Int J Clin Exp Med 2016;9(2):2881-2888
www.ijcem.com /ISSN:1940-5901/IJCEM0014543

Original Article

Current evidence on XPC rs2228001 A/C polymorphism and bladder cancer susceptibility

He-Yun Sun[1*], Li Zuo[1,3*], Jian-Gang Zou[1*], Li-Feng Zhang[1], Xiao-Peng Wu[1], Yuan-Yuan Mi[2], Takahiro Yasui[3], Atsushi Okada[3]

[1]Department of Urology, Changzhou No. 2 People's Hospital Affiliated to Nanjing Medical University, Changzhou 213003, Jiangsu Province, China; [2]Department of Urology, Third Affiliated Hospital of Nantong University, 585 Xingyuan Road, Wuxi 214041, Jiangsu Province, China; [3]Department of Nephrourology, Nagoya City University Graduate School of Medical Sciences, Aichi 4678601, Japan. [*]Equal contributors.

Received August 12, 2015; Accepted November 16, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: The xeroderma pigmentosum group C (XPC) gene plays a significant role in DNA damage recognition during nucleotide excision repair process. Polymorphisms of the XPC gene have been analyzed in numerous case-control studies to evaluate bladder cancer risk attributed to XPC genetic variation; however, published data on the association between XPC rs2228001 A/C and bladder cancer risk are inconclusive. To assess the impact of XPC rs2228001 polymorphism on bladder cancer risk, we performed a meta-analysis on all available studies including 4,741 patients and 5,065 control subjects. The overall results indicated a positive association of the variant on bladder cancer risk using an allelic contrast, homozygote comparison and the recessive genetic model. When stratified by ethnicity, obvious associations were found in Asian descendants by using an allelic contrast (odds ratio [OR] = 1.33, 95% confidence interval [CI] = 1.06-1.66, $P_{heterogeneity}$ = 0.002), homozygote comparison (OR = 1.91, 95% CI = 1.30-2.82, $P_{heterogeneity}$ = 0.040) and the recessive genetic model (OR = 1.64, 95% CI = 1.25-2.15, $P_{heterogeneity}$ = 0.128). Furthermore, a significant association was found in smokers by using an allelic contrast (OR = 2.08, 95% CI = 1.04-4.17, $P_{heterogeneity}$ = 0.039), homozygote comparison (OR = 4.66, 95% CI = 1.22-17.76, $P_{heterogeneity}$ = 0.024) and the recessive genetic model (OR = 3.79, 95% CI = 1.18-12.20, $P_{heterogeneity}$ = 0.027). In conclusion, XPC rs2228001 A/C polymorphism may contribute to the risk for developing bladder cancer in Asian descendants and may interact with smoking exposure. Further studies based on larger, more diverse case-control populations are warranted to further evaluate the association.

Keywords: XPC, polymorphism, bladder cancer, meta-analysis

Introduction

Transitional cell carcinoma of the bladder is one of the most common types of neoplasm in the Western world [1]. In the United States, bladder cancer is the fifth most prevalent cancer, with 70,980 new cases predicted to occur in 2009 [2]. In China, bladder cancer was the tenth most common cancer in 2005 [3]. Epidemiological studies indicate that cigarette smoking is strongly associated with the bladder carcinoma risk. Cigarette smoke contains several potent chemical carcinogens that are estimated to contribute up to approximately 65% of bladder cancer occurrence in men and up to 20-30% in women [4, 5]. Carcinogens from tobacco smoking cause DNA damage via the introduction of crosslinks, bulky adducts, and single or double-stranded breaks [6].

Repairing damaged DNA is the prevalent defense mechanism against mutagenic exposure. Many chemical carcinogenic metabolites generate bulky DNA adducts, which are mainly removed by the nucleotide excision repair (NER) pathway. This pathway also repairs endogenously generated oxidative DNA lesions [7]. Xeroderma pigmentosum group C (XPC), spans 33 kb on chromosome 3 and includes 16 exons and 15 introns. XPC encodes a protein that recognizes and binds to helix-distorting DNA adducts and plays a significant role in damage detection and initiation of the NER pathway [8, 9]. XPC mutations can lead to xeroderma pig-

mentosum, a rare autosomal recessive disease with accumulated sensitivity to sunlight and the development of skin carcinoma at an early age [10]. XPC knockout mice demonstrate a defective NER pathway, developing skin carcinomas following exposure to ultraviolet B radiation and have increased susceptibility to common cancers, including bladder, lung and liver cancer, following exposure to the chemical carcinogen, acetylaminofluorene [11, 12].

Numerous epidemiological studies have been canducted to explore the association of XPC polymorphisms with bladder cancer risk. One of the most widely investigated XPC polymorphism is an A to C substitution in exon 15 (rs2228001) at position 939 (Lys939Gln), resulting in a lysine-to-glutamine substitution. However, the association between XPC rs2228001 A/C polymorphism and bladder cancer risk remains controversial due to conflicting results from various case-control studies. Hence, we utilized the enhanced statistical power of a meta-analysis to obtain a summary result on the association of XPC rs2228001 A/C polymorphism bladder cancer using accumulated data from eligible studies published to date [13-24]. Additionally, the potential interaction between XPC rs2228001 A/C polymorphism and total smoking exposure on bladder cancer risk was evaluated.

Materials and methods

Search strategy and identification of relevant studies

PubMed database searches were conducted using the following keywords: 'Xeroderma pigmentosum group C' or 'XPC', 'bladder cancer' and 'polymorphism' (last search updated on August 01, 2015). References of the identified manuscripts were also manually screened for eligibility. Eligible manuscripts met all of the following criteria: (a) used a case-control design with unrelated individuals; (b) contained information about genotype frequency; (c) the genotype distribution of the control population was in accord with Hardy-Weinberg equilibrium (HWE); (d) the study was published in English; and (e) was a full-text article. The following exclusion criteria were utilized: (1) study lack of available genotype frequency data; (2) lack of the control population; (3) study was the duplicate.

Data extraction and quality assessment

For each eligible publication, data extraction and methodological quality assessment were conducted by two of the co-authors independently. Disagreement was resolved by discussion between the two co-authors. If a consensus could not be reached, additional co-authors were included in the discussion until a consensus was reached. The following parameters from each study were recorded: first author's name, publication date, ethnicity, the source of cancer cases and controls, sample size of cases and controls, and the number of cases and controls with wild type and variant allele, respectively.

Statistical analysis

Crude odds ratios (ORs) with 95% confidence intervals (CIs) were utilized to evaluate the strength of the association between XPC rs2228001 polymorphism and bladder cancer based on the genotype frequencies in cases and controls. For XPC rs2228001 A/C, we investigated the relationship between genetic variants and bladder cancer risk in allelic contrast (C-allele vs. A-allele), homozygote comparison (CC vs. AA), heterozygote comparison (CA vs. AA), dominant genetic model (CC + CA vs. AA) and recessive genetic model (CC vs. CA + AA). Subgroup analyses were conducted, stratifying by ethnicity, source of control subject (hospital-based or population-based), and smoking exposure. We utilized the random effects model and fixed effects model to calculate the pooled OR. The heterogeneity assumption was evaluated by a chi-square-based *Q*-test among the studies. *P* values greater than 0.05 for the *Q*-test indicates lack of heterogeneity among studies, in which case the pooled OR was examined using a fixed-effects model (the Mantel-Haenszel method) [25]; otherwise, a random effects model (DerSimonian and Laird method [26]) was performed. Significant departures of allele frequencies of XPC rs2228001 polymorphism from expectation under HWE were evaluated in controls utilizing the Pearson's chi-square test. $P < 0.05$ was considered statistically significant. A *Z*-test was used to evaluate the statistical significance of the summary OR with a *P* value of < 0.05 considered significant. We also utilized the statistic of I^2 to efficiently test for heterogeneity, with $I^2 >$ 75%, 25-75% and < 25% to representing a high,

Table 1. Study characteristics of XPC rs2228001 A/C polymorphism included in this meta-analysis

First author	Year	Country	Ethnicity	Source of control	Genotyping methods	Sample size of case				Sample size of control				P_{HWE}
						CC	CA	AA	Total	CC	CA	AA	Total	
Wen	2013	China	Asian	Hospital-based	TaqMan	25	56	49	130	22	96	185	303	0.059
Zhi	2012	China	Asian	Hospital-based	PCR-RFLP	48	136	118	302	35	138	138	311	0.955
Mittal	2012	India	Asian	Hospital-based	PCR-RFLP	28	73	94	195	19	104	127	250	0.717
Liu	2012	China	Asian	Population-based	PCR-RFLP	92	272	236	600	75	281	253	609	0.824
Rouissi	2011	Tunisia	African	Hospital-based	PCR-RFLP	20	52	53	125	16	52	57	125	0.449
Verdier	2010	Sweden	European	Population-based	PCR-RFLP	51	141	113	305	34	161	133	328	0.147
Gangwar	2010	India	Asian	Hospital-based	PCR-RFLP	25	86	97	208	16	116	113	245	0.054
Fontana	2008	France	European	Hospital-based	TaqMan	22	22	7	51	6	24	15	45	0.456
Zhu	2007	USA	European	Population-based	TaqMan	80	271	199	550	93	262	199	554	0.408
Garcia	2006	Spain	European	Population-based	SNP500Cancer	188	575	374	1137	191	536	411	1138	0.470
Wu	2006	USA	European	Population-based	PCR-RFLP	94	293	219	606	101	284	211	596	0.744
Sak	2005	UK	European	Population-based	TaqMan	87	241	204	532	84	285	192	561	0.306

HWE: Hardy-Weinberg equilibrium of controls, RFLP: restriction fragment length polymorphism.

moderate and low degree of inconsistency, respectively [27]. We determined significance of the intercept by a t-test as suggested by Egger and a $P < 0.01$ was considered representative of a significant publication bias [28]. All statistical analyses were performed with STATA version 10.0 (Stata Corporation, College Station, TX), utilizing two-sided *P* values.

Results

Study characteristics

A total of 12 publications met all inclusion criteria and were included in the meta-analysis. The genotype distribution in the control population was consistent with HWE in all the publications. Study characteristics of eligible publications are summarized in **Table 1**. The meta-analysis included 4,741 bladder cancer patients and 5,065 control subjects. Six of the studies were performed with European descendants, 5 with Asian descendants and one with African descendants. Hospital-based controls were used in 6 of the studies. Polymerase chain reaction-restriction fragment length polymorphism (RFLP), the classical genotyping method, was used in 7 comparisons while 4 studies utilized TaqMan real-time polymerase chain reaction (PCR). Furthermore, 4 publications included smoking status (categorized as smokers and non-smokers).

Quantitative synthesis

Using the pooled data, (**Table 2**) a positive association of the XPC variant on bladder cancer risk was found using an allelic contrast (random-effects OR = 1.18, 95% CI = 1.04-1.33, $P_{heterogeneity} < 0.001$, $P = 0.009$, $I^2 = 74.2$), homozygote comparison (random-effects OR = 1.44, 95% CI = 1.12-1.85, $P_{heterogeneity} < 0.001$, $P = 0.004$, $I^2 = 71.6$) and the recessive genetic model (random-effects OR = 1.38, 95% CI = 1.10-1.72, $P_{heterogeneity} < 0.001$, $P = 0.005$, $I^2 = 69.2$). Further, in a subgroup analysis stratified by ethnicity, obvious associations between XPC rs2228001 A/C polymorphism and bladder cancer risk were observed in Asian descendants using an allelic comparison (random-effects OR = 1.33, 95% CI = 1.06-1.66, $P_{heterogeneity} = 0.002$, $P = 0.015$, $I^2 = 76.2$), but not in European descendants (fixed-effects OR = 1.07, 95% CI = 0.93-1.23, $P_{heterogeneity} = 0.006$, $P = 0.367$, $I^2 = 69.1$) nor African descendants (OR = 1.15, 95% CI = 0.80-1.66, $P = 0.454$) (**Figure 1**). A significant dose-response association was found in smokers by using an allelic contrast (random-effects OR = 2.08, 95% CI = 1.04-4.17, $P_{heterogeneity} < 0.001$, $P = 0.039$, $I^2 = 86.8$) (**Figure 2**), homozygote comparison (random-effects OR = 4.66, 95% CI = 1.22-17.76, $P_{heterogeneity} = 0.024$, $P = 0.013$, $I^2 = 72.3$) and the recessive genetic model (random-effects OR = 3.79, 95% CI = 1.18-12.20, $P_{heterogeneity} = 0.027$, $P = 0.026$, $I^2 = 67.2$). Furthermore, a significant association between the XPC rs2228001 polymorphism and bladder cancer was also found in hospital-based studies by using an allelic comparison (random-effects OR = 1.46, 95% CI = 1.13-1.89, $P_{heterogeneity} = 0.001$, $P = 0.004$, $I^2 = 74.8$), homozygote comparison (random-effects OR = 2.26, 95% CI = 1.47-3.48, $P_{heterogeneity} = 0.045$, $P < 0.001$, $I^2 = 56.0$), the dominant genetic model (random-effects OR = 1.40, 95%

Table 2. Stratified analyses of the XPC rs2228001 A>C polymorphism on urinary-bladder cancer risk

Variables	N[a]	Cases/ Controls	C-allele vs. A-allele				CC vs. AA				CC vs. CA+AA			
			OR (95% CI)	P_{heter}[b]	*P*	I^2	OR (95% CI)	P_{heter}[b]	*P*	I^2	OR (95% CI)	P_{heter}[b]	*P*	I^2
Total	12	4741/5065	1.18 (1.04-1.33)	< 0.001	0.009	74.2	1.44 (1.12-1.85)	< 0.001	0.004	71.6	1.38 (1.10-1.72)	< 0.001	0.005	69.2
Ethnicity														
European	6	3181/3222	1.07 (0.93-1.23)	0.006	0.367	69.1	1.15 (0.86-1.54)	0.007	0.353	68.7	1.14 (0.87-1.49)	0.006	0.339	69.5
Asian	5	1435/1718	1.33 (1.06-1.66)	0.002	0.015	76.2	1.91 (1.30-2.82)	0.040	0.001	60.1	1.64 (1.25-2.15)	0.128[c]	< 0.001	44.1
African	1	125/125	1.15 (0.80-1.66)	-	0.454	-	1.34 (0.63-2.86)	-	0.443	-	1.30 (0.64-2.64)	-	0.472	-
Source of control														
Hospital-based	6	1011/1279	1.46 (1.13-1.89)	0.001	0.004	69.1	2.26 (1.47-3.48)	0.045	< 0.001	56.0	1.83 (1.40-2.40)	0.235[c]	< 0.001	26.6
Population-based	6	3730/3786	1.02 (0.97-1.07)	0.269[c]	0.446	21.9	1.05 (0.93-1.19)	0.160[c]	0.444	37.0	1.06 (0.91-1.22)	0.103[c]	0.478	45.4
Smoking exposure														
Non-smokers	4	386/693	1.15 (0.92-1.44)	0.213	0.070	57.5	1.31 (0.87-1.98)	0.199[c]	0.197	35.8	1.35 (0.87-1.99)	0.251[c]	0.193	26.7
Smokers	4	503/389	2.08 (1.04-4.17)	0.039	< 0.001	86.8	4.66 (1.22-17.76)	0.024	0.013	72.3	3.79 (1.18-12.20)	0.027	0.026	67.2

[a]Number of comparisons, [b]*P* value of *Q*-test for heterogeneity test (P_{heter}), [c]Random effects model was performed when P_{heter} < 0.05; otherwise, fixed effects model was used.

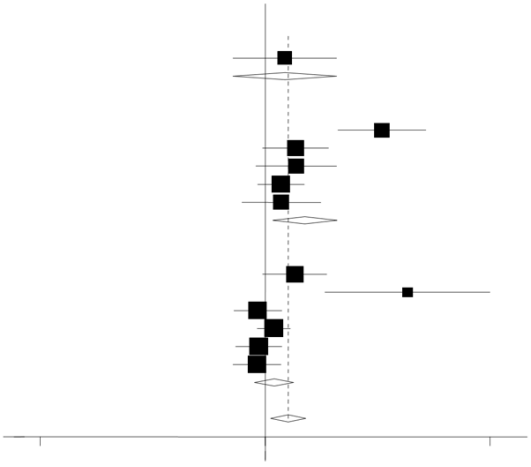

Figure 1. Forest plot of bladder cancer risk associated with the XPC rs2228001 A/C polymorphism (allelic contrast of C-allele vs. A-allele) in the stratified analyses by ethnicity. The *squares* and *horizontal lines* represent the study-specific OR and 95% CI. The area of the *squares* reflects the weight (inverse of the variance). The *diamond* corresponds to the summary OR and 95% CI. Separate details were summarized in **Table 1**.

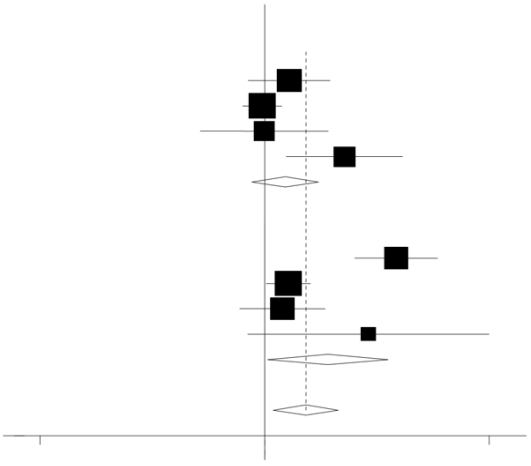

Figure 2. Association between the XPC rs2228001 A/C polymorphism, smoking and the risk of bladder cancer, evaluated by the allelic contrast (C-allele vs. A-allele). The area of the *squares* reflects the weight. The *squares* and *horizontal lines* represent the study-specific OR and 95% CI. The *diamond* corresponds to the summary OR and 95% CI.

CI = 1.01-1.94, $P_{heterogeneity}$ = 0.006, P = 0.043, I^2 = 69.5), and the recessive genetic model (random-effects OR = 1.83, 95% CI = 1.40-2.40, $P_{heterogeneity}$ = 0.235, P < 0.001, I^2 = 26.6), while no association existed among population-based studies (allelic comparison: fixed-effects

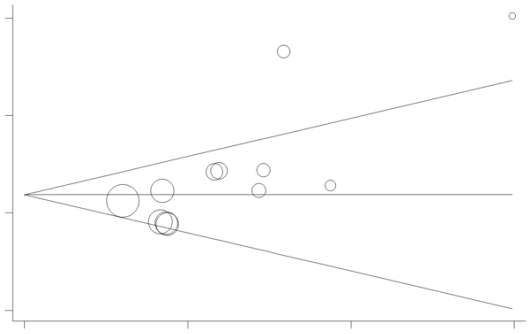

Figure 3. Begg's funnel plot for publication bias test (C-allele vs. A-allele). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line, mean effect size.

OR = 1.02, 95% CI = 0.97-1.07, $P_{heterogeneity}$ = 0.269, P = 0.446, I^2 = 21.9; homozygote comparison: fixed-effects OR = 1.05, 95% CI = 0.93-1.19, $P_{heterogeneity}$ = 0.160, P = 0.444, I^2 = 37.0; dominant genetic model: fixed-effects OR = 1.01, 95% CI = 0.98-1.05, $P_{heterogeneity}$ = 0.358, P = 0.492, I^2 = 9.1; recessive genetic model: fixed-effects OR = 1.06, 95% CI = 0.91-1.22, $P_{heterogeneity}$ = 0.103, P = 0.478, I^2 = 45.4).

Publication bias

The Egger's test and Begg's funnel plot were carried out to assess potential publication bias in the literature. The shape of the funnel plots seemed asymmetrical in allelic comparison for XPC rs2228001 A/C polymorphism, suggesting no publication bias (**Figure 3**). Egger's test was also conducted to evaluate the publication bias to provide statistical evidence of funnel plot symmetry, and data did not reveal evidence of publication bias (**Table 3**).

Discussion

Genetic susceptibility to cancers has led to increased attention to polymorphisms in genes involved in the process of carcinogenesis. Accumulating evidence demonstrates that reduced DNA repair capacity due to genetic variation is associated with an increased risk for human malignancies [29, 30]. Among them, bladder cancer is strongly associated with environmental and occupational exposure to chemical carcinogens. Given the high prevalence of cigarette smoking, it is likely responsible for more cases of bladder cancer than any other

Table 3. Publication bias tests (Begg's funnel plot and Egger's test) for XPC rs2228001 A/C polymorphism

Compared genotype model	Begg's test		Egger's test	
	z-value	*p*-value	t-value	*p*-value
Allelic contrast	2.13	0.034	3.02	0.013
Homozygote comparison	2.26	0.024	3.92	0.003
Heterozygote comparison	0.62	0.537	0.82	0.432
Dominant genetic model	1.44	0.150	1.80	0.103
Recessive genetic model	2.54	0.011	4.88	0.001

risk factor [31]. The damage from cigarette smoke is predominantly repaired by the NER pathway that includes XPC [32]. Nevertheless, the association between XPC rs2228001 A/C polymorphism and bladder cancer risk remains inconclusive. For example, de Verdier et al. demonstrated that the XPC rs2228001 A/C variant significantly increased cancer risk [15]. However, Liu et al. did not find this variation to be associated with an elevated bladder cancer risk [13]. The goal of this meta-analysis was to combine results from previous research to yield summary conclusions, which is quite useful when individual studies may have been too small to achieve a valid conclusion. In addition, our meta-analysis revealed new information regarding the association of XPC rs2228001 polymorphism with bladder cancer.

Our results suggest that XPC rs2228001 A/C polymorphism is associated with increased bladder cancer risk in Asian descendants (under allelic contrast, homozygote comparison and the recessive genetic model) in a stratified analysis. Furthermore, a significant association was observed in smokers using an allelic contrast, homozygote comparison and the recessive genetic model when stratified by smoking exposure. In the analysis stratified by the source of control subjects, the XPC rs2228001 variant was found to increase bladder cancer risk in hospital-based studies (using an allelic contrast, homozygote comparison, and the dominant and recessive genetic models). However, some challenges may limit the generalization of these results. First, the diversity of ethnic backgrounds was limited with only one study using African descendants while 5 were based on Asian descendants. In addition, only four publications included information on the interaction of smoking exposure with XPC rs2228001 polymorphism on bladder cancer risk. Second, the studies may have differed in the histological types of carcinoma that may be associated with different susceptibility. Although we attempted to evaluate the effect of XPC rs2228001 polymorphism on the susceptibility in different types of bladder cancer, the available data were too limited. Third, positive results tend to be published more quickly than 'negative' results, creating a time-lag bias [33]. Fourth, other potential environmental-gene interactions including dietary factors, radiation, toxins and infectious agents should be examined in the future with the growing of more compatible data. Fifth, while XPC rs2228001 polymorphism may contribute to carcinoma, the combined effects of multiple genes or environmental factors might predominate in the development or metastasis of carcinoma [34]. Sixth, the meta-analysis was mainly based on unadjusted estimates. A more precise analysis could be conducted if the individual data were available [35]. Despite these limitations, the present pooled analysis has some key advantages compared with the individual studies. First, a substantial number of cases and controls were extracted from the various studies, which can significantly increase statistical power. Second, the quality of case-control studies included in this analysis was satisfactory based on our selection criteria. Third, no obvious publication bias was detected, suggesting that the results are relatively stable and did not influence the results of our meta-analysis.

In conclusion, this meta-analysis demonstrated that XPC rs2228001 A/C polymorphism may contribute to the risk of developing bladder cancer in the Asian population, but not with other descendants. Furthermore, an elevated risk of bladder cancer was significantly associated with an interaction between XPC rs2228001 polymorphism and smoking status. Future well-designed large studies, particularly referring to gene-environment interactions, are warranted. These future studies should lead to a more comprehensive understanding of the association between XPC rs2228001 A/C polymorphism and bladder cancer risk.

Disclosure of conflict of interest

None.

Address correspondence to: Li-Feng Zhang, Department of Urology, Changzhou No. 2 People's Hospital Affiliated to Nanjing Medical University, Changzhou 213003, Jiangsu Province, China. Tel: +86 519 88132663; Fax: +86 519 88132663; E-mail: nj-likky@163.com; Yuan-Yuan Mi, Department of Urology, Third Affiliated Hospital of Nantong University, 585 Xingyuan Road, Wuxi 214041, China. E-mail: 136-51505691@139.com

References

[1] Franekova M, Halasova E, Bukovska E, Luptak J, Dobrota D. Gene polymorphisms in bladder cancer. Urol Oncol 2008; 26: 1-8.

[2] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009; 59: 225-249.

[3] Yang L, Parkin DM, Li LD, Chen YD, Bray F. Estimation and projection of the national profile of cancer mortality in China: 1991-2005. Br J Cancer 2004; 90: 2157-2166.

[4] Baris D, Karagas MR, Verrill C, Johnson A, Andrew AS, Marsit CJ, Schwenn M, Colt JS, Cherala S, Samanic C, Waddell R, Cantor KP, Schned A, Rothman N, Lubin J, Fraumeni JF Jr, Hoover RN, Kelsey KT, Silverman DT. A case-control study of smoking and bladder cancer risk: emergent patterns over time. J Natl Cancer Inst 2009; 101: 1553-1561.

[5] Hirao Y, Kim WJ, Fujimoto K. Environmental factors promoting bladder cancer. Curr Opin Urol 2009; 19: 494-499.

[6] IARC Working Group on the Evaluations of carcinogenic risks to humans. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum 2004; 83: 1-1438.

[7] Friedberg EC. How nucleotide excision repair protects against cancer. Nat Rev Cancer 2001; 1: 22-33.

[8] Sugasawa K, Ng JM, Masutani C, Iwai S, van der Spek PJ, Eker AP, Hanaoka F, Bootsma D, Hoeijmakers JH. Xeroderma pigmentosum group C protein complex is the initiator of global genome nucleotide excision repair. Mol Cell 1998; 2: 223-232.

[9] Khan SG, Muniz-Medina V, Shahlavi T, Shahlavi T, Baker CC, Inui H, Ueda T, Emmert S, Schneider TD, Kraemer KH. The human XPC DNA repair gene: arrangement, splice site information content and influence of a single nucleotide polymorphism in a splice acceptor site on alternative splicing and function. Nucleic Acids Res 2002; 30: 3624-3631.

[10] Kraemer KH, Lee MM, Andrews AD, Lambert WC. The role of sunlight and DNA repair in melanoma and nonmelanoma skin cancer. The xeroderma pigmentosum paradigm. Arch Dermatol 1994; 130: 1018-1021.

[11] Friedberg EC, Bond JP, Burns DK, Cheo DL, Greenblatt MS, Meira LB, Nahari D, Reis AM. Defective nucleotide excision repair in xpc mutant mice and its association with cancer predisposition. Mutat Res 2000; 459: 99-108.

[12] Sands AT, Abuin A, Sanchez A, Conti CJ, Bradley A. High susceptibility to ultraviolet-induced carcinogenesis in mice lacking XPC. Nature 1995; 377: 162-165.

[13] Liu Y, Wang H, Lin T, Wei Q, Zhi Y, Yuan F, Song B, Yang J, Chen Z. Interactions between cigarette smoking and XPC-PAT genetic polymorphism enhance bladder cancer risk. Oncol Rep 2012; 28: 337-345.

[14] Rouissi K, Ouerhani S, Hamrita B, Bougatef K, Marrakchi R, Cherif M, Ben Slama MR, Bouzouita M, Chebil M, Ben Ammar Elgaaied A. Smoking and Polymorphisms in Xenobiotic Metabolism and DNA Repair Genes are Additive Risk Factors Affecting Bladder Cancer in Northern Tunisia. Pathol Oncol Res 2011; 17: 879-886.

[15] de Verdier PJ, Sanyal S, Bermejo JL, Steineck G, Hemminki K, Kumar R. Genotypes, haplotypes and diplotypes of three XPC polymorphisms in urinary-bladder cancer patients. Mutat Res 2010; 694: 39-44.

[16] Gangwar R, Mandhani A, Mittal RD. XPC gene variants: a risk factor for recurrence of urothelial bladder carcinoma in patients on BCG immunotherapy. J Cancer Res Clin Oncol 2010; 136: 779-786.

[17] Fontana L, Bosviel R, Delort L, Guy L, Chalabi N, Kwiatkowski F, Satih S, Rabiau N, Boiteux JP, Chamoux A, Bignon YJ, Bernard-Gallon DJ. DNA repair gene ERCC2, XPC, XRCC1, XRCC3 polymorphisms and associations with bladder cancer risk in a French cohort. Anticancer Res 2008; 28: 1853-1856.

[18] Zhu Y, Lai M, Yang H, Lin J, Huang M, Grossman HB, Dinney CP, Wu X. Genotypes, haplotypes and diplotypes of XPC and risk of bladder cancer. Carcinogenesis 2007; 28: 698-703.

[19] García-Closas M, Malats N, Real FX, Welch R, Kogevinas M, Chatterjee N, Pfeiffer R, Silverman D, Dosemeci M, Tardón A, Serra C, Carrato A, García-Closas R, Castaño-Vinyals G, Chanock S, Yeager M, Rothman N. Genetic variation in the nucleotide excision repair pathway and bladder cancer risk. Cancer Epidemiol Biomarkers Prev 2006; 15: 536-542.

[20] Wu X, Gu J, Grossman HB, Amos CI, Etzel C, Huang M, Zhang Q, Millikan RE, Lerner S, Dinney CP, Spitz MR. Bladder cancer predisposition: a multigenic approach to DNA-repair and cell-cycle-control genes. Am J Hum Genet 2006; 78: 464-479.

[21] Sak SC, Barrett JH, Paul AB, Bishop DT, Kiltie AE. The polyAT, intronic IVS11-6 and Lys939Gln

XPC polymorphisms are not associated with transitional cell carcinoma of the bladder. Br J Cancer 2005; 92: 2262-2265.
[22] Mittal RD, Mandal RK. Genetic variation in nucleotide excision repair pathway genes influence prostate and bladder cancer susceptibility in North Indian population. Indian J Hum Genet 2012; 18: 47-55.
[23] Zhi Y, Yu J, Liu Y, Wei Q, Yuan F, Zhou X, Song B, Chen Z, Yang J. Interaction between polymorphisms of DNA repair genes significantly modulated bladder cancer risk. Int J Med Sci 2012; 9: 498-505.
[24] Wen H, Feng CC, Fang ZJ, Xia GW, Jiang HW, Xu G, Huang XD, Ding Q. Study on bladder cancer susceptibility and genetic polymorphisms of XPC, XPG, and CYP in smokers and non-smokers. Actas Urol Esp 2013; 37: 259-265.
[25] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.
[26] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
[27] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.
[28] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.
[29] Ribas G, Gonzalez-Neira A, Salas A, Milne RL, Vega A, Carracedo B, González E, Barroso E, Fernández LP, Yankilevich P, Robledo M, Carracedo A, Benítez J. Evaluating HapMap SNP data transferability in a large-scale genotyping project involving 175 cancer-associated genes. Hum Genet 2006; 118: 669-679.
[30] Zhang L, Zhang Z, Yan W. Single nucleotide polymorphisms for DNA repair genes in breast cancer patients. Clin Chim Acta 2005; 359: 150-155.
[31] Zeegers MP, Tan FE, Dorant E, van Den Brandt PA. The impact of characteristics of cigarette smoking on urinary tract cancer risk: a meta-analysis of epidemiologic studies. Cancer 2000; 89: 630-639.
[32] Zasimauskas D, Zekonis G. Effect of smoking on neutrophil oxidative metabolism. Medicina 2008; 443: 195-200.
[33] Ioannidis JP. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. JAMA 1998; 279: 281-286.
[34] Wei Q, Cheng L, Amos CI, Wang LE, Guo Z, Hong WK, Spitz MR. Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. J Natl Cancer Inst 2000; 92: 1764-1772.
[35] Hirschhorn JN, Lohmueller K, Byrne E. A comprehensive review of genetic association studies. Genet Med 2002; 4: 45-61.