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Original Article

XPG Asp1104His polymorphism and gastrointestinal cancers risk: a meta-analysis

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Abstract: Several studies have reported the association between the Asp1104His polymorphism in xeroderma pigmentosum group G (XPG) gene and risk of gastrointestinal cancers. However, the results are inconsistent. This meta-analysis was performed to assess the association between XPG Asp1104His polymorphism and gastrointestinal cancers risk. Relevant studies were identified using PubMed, Web of Science, CNKI, WanFang and VIP databases up to July 22, 2014. The pooled odds ratio (OR) with a 95% confidence interval (CI) was calculated using the fixed- or random effects model. 13 case-control studies from twelve publications with 4275 patients and 5735 controls were included. Overall, a significant association was found between the XPG Asp1104His polymorphism and the risk of gastrointestinal cancers (dominant model: OR = 1.15, 95% CI: 1.05-1.26; His/His vs. Asp/Asp: OR = 1.15, 95% CI: 1.01-1.32). When the analysis was stratified by ethnicity, similar results were observed in Asians under homozygote model; in stratification analysis by cancer type, increased cancer risk was detected in colorectal and hepatocellular carcinoma, but not for other gastrointestinal cancers. Furthermore, in subgroup analysis by source of control, we failed to detect any association among population, hospital and family-based populations. This meta-analysis indicated that the XPG Asp1104His polymorphism may be a risk factor for gastrointestinal cancers, especially of colorectal cancer.

Keywords: XPG, polymorphism, gastrointestinal cancers, meta-analysis

Introduction

Gastrointestinal cancers referring to a group of malignancies, including esophagus, gastric, hepatocellular, bowels, pancreas, gallbladder, and anus, are the most common cancer worldwide. There were estimated 3.4 million new cases worldwide each year, and their mortality rates have increased gradually over the past decade [1]. The exact mechanism of carcinogenesis is still not fully understood. It is well established that some risk factors (such as dietary, racial and socioeconomic) and interactions between genetic and environmental factors play important roles in the pathogenesis of cancer [2, 3].

DNA repair deregulation is a crucial factor in the multistep process of carcinogenesis. Normally, a variety of DNA repair machinery has been developed to ensure genome integrity in humans, and the xeroderma pigmentosum group G (XPG) gene is a vital component of the DNA repair machinery. The XPG gene, also known as excision repair cross complementing group 5 (ERCC5), is a member of the flap structure-specific endonuclease 1 family and encodes a protein of 1.186 amino acids. The primary structure of the human XPG protein harbors the N- and Inuclease domains that are highly conserved, which together form the nuclease core [4]. The XPG gene is located on chromosome 13q22-q33, consists of 15 exons and 14 introns [5]. To date, several single nucleotide polymorphisms (SNPs) in XPG gene have been identified, and have been studied for their association with cancer risk, such as rs17655G>C (Asp1104His), rs2296147T>C, rs2094258C>T, rs873601G>A, rs1047768T>C, rs2018836G>A, rs3818356G>A and rs751402A>G [6-9]. Of these, the Asp1104His polymorphism is common (minor allele frequency > 0.05) and regarded as a tagger, which was most frequently investigated for its association with cancer risk.

Recently, the Asp1104His polymorphism in XPG gene has been reported to be associated with gastrointestinal cancers (e.g. esophageal,

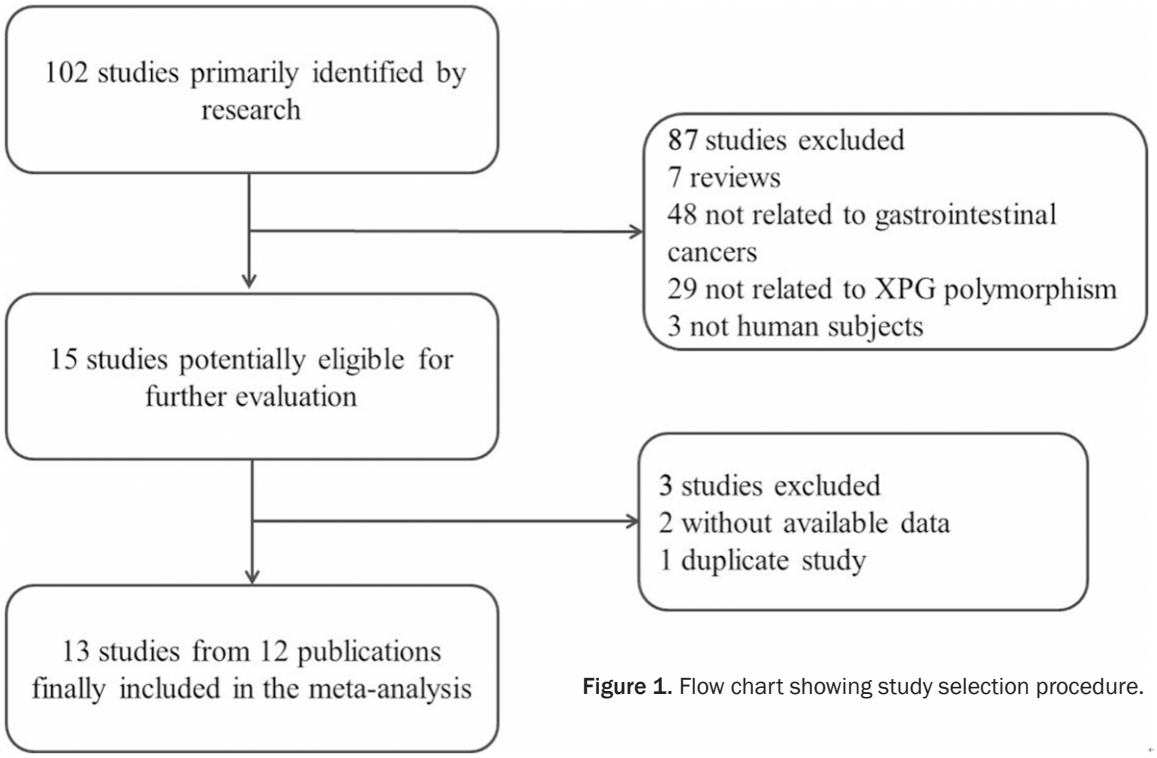

Figure 1. Flow chart showing study selection procedure.

colorectal, gastric and hepatocellular) [10-23]. However, the results have been inconclusive or inconsistent. Therefore, we conducted a meta-analysis to evaluate the association between the XPG Asp1104His polymorphism and susceptibility to gastrointestinal cancers.

Materials and methods

Search strategy

We searched the electronic literature PubMed, Web of Science, CNKI, WanFang and VIP databases for all relevant articles. The last search update was July 22, 2014, using the search terms: "xeroderma pigmentosum group G or XPG or ERCC5 or DNA repair gene or NER" and "genetic polymorphism or polymorphisms or variant" and "gastrointestinal cancers or digestive system cancer or gastric cancer or colorectal cancer or hepatocellular carcinoma or esophageal cancer or pancreatic cancer". The search was restricted to humans without language restrictions. Additional studies were identified by a hand search of references of original or review articles on this topic.

Inclusion criteria and exclusion criteria

Studies included in this meta-analysis have to meet the following criteria: (1) studies that evaluated the association between the XPG Asp1104His polymorphism and gastrointestinal cancers, (2) in a case-control study design, (3) had detailed genotype frequency of cases and controls or could be calculated from the article text. While major exclusion criteria were: (1) case-only study, case reports, and review articles, (2) studies without the raw data of the XPG Asp1104His genotype, (3) repetitive publications.

Data extraction

For each study, the following data were extracted independently by two investigators: the first author's name, year of publication, country of origin, ethnicity, source of controls, genotype methods, number of cases and controls, and Hardy-Weinberg equilibrium (HWE) in controls (*P* value). The results were compared, and disagreements were discussed among all authors and resolved with consensus.

Statistical analysis

HWE was evaluated for each study using an internet-based HWE calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The risk of gastrointestinal cancers associated with the XPG Asp1104His polymorphism was estimated for each study by odds ratio (OR) and 95% confi-

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

Study	Year	Country	Ethnicity	Tumor type	Source of controls	Genotype methods	Genotype (case/control)				P_{HWE}
							Total	Asp/Asp	Asp/His	His/His	
Canbay, et al. [10]	2010	Turkey	Caucasian	Gastric	PB	PCR-RFLP	40/247	25/148	12/83	3/16	0.352
Canbay, et al. [11]	2011	Turkey	Caucasian	Colorectal	PB	PCR-RFLP	79/247	43/148	34/83	2/16	0.352
Gli, et al. [12]	2012	Poland	Caucasian	Colorectal	HB	PCR-RFLP	132/100	86/64	35/31	11/5	0.625
Guo, et al. [13]	2009a	China	Asian	Esophageal	PB	PCR-RFLP	327/612	59/134	174/326	94/152	0.101
Guo, et al. [13]	2009b	China	Asian	Gastric	PB	PCR-RFLP	253/612	70/134	124/326	59/152	0.101
Hussain, et al. [14]	2009	China	Asian	Gastric	PB	SNPlex assay	173/370	36/93	101/185	36/92	0.999
Joshi, et al. [15]	2009	USA	Caucasian	Colorectal	FB	TaqMan	308/361	183/213	114/137	11/11	0.046
Li, et al. [16]	2010	China	Asian	Hepatocellular	HB	TaqMan	500/507	93/91	233/265	174/151	0.175
Li, et al. [17]	2011	China	Asian	Gastric	HB	MALDI-TOF MS	100/126	26/33	50/63	24/30	0.995
Liu, et al. [18]	2012	China	Asian	Colorectal	PB	PCR-RFLP	1028/1085	233/329	603/537	192/219	0.996
Pan, et al. [19]	2009	USA	Caucasian	Esophageal	HB	TaqMan	382/457	222/287	145/155	15/15	0.281
Pardini, et al. [20]	2008	Czech	Caucasian	Colorectal	HB	PCR-RFLP	532/532	334/356	177/153	21/23	0.211
Xie, et al. [21]	2007	China	Asian	Hepatocellular	PB	PCR-RFLP	421/479	143/169	199/248	79/62	0.508

HWE: Hardy-Weinberg equilibrium; MALDI-TOF MS: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism. PB: population-based; HB: hospital-based; FB: family-based.

Table 2. Summary of OR of the XPG Asp1104His polymorphism and gastrointestinal cancers risk

Variables	N[a]	dominant model			recessive model			Asp/His vs. Asp/Asp			His/His vs. Asp/Asp		
		OR (95% CI)	P[b]	I^2	OR (95% CI)	P[b]	I^2	OR (95% CI)	P[b]	I^2	OR (95% CI)	P[b]	I^2
Total	13	1.15 (1.05, 1.26)	0.11	34	1.07 (0.95, 1.19)	0.29	15	1.10 (0.95,1.27)	0.01	52	1.15 (1.01, 1.32)	0.62	0
Ethnicity													
Asian	7	1.11 (0.90, 1.35)	0.01	62	1.07 (0.95, 1.21)	0.09	46	1.08 (0.85, 1.38)	0.002	72	1.17 (1.01, 1.35)	0.28	20
Caucasian	6	1.12 (0.97, 1.30)	0.82	0	1.04 (0.73, 1.47)	0.69	0	1.13 (0.97, 1.31)	0.01	0	1.08 (0.76, 1.54)	0.80	0
Cancer type													
Gastric	4	0.92 (0.73, 1.16)	0.26	26	0.90 (0.70, 1.15)	0.89	0	0.94 (0.74, 1.20)	0.16	42	0.87 (0.65, 1.17)	0.77	0
Colorectal	5	1.26 (1.11, 1.43)	0.17	37	0.92 (0.76, 1.12)	0.56	0	1.23 (0.98, 1.54)	0.30	57	1.17 (0.94, 1.46)	0.63	0
Esophageal	2	1.24 (1.00, 1.54)	0.84	0	1.22 (0.92, 1.61)	0.97	0	1.21 (0.97, 1.51)	0.99	0	1.38 (0.97, 1.96)	0.85	0
Hepatocellular	2	1.01 (0.82, 1.25)	0.64	0	1.35 (1.09, 1.68)	0.36	0	0.91 (0.73, 1.13)	0.67	0	1.28 (0.98, 1.68)	0.29	9
Source of control													
PB	7	1.14 (0.92, 1.40)	0.02	59	1.02 (0.89, 1.16)	0.09	46	1.14 (0.89, 1.47)	0.004	68	1.17 (0.99, 1.37)	0.17	34
HB	5	1.11 (0.96, 1.29)	0.73	0	1.19 (0.96, 1.47)	0.80	0	1.09 (0.93, 1.27)	0.40	1	1.13 (0.87, 1.46)	0.93	0
FB	1	0.98 (0.72, 1.34)	NA	NA	1.18 (0.50, 2.76)	NA	NA	0.97 (0.71, 1.33)	NA	NA	1.16 (0.49, 2.75)	NA	NA

[a]Number of comparisons. [b]Test for heterogeneity. NA, not applicable.

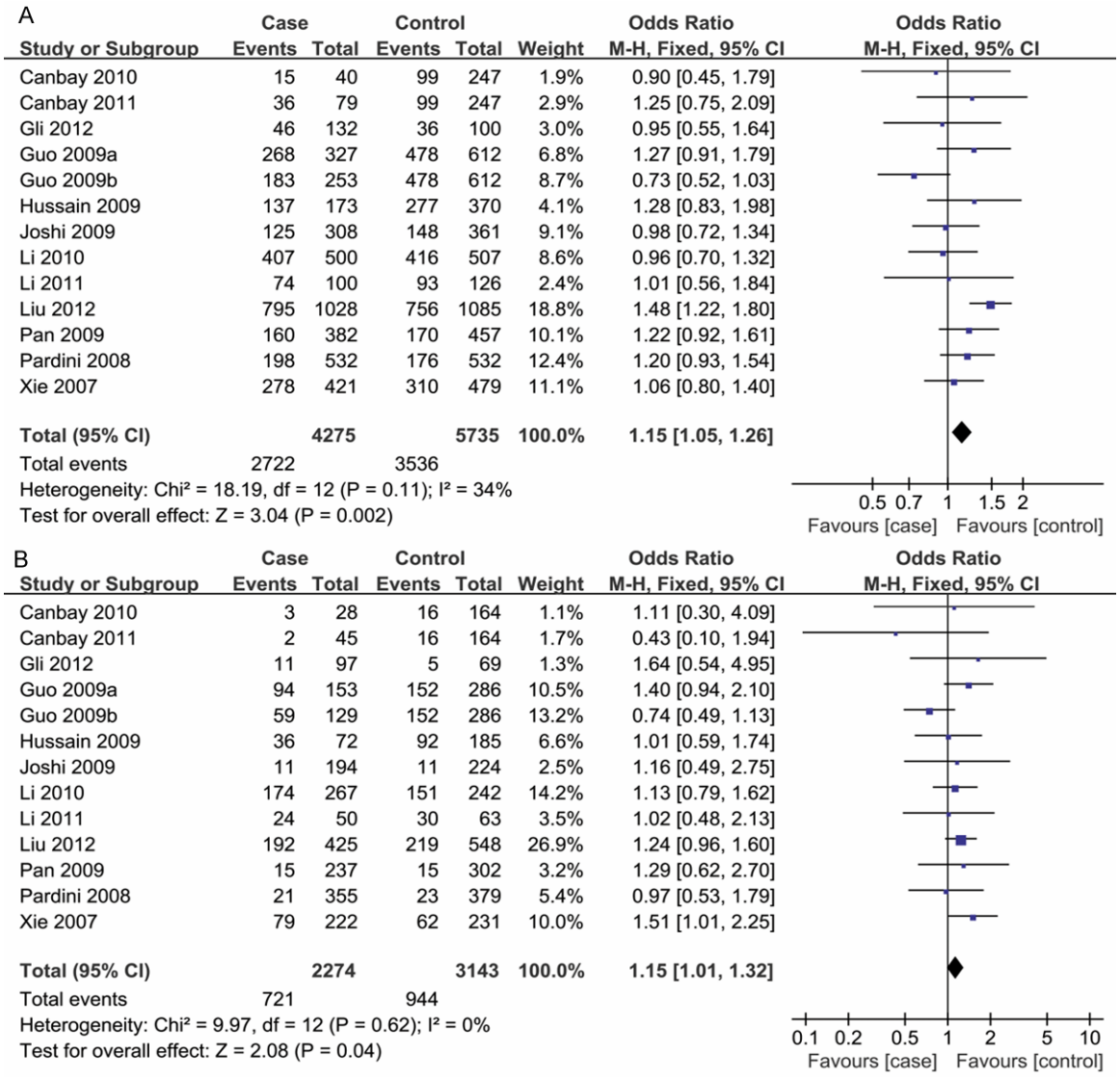

Figure 2. Forest plots for the association of XPG Asp1104His polymorphism and gastrointestinal cancers risk. (A: dominant model; B: His/His vs. Asp/Asp).

dence interval (95% CI). Four different ORs were calculated: the dominant model (Asp/His+His/His vs. Asp/Asp), the recessive model (His/His vs. Asp/Asp+Asp/His), heterozygote comparison (Asp/His vs. Asp/Asp), and homozygote comparison (His/His vs. Asp/Asp). A χ^2-test-based Q statistic test was performed to assess the between-study heterogeneity [24]. We also quantified the effect of heterogeneity by I^2 test. When a significant Q test ($P > 0.05$) or $I^2 < 50\%$ indicated homogeneity across studies, the fixed effects model was used [25], or else the random effects model was used [26]. Then, we performed stratification analyses on ethnicity, tumor type and source of control. Analysis of sensitivity was performed to evaluate the stability of the results. Finally, potential publication bias was investigated using Begg's funnel plot and Egger's regression test [27, 28]. $P < 0.05$ was considered statistically significant.

All analyses were performed using the Cochrane Collaboration RevMan 5.2 and STATA package version 12.0 (Stata Corporation, College Station, Texas).

Results

Study characteristics

After an initial search, a total of 102 published articles relevant to the topic were identified. According to the inclusion criteria, 14 studies

[10-23] with full-text were included in this meta-analysis and 88 studies were excluded. The flow chart of study selection in summarized in **Figure 1**. Because the study by Guo et al [13] included two types of cancers, we treated them separately in this meta-analysis, moreover, we excluded two studies because they did not present detailed genotyping information [22, 23]. Therefore, as shown in **Table 1**, there were 13 case-control studies [10-21] with 4275 cases and 5735 controls concerning XPG polymorphism. Of the 13 eligible studies, eight studies [10-12, 14, 15, 18-20] were written in English and five studies [13, 16, 17, 21] in Chinese. Four cancer types were addressed: four studies [10, 13, 14, 17] involved gastric cancers, five [11, 12, 15, 18, 20] involved colorectal cancers, two [13, 19] involved esophageal cancers and two [16, 21] involved hepatocellular cancers. Two ethnicities were addressed: seven studies [13, 14, 16-18, 21] were conducted on Asian populations and six studies [10-12, 15, 19, 20] on Caucasian populations. Except for study [16], the distribution of genotypes in the controls was consistent with the HWE for all other selected studies.

Quantitative data synthesis

As shown in **Table 2**, overall, a significantly increased risk was found between the XPG Asp1104His polymorphism and the risk of gastrointestinal cancers (dominant model: OR = 1.15, 95% CI: 1.05-1.26; His/His vs. Asp/Asp: OR = 1.15, 95% CI: 1.01-1.32) (**Figure 2**); while, no obvious associations were observed under other two models (recessive model: OR = 1.07, 95% CI: 0.95-1.19; Asp/His vs. Asp/Asp: OR = 1.10, 95% CI: 0.95-1.27).

In subgroup analysis by ethnicity, a significant association was detected in Asians under homozygote model (His/His vs. Asp/Asp: OR = 1.17, 95% CI: 1.01-1.35), but not for the other three models; besides, we failed to found any association in Caucasians populations (**Table 2**).

Stratification by tumor type indicated that the XPG Asp1104His polymorphism was associated with an increased risk of colorectal cancer (OR = 1.26, 95% CI: 1.11-1.43) and hepatocellular carcinoma (OR = 1.35, 95% CI: 1.09-1.68); However, no significant association was found for gastric and esophageal cancers (**Table 2**).

When the analysis was stratified by source of control, we found that the XPG Asp1104His polymorphism was not associated with risk of gastrointestinal cancers among population-based, hospital-based and family-based populations (**Table 2**).

Heterogeneity and sensitivity analyses

Substantial heterogeneities were observed among studies for the association between the XPG polymorphisms and gastrointestinal cancers risk under heterozygote comparison model (I^2 = 52%, P = 0.01). We therefore assessed the source of heterogeneity by ethnicity and tumor type. The heterogeneity was partly decreased or removed among gastric, esophageal, hepatocellular cancers and Caucasian populations. However, there was still significant heterogeneity in colorectal cancer and Asian population. Then, sensitivity analysis was performed to evaluate the stability of the results. The statistical significance of the results was not altered when any single study was omitted, confirming the stability of the results.

Publication bias

We used the Begg's funnel plot and Egger's test to address potential publication bias in the available literature. The shape of funnel plots did not reveal any evidence of funnel plot asymmetry (**Figure 3**). Egger's test also showed that there was no statistical significance for the evaluation of publication bias (dominant model: P = 0.106, Asp/His vs. Asp/Asp: P = 0.132, His/His vs. Asp/Asp: P = 0.399, recessive model: P = 0.939).

Discussion

Evidence suggests that reduced DNA repair capacity may lead to genetic instability and carcinogenesis, genes involved in DNA repair have been proposed as candidate cancer susceptibility genes [29]. The nucleotide excision repair (NER) pathway may be an important pathway modulating susceptibility to cancer, because it is the primary mechanism for the repair of a wide variety of DNA damage [30-32]. There were several core genes in the NER pathway (e.g. ERCC1, XPA, XPB/ERCC3, XPC, XPD/ERCC2, XPE/DDB1, XPF/ERCC4, and XPG/ERCC5). Of those, The XPG gene is one of the central players in the NER pathway; it plays vital roles in repairing DNA damage and maintaining

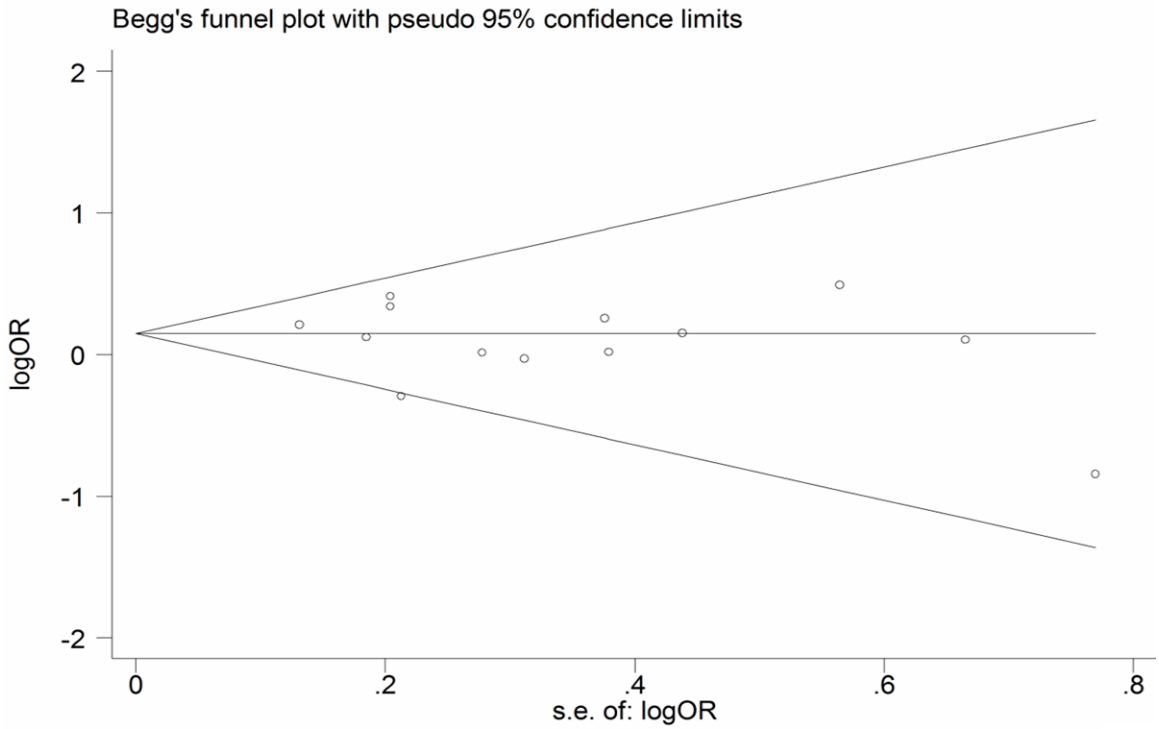

Figure 3. Begg's funnel plot for publication bias. (His/His vs. Asp/Asp).

genome integrity [33, 34]. Recently, the XPG Asp1104His polymorphism was reported to confer the risk of gastrointestinal cancers. Furthermore, a number of epidemiological studies have evaluated the association between the polymorphism and risk of gastrointestinal cancers, but the results remain inconclusive. Canbay et al [10, 11] reported that the XPG Asp1104His polymorphism is not association with the risk of gastric or colorectal cancer in a Turkish population; similarly, in a study from Poland, Gil et al [12] suggested the Asp1104His polymorphism may not play a crucial role in the modulation of an individual's susceptibility to sporadic colorectal cancer; however, Liu et al [18] found that XPG Asp1104His polymorphisms might contribute to the identification of patients with increased risk for colorectal cancer.

Recently, a previous meta-analysis [35] have evaluated the association between XPG Asp1104His polymorphism and cancer risk, and reported that the XPG Asp1104His polymorphism appeared to be unlikely to confer susceptibility to cancers. However, only 7 studies focusing on gastrointestinal cancers (3 studies for colorectal, 2 studies for gastric, and one study for esophageal and hepatocellular, respectively) were included in the above meta-analysis, due to the limited studies, further analyses was not conducted. Compared with it, we conducted a comprehensive literature search in different databases (i.e. Web of science, CNKI, WanFang and VIP) and included several additional studies [13, 15, 17, 18, 21], which allowed for a larger number of subjects and more precise risk estimation. In this meta-analysis, we pooled 13 studies to explore the association between the Asp1104His polymorphism and risk of gastrointestinal cancers. The results demonstrated that the XPG Asp1104His polymorphism may be a risk factor for gastrointestinal cancers. The results seem to contradict the previous meta-analysis. The discrepancies are probably due to the small size of the Asp1104His in determining susceptibility to gastrointestinal cancers in the previous meta-analysis. In addition, the biological mechanisms of the XPG gene in carcinogenesis were complicated, which may be mediated by the activities of multiple genes (such as XPB, and XPD) in the NER pathway and the function of which may be differ from the gastrointestinal cancers and other cancers. Generally, the XPG polymorphism confers to risk of cancers via

leading to an amino acid change in the protein product and modulating the individual DNA repair capacity phenotype.

Since the outcomes from meta-analysis can be affected by several factors such as ethnicity, cancer origins and control selection. Therefore, subgroup analyses were conducted. In this study, stratification by ethnicity, there was significant association in Asian descents, but not in Caucasian populations. The possible reason could be that individuals from different ethnicities may have diverse genetic backgrounds and environmental factors, and consequently, the same polymorphism may play different roles in different populations [36]. When stratified by tumor type, we found that the Asp1104His polymorphism was associated with an increased risk of hepatocellular and colorectal cancers; however, no significant associations were observed in esophageal or gastric cancer. As we know, the pathogenesis of different cancers may be diverse from each other, besides, it is noteworthy that the negative associations between the Asp1104His polymorphism and esophageal or gastric cancer were probably due to the small size (only two studies), and we should sensibly consider the conclusions. In addition, when the subgroups based on source of control were examined, we failed to detect any association among population-based, hospital-based and family-based populations.

Heterogeneity is a potential problem when interpreting the results of all meta-analysis. In this meta-analysis, heterogeneity was found in overall comparison under heterozygote model, when stratified by ethnicity and tumor type, the heterogeneity was partly decreased or removed among gastric, esophageal, hepatocellular cancers and Caucasian populations. However, heterogeneity still existed in colorectal cancer and Asian population. In addition, when excluded the study by Liu et al or Guo et al, the heterogeneity decreased. The results above suggest that the ethnic background, different tumor types and particular study might be the source of heterogeneity. Then sensitivity analyses were conducted by successively excluding one study, the estimated pooled odd ratio changed quite little, strengthening the results from this meta-analysis. In addition, no publication bias was shown suggesting this possible true result.

This meta-analysis has limitations that must be acknowledged. First, because of incomplete raw data or publication limitations, some relevant studies could not be included in our analysis. Second, the data from the esophageal and hepatocellular carcinoma were relatively small, and significant heterogeneity was found in some models, which might lead the failure to confirm marginal associations. Third, our results were based on unadjusted estimates, which may cause serious confounding bias. In addition, cancer is a multi-factorial disease that results from complex interactions between many environmental and genetic factors. Therefore, when we only consider suspected gene polymorphism in gastrointestinal cancers neglecting the role of other genes and environmental factors, we might fail to conclude a real association.

Conclusion

In conclusion, this meta-analysis suggests that the XPG Asp1104His polymorphism may be a risk factor for gastrointestinal cancers, especially of colorectal cancer. However, considering the limitations in our study, large and well-designed studies are warranted to validate our findings.

Disclosure of conflict of interest

None.

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