	0.03	0.86
Gender						
Male	168	68.29	168	68.29		
Female	78	31.71	78	31.71	0.00	1.00
Tobacco smoking						
Non-smokers	114	46.34	151	61.38		
Smokers	132	53.66	95	38.62	11.20	0.001
Alcohol drinking						
Non-drinkers	106	43.09	141	57.32		
Drinkers	140	56.91	105	42.68	9,96	0.002
Body Mass Index (BMI)						
≤24	136	55.28	168	68.29		
>24	110	44.72	78	31.71	8.82	0.003
Type 2 diabetes						
No	39	15.85	26	10.57		
Yes	207	84.15	220	89.43	2.99	0.08
Family history of pancreatic cancer in the first relatives						
No	232	94.31	246	100.00		
Yes	14	5.69	0	0.00	14.41	<0.001

genes involved in the DNA damage incision [8, 9], ERCC2 and ERCC3 are two genes and responsible for the damage unwinding process [10, 11], and XPA, XPC and DDB2 are involved in the DNA damage recognition [12]. Until now, few studies have been conducted to investigate the role of genes in NER pathways in the development of pancreatic cancer risk. In our study, we conducted a case-control study to investigate the association of ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, XPA, XPC and DDB2 gene polymorphisms in the risk of pancreatic cancer.

Materials and methods

Subjects

Between May 2012 and May 2014, a total of 265 patients with who were newly diagnosed with histopathologically confirmed primary pancreatic cancer were selected from Zhumadian Central Hospital. Patients who had primary tumors other than pancreatic cancer and tumors of an unknown origin were excluded from this study. Finally, 246 patients are according to the inclusion criteria and included into this study, and the participation rate is 92.83%.

The control group consisted of 246 subjects without malignant pathologies consulting at Orthopedics, Dermatology and Pneumology departments in the same hospital. The controls were matched with patients in terms of age and gender.

Cases and controls were interviewed using a standardized questionnaire including sociodemographic characteristics, such as gender, age, tobacco smoking, alcohol drinking, body mass index and type 2 diabetes as well as family history of pancreatic cancer. Tobacco smokers were divided into smokers and non-smokers. Smokers were defined as those who had smoked a pack of cigarettes once a week for more than half a year. Drinkers were defined as those who had drunk alcoholic beverages at least once a week for more than half a year previously. All individuals voluntarily participated in the study and gave their informed consent. The project was approved by the Ethics Committee of Zhumadian Central Hospital.

DNA extraction and SNPs genotyping

5 ml peripheral blood sample was drawn from each patient with pancreatic cancer and control subject, and the peripheral blood samples were kept in -20°C until use. DNA was extracted from peripheral blood samples collected from patients and controls using the conventional phenol/chloroform extraction method. Genotyping of ERCC1 rs3212986 and rs11615, ERCC2 rs13181, ERCC3 rs4150441, ERCC4 rs6498486, ERCC5 rs873601, XPA rs2808668, XPC rs2228000, XPC rs2228001 and DDB2 rs2029298 were analyzed using polymerase chain reaction (PCR) coupled with restriction fragment length polymorphism (RFLP). The PCR fragments of the investigated polymorphisms were subsequently digested with their specific restriction enzyme. The reaction condition for PCR was conducted at 95°C for 5 min for the initial denaturation, following

Table 2. Association between DNA gene polymorphisms and risk of pancreatic cancer

Polymorphisms	Cases	%	Controls	%	HWE	χ^2-test	*P* value	Adjusted OR (95% CI)[1]	*P* value
ERCC1 rs3212986									
GG	80	32.52	105	42.68				1.0 (Ref.)	-
GT	124	50.41	118	47.97				1.38 (0.92-2.07)	0.10
TT	42	17.07	23	9.35	0.21	9.08	0.011	2.40 (1.29-4.52)	0.003
ERCC1 rs11615									
CC	111	45.12	120	48.78				1.0 (Ref.)	-
CT	108	43.90	104	42.28	0.94	0.94	0.63	1.12 (0.76-1.66)	0.54
TT	27	10.98	22	8.94				1.33 (0.68-2.60)	0.37
ERCC2 rs13181									
TT	131	53.25	159	64.63				1.0 (Ref.)	-
TG	72	29.27	64	26.02				1.37 (0.89-2.10)	0.13
GG	43	17.48	23	9.35	<0.001	9.23	0.01	2.27 (1.26-4.15)	0.003
ERCC3 rs4150506									
GG	90	36.59	96	39.02				1.0 (Ref.)	-
GA	115	46.75	112	45.53				1.10 (0.73-1.64)	0.65
AA	41	16.67	38	15.45	0.57	0.32	0.85	1.15 (0.66-2.02)	0.60
ERCC4 rs6498486									
AA	125	50.81	133	54.07				1.0 (Ref.)	-
AC	94	38.21	90	36.59				1.11 (0.75-1.65)	0.58
CC	27	10.98	23	9.35	0.18	0.66	0.72	1.25 (0.65-2.41)	0.47
ERCC5 rs873601									
GG	105	42.68	118	47.97				1.0 (Ref.)	-
GA	111	45.12	107	43.50				1.17 (0.79-1.72)	0.42
AA	30	12.20	21	8.54	0.64	2.42	0.30	1.61 (0.83-3.13)	0.13
XPA rs2808668									
TT	85	34.55	95	38.62				1.0 (Ref.)	-
TC	132	53.66	126	51.22				1.17 (0.79-1.75)	0.42
CC	29	11.79	25	10.16	0.07	0.99	0.61	1.30 (0.67-2.50)	0.40
XPC rs2228000									
CC	119	48.37	131	53.25				1.0 (Ref.)	-
CT	95	38.62	85	34.55				1.23 (0.82-1.84)	0.29
TT	32	13.01	30	12.20	<0.001	1.20	0.55	1.17 (0.65-2.13)	0.57
XPC rs2228001									
AA	117	47.56	127	51.63				1.0 (Ref.)	-
AC	109	44.31	106	43.09				1.12 (0.76-1.64)	0.56
CC	21	8.54	13	5.28	0.13	2.33	0.31	1.75 (0.79-3.99)	0.13
DDB2 rs2029298									
GG	100	40.65	112	45.53				1.0 (Ref.)	-
GA	110	44.72	104	42.28				1.18 (0.80-1.76)	0.38
AA	36	14.63	30	12.20	0.44	1.39	0.50	1.34 (0.74-2.44)	0.30

[1]Adjusted for sex, age, tobacco smoking, alcohol drinking, body mass index and family history of pancreatic cancer in the first relatives.

30 cycles of denaturation at 95°C for 30 s, annealing at 62°C for 45 s, extension at 72°C for 30 s and final extension at 72°C for 5 mins. Digestion products were separated by electrophoresis on ethidium bromide stained agarose gel and visualized under UV light.

Statically analysis

Means of quantitative variables were compared between groups using Student t-test, while distributions of categorical variables were compared by Pearson χ^2 test. Hardy-Weinberg equi-

Table 3. Interaction between ERCC1 rs3212986 and ERCC2 rs1318 gene polymorphisms and tobacco smoking and alcohol drinking in the risk of pancreatic cancer

	ERCC1 rs3212986						ERCC2 rs1318					
	GG		GT+TT		OR (95% CI)[1]	*P* value	TT		TG+GG		OR (95% CI)	*P* value
	Patients	Controls	Patients	Controls			Patients	Controls	Patients	Controls		
Tobacco smoking												
Non-smokers	41	63	73	88	1.27 (0.75-2.17)	0.34	68	99	46	52	1.29 (0.76-2.19)	0.32
Smokers	39	42	93	53	1.89 (1.05-3.40)	0.02	63	60	69	35	1.88 (1.06-3.34)	0.02
Alcohol drinking												
Non-drinkers	35	60	71	81	1.50 (0.86-2.63)	0.13	56	91	50	50	1.63 (0.94-2.81)	0.06
Drinkers	45	45	95	60	1.58 (0.91-2.77)	0.09	75	68	65	37	1.59 (0.92-2.78)	0.08

[1]Adjusted for sex, age, body mass index and family history of pancreatic cancer in the first relatives.

librium (HWE) was examined using a χ^2-test with one degree of freedom. Multiple conditional logistic regression models were established to estimate relative risks of tobacco and alcohol consumption as well as risks related to each SNP after adjustment for gender, age, tobacco smoking, alcohol drinking, body mass index and type 2 diabetes as well as family history of pancreatic cancer. Additional regression models were designed where subjects were stratified on demographic characteristics and genetic polymorphisms of the study variations. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. All tests were two-sided with a significant level of *P*-value <0.05. Statistical analysis was conducted using the SPSS 21.0 package (SPSS Inc., Chicago, IL, USA).

Results

The demographic characteristics of patients with pancreatic cancer and control subjects were summarized in **Table 1**. The mean ages of patients with pancreatic cancer and control subjects were 57.3±7.9 and 56.8±8.1 years old, respectively. By χ^2-test, no significant differences were found between patients with pancreatic cancer and control subjects in terms of age, gender and type 2 diabetes. When compared with control subjects, patients with pancreatic cancer were more likely to be tobacco smokers and alcohol drinkers, and have higher BMI and family history of pancreatic cancer in the first relatives.

The genotype distributions of ERCC1 rs3212986 and rs11615, ERCC3 rs4150506, ERCC4 rs6498486, ERCC5 rs873601, XPA rs2808668, XPC rs2228001 and DDB2 rs2029298 confirmed with the Hardy-Weinberg equilibrium in the controls (*P* value >0.05), but ERCC2 rs13181 and XPC rs2228000 were not (*P* value <0.05) (**Table 2**). By χ^2-test, there were significant differences between patients with pancreatic cancer and control subjects in terms of genotype distributions of ERCC1 rs3212986 (χ^2=9.08, *P* value =0.011) and ERCC2 rs13181 (χ^2=9.23, *P* value =0.01). By conditional logistic regression analysis, individuals carrying with TT genotype of ERCC1 rs3212986 and GG genotype of ERCC2 rs13181 were associated with increased risk of pancreatic cancer when compared with wide-type genotype, and the adjusted ORs (95% CI) were 2.40 (1.29-4.52) and 2.27 (1.26-4.15), respectively. However, we did not find significant difference association of ERCC1 rs11615, ERCC3 rs4150506, ERCC4 rs6498486, ERCC5 rs873601, XPA rs2808668, XPC rs2228000, XPC rs2228001 and DDB2 rs2029298 with the risk of pancreatic cancer.

We further analyzed the association between ERCC1 rs3212986 and ERCC2 rs1318 gene polymorphisms and risk of pancreatic cancer stratified by tobacco smoking and alcohol drinking (**Table 3**). We found that individuals carrying with GT+TT genotype of ERCC1 rs3212986 and TG+GG genotype of ERCC2 rs1318 gene polymorphisms were correlated with higher risk of pancreatic cancer in smokers when compared with non-smokers, and the adjusted ORs (95% CI) were 1.89 (1.05-3.40) and 1.88 (1.06-3.34), respectively.

Discussion

Polymorphisms have an effect on the regulation of gene expression, and they can contribute to the differences between individuals in the susceptibility to a disease and its severity. The regulation of DNA repair plays an important role in the multistep process of carcinogenesis, and NER pathway is an important DNA repair process, and it has steps of damage recognition, damage demarcation and unwinding, damage incision, and new strand ligation [13, 14]. Polymorphisms in DNA repair genes resulting in variation of DNA repair efficiency may therefore be associated with risk of cancers. In the present study, we investigate the role of ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, XPA, XPC and DDB2 gene polymorphisms of the NER pathway in the risk of pancreatic cancer, and we found that ERCC1 rs3212986 and ERCC2 rs1318 gene polymorphisms contribute to the development of pancreatic cancer.

The excision repair cross complementation group 1 (ERCC1) enzyme belongs to nucleotide excision repair (NER) system which has the ability of repairing DNA adducts and other DNA helix-distorting lesions [15]. ERCC1 has interaction with XPA, XPF and/or RPA, guiding the 5' cleavage activity in the NER pathway [16, 17]. Cells from ERCC1-deficient mice show a high mutation frequency, an elevated level of genomic instability and a reduced frequency of S-phase-dependent illegitimate chromosome

exchange, a response adopted by rodent cells to prevent the accumulation of DNA double strand breaks [18]. Therefore, functional SNPs in ERCC1 could influence cellular DNA repair capacity and thus may be important for the development of cancers. Previous studies have reported that the ERCC1 rs3212986 polymorphism is associated with development of several kinds of cancer, such as colorectal cancer, lung cancer, breast cancer and glioma [19, 22]. A recent meta-analysis with 48 case-control studies reported that no association between ERCC1 rs3212986 and susceptibility to cancers [23]. For the association between ERCC1 rs3212986 polymorphism and risk of pancreatic cancer, only study reported that ERCC1 rs3212986 polymorphism could not influence the development of pancreatic cancer [24]. However, we found that ERCC1 rs3212986 was associated with an increased risk of pancreatic cancer. The discrepancy of the different results may be caused by different in ethnicities, study design, source of patients, sample size, and by chance.

The ERCC2 protein, encoded by the gene located at chromosome 19q13.3, possesses both single strand DNA-dependent ATPase and 5'-3' DNA helicase activities and participates in DNA unwinding during NER [25, 26]. Polymorphisms in the ERCC2 gene are thought to reduce the helicase activity, resulting in a lower DNA repair capacity of NER pathway and influencing cancer susceptibility [27, 28]. Previous studies have reported that ERCC2 rs1318 gene polymorphism is associated with many kinds of cancers, such as esophageal cancer, hepatocellular cancer, skin cancer and breast cancer [29-32]. Two studies reported the association between ERCC2 rs1318 gene polymorphism and pancreatic cancer [33, 34]. Jiao et al. reported that ERCC2 rs1318 gene polymorphism could be a genetic risk modifier for smoking-related pancreatic cancer in a Chinese population [33]. Duell et al. also found that ERCC2 rs1318 gene polymorphism in combination with cigarette smoking may increase the risk for pancreatic cancer [34]. In our study, we found that ERCC2 rs1318 gene polymorphism influence the development of pancreatic cancer, especially in smokers, which are in line with previous studies.

There were several limitations in our study. First, ERCC2 rs13181 and XPC rs2228000 were not in line with Hardy-Weinberg equilibrium, which suggest that the controls may not present the general population. Second, cases and controls were selected from one hospital, selection bias may be considered in our study. Third, tobacco smoking and alcohol drinking were recalled by included subjects, and information bias may be existed. Fourth, the sample size of this study is relatively small, and small sample size may limit the statistical power to find differences between groups.

In conclusion, our study suggests that ERCC1 rs3212986 and ERCC2 rs1318 gene polymorphisms contribute to the development of pancreatic cancer, especially in smokers. Further large sample studies are greatly warranted to elucidate our finding.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yuhong Shang, Department of Tumor, The First Affiliated Hospital of Zhengzhou University, No. 1 of Jian She Dong Road, Zhengzhou 450052, China. Tel: +86-371-66295541; Fax: +86-371-66295541; E-mail: shangyudongd@sina.com

References

[1] Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet 2011; 378: 607-20.
[2] Hidalgo M. Pancreatic cancer. N Engl J Med 2010; 362: 1605-17.
[3] International Agency for Research on Cancer. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012.
[4] Pandol S, Gukovskaya A, Edderkaoui M, Dawson D, Eibl G, Lugea A. Epidemiology, risk factors, and the promotion of pancreatic cancer: role of the stellate cell. J Gastroenterol Hepatol 2012; 27 Suppl 2: 127-34.
[5] Krejs GJ. Pancreatic cancer: Epidemiology and risk factors. Dig Dis 2010; 28: 355-8.
[6] Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol Biomarkers Prev 2002; 11: 1513-30.
[7] Nouspikel T. DNA repair in mammalian cells: Nucleotide excision repair: variations on versatility. Cell Mol Life Sci 2009; 66: 994-1009.
[8] Enzlin JH, Scharer OD. The active site of the DNA repair endonuclease XPF-ERCC1 forms a highly conserved nuclease motif. EMBO J 2002; 21: 2045-53.

[9] Matsunaga T, Mu D, Park CH, Reardon JT, Sancar A. Human DNA repair excision nuclease. Analysis of the roles of the subunits involved in dual incisions by using anti-XPG and anti-ERCC1 antibodies. J Biol Chem 1995; 270: 20862-9.
[10] Coin F, Oksenych V, Egly JM. Distinct roles for the XPB/p52 and XPD/p44 subcomplexes of TFIIH in damaged DNA opening during nucleotide excision repair. Mol Cell 2007; 26: 245-56.
[11] Evans E, Moggs JG, Hwang JR, Egly JM, Wood RD. Mechanism of open complex and dual incision formation by human nucleotide excision repair factors. EMBO J 1997; 16: 6559-73.
[12] Sugasawa K. Multiple DNA damage recognition factors involved in mammalian nucleotide excision repair. Biochemistry (Mosc) 2011; 76: 16-23.
[13] Kamileri I, Karakasilioti I, Garinis GA. Nucleotide excision repair: new tricks with old bricks. Trends Genet 2012; 28: 566-73.
[14] Ng JM, Vermeulen W, van der Horst GT, Bergink S, Sugasawa K, Vrieling H, Hoeijmakers JH. A novel regulation mechanism of DNA repair by damage-induced and RAD23-dependent stabilization of xeroderma pigmentosum group C protein. Genes Dev 2003; 17: 1630-45.
[15] de Laat WL, Jaspers NG, Hoeijmakers JH. Molecular mechanism of nucleotide excision repair. Genes Dev 1999; 13: 768-85.
[16] Volker M, Mone MJ, Karmakar P, van Hoffen A, Schul W, Vermeulen W, Hoeijmakers JH, van Driel R, van Zeeland AA, Mullenders LH. Sequential assembly of the nucleotide excision repair factors in vivo. Mol Cell 2001; 8: 213-24.
[17] Sijbers AM, de Laat WL, Ariza RR, Biggerstaff M, Wei YF, Moggs JG, Carter KC, Shell BK, Evans E, de Jong MC, Rademakers S, de Rooij J, Jaspers NG, Hoeijmakers JH, Wood RD. Xeroderma pigmentosum group F caused by a defect in a structure-specific DNA repair endonuclease. Cell 1996; 86: 811-22.
[18] Melton DW, Ketchen AM, Nunez F, Bonatti-Abbondandolo S, Abbondandolo A, Squires S, Johnson RT. Cells from ERCC1-deficient mice show increased genome instability and a reduced frequency of S-phase-dependent illegitimate chromosome exchange but a normal frequency of homologous recombination. J Cell Sci 1998; 111 Pt 3: 395-404.
[19] Hou R, Liu Y, Feng Y, Sun L, Shu Z, Zhao J, Yang S. Association of single nucleotide polymorphisms of ERCC1 and XPF with colorectal cancer risk and interaction with tobacco use. Gene 2014; 548: 1-5.
[20] Zhu J, Hua RX, Jiang J, Zhao LQ, Sun X, Luan J, Lang Y, Sun Y, Shang K, Peng S, Ma J. Association studies of ERCC1 polymorphisms with lung cancer susceptibility: a systematic review and meta-analysis. PLoS One 2014; 9: e97616.
[21] Pei XH, Yang Z, Lv XQ, Li HX. Genetic variation in ERCC1 and XPF genes and breast cancer risk. Genet Mol Res 2014; 13: 2259-67.
[22] Zhang N, Lin LY, Zhu LL, Wu F, Wen H, Pan D, Huang YC, Chen DQ. ERCC1 polymorphisms and risk of adult glioma in a Chinese population: a hospital-based case-control study. Cancer Invest 2012; 30: 199-202.
[23] Zhang L, Wang J, Xu L, Zhou J, Guan X, Jiang F, Wu Y, Fan W. Nucleotide excision repair gene ERCC1 polymorphisms contribute to cancer susceptibility: a meta-analysis. Mutagenesis 2012; 27: 67-76.
[24] McWilliams RR, Bamlet WR, Cunningham JM, Goode EL, de Andrade M, Boardman LA, Petersen GM. Polymorphisms in DNA repair genes, smoking, and pancreatic adenocarcinoma risk. Cancer Res 2008; 68: 4928-35.
[25] Sung P, Bailly V, Weber C, Thompson LH, Prakash L, Prakash S. Human xeroderma pigmentosum group D gene encodes a DNA helicase. Nature 1993; 365: 852-5.
[26] de Boer J, Hoeijmakers JH. Nucleotide excision repair and human syndromes. Carcinogenesis 2000; 21: 453-60.
[27] Zhang J, Gu SY, Zhang P, Jia Z, Chang JH. ERCC2 Lys751Gln polymorphism is associated with lung cancer among Caucasians. Eur J Cancer 2010; 46: 2479-84.
[28] Xue H, Lu Y, Lin B, Chen J, Tang F, Huang G. The effect of XPD/ERCC2 polymorphisms on gastric cancer risk among different ethnicities: a systematic review and meta-analysis. PLoS One 2012; 7: e43431.
[29] Guo XF, Wang J, Lei XF, Zeng YP, Dong WG. XPD Lys751Gln polymorphisms and the risk of esophageal cancer: an updated meta-analysis. Intern Med 2015; 54: 251-9.
[30] Peng Q, Li S, Lao X, Chen Z, Li R, Qin X. Association between XPD Lys751Gln and Asp312Asn polymorphisms and hepatocellular carcinoma risk: A systematic review and meta-analysis. Medicine (Baltimore) 2014; 93: e330.
[31] Zhu HL, Bao JM, Lin PX, Li WX, Zou ZN, Huang YE, Chen Q, Shen H. XPD Lys751Gln and Asp312Asn polymorphisms and susceptibility to skin cancer: a meta-analysis of 17 case-control studies. Asian Pac J Cancer Prev 2014; 15: 6619-25.
[32] Wang T, Wang H, Guo H, Yang S, Zhu G, Guo H, Wang L, Li Y, Yang K, Li H, Min J, Li X, Hu Q, Wang Y, Liu Y, Zhang B, Chen X, Su H. Polymorphisms in the DNA repair gene ERCC2/XPD and breast cancer risk: A HapMap-based case-

control study among Han Women in a Chinese less-developed area. Genet Test Mol Biomarkers 2014; 18: 703-10.

[33] Jiao L, Hassan MM, Bondy ML, Abbruzzese JL, Evans DB, Li D. The XPD Asp312Asn and Lys-751Gln polymorphisms, corresponding haplotype, and pancreatic cancer risk. Cancer Lett 2007; 245: 61-8.

[34] Duell EJ, Bracci PM, Moore JH, Burk RD, Kelsey KT, Holly EA. Detecting pathway-based gene-gene and gene-environment interactions in pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2008; 17: 1470-9.