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Original Article

XPC Ala499Val and XPG Asp1104His polymorphisms and digestive system cancer risk: a meta-analysis based on model-free approach

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Abstract: Many studies have reported the association between XPC Ala499Val and XPG Asp1104His polymorphisms and digestive system cancer susceptibility, but the results were inconclusive. We performed a meta-analysis, using a comprehensive strategy based on the allele model and a model-free approach, to derive a more precise estimation of the relationship between XPC Ala499Val and XPG Asp1104His polymorphisms with digestive system cancer risk. For XPC Ala499Val, no significant cancer risk was found in the allele model (OR = 0.98, 95% CI: 0.86-1.11) and with model-free approach (OR_G = 0.97, 95% CI: 0.83-1.13). For XPG Asp1104His, there was also no association between this polymorphism and cancer risk in the allele model (OR = 1.03, 95% CI: 0.96-1.11) and with the model-free approach (OR_G = 1.04, 95% CI: 0.95-1.14). Therefore, this meta-analysis suggests that the XPC Ala499Val and XPG Asp1104His polymorphisms were not associated with digestive system cancer risk. Further large and well-designed studies are needed to confirm these findings.

Keywords: XPC, XPG, digestive system cancer, polymorphism, meta-analysis

Introduction

Digestive system cancers are types of the most common malignant tumors worldwide. In 2014, an estimated 71,830 men and 65,000 women will be diagnosed with colorectal cancer and 26,270 men and 24,040 women will die of the disease [1]. Various etiological factors of carcinogenesis include hereditary mutations and susceptibility polymorphisms, inflammation due to infectious agents, environmental and dietary factors. Hereditary and genetic abnormalities usually influence the risk of digestive carcinomas slightly or moderately [2-4].

DNA repair is the basic mechanism in the function of human cells and stimulated in response to DNA damage. Further, DNA repair is a complex process in maintaining the integrity of the genome, which is made up of a series of DNA repair pathways, including more than 130 genes. In humans, there are at least four DNA repair pathways. One of the four pathways, base excision repair (BER) pathway, is responsible for DNA damage repair in exposure to various endogenous and exogenous carcinogens. This pathway is to eliminate error and damaged bases, and can specifically remove methylated, oxidized, or reduced single base pair alterations [5]. At least eight core genes (i.e., ERCC1, XPA, XPB/ERCC3, XPC, XPD/ERCC2, XPE/DDB1, XPF/ERCC4, and XPG/ERCC5) in the NER pathway play an important role in DNA damage repair and maintenance of genome integrity [6, 7].

Xeroderma pigmentosum group C (XPC) is located at chromosome 3p25, which is one of the eight core genes in the NER pathway, particular plays an important role in the early steps (damage recognition, open complex formation and reparation) of genome NER [8, 9]. Recent studies have showed that polymorphisms of XPC gene may alter the DNA repair capacity (DRC) and modulate the susceptibility to cancer. The Ala499Val (C/T) in exon 9 of XPC gene has been

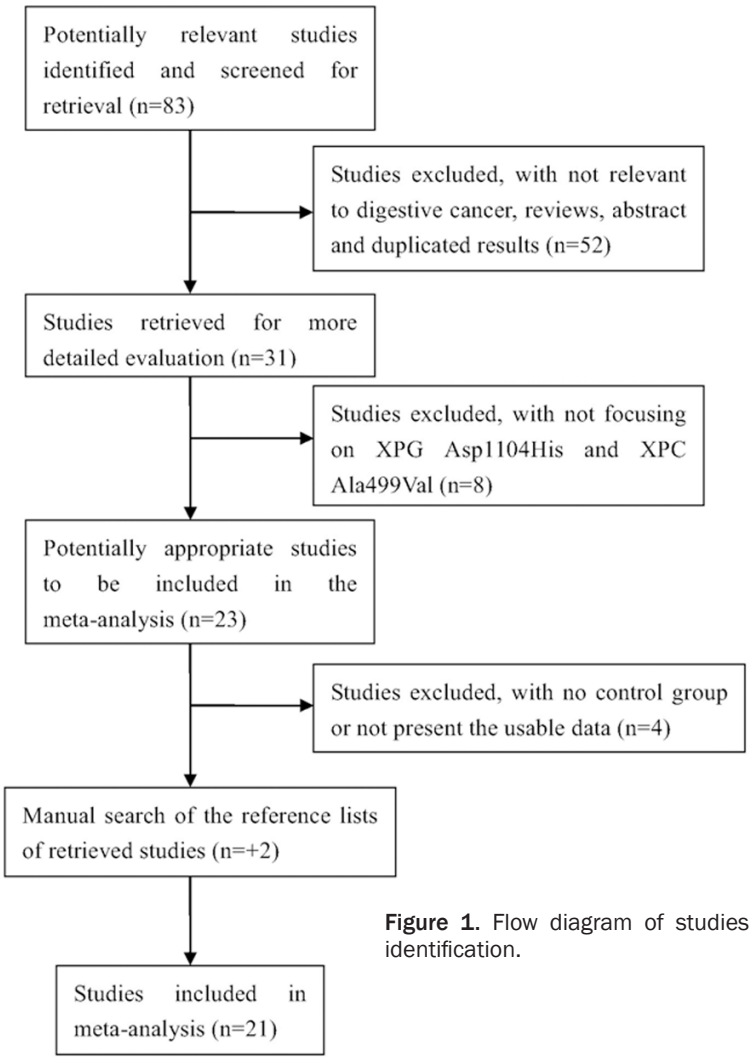

Figure 1. Flow diagram of studies identification.

previously identified in several tumors. Xeroderma pigmentosum group G (XPG) is also one of the NER genes and responsible for 1,186 amino acid structure specific endonuclease activity, thereby playing a key role in NER of helix-distorting DNA damage [6]. It has been observed that there is a relationship between the SNP in exon 15 (G3507C, Asp1104His) and cancer susceptibility.

Recently, many studies indicated that the XPC Ala499Val and XPG Asp1104His genetic polymorphism was correlated with cancer risk in many cancer types [10-30]. However, this relationship remains controversial in digestive system cancer. Therefore, this meta-analysis was performed to evaluate the association between the XPC Ala499Val and XPG Asp1104His genetic polymorphism and digestive system cancer risk.

Materials and methods

Search strategy

We extracted Eligible case-control studies by searching databases and manual search of references of relative reviews and articles. To identify all the studies that examined the association of XPC Ala499Val and XPG Asp-1104H is polymorphism and cancer risk, we conducted a computerized literature search of Embase, PubMed and China National Knowledge Infrastructure (CNKI). The combination of the following key words were used as search terms: “ERCC5” or “XPG”; “XPC”; “Cancer”, ‘‘carcinoma’’ or ‘‘tumor’’; “polymorphism” or ‘‘variation’’. There was no limitation of research and the last research was carried out on Oct 30, 2014. To explore potentially additional studies, we also examined the references of articles and reviews

Selection criteria

Studies were selected according to the following inclusion criteria: (1) case-control studies which evaluated the association between XPC Ala499Val or XPG Asp1104His polymorphisms and digestive system cancer; (2) Genotype and allele data available; and (3) the control population did not contain malignant tumor patients. Studies were excluded if one of the following existed: (1) no control population; (2) duplicate of previous publication; and (3) data unavailable for calculating genotype or allele frequencies.

Data extraction

All the available data were extracted from each study by two investigators independently according to the inclusion criteria listed above. For each study, we recorded the first author, year of publication, country of origin, ethnicity, cancer type, the method of genotyping, the

Table 1. Characteristics of studies included in this meta-analysis

Author	Year	Country	Ethnicity	Cancer type	Genotyping methods	Sample size (case/control)	Case			Control			P_{HWE}
XPC Ala499Val							CC	CT	TT	CC	CT	TT	
Berndt	2006	USA	Caucasian	Colorectal	Taqman	219/28897	123	85	11	16983	10515	123	< 0.001
Huang	2006	USA	Mixed	Colorectal	Taqman	689/703	397	261	31	403	259	397	0.942
Zhou	2006	China	Asian	ESCC and GCA	PCR-RFLP	461/612	297	131	33	272	282	297	0.217
McWilliams	2008	USA	Caucasian	Pancreatic	SNPstream	457/582	246	182	29	339	211	246	0.911
Dong	2008	China	Asian	Gastric	PCR-RFLP	253/612	141	90	22	272	282	141	0.217
Guo	2008	China	Asian	Esophageal	PCR-RFLP	327/612	156	133	38	272	282	156	0.217
Pan	2009	USA	Caucasian	Esophageal	Taqman	383/450	228	129	26	251	178	228	0.133
Long	2010	China	Asian	Gastric	Taqman	361/616	170	156	35	280	274	170	0.673
Li	2010	China	Asian	Liver	Taqman	500/507	163	248	89	169	250	163	0.787
Jiao	2011	China	Asian	Gallbladder	PCR-RFLP	334/329	127	177	30	163	146	127	0.087
Wu	2011	China	Asian	Colorectal	PCR-RFLP	419/838	172	195	52	315	406	172	0.447
Sun	2014	China	Asian	Colorectal	PCR-RFLP	890/910	276	465	149	321	510	276	< 0.001
Li D	2014	China	Asian	Gastric	PCR-RFLP	202/327	92	91	19	144	153	92	0.238
XPG Asp1104His							GG	GC	CC	GG	GC	CC	
Bigler	2005	USA	Mixed	Colorectal	Taqman	719/616	440	243	36	353	226	37	0.917
Huang	2006	USA	Mixed	Colorectal	Taqman	679/697	407	243	29	403	265	29	0.073
Pardini	2008	Czech	Caucasian	Colorectal	PCR-RFLP or Taqman	532/532	334	177	21	356	153	23	0.211
Hussain	2009	China	Asian	Gastric	SNPlex	181/361	38	104	39	90	180	91	0.958
Pan	2009	USA	Caucasian	Esophageal	Taqman	382/457	222	145	15	287	155	15	0.281
Li	2010	China	Asian	Liver	Taqman	500/507	174	233	93	151	265	91	0.175
Canbay	2010	Turkey	Caucasian	Gastric	PCR-RFLP	40/247	25	12	3	148	83	16	0.352
Liu	2011	China	Asian	Colorectal	PCR-RFLP	1028/1085	233	603	192	329	537	219	0.996
Canbay	2011	Turkey	Caucasian	Colorectal	PCR-RFLP	192/208	105	77	10	109	74	25	0.031
Gil	2012	Poland	Caucasian	Colorectal	PCR-RFLP	132/100	86	35	11	64	31	5	0.625
Du	2014	China	Asian	Lung	Taqman	878/884	286	459	133	355	405	124	0.623
Sun	2014	China	Asian	Colorectal	PCR-RFLP	890/910	216	476	198	227	497	186	0.004

ESCC: Esophageal Squamous Cell Carcinoma; GCA: Gastric Cardiac Adenocarcinoma; PCR-RFLP: Polymerase Chain Reaction-restriction Fragment Length Polymorphism; HWE: Hardy-Weinberg. Equilibrium.

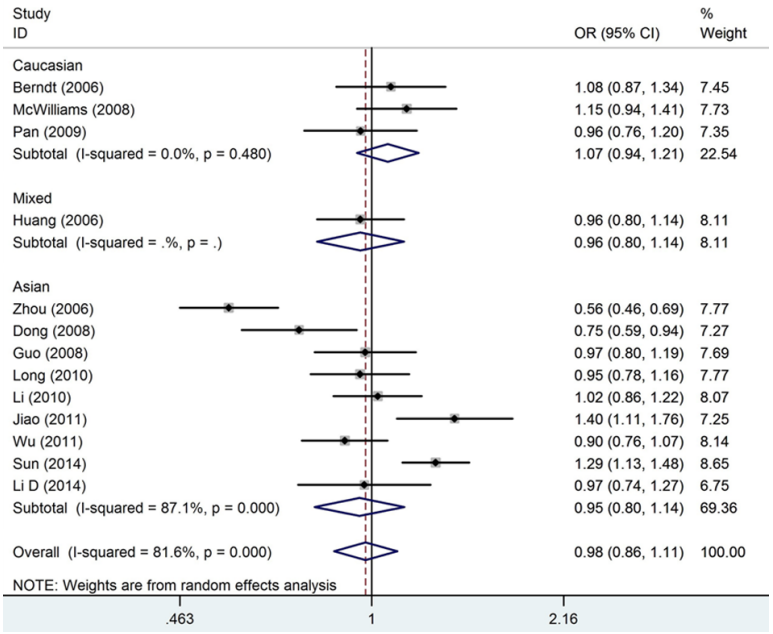

Figure 2. Odds ratios (OR) and 95% confidence interval (CI) of individual studies and pooled data for the association of the XPC Ala499Val polymorphism and digestive system cancer risk in allele model.

number of cases and controls and genotype distributions in cases and controls.

Statistical analysis

Hardy-Weinberg equilibrium was examined by chi-square goodness-of-fit test ($P > 0.05$) using gene frequencies of the healthy individuals. Zintzaras reported a novel method to calculate the generalized odds ratio (OR_G) based on a genetic model-free approach, which may overcome the short-comings of multiple model testing or erroneous model specification [31]. Thus, the OR_G calculations were also performed.

The heterogeneity of the studies was assessed using the Cochran's Q test (considered significant for $P < 0.10$) and was quantified by the I^2 statistic. Both fixed effects (Mantel-Haenszel) and random effects (Der Simonian and Laird) models were used to combine the data. Relative influence of each study on the pooled estimate was assessed by omitting one study at a time for sensitivity analysis. Publication bias was evaluated by visual inspection of symmetry of Begg's funnel plot and assessment of Egger's test ($P < 0.05$ was regarded as representative of statistical significance). Statistical analyses were done in ORGGASMA and STATA software, version 11.0 (STATA Corp., College Station, TX, USA), and all tests were two-sided.

Results

Characteristics of the studies

There were 83 papers relevant to the search words. The flow chart of selection of studies and reasons for exclusion is presented in **Figure 1** Overall, 21 articles were included in the final meta-analysis. There were 13 articles with 5495 cases and 35995 controls for the XPC Ala499Val polymorphism, and 12 studies with 6153 cases and 6604 controls for the XPG Asp1104His polymorphism. For the XPC Ala499Val polymorphism, there were three studies conducted in Caucasians, nine studies in Asians, and one study in mixed ethnic group. As to the XPG Asp1104His polymorphism, there were five studies conducted in Caucasians, five studies in Asians, two studies in mixed ethnic group. Study characteristics are summarized in **Table 1**. The genotype distributions in the controls of all studies were consistent with HWE except for three studies [18, 21, 23].

Quantitative synthesis

For the allele contrast, 13 studies (5495 case and 35995 control) that researched the relationship between XPC Ala499Val polymorphism and the risk of digestive system cancers were included in the meta-analysis. The results showed that there was large heterogeneity among studies ($I^2 = 81.6\%$, $P_{heterogeneity} < 0.001$); therefore, the random-effects model was used; OR = 0.98 (0.86-1.11). In subgroup analysis based on ethnicity, there was no heterogeneity among the studies performed in Caucasian but large heterogeneity in studies on Asians. And the pooled ORs were no significant: 1.07 (0.94-1.21), and 0.95 (0.80-1.14), respectively (**Figure 2**). We also examined the association of the XPC Ala499Val polymorphism and cancer risk according to cancer type. No significant

Table 2. Meta-analysis of the XPC Ala499Val and XPG Asp1104His polymorphisms and digestive system cancer risk

Study characteristics		Case/controls	Genetic model	OR (95% CI)	I^2 (%)	*P* for heterogeneity
XPC Ala499Val						
Total (N = 13)		5495/35995	Allele Model	0.98 (0.86-1.11)	81.6	< 0.001
			OR_G	0.97 (0.83-1.13)	83.2	< 0.001
Ethnicity	Caucasian (N = 3)	1059/29929	Allele Model	1.07 (0.94-1.21)	0	0.480
			OR_G	1.07 (0.93-1.23)	16.1	0.304
	Asian (N = 9)	3747/5363	Allele Model	0.95 (0.80-1.14)	87.1	< 0.001
			OR_G	0.94 (0.75-1.17)	88.1	< 0.001
	Mixed (N = 1)	689/703	Allele Model	0.96 (0.80-1.14)		
			OR_G	0.97 (0.79-1.18)		
Cancer type	Colorectal (N = 4)	2217/31348	Allele Model	1.05 (0.88-1.26)	77.4	0.004
			OR_G	1.07 (0.87-1.32)	76.9	0.005
	Gastric (N = 3)	816/1555	Allele Model	0.89 (0.75-1.04)	35.3	0.213
			OR_G	0.86 (0.73-1.00)	44.5	0.165
	Esophageal (N = 2)	710/1062	Allele Model	0.97 (0.83-1.12)	0	0.902
			OR_G	0.92 (0.78-1.10)	0	0.827
	Other (N = 4)	1752/2030	Allele Model	0.98 (0.68-1.42)	92.8	< 0.001
			OR_G	0.98 (0.62-1.56)	93.5	< 0.001
HWE	Yes (N = 11)	4386/6188	Allele Model	0.94 (0.82-1.07)	78.2	< 0.001
			OR_G	0.92 (0.78-1.09)	80.6	< 0.001
	No (N = 2)	1109/29807	Allele Model	1.21 (1.02-1.43)	47.5	0.168
			OR_G	1.28 (1.12-1.47)	50.2	0.156
XPG Asp1104His						
Total (N = 12)		6153/6604	Allele Model	1.03 (0.96-1.11)	37.3	0.093
			OR_G	1.04 (0.95-1.14)	42.3	0.060
Ethnicity	Caucasian (N = 5)	1278/1544	Allele Model	1.05 (0.92-1.21)	8.7	0.357
			OR_G	1.09 (0.94-1.26)	0	0.477
	Asian (N = 5)	3477/3747	Allele Model	1.08 (0.98-1.18)	41.0	0.148
			OR_G	1.09 (0.97-1.23)	51.2	0.084
	Mixed (N = 2)	1398/1313	Allele Model	0.91 (0.80-1.03)	0	0.535
			OR_G	0.89 (0.77-1.03)	0	0.591
Cancer type	Colorectal (N = 8)	5050/5032	Allele Model	1.04 (0.95-1.14)	50.3	0.05
			OR_G	1.05 (1.00-1.16)	53.2	0.037
	Gastric (N = 2)	221/608	Allele Model	1.00 (0.79-1.26)	0	0.875
			OR_G	0.99 (0.75-1.30)	0	0.819
	Other (N = 2)	882/964	Allele Model	1.02 (0.80-1.30)	63.4	0.098
			OR_G	1.02 (0.76-1.38)	68.2	0.076
HWE	Yes (N = 10)	5071/5486	Allele Model	1.04 (0.96-1.13)	37.8	0.106
			OR_G	1.05 (0.95-1.17)	47.6	0.046
	No (N = 2)	1082/1118	Allele Model	0.95 (0.73-1.23)	61.5	0.107
			OR_G	1.02 (0.88-1.18)	35.8	0.212

OR_G: The Generalized Odds Ratio.

association was found between XPC Ala499Val polymorphism and cancer risk according to cancer type (**Table 2**). Examining genotype frequencies in the controls, significant deviation from HWE was detected in the two studies [21, 23]. When the two studies were excluded,

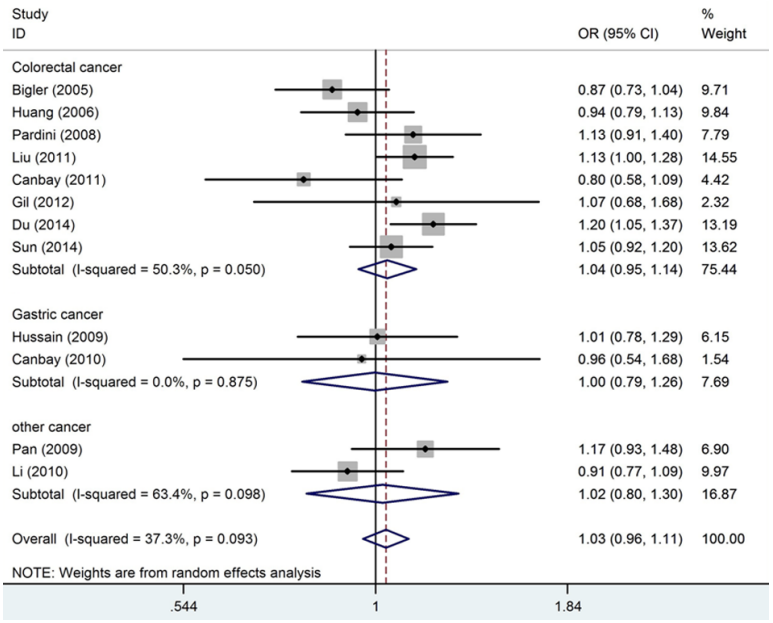

Figure 3. Forest plot of the odds ratio (OR) and 95% confidence intervals (CIs) of studies on the association between digestive system cancer and the XPG Asp1104His polymorphism based on allele model.

results showed that there still was large heterogeneity among studies (I^2 = 78.2%, $P_{heterogeneity}$ < 0.001); hence, the random-effects model was used; OR = 0.94 (0.82-1.07).

Similarly, for the model-free approach, 13 studies were included. The results showed that there was large heterogeneity among studies (I^2 = 83.2%, $P_{heterogeneity}$ < 0.001), and the random-effects model was used; OR_G = 0.97 (0.83-1.13). In subgroup analysis based on ethnicity, no significant heterogeneity was found in Caucasian and the fixed-effect OR_G equalled 1.07 (0.93-1.23). But in Asians, large heterogeneity existed (I^2 = 88.1%, $P_{heterogeneity}$ < 0.001), and random-effects model was used to estimate the pooled OR_G = 0.94 (0.75-1.17; **Table 2**). In subgroup analysis based on cancer type, no significant association was found between XPC Ala499Val polymorphism and cancer risk. When the two studies deviation from HWE were excluded, results showed that there still was large heterogeneity among studies (I^2 = 80.6%, $P_{heterogeneity}$ < 0.001), and the random-effects model was used; OR_G = 0.92(0.78-1.09) (**Table 2**).

For the allele contrast, there were 12 articles (6153 case and 6604 control) studying the association between XPG Asp1104His polymorphism and the risk of digestive system cancers. The results showed moderate heterogeneity among studies (I^2 = 37.3%, $P_{heterogeneity}$ = 0.093), and the random-effects OR = 1.03 (0.96-1.11; **Figure 3**). When the two studies deviation from HWE were excluded [18, 21], results showed no heterogeneity among studies (I^2 = 37.8%, P = 0.106), and the fixed-effects OR was not significant either: OR = 1.04 (0.96-1.13). Same situations were encountered in subgroup analysis based on ethnicity and cancer type (**Figure 3**), namely, no significant associations were found (**Table 2**).

For the model-free approach, 12 studies were included. The results also showed moderate heterogeneity among studies (I^2 = 42.3%, $P_{heterogeneity}$ = 0.060), and the random effect was used; OR_G = 1.04 (0.95-1.14). When the two studies deviation from HWE were excluded, results showed a similar pattern: OR_G = 1.05 (0.95-1.17), with moderate heterogeneity (I^2 = 47.6%, $P_{heterogeneity}$ = 0.046). Same situations were encountered in subgroup analysis based on ethnicity and cancer type, namely, no signifiant associations were found (**Table 2**).

Sensitive analysis

Sensitivity analyses were performed to assess the influence of individual dataset on the pooled ORs by sequential removing each eligible study. As seen in **Figure 4**, any single study was omitted, while the overall statistical significance does not change, indicating that our results are statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to assess publication bias among the literatures. As shown in **Figure 5**, there was no evidence of publication bias for XPC Ala499Val in allele model (Begg's test P = 0.760; Egger's test P = 0.303) and XPG Asp1104His in allele model (Begg's test P = 0.451; Egger's test P = 0.253).

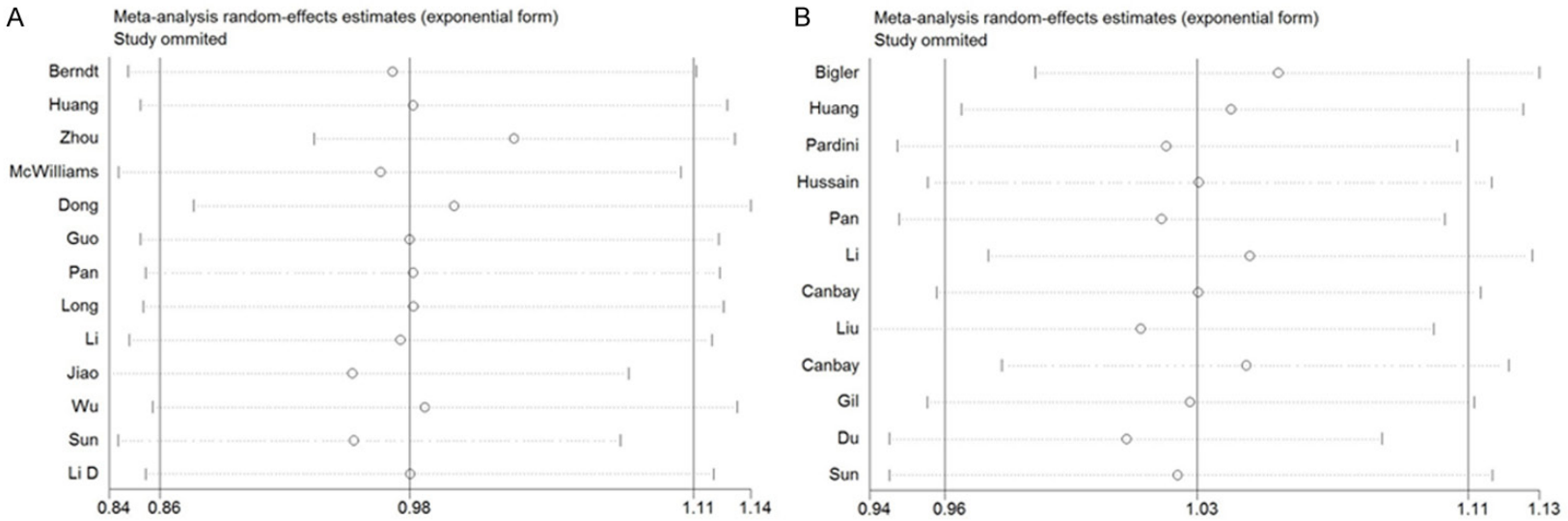

Figure 4. Sensitivity analysis: examining the influence of individual studies to pooled odds ratios (OR). A. XPC Ala499Val polymorphism in allele model; B. XPG Asp1104His polymorphism in allele model.

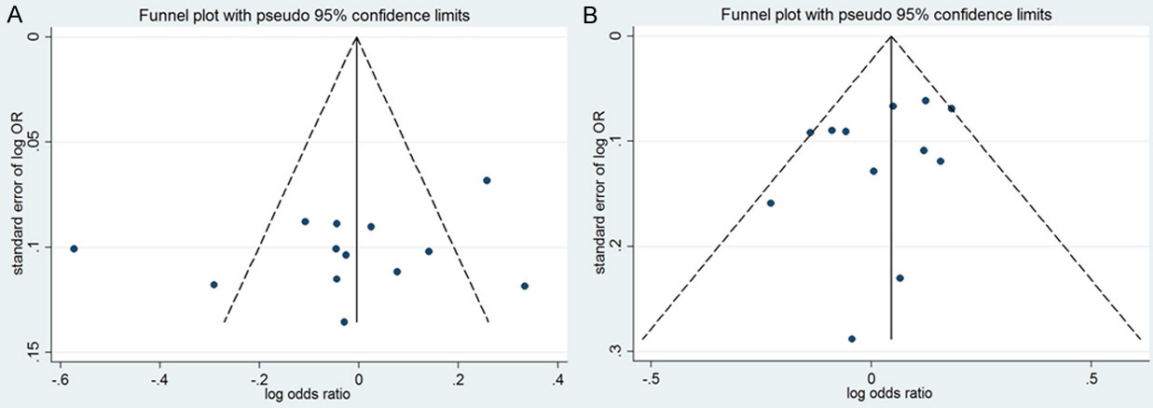

Figure 5. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. A. Funnel plot for allele model of XPC Ala499Val polymorphism; B. Funnel plot for allele model of XPG Asp1104His polymorphism.

Discussion

At present, the majority of meta-analyses of genetic association studies are usually conducted by comparing genotype frequencies between cases and controls under various genetic models. However, these genetic models are not independent, and a priori knowledge or biological justification for model selection is seldom available [32, 33]. But in our study, the model-free approach was used. The application of OR_G might overcome the drawbacks of multiple model testing or erroneous model specification and make the interpretation of the results easier [31].

To our knowledge, the current meta-analysis is the largest one to investigate the association between XPC Ala499Val and XPG Asp1104His polymorphisms and digestive system cancer risk. Pooled analysis for the XPC Ala499Val polymorphism contained 13 studies with a total of 5495 cases and 35995 controls; meanwhile, pooled analysis for the XPG Asp1104His polymorphism encompassed 12 studies with 6153 cases and 6604 controls. The meta-analysis observed no significant association between XPC Ala499Val and XPG Asp1104His polymorphisms and digestive system cancer risk in the overall population and in the subgroup analysis by ethnicity and cancer type.

The XPC Ala499Val and XPG Asp1104His polymorphisms and cancer risk have been investigated by several meta-analyses [34, 35]. Recently, He et al conducted a comprehensive meta-analysis about XPG Asp1104His polymorphisms and cancer susceptibility, and found that the XPG Asp1104His polymorphism confer significantly susceptibility to cancer risk [34]. Compared with He's work, we only focus on the association of XPG Asp1104His polymorphism and digestive system cancer, while He et al. analyzed a variety of cancers, including breast cancer, lung cancer, bladder cancer, and glioma, etc. Additionally, two recently published studies [20, 21] were not included in that meta-analysis. Therefore, we identified more eligible studies and performed a detailed analysis by the allele model and model-free approach. Compared with another meta-analysis about XPC Ala499Val polymorphism and digestive system risk reported by Jiang et al [35], we identified more eligible studies and performed analysis by a comprehensive strategy, while they only analyzed six studies about XPC Ala499Val polymorphism.

The current study has some inevitable limitations that should be acknowledged. First, our results were based on an unadjusted estimated, a more precise analysis would have been conducted if more detailed individual data were available. Second, there was significant heterogeneity among included studies. Even though we used the random-effect model to calculate pool ORs, the precision of outcome would be affected. Third, only published studies were included in this meta-analysis, which may have biased our results.

In summary, we concluded that the XPC Ala499Val and XPG Asp1104His polymorphisms were not associated with digestive sys-

tem cancer risk. However, future well designed large studies, particularly stratified by gene-gene and gene-environment interactions might be necessary to clarify the possible role of the XPC Ala499Val and XPG Asp1104His polymorphisms in the susceptibility to digestive system cancer.

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Disclosure of conflict of interest

None.

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References

[1] Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin 2014; 64: 104-17.

[2] Burn J, Mathers J, Bishop DT. Genetics, inheritance and strategies for prevention in populations at high risk of colorectal cancer (CRC). Recent Results Cancer Res 2013; 191: 157-83.

[3] Pellegrini ML, Argibay P, Gomez DE. Genetics and epigenetics of colorectal cancer. Acta Gastroenterol Latinoam 2011; 41: 247-261.

[4] Vogelaar IP, van der Post RS, Bisseling TM, van Krieken JH, Ligtenberg MJ, Hoogerbrugge N. Familial gastric cancer: detection of a hereditary cause helps to understand its etiology. Hered Cancer Clin Pract 2012; 10: 18.

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

[6] Wakasugi M, Reardon JT, Sancar A. The noncatalytic function of XPG protein during dual incision in human nucleotide excision repair. J Biol Chem 1997; 272: 16030-16034.

[7] O'Donovan A, Davies AA, Moggs JG, West SC, Wood RD. XPG endonuclease makes the 3' incision in human DNA nucleotide excision repair. Nature 1994; 371: 432-435.

[8] Li L, Peterson C, Legerski R. Sequence of the mouse XPC cDNA and genomic structure of the human XPC gene. Nucleic Acids Res 1996; 24: 1026-1028.

[9] Sugasawa K, Ng JM, Masutani C. Xeroderma pigmentosum group C protein complex is the initiator of global genome nucleotide excision repair. Mol Cell 1998; 2: 223-232.

[10] Bigler J, Ulrich CM, Kawashima T, Whitton J, Potter JD. DNA repair polymorphisms and risk of colorectal adenomatous or hyperplastic polyps. Cancer Epidemiol Biomarkers Prev 2005; 14: 2501-2508.

[11] Huang WY, Berndt SI, Kang D, Chatterjee N, Chanock SJ. Nucleotide excision repair gene polymorphisms and risk of advanced colorectaladenoma: XPC polymorphisms modify smoking-related risk. Cancer Epidemiol Biomarkers Prev 2006; 15: 306-311.

[12] Pardini B, Naccarati A, Novotny J, Smerhovsky Z, Vodickova L. DNA repair genetic polymorphisms and risk of colorectal cancer in the Czech Republic. Mutat Res 2008; 638: 146-153.

[13] Hussain SK, Mu LN, Cai L, Chang SC, Park SL. Genetic variation in immune regulation and DNA repair pathways and stomach cancer in China. Cancer Epidemiol Biomarkers Prev 2009; 18: 2304-2309.

[14] Pan J, Lin J, Izzo JG, Liu Y, Xing J. Genetic susceptibility to esophageal cancer: the role of the nucleotide excision repair pathway Carcinogenesis 2009; 30: 785-792.

[15] Li LM, Zeng XY, Ji L, Fan XJ, Li YQ. Association of XPC and XPG polymorphisms with the risk of hepatocellular carcinoma. Zhong Hua Gan Zang Bing Za Zhi 2010; 18: 271-275.

[16] Canbay E, Agachan B, Gulluoglu M, Isbir T, Balik E. Possible associations of APE1 polymorphism with susceptibility and HOGG1 polymorphism with prognosis in gastric cancer. Anticancer Res 2010; 30: 1359-1364.

[17] Liu D, Wu HZ, Zhang YN, Kang H, Sun MJ. DNA repair genes XPC, XPG polymorphisms: Relation to the risk of colorectal carcinoma and therapeutic outcome with oxaliplatin-based adjuvant chemotherapy. Mol Carcinog 2012; 51 Suppl 1: e83-93.

[18] Canbay E, Cakmakoglu B, Zeybek U, Sozen S, Cacina C. Association of APE1 and hOGG1 polymorphisms with colorectal cancer risk in a Turkish population. Curr Med Res Opin 2011; 27: 1295-1302.

[19] Gil J, Ramsey D, Stembalska A, Karpinski P, Pesz KA, Laczmanska I, Leszczynski P, Grzebi-

eniak Z, Sasiadek MM. The C/A polymorphism in intron 11 of the XPC gene plays a crucial role in the modulation of an individual's susceptibility to sporadic colorectal cancer. Mol Biol Rep 2012; 39: 527-534.
[20] Du H, Zhang X, Du M, Guo N, Chen Z, Shu Y, Zhang Z, Wang M, Zhu L. Association study between XPG Asp1104His polymorphism and colorectal cancer risk in a Chinese population. Sci Rep 2014; 4: 6700.
[21] Sun K, Gong A, Liang P. Predictive impact of genetic polymorphisms in DNA repair genes on susceptibility and therapeutic outcomes to colorectal cancer patients. Tumour Biol 2014; 36: 1549-59.
[22] Li D, Hou H, Xu C, Ning T. The relationship between XPC gene polymorphism and gastric cancer risk. Shandong Medical Journal 2014; 54: 24-26.
[23] Berndt SI, Platz EA, Fallin MD. Genetic variation in the nucleotide excision repairpathway and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2006; 15: 2263-9.
[24] Zhou RM, Wang N, Guo W. Correlation of polymorphisms in xeroderma pigmentosum group C to the risk of ovarian carcinoma. Zhonghua Liu Xing Bing Xue Za Zhi 2008; 29: 91-2.
[25] Guo W, Zhou RM, Wan LL. Polymorphisms of the DNA repair genexeroderma pigmentosum groups A and C and risk of esophageal squamous cell carcinoma in a population of high incidence region of North China. J Cancer Res Clin Oncol 2008; 134: 263-70.
[26] Dong Z, Guo W, Zhou R. Polymorphisms of the DNA repair gene XPA and XPC and its correlation with gastric cardiac adenocarcinoma in a high incidence population in North China. J Clin Gastroen Terol 2008; 42: 910-5.
[27] McWilliams RR, Bamlet WR, Cunningham JM. Polymorphisms in DNA repair genes, smoking, and pancreatic adenocarcinoma risk. Cancer Res 2008; 68: 4928-35.
[28] Wu Y, Jin M, Liu B. The association of XPC polymorphisms and tea drinking with colorectal cancer risk in a Chinese population. Mol Carcinog 2011; 50: 189-98.
[29] Jiao X, Ren J, Chen H. Ala499Val (C > T) and Lys939Gln (A > C) polymorphisms of the XPC gene: their correlation with the risk of primary gallbladder adenocarcinoma-a case control study in China. Carc Inogenesis 2011; 32: 496-501.
[30] Long XD, Ma Y, Huang YZ. Genetic polymorphisms in DNA repair genes XPC, XPD, and XRCC4, and susceptibility to Helicobacter pylori infection-related gastric antrum adenocarcinoma in Guangxi population, China. Mol Carcinog 2010; 49: 611-8.
[31] Zintzaras, E. The generalized odds ratio as a measure of genetic risk effect in the analysis and meta-analysis of association studies. Stat Appl Genet Mol Biol 2010; 9: Article21.
[32] Kavvoura FK, Ioannidis JP. Methods for meta-analysis in genetic association studies: a review of their potential and pitfalls. Hum Genet 2008; 123: 1-14.
[33] Salanti G, Sanderson S, Higgins JP. Obstacles and opportunities in meta-analysis of genetic association studies. Genet Med 2005; 7: 13-20.
[34] He XF, Liu LR, Wei W, Liu Y, Su J, Wang SL, Shen XL, Yang XB. Association between the XPG Asp1104His and XPF Arg415Gln polymorphisms and risk of cancer: a meta-analysis. PLoS One 2014; 9: e88490.
[35] Jiang X, Zhou LT, Zhang SC, Chen K. XPC Polymorphism Increases Risk of Digestive System Cancers: Current Evidence from A Meta-Analysis. Chin J Cancer Res 2012; 24: 181-9.