

# XPA A23G polymorphism and risk of digestive system cancers: a meta-analysis

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**Background:** Several studies have reported an association between the A23G polymorphism (rs 1800975) in the *xeroderma pigmentosum group A (XPA)* gene and risk of digestive system cancers. However, the results are inconsistent. In this study, we performed a meta-analysis to assess the association between XPA A23G polymorphism and the risk of digestive system cancers.

**Methods:** Relevant studies were identified using the PubMed, Web of Science, China National Knowledge Infrastructure, WanFang, and VIP databases up to August 30, 2014. The pooled odds ratio (OR) with a 95% confidence interval (CI) was calculated using the fixed or random effects model.

**Results:** A total of 18 case-control studies from 16 publications with 4,170 patients and 6,929 controls were included. Overall, no significant association was found between XPA A23G polymorphism and the risk of digestive system cancers (dominant model: GA + AA versus GG, OR 0.89, 95% CI 0.74–1.08; recessive model: AA versus GA + GG, OR 0.94, 95% CI 0.74–1.20; GA versus GG, OR 0.89, 95% CI 0.77–1.03; and AA versus GG, OR 0.87, 95% CI 0.64–1.19). When the analysis was stratified by ethnicity, similar results were observed among Asians and Caucasians in all genetic models. In stratified analysis based on tumor type, we also failed to detect any association between XPA A23G polymorphism and the risk of esophageal, gastric, or colorectal cancers.

**Conclusion:** This meta-analysis indicates that the XPA A23G polymorphism is not associated with a risk of digestive system cancers.

**Keywords:** xeroderma pigmentosum group A, polymorphism, digestive system cancer, meta-analysis

## Introduction

Gastrointestinal cancers, referring to a group of malignancies affecting the esophagus, stomach, liver, bowel, pancreas, gallbladder, and anus, are the most common cancers worldwide.<sup>1</sup> There are an estimated 3.4 million new cases worldwide each year, and their mortality rates have increased gradually over the past decade.<sup>1</sup> The exact mechanism of carcinogenesis is still not fully understood. It is well established that some risk factors (eg, dietary, racial, and socioeconomic) and interactions between genetic and environmental factors play important roles in the pathogenesis of cancer.<sup>2,3</sup>

Deregulation of DNA repair is a crucial factor in the multistep process of carcinogenesis. A variety of mechanisms for DNA repair have been developed to ensure integrity of the genome in humans, and the *xeroderma pigmentosum group A (XPA)* gene is a vital component of the DNA repair machinery. The *XPA* gene is located on chromosome 9q22.3 and encodes a zinc finger DNA-binding protein participating in DNA excision repair to maintain genomic integrity.<sup>4</sup> The XPA protein plays a central role

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in nucleotide excision repair (NER) through its interaction with replication protein A, transcription factor II H, and the excision repair cross-complementing group 1-xeroderma pigmentosum group F protein complex.<sup>5,6</sup> In addition, XPA is involved in both global genome and transcription-coupled repair pathways,<sup>7</sup> and interacts with many core repair factors during the DNA repair process.<sup>8</sup> In the *XPA* gene, a polymorphic site has been identified in the 5' untranslated region and consists of an A to G substitution in the fourth nucleotide before the ATG start codon (XPA A23G, rs 1800975). It has been shown that the polymorphism could affect protein levels in the cell.<sup>9,10</sup> To date, a large number of molecular epidemiologic studies have been conducted to assess the role of A23G polymorphism in *XPA* gene on various types of cancers, especially those affecting the digestive system.<sup>11–30</sup> However, the results have been inconclusive or inconsistent. Individual studies might have been underpowered to detect the effect of this polymorphism on susceptibility to cancer. Therefore, we conducted a meta-analysis to evaluate the association between XPA A23G polymorphism and the susceptibility to digestive system cancers.

## Methods

### Search strategy

We searched the electronic literature in the PubMed, Web of Science, China National Knowledge Infrastructure, WanFang, and VIP databases for all relevant articles. The last search update was August 30, 2014, using the search terms: “xeroderma pigmentosum group A or XPA or DNA repair gene or NER”, “genetic polymorphism or polymorphisms or variant”, and “digestive system cancer or gastrointestinal cancers 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. If more than one geographic or cancer type was reported in one report, each was extracted separately. If data or data subsets were published in more than one article, only the publication with the largest sample size was included.

### Inclusion and exclusion criteria

Studies included in this meta-analysis had to meet the following criteria: studies that evaluated the association between XPA A23G polymorphism and digestive system cancers, in a case-control study design, and had detailed genotype frequency of cases and controls or could be calculated from the article text. We excluded case-only studies, case reports,

review articles, studies without raw data for the XPA A23G genotype, and 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, age, sex, source of controls, genotype methods, number of cases and controls (total and genotypes), and Hardy–Weinberg equilibrium (HWE) in controls (*P*-value). The results were compared, and disagreements were discussed among all authors and resolved with consensus. Different ethnicity was categorized as Asian and Caucasian.

### Quality assessment

The quality of the eligible studies was assessed using Newcastle–Ottawa Scale (NOS), which is widely used for assessment of the quality of observational studies, including cohort or case–control studies.<sup>31</sup> NOS, consisting of three parts (selection, comparability, and exposure), is a star-rewarded scale. A total of four, two, and three stars, respectively, will be rewarded if the criteria are met. A study with seven or more stars was categorized as high quality, otherwise, the study was categorized as low quality.

### 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 digestive system cancers associated with XPA A23G polymorphism was estimated for each study by odds ratio (OR) and 95% confidence interval (CI). The most common G allele was considered the reference genotype and the rare A allele was examined as the variant in this analysis. Four different ORs were calculated: the dominant model (AG + AA versus GG), the recessive model (AA versus AG + GG), heterozygote comparison (AG versus GG), and homozygote comparison (AA versus GG). A  $\chi^2$ -test-based *Q* statistic test was performed to assess between-study heterogeneity.<sup>32</sup> We also quantified the effect of heterogeneity by *I*<sup>2</sup> test. When a significant *Q* test (*P*>0.1) or *I*<sup>2</sup><50% indicated homogeneity across studies, the fixed effects model was used,<sup>33</sup> or else the random effects model was used.<sup>34</sup> We then performed stratification analyses on ethnicity, tumor type, and source of control. Analysis of sensitivity was performed to evaluate the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set on the pooled OR. Finally, potential publication bias was investigated using Begg's funnel plot

and Egger's regression test.<sup>35,36</sup>  $P < 0.05$  was considered to be statistically significant. All analyses were performed using the Cochrane Collaboration RevMan 5.2 and Stata package version 12.0 (Stata Corp, College Station, TX, USA).

## Results

### Study characteristics

After an initial search, a total of 101 published articles relevant to the topic were identified. According to the inclusion criteria, 20 studies<sup>11–30</sup> with full text were included in this meta-analysis and 81 studies were excluded. The flow chart for study selection is summarized in Figure 1. Because the study by Huang et al<sup>17</sup> included two types of cancer, we treated them separately in this meta-analysis; three articles<sup>27–29</sup> that had overlapped study data were also excluded. Moreover, we excluded one study<sup>30</sup> because it did not present detailed genotyping information. Therefore, as shown in Table 1, there were 18 case-control studies<sup>11–26</sup> with 4,170 cases and 6,929 controls concerning XPA A23G polymorphism. Of the 18 eligible studies, nine studies<sup>12,14,15,17,20,22,24–26</sup> involved esophageal cancers, four studies<sup>11,17,21</sup> involved gastric cancers, four<sup>13,16,18,19</sup> involved colorectal cancers, and one<sup>23</sup> involved hepatocellular carcinoma. Two ethnicities were addressed: eleven studies<sup>11,12,14,17,20,23–26</sup> were conducted in Asian populations and seven studies<sup>13,15,16,18,19,21,22</sup> in Caucasian populations. The distribution of genotypes in the controls was consistent with HWE for all selected studies. The quality of all eligible studies was categorized as high except for one study.<sup>20</sup>

### Quantitative data synthesis

As shown in Table 2, overall no significant association was found between XPA A23G polymorphism and the risk of

digestive system cancers (dominant model: OR 0.89, 95% CI 0.74–1.08; recessive model: OR 0.94, 95% CI 0.74–1.20; GA versus GG, OR 0.89, 95% CI 0.77–1.03; and AA versus GG, OR 0.87, 95% CI 0.64–1.19, Figure 2).

In subgroup analysis by ethnicity, there was no significant association between XPA A23G polymorphism and the risk of digestive system cancers in either Asians or Caucasians (Table 2, Figure 3).

In stratified analysis based on tumor type, we also failed to detect any association between XPA A23G polymorphism and the risk of esophageal, gastric, or colorectal cancers. In addition, only one study focused on hepatocellular carcinoma, and the results showed no association between XPA A23G polymorphism and the risk of hepatocellular carcinoma (Table 2, Figure 4).

When the analysis was stratified by source of control, we found that XPA A23G polymorphism was associated with a decreased risk of digestive system cancers in population-based models (GA versus GG, OR 0.86, 95% CI 0.77–0.96), but not in other genetic models or hospital-based populations (Table 2). However, it is worth noting that there was moderate heterogeneity ( $I^2=40\%$ ) in the subgroup analysis; when the study by Zhen et al was excluded, the heterogeneity disappeared ( $I^2=0\%$ ), and the pooled results showed no significant differences in genotype distribution between digestive system cancer cases and controls (OR 0.92, 95% CI 0.82–1.04). Therefore, the results that included the study by Zhen et al should be cautiously interpreted.

### Heterogeneity and sensitivity analyses

Substantial heterogeneity was observed between studies for the association between XPA A23G polymorphism and digestive system cancer risk in all genetic models (dominant

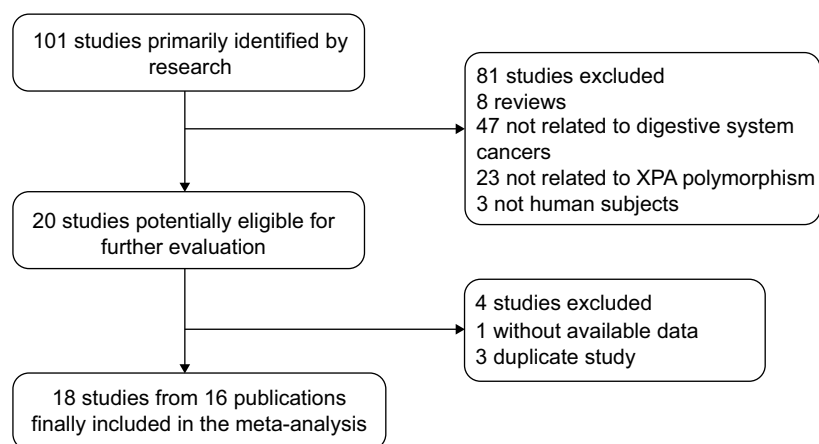


Figure 1 Flow chart showing study selection procedure.

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

Study	Year	Country	Ethnicity	Age, years		Sex (male/female)		Cancer type	Source of controls	Genotype methods	Genotype (case/control)			P <sub>HWE</sub>	NOS	
				Case	Control	Case	Control				Total	GG	GA			AA
Dong et al <sup>11</sup>	2008	People's Republic of China	Asian	60.4±8.30	60.4±8.42	165/88	385/227	Gastric	PB	PCR-RFLP	253/612	47/128	120/322	86/162	0.169	8
Feng et al <sup>12</sup>	2008	People's Republic of China	Asian	59.09±8.43	58.81±8.58	125/71	130/71	Esophageal	HB	PCR-RFLP	196/201	28/56	83/91	85/54	0.181	7
Gil et al <sup>13</sup>	2012	Poland	Caucasian	63.22±11.36	74.89±7.63	NR	NR	Colorectal	HB	PCR-RFLP	100/133	26/50	58/67	16/16	0.369	8
Guo et al <sup>14</sup>	2008	People's Republic of China	Asian	60.0±9.33	60.4±8.42	218/109	385/227	Esophageal	PB	PCR-RFLP	327/612	65/128	139/322	123/162	0.169	8
Hall et al <sup>15</sup>	2007	Europe	Caucasian	NR	NR	NR	NR	Esophageal	HB	TaqMan	171/974	75/398	81/451	15/125	0.875	9
Hansen et al <sup>16</sup>	2007	Denmark	Caucasian	59 (51–64)	56 (50–63)	219/178	434/366	Colorectal	PB	NR	394/788	176/339	187/359	31/90	0.731	8
Huang et al <sup>17</sup>	2007 <sup>a</sup>	People's Republic of China	Asian	NR	NR	112/38	301/101	Esophageal	PB	PCR-RFLP	150/402	22/32	69/160	59/210	0.843	7
Huang et al <sup>17</sup>	2007 <sup>b</sup>	People's Republic of China	Asian	NR	NR	116/29	130/50	Cardiac	PB	PCR-RFLP	145/180	20/13	60/55	65/112	0.097	7
Huang et al <sup>17</sup>	2007 <sup>c</sup>	People's Republic of China	Asian	NR	NR	111/35	130/50	Gastric	PB	PCR-RFLP	146/180	12/13	57/55	77/112	0.097	7
Jelonek et al <sup>18</sup>	2010	Poland	Caucasian	NR	NR	NR	NR	Colorectal	HB	PCR-RFLP	66/133	29/46	33/70	4/17	0.225	8
Joshi et al <sup>19</sup>	2009	USA	Caucasian	60.0±11.3	59.3±11.8	NR	NR	Colorectal	PB	TaqMan	302/349	136/149	133/170	33/30	0.056	8
Liu et al <sup>20</sup>	2007	People's Republic of China	Asian	63.67±9.58	62.50±9.39	56/41	56/41	Esophageal	PB	PCR-RFLP	96/96	11/11	35/47	50/38	0.535	6
Palli et al <sup>21</sup>	2010	Italy	Caucasian	68.8±9.9	55.5±7.0	177/137	270/278	Gastric	PB	TaqMan	284/523	134/249	115/215	35/59	0.227	8
Pan et al <sup>22</sup>	2009	USA	Caucasian	63.13±10.60	62.91±10.38	343/44	397/65	Esophageal	HB	PCR-RFLP	380/458	179/151	166/219	35/88	0.589	8
Xie et al <sup>23</sup>	2007	People's Republic of China	Asian	49.1 (17–80)	48.6 (28–79)	377/57	384/96	Hepatocellular	PB	PCR-RFLP	415/479	139/144	203/219	73/116	0.071	7
Zhang et al <sup>24</sup>	2006	People's Republic of China	Asian	NR	NR	NR	NR	Esophageal	HB	PCR-RFLP	206/206	33/44	82/96	91/66	0.412	7
Zhen et al <sup>25</sup>	2012	People's Republic of China	Asian	NR	NR	237/114	258/142	Esophageal	PB	PCR-RFLP	351/400	99/53	145/188	107/159	0.826	7
Zhu et al <sup>26</sup>	2008	People's Republic of China	Asian	61.03	60.77	105/83	126/77	Esophageal	PB	PCR-SSCP	188/203	50/52	69/88	69/63	0.063	7

**Notes:** Age is expressed either as mean ± standard deviation or median (interquartile range). <sup>a</sup>Esophageal study; <sup>b</sup>cardiac study; <sup>c</sup>gastric study.  
**Abbreviations:** HWE: Hardy-Weinberg equilibrium; PCR-RFLP, polymerase chain reaction–restriction fragment length polymorphism; PCR-SSCP, polymerase chain reaction–single strand conformation polymorphism; PB, population-based; HB, hospital-based; NR, not reported; NOS, Newcastle–Ottawa Scale.

Table 2 Summary of odds ratios for the risk of the XPG Asp1104His polymorphism and gastrointestinal cancers

Variables	N <sup>a</sup>	Dominant model			Recessive model			GA versus GG			AA versus GG		
		OR (95% CI)	P <sup>b</sup>	I <sup>2</sup>	OR (95% CI)	P <sup>b</sup>	I <sup>2</sup>	OR (95% CI)	P <sup>b</sup>	I <sup>2</sup>	OR (95% CI)	P <sup>b</sup>	I <sup>2</sup>
Total	18	0.89 (0.74–1.08)	<0.00001	73	0.94 (0.74–1.20)	<0.00001	83	0.89 (0.77–1.03)	0.005	52	0.87 (0.64–1.19)	<0.00001	83
Ethnicity													
Asian	11	0.90 (0.66–1.21)	<0.00001	78	1.04 (0.77–1.41)	<0.00001	86	0.87 (0.68–1.10)	0.007	59	0.95 (0.62–1.44)	<0.00001	86
Caucasian	7	0.88 (0.71–1.10)	0.007	66	0.78 (0.55–1.13)	0.006	67	0.90 (0.79–1.03)	0.09	45	0.76 (0.49–1.18)	0.0004	76
Tumor type													
Esophageal	9	0.87 (0.61–1.23)	<0.00001	84	1.04 (0.71–1.52)	<0.00001	88	0.81 (0.62–1.06)	0.002	68	0.89 (0.52–1.54)	<0.00001	90
Gastric	4	0.99 (0.80–1.22)	0.22	32	0.86 (0.53–1.41)	0.0006	83	0.98 (0.78–1.23)	0.85	0	0.88 (0.52–1.50)	0.02	69
Colorectal	4	0.96 (0.80–1.14)	0.14	45	0.91 (0.56–1.47)	0.08	56	0.98 (0.82–1.17)	0.21	33	0.92 (0.52–1.62)	0.04	63
Hepatocellular	1	0.85 (0.64–1.13)	NA	NA	0.67 (0.48–0.93)	NA	NA	0.96 (0.71–1.30)	NA	NA	0.65 (0.45–0.95)	NA	NA
Source of control													
PB	12	0.83 (0.69–1.00)	0.002	63	0.93 (0.72–1.20)	<0.00001	81	0.86 (0.77–0.96)	0.08	40	0.81 (0.60–1.11)	<0.00001	77
HB	6	1.09 (0.69–1.73)	<0.00001	85	0.96 (0.52–1.76)	<0.00001	87	1.04 (0.74–1.47)	0.005	70	1.00 (0.44–2.27)	<0.00001	90

Notes: <sup>a</sup>Number of comparisons; <sup>b</sup>test for heterogeneity.

Abbreviations: CI, confidence interval; HB, hospital-based; NA, not applicable; OR, odds ratio; PB, population-based.

model:  $I^2=73%$ ,  $P<0.00001$ ; recessive model:  $I^2=83%$ ,  $P<0.00001$ ; GA versus GG,  $I^2=52%$ ,  $P=0.005$ ; and AA versus GG,  $I^2=83%$ ,  $P<0.00001$ ). We therefore assessed the source of heterogeneity by ethnicity, tumor type, and source of control. The heterogeneity was partly decreased or removed for gastric cancers, colorectal cancers, Caucasians, and population-based studies. However, there was still significant heterogeneity for esophageal cancer, Asians, and hospital-based populations. Sensitivity analysis was then 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 findings.

## 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 the funnel plots did not reveal any evidence of funnel plot asymmetry (Figure 5). Egger's test also showed that there was no statistical significance for the evaluation of publication bias (dominant model:  $P=0.703$ ; GA versus GG,  $P=0.792$ ; AA versus GG,  $P=0.895$ ; recessive model,  $P=0.678$ ).

## Discussion

The 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.<sup>37</sup> The NER pathway may be important in modulating susceptibility to cancer, because it is the primary mechanism for repair of a wide variety of types of DNA damage.<sup>38–40</sup> There are several core genes in the NER pathway (eg, ERCC1, XPA, XPB/ERCC3, XPC, XPD/ERCC2, XPE/DDB1, XPF/ERCC4, and XPG/ERCC5). Of these, the *XPA* gene is one of the central players, with a vital role in repairing DNA damage and maintaining the integrity of the genome.<sup>4</sup> Recently, A23G polymorphism of the *XPA* gene was reported to confer a risk of digestive system cancers. Furthermore, a number of epidemiological studies have evaluated the association between this polymorphism and risk of digestive system cancers, but the results remain inconclusive. Dong et al<sup>11</sup> and Guo et al<sup>14</sup> reported that the XPA A23G polymorphism was associated with a decreased risk of esophageal squamous cell carcinoma and gastric cardiac adenocarcinoma in a high-incidence population in northern China; however, in a study from the USA, Pan et al<sup>22</sup> suggested that the heterozygous AG genotype of the XPA 5' untranslated region was associated with a 2.11-fold increased risk, and the increased risk reached 3.10-fold

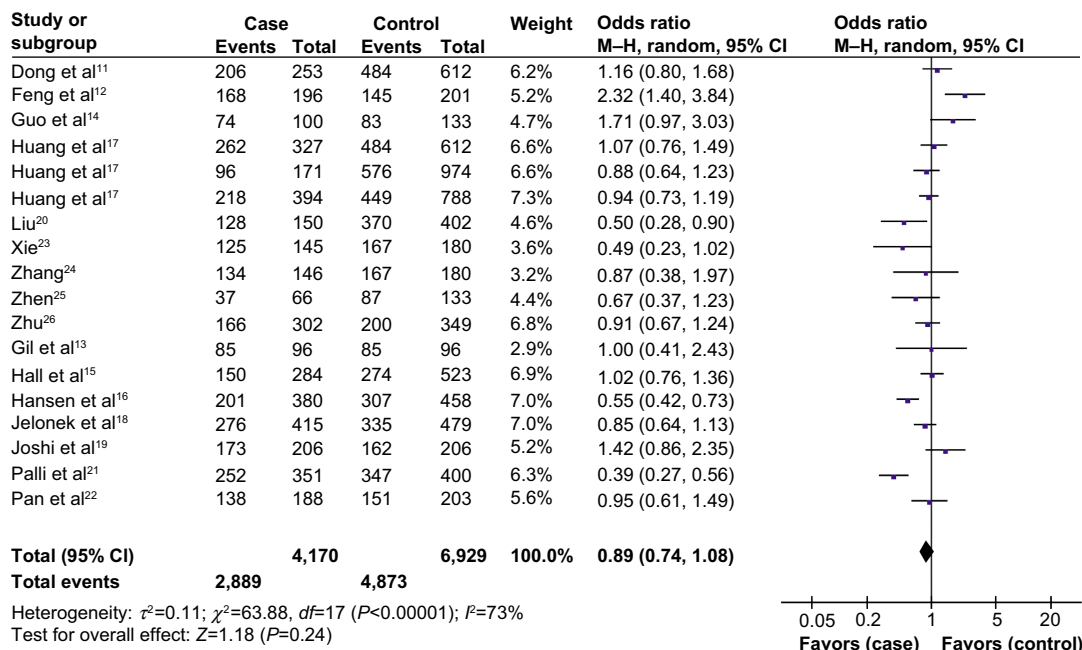


Figure 2 Forest plots of odds ratios for the association of XPA A23G polymorphism and digestive system cancer risk (dominant model).

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel method.

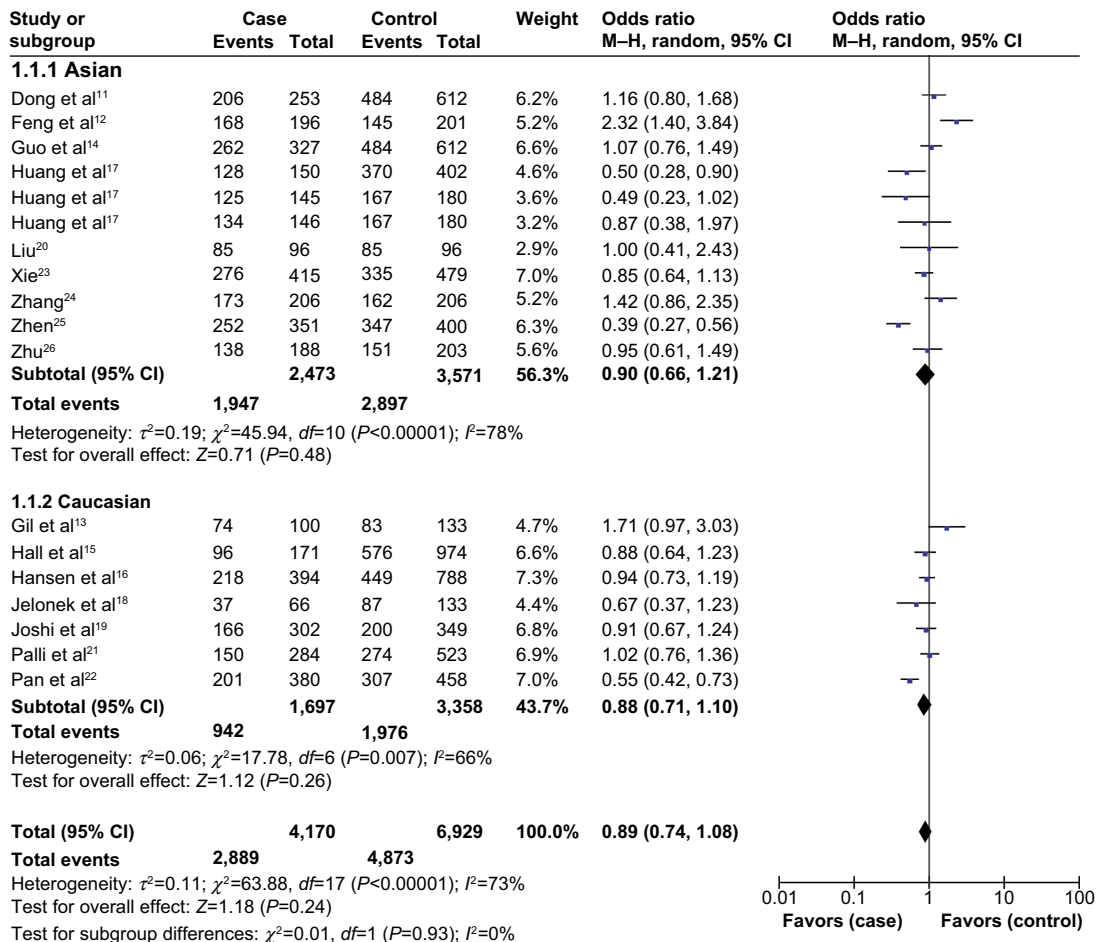
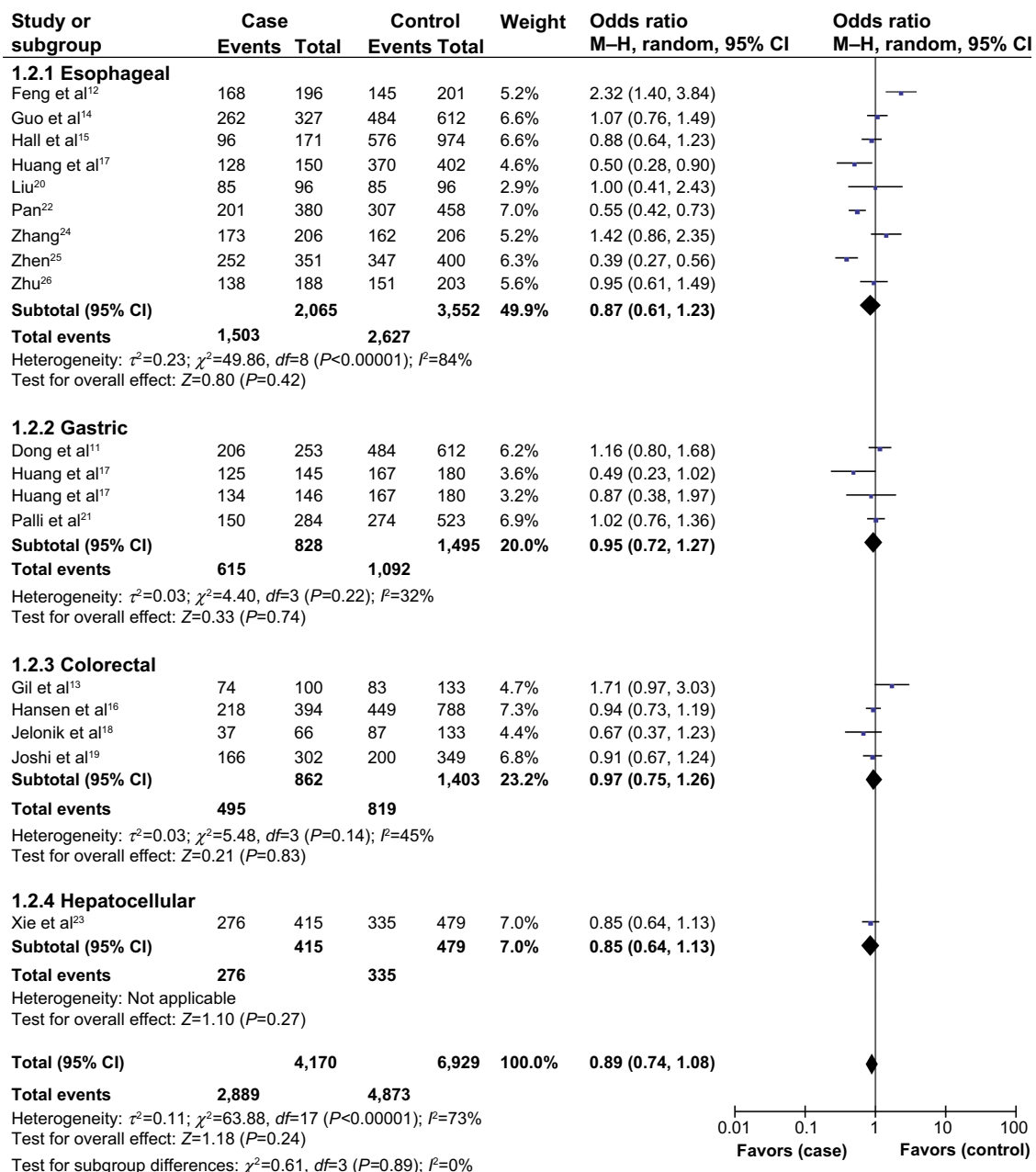


Figure 3 Subgroup analysis by ethnicity of odds ratios for the association of XPA A23G polymorphism and digestive system cancer risk (dominant model).

Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel method.

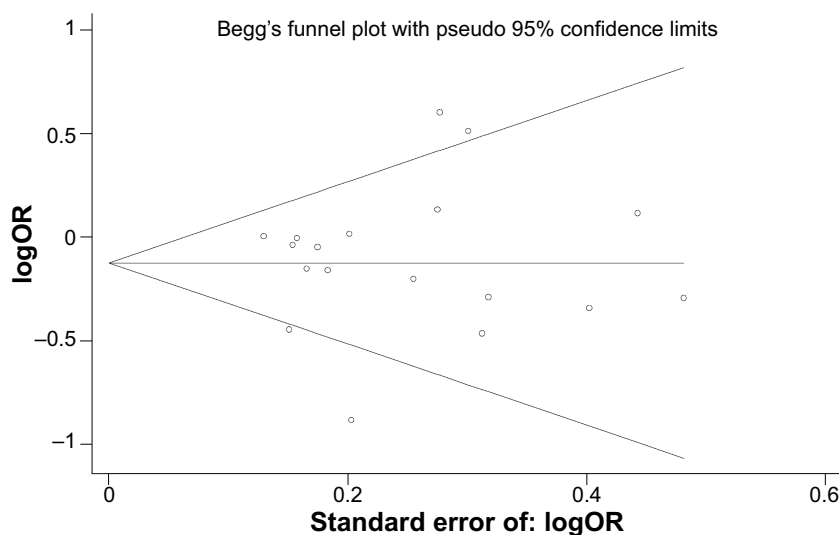


**Figure 4** Subgroup analysis by tumor type of odds ratios for the association of XPA A23G polymorphism and digestive system cancer risk (dominant model).  
**Abbreviations:** CI, confidence interval; M-H, Mantel-Haenszel method.

for the homozygous variant GG genotype in esophageal cancer. Furthermore, Gil et al<sup>13</sup> found that the XPA A23G polymorphism may be unrelated to the risk of sporadic colorectal cancer; similarly, Hansen et al<sup>16</sup> failed to detect an association between the polymorphism and risk of colorectal cancer in a Danish population. These inconsistent results may be attributed to differences in genetic backgrounds, environmental factors, and other factors.

A recent meta-analysis<sup>41</sup> evaluated the association between XPA A23G polymorphism and cancer risk, and reported that this

polymorphism is associated with an increased lung cancer risk and may be a low-penetrant risk factor for development of cancer in people of Asian ethnicity. Subsequently, Liu et al<sup>42</sup> conducted another meta-analysis to assess the association between A23G polymorphism and risk of cancer, and suggested that the XPA A23G G allele is a low-penetrant risk factor for development of cancer. However, only few studies focusing on digestive system cancers (eight and nine studies, respectively) were included in the above meta-analysis, and due to the limited study number, further analyses was not conducted. Compared with those stud-



**Figure 5** Begg's funnel plot for publication bias (GA versus GG).

ies, we conducted a more comprehensive literature search in different databases (including Web of Science, China National Knowledge Infrastructure, WanFang, and VIP) and included several additional studies,<sup>17,19,20,23–26</sup> which allowed for a larger number of subjects and more precise risk estimation. In this meta-analysis, we pooled 18 studies to explore the association between A23G polymorphism and risk of gastrointestinal cancers. The results demonstrated that XPA A23G polymorphism is not associated with digestive system cancer risk.

The outcomes from meta-analysis can be affected by several factors, such as ethnicity, cancer origin, and control selection. Therefore, subgroup analyses were conducted. In this study, stratification by ethnicity, tumor type, and source of control revealed no significant association. The results seem to contradict the previous meta-analyses. The discrepancies are probably due to the small size of the A23G polymorphism in determining susceptibility to digestive system cancers in the previous meta-analyses. Moreover, the biological mechanisms of the *XPA* gene in carcinogenesis are complicated, and may be mediated by the activities of multiple genes (such as ERCC1 and XPF) in the NER pathway, the function of which may be different in digestive system cancers than in other cancers. In addition, cancer is a multifactorial disease that results from complex interactions between many environmental and genetic factors. Therefore, when we only consider suspected gene polymorphism in digestive system cancers and ignore the role of other genes and environmental factors, we might fail to conclude a real association.

Two significant issues should be addressed in this study, ie, heterogeneity and publication bias, which may influence the results of a meta-analysis. We did not detect a significant

publication bias in this meta-analysis, suggesting that our results are reliable. With regard to heterogeneity, in this meta-analysis, heterogeneity was found in overall comparison under all genetic models, when stratified by ethnicity, tumor type, and source of control, the heterogeneity was partly decreased or removed among gastric and colorectal cancers, Caucasians, and population-based subgroups. However, heterogeneity still existed for esophageal cancer, Asians, and hospital-based populations. In addition, when the study by Zhen et al was excluded, the heterogeneity decreased. Our results suggest that the ethnic background, different types of tumor, and the 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, indicating that the results of this meta-analysis were stable.

This meta-analysis has limitations that must be acknowledged. First, all case-control studies included were done in Asians and Caucasians, so our results may be applicable only to these populations. More studies on Africans and other ethnic groups are needed. Second, the controls included in our analysis were selected variously from either population-based or hospitals. Therefore, misclassification bias was possible because these studies may have included control groups that have different risks for developing digestive system cancers. Third, our results were based on unadjusted estimates, without adjustment for family history or other risk factors, which may cause serious confounding bias.

## Conclusion

In summary, this meta-analysis suggests that XPA A23G polymorphism is not associated with a risk of digestive



system cancers. However, large and well-designed studies taking into consideration gene–gene and gene–environment interactions are warranted to validate our findings.

## Disclosure

The authors report no conflicts of interest in this work.

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