World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i16.5081

*World J Gastroenterol* 2015 April 28; 21(16): 5081-5089
ISSN 1007-9327 (print) ISSN 2219-2840 (online)


META-ANALYSIS

# Relationship between apurinic endonuclease 1 Asp148Glu polymorphism and gastrointestinal cancer risk: An updated meta-analysis

Zhi-Jun Dai, Yong-Ping Shao, Hua-Feng Kang, Wei Tang, Dan Xu, Yang Zhao, Di Liu, Meng Wang, Peng-Tao Yang, Xi-Jing Wang

Zhi-Jun Dai, Hua-Feng Kang, Yang Zhao, Di Liu, Meng Wang, Peng-Tao Yang, Xi-Jing Wang, Department of Oncology, the Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China
Zhi-Jun Dai, Yong-Ping Shao, Dan Xu, Center for Translational Medicine, Frontier Institute of Science and Technology, Xi'an Jiaotong University, Xi'an 710049, Shaanxi Province, China
Wei Tang, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an 710061, Shaanxi Province, China
Author contributions: Dai ZJ, Shao YP and Kang HF contributed equally to this work; Dai ZJ, Kang HF and Wang XJ designed the research; Shao YP, Xu D, Zhao Y, Liu D and Yang PT performed the research; Tang W, Wang M and Wang XJ analyzed the data; Dai ZJ and Shao YP wrote the paper.
Supported by National Natural Science Foundation of China, No. 81471670 and No. 81102711; the International Cooperative Project of Shaanxi Province, China, No. 2013KW-32-01; and the Fundamental Research Funds for the Central Universities, China and Specialized Research Fund of the Second Affiliated Hospital of Xi'an Jiaotong University, China, No. RC (GG) 201203.

Correspondence to: Zhi-Jun Dai, MD, PhD, Department of Oncology, the Second Affiliated Hospital of Xi'an Jiaotong University, No. 157, West 5th Road, Xi'an 710004, Shaanxi Province, China. dzj0911@126.com
Telephone: +86-29-87679226
Fax: +86-29-87679282
Received: August 21, 2014
Peer-review started: August 21, 2014
First decision: September 27 ,2014
Revised: October 28, 2014
Accepted: December 5, 2014
Article in press: December 8, 2014
Published online: April 28, 2015

## Abstract

**AIM:** To evaluate the relationship between apurinic endonuclease 1 (APE1) Asp148Glu polymorphism and the susceptibility to gastrointestinal (GI) cancers.

**METHODS:** We searched PubMed, ISI Web of Knowledge, and Chinese National Knowledge Infrastructure (CNKI) databases updated on July 15, 2014 for relevant studies. Only case-control studies comparing APE1 Asp148Glu polymorphism and GI cancer risk were included. We excluded studies reporting only standardized incidence ratios without control groups and those without detailed genotyping data. Meta-analysis was performed on 17 studies involving 4856 cancer patients and 6136 cancer-free controls. Review Manager version 5.1 was used to perform the meta-analysis. The pooled odds ratios (ORs) and 95% confidence intervals (CIs) were estimated under the allele contrast, homozygous, heterozygous, dominant and recessive genetic models. We also conducted subgroup analyses stratified by ethnicity and cancer type. Publication bias was evaluated using Begg's test.

**RESULTS:** The meta-analysis showed a significant association between APE1 Asp148Glu polymorphism and GI cancer risk in three genetic models in the overall population (G *vs* T: OR = 1.18; 95%CI: 1.05-1.32; TG *vs* TT: OR = 1.28; 95%CI: 1.08-1.52; TG + GG *vs* TT: OR = 1.32; 95%CI: 1.10-1.57). Stratified analysis by ethnicity revealed a statistically increased GI cancer risk in Asians (G *vs* T: OR = 1.27; 95%CI: 1.07-1.51; GG *vs* TT: OR = 1.58; 95%CI: 1.05-2.38; TG *vs* TT: OR = 1.30; 95%CI, 1.01- 1.67; and TG + GG *vs* TT: OR = 1.38; 95%CI: 1.07-1.78), but not in Caucasians. Further

subgroup analysis by cancer type indicated that APE1 Asp148Glu polymorphism may contribute to gastric cancer risk. However, Asp148Glu has no significant association with colorectal or esophageal cancer risk in any genetic model.

**CONCLUSION:** This meta-analysis suggests that the APE1 Asp148Glu polymorphism G allele is associated with an increased GI cancer risk, especially in gastric cancer.

**Key words:** Apurinic endonuclease 1; Single nucleotide polymorphism; Gastrointestinal cancers; Cancer risk; Meta-analysis



**Core tip:** Apurinic endonuclease 1 (APE1) plays an important role in the DNA repair system and therefore has been implicated in human carcinogenesis. Many studies have suggested an association between the APE1 Asp148Glu polymorphism and gastrointestinal cancer susceptibility. However, the results remained inconclusive. We performed a meta-analysis on pooled data from previously published studies. The results showed that the APE1 Asp148Glu polymorphism G allele is associated with an increased gastrointestinal cancer risk, especially in gastric cancer.

Dai ZJ, Shao YP, Kang HF, Tang W, Xu D, Zhao Y, Liu D, Wang M, Yang PT, Wang XJ. Relationship between apurinic endonuclease 1 Asp148Glu polymorphism and gastrointestinal cancer risk: An updated meta-analysis. *World J Gastroenterol* 2015; 21(16): 5081-5089 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i16/5081.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i16.5081

## INTRODUCTION

Gastrointestinal (GI) cancers, especially esophageal, gastric, and colorectal cancers, are the leading causes of cancer-related death worldwide[1]. GI cancers are multifactorial diseases caused by complex interactions between many genetic and environmental factors[1,2]. Allelic variations in oncogenes are candidate genetic risk factors that may alter the onset and outcome of GI cancers[3].

Apurinic/apyrimidinic endonuclease 1 (APE1) is an essential enzyme in the base excision repair pathway[4]. APE1 plays an important role in the DNA repair system and therefore has been implicated in human carcinogenesis[5]. The human APE1 is located on chromosome 14q11.2 and consists of five exons, spanning roughly 2.5 to 3 kb of DNA[6]. Many single nucleotide polymorphisms in the APE1 gene have been reported, including the commonly occurring Asp148Glu in the fifth exon and -141T/G in the promoter region[7]. These nonconservative amino acid alterations have been reported to reduce the DNA repair activity of APE1 and consequently increase cancer risk[8]. Our previous study has suggested that the APE1 -141T/G but not the Asp148Glu polymorphism may influence the susceptibility to and progression of breast cancer in the Chinese population[9]. However, a recent study reported that the APE1 148 GG genotype is associated with an increased risk of colorectal cancer (CRC)[10].

It is important to summarize inconclusive results from different studies to further validate the association of one polymorphism with cancer risk[11]. To clarify the role of the APE1 Asp148Glu polymorphism in GI cancer risk, we performed a meta-analysis on all eligible case-control studies to estimate the overall cancer risk associated with the APE1 Asp148Glu polymorphism. Furthermore, we conducted subgroup analyses stratified by ethnicity and cancer type.

## MATERIALS AND METHODS

### *Methods*

The procedures performed in this meta-analysis are in accordance with recent guidelines for the reporting of meta-analyses (PRISMA guidelines).

### *Publication search*

We searched the electronic databases of PubMed, Web of Knowledge and Chinese National Knowledge Infrastructure databases to collect articles reporting case-control studies related to the association of APE1 Asp148Glu polymorphisms with GI cancer risk. The keywords used for search were as follows: apurinic/apyrimidinic endonuclease-1/APE1/APEX/HAP1/REF-1, gastrointestinal/esophageal/gastric/colorectal, cancer/carcinoma/tumor/neoplasm, polymorphism/genotype/SNP/variation. The latest search was updated on July 15, 2014. Furthermore, reference lists of main reports and review articles were also reviewed manually to identify additional relevant publications.

### *Selection criteria*

The following criteria were used to select studies for further meta-analysis: (1) case-control studies; (2) studies that evaluated the associations between APE1 Asp148Glu polymorphism and GI cancer risk; (3) studies that contained at least two comparison groups (cancer *vs* control); and (4) studies that included detailed genotyping data.

### *Data extraction and synthesis*

Articles were reviewed independently by two reviewers and data with discrepancies were discussed by all authors. For each included study, the following information was collected: first author, year of publication, country of origin, ethnicity, source of control, total numbers of cases and controls, genotyping methods as well as numbers of cases and controls with the different genotypes. Different ethnic groups were categorized as Caucasian,

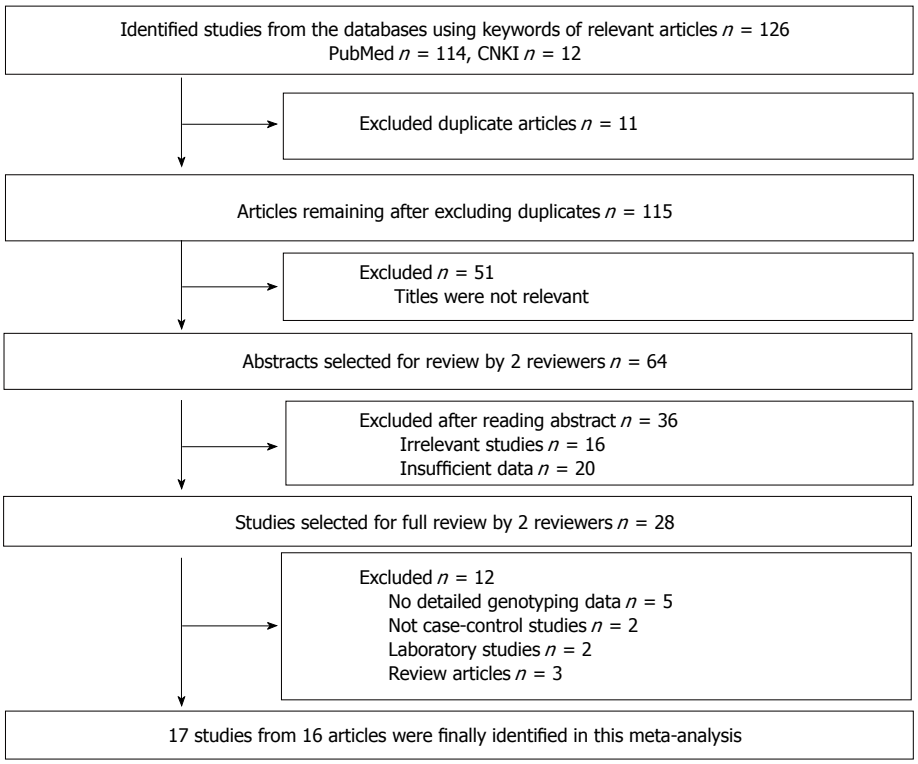


**Figure 1 Flow diagram of study identification and selection.**

Asian, African, and "mixed". All the case and control groups were well controlled. The non-cancer controls had no history of gynecologic disease, and there was no present evidence of any malignant disease.

### *Statistical analysis*

The associations between APE1 Asp148Glu polymorphism and GI cancer risk were measured by odds ratio (OR) with 95% confidence interval (CI). The significance of the pooled OR was determined by the *Z*-test.

The meta-analysis assessed association by using five different genetic models: (1) allele contrast genetic model - A *vs* a (where "a" is the wild-type allele and "A" is the variant allele); (2) homozygous genetic model-comparison between the 2 homozygous genotypes (AA *vs* aa); (3) heterozygous genetic model-comparison between the heterozygous and homozygous wild-type genotype groups (Aa *vs* aa); (4) dominant genetic model-comparison between the wild-type homozygous genotype *vs* the variant allele-positive genotypes (AA + Aa *vs* aa); and (5) recessive genetic model-comparison between the variant homozygous genotype *vs* the rest (AA *vs* aa + Aa).

Statistical heterogeneity among studies was assessed with the *Q* and $I^2$ statistics. If the *P*-value of heterogeneity test was more than 0.1 ($P \geqslant 0.1$), the pooled OR estimate of the study was calculated using the fixed-effects model. Otherwise, the random-effects model was used[11]. The value of the $I$ index was used to assess the degree of heterogeneity ($I^2$ < 25%: no heterogeneity; 25% < $I^2$ < 50%: moderate heterogeneity; 50% < $I^2$ < 75%: high heterogeneity; $I^2$ > 75%: extremely high heterogeneity). Publication bias was evaluated by the funnel plot and further assessed by the method of Egger's linear regression test. All statistical analyses were carried out with the Review Manager version 5.1 (Revman; The Cochrane Collaboration, Oxford, United Kingdom).

## RESULTS

### *Characteristics of the included studies*

As shown in Figure 1, a total of 126 potential publications were initially extracted. After reading the abstracts, we excluded 67 irrelevant studies, 20 studies with insufficient data, and 11 duplicated studies. After reading the full-texts, we excluded 5 articles with no detailed genotyping data, 2 non-case-control studies, 2 laboratory studies and 3 review articles. Finally, 17 studies from 16 articles were included in this meta-analysis.

Overall, 17 studies on APE1 Asp148Glu polymorphism and GI cancer risk were identified[10,12-26], including a total of 4856 cases and 6136 case-free controls. The characteristics of the included studies are listed in Table 1. Among the eligible 17 studies, nine were carried out in Caucasians from United States, Italy, Czech, Spain, Poland and Turkey, seven were based on Asian background and carried out in China and Japan, and one was based on mixed ethnic groups. All studies were case-controlled, including 11 CRC studies, 4 gastric cancer (GC) studies and 2 esophageal

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

| Ref. | Year | Country | Ethnicity | Cancer type | Genotyping method | Source of controls | Total sample size (cases/controls) |
|---|---|---|---|---|---|---|---|
| Zhang *et al*[10] | 2014 | China | Asian | CRC | PCR-CTPP | PB | 247/300 |
| Li *et al*[12] | 2013 | China | Asian | CRC | PCR-RFLP | HB | 451/631 |
| Canbay *et al*[13] | 2011 | Turkey | Caucasian | CRC | PCR-RFLP | PB | 79/247 |
| Gu *et al*[14] | 2011 | China | Asian | GC | PCR-RFLP | PB | 572/547 |
| Li *et al*[15] | 2011 | China | Asian | GC | PCR-RFLP | PB | 126/156 |
| Canbay *et al*[16] | 2010 | Turkey | Caucasian | GC | PCR-RFLP | PB | 40/247 |
| Brevik *et al*[17] | 2010 | United States | Caucasian | CRC | TaqMan | HB | 304/359 |
| Jelonek *et al*[18] | 2010 | Poland | Caucasian | CRC | PCR-RFLP | PB | 153/273 |
| Palli *et al*[19] | 2010 | Italy | Caucasian | GC | TaqMan | PB | 314/548 |
| Ye *et al*[20] | 2010 | China | Asian | CRC | MassARRAY | HB | 123/158 |
| Kasahara *et al*[21] | 2008 | Japan | Asian | CRC | PCR-RFLP | HB | 68/121 |
| Pardini *et al*[22] | 2008 | Czech | Caucasian | CRC | TaqMan | HB | 532/532 |
| Tse *et al*[23] | 2008 | United States | Caucasian | EC | TaqMan | HB | 312/454 |
| Berndt *et al*[24] | 2007 | United States | Caucasian | CRC | TaqMan | PB | 720/725 |
| Berndt *et al*[24] | 2007 | United States | Mixed | CRC | TaqMan | PB | 47/48 |
| Moreno *et al*[25] | 2006 | Spain | Caucasian | CRC | Arrayed primer extension | PB | 359/312 |
| Hao *et al*[26] | 2004 | China | Asian | EC | PCR-RFLP | PB | 409/478 |

CRC: Colorectal cancer; GC: Gastric cancer; EC: Esophageal cancer; PCR-CTPP: Polymerase chain reaction with confronting two-pair primers; PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; PB: Population based; HB: Hospital based.

**Table 2 Apurinic endonuclease 1 Asp148Glu polymorphism genotype distribution and allele frequency in cases and controls**

| Ref. | Genotype (*n*) | | | | | | | | Allele frequency (*n*) | | | | MAF |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | | | | Controls | | | | Cases | | Controls | | |
| | Total | TT | TG | GG | Total | TT | TG | GG | T | G | T | G | |
| Zhang *et al*[10] | 247 | 87 | 90 | 70 | 300 | 121 | 137 | 41 | 264 | 230 | 381 | 219 | 0.47 |
| Li *et al*[12] | 451 | 123 | 247 | 81 | 631 | 186 | 335 | 110 | 493 | 409 | 707 | 555 | 0.45 |
| Canbay *et al*[13] | 79 | 28 | 43 | 8 | 247 | 151 | 63 | 33 | 99 | 59 | 365 | 129 | 0.37 |
| Gu *et al*[14] | 338 | 69 | 185 | 84 | 362 | 110 | 183 | 69 | 323 | 353 | 403 | 321 | 0.52 |
| Li *et al*[15] | 126 | 26 | 64 | 36 | 156 | 56 | 70 | 30 | 116 | 136 | 182 | 130 | 0.54 |
| Canbay *et al*[16] | 40 | 14 | 18 | 8 | 247 | 151 | 63 | 33 | 46 | 34 | 365 | 129 | 0.42 |
| Brevik *et al*[17] | 304 | 102 | 137 | 65 | 359 | 108 | 167 | 84 | 341 | 267 | 383 | 335 | 0.44 |
| Jelonek *et al*[18] | 113 | 49 | 59 | 5 | 273 | 70 | 141 | 62 | 157 | 69 | 163 | 143 | 0.31 |
| Palli *et al*[19] | 298 | 103 | 147 | 48 | 546 | 208 | 243 | 95 | 353 | 243 | 659 | 433 | 0.41 |
| Ye *et al*[20] | 123 | 37 | 86 | 0 | 158 | 52 | 106 | 0 | 160 | 86 | 210 | 106 | 0.35 |
| Kasahara *et al*[21] | 68 | 23 | 45 | 0 | 121 | 70 | 51 | 0 | 91 | 45 | 191 | 51 | 0.33 |
| Pardini *et al*[22] | 531 | 140 | 261 | 130 | 530 | 157 | 267 | 106 | 541 | 521 | 581 | 479 | 0.49 |
| Tse *et al*[23] | 311 | 75 | 162 | 74 | 454 | 123 | 228 | 103 | 312 | 310 | 474 | 434 | 0.50 |
| Berndt *et al*[24] | 692 | 175 | 364 | 153 | 710 | 204 | 335 | 171 | 714 | 670 | 743 | 677 | 0.48 |
| Berndt *et al*[24] | 47 | 11 | 23 | 13 | 48 | 18 | 22 | 7 | 45 | 49 | 58 | 36 | 0.48 |
| Moreno *et al*[25] | 359 | 95 | 177 | 87 | 312 | 99 | 147 | 66 | 367 | 351 | 345 | 279 | 0.49 |
| Hao *et al*[26] | 409 | 126 | 211 | 72 | 477 | 149 | 243 | 95 | 463 | 355 | 541 | 433 | 0.43 |

MAF: Minor allele frequency.

cancer (EC) studies. All GI cancers were confirmed by histology or pathology. The histological type of cancers in the included studies was adenocarcinoma except one EC study[26]. Moreover, controls were matched mainly by age. Eleven studies were population-based and six were hospital-based. Several genotyping methods were used in the studies, including polymerase chain reaction-restriction fragment length polymorphism, PCR-ligase detection reaction, TaqMan, MassARRAY, and Arrayed primer extension.

### *Meta-analysis results*

As shown in Table 2, the frequency of the G allele varied widely across the 12 studies, ranging from 0.31 to 0.54. The average frequency of the G allele in the overall population, Caucasian population and Asian population was 0.47, 0.46, and 0.47, respectively. There was no significant difference between Asians and Caucasians ($P > 0.05$). The average frequency of the G allele in CRC, GC and EC was 0.46, 0.50, and 0.46, respectively.

Overall, there was evidence of an association between GI cancer risk and the variant genotypes when all the eligible studies were pooled into the meta-analysis. As show in Figure 2 and Table 3, there was a significant association between APE1 Asp148Glu polymorphism and GI cancer risk in three genetic models in the overall population (G *vs* T: OR = 1.18,

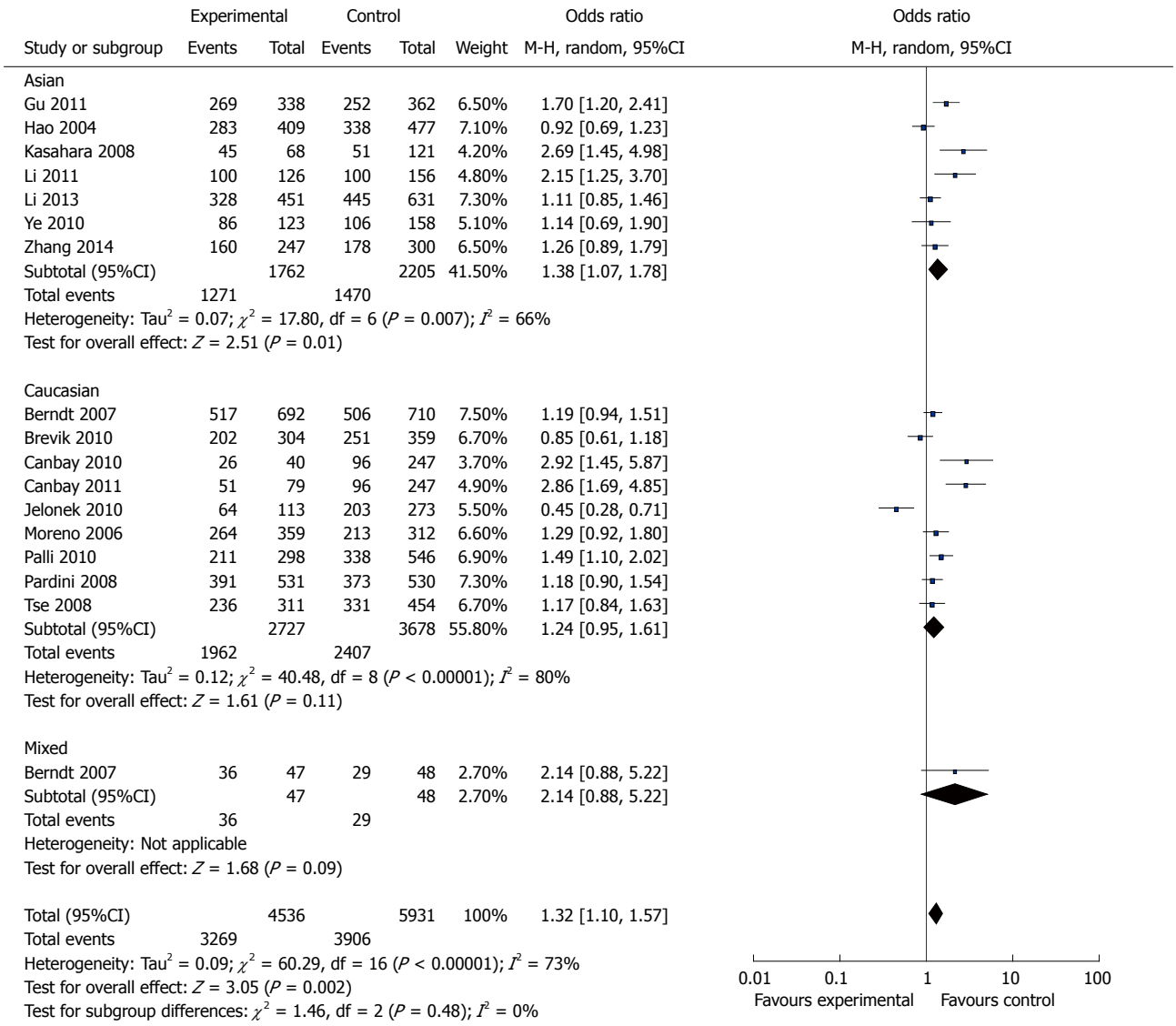


**Figure 2 Forest plot of association of apurinic endonuclease 1 Asp148Glu polymorphism with gastrointestinal cancer risk stratified by ethnicity (TG + GG *vs* TT).**

95%CI = 1.05-1.32, *P* = 0.004; TG *vs* TT: OR =1.28, 95%CI = 1.08-1.52, *P* = 0.004; TG + GG *vs* TT: OR = 1.32, 95%CI =1.10-1.57, *P* = 0.002). However, there was no significant association in the other two genetic models (GG *vs* TT: OR = 1.25, 95%CI = 0.98-1.59, *P* = 0.07; GG *vs* TT + TG: OR = 1.10, 95%CI = 0.90-1.34, *P* = 0.33).

In the stratified analysis by population, as shown in Figure 2 and Table 3, meta-analysis showed that Asp148Glu polymorphism had no association with GI cancer risk in Caucasians in all genetic models (allele contrast genetic model: OR = 1.09, 95%CI = 0.94-1.26, *P* = 0.24; homozygote comparison: OR = 1.25, 95%CI = 0.98-1.59, *P* = 0.81; heterozygote comparison: OR = 1.26, 95%CI = 0.98- 1.63, *P* = 0.07; the dominant model: OR = 1.24, 95%CI = 0.95-1.61, *P* = 0.11; and the recessive model: OR = 0.95, 95%CI = 0.75-1.20, *P* = 0.66).

There were 7 studies with 1587 cases and 1913 controls for assessing the relationship between Asp148Glu polymorphism and GI cancer susceptibility in Asians. As shown in Figure 2 and Table 3, Asp148Glu polymorphism was significantly associated with GI cancer risk in four genetic models (allele contrast genetic model: OR = 1.27, 95%CI = 1.07-1.51, *P* = 0.007; homozygote comparison: OR = 1.58, 95%CI = 1.05-2038, *P* = 0.03; heterozygote comparison: OR = 1.30, 95%CI = 1.01-1.67, *P* = 0.04; and the dominant model: OR = 1.38, 95%CI = 1.07-1.78, *P* = 0.01.

In the stratified analysis by cancer type, 11 studies including 3083 cases and 3706 controls were used to evaluate the relationship between APE1 Asp148Glu polymorphism and CRC risk. As shown in Table 3 and Figure 3, there was no significant association between APE1 Asp148Glu polymorphism and CRC risk under all genetic models (allele contrast genetic model: OR = 1.15, 95%CI = 0.99-1.33, *P* = 0.06; homozygote comparison: OR = 1.12, 95%CI = 0.79-1.59, *P* = 0.51; heterozygote comparison: OR = 1.23, 95%CI = 0.98-1.54, *P* = 0.08; the dominant model: OR =

**Table 3 Meta-analysis results**

| Comparison | OR | 95%CI | *P* value | Heterogeneity | | Effects model |
|---|---|---|---|---|---|---|
| | | | | $I^2$ | *P* value | |
| G *vs* T | 1.18 | 1.05-1.32 | 0.004[1] | 71% | < 0.00001 | Random |
| Caucasian | 1.09 | 0.94-1.26 | 0.24 | 72% | 0.0004 | Random |
| Asian | 1.27 | 1.07-1.51 | 0.007[1] | 70% | 0.003 | Random |
| Colorectal cancer | 1.15 | 0.99-1.33 | 0.06 | 73% | < 0.0001 | Random |
| Gastric cancer | 1.41 | 1.09-1.83 | 0.009[1] | 70% | 0.02 | Random |
| Esophageal cancer | 1.01 | 0.88-1.16 | 0.87 | 0% | 0.40 | Fixed |
| GG *vs* TT | 1.25 | 0.98-1.59 | 0.07 | 73% | < 0.00001 | Random |
| Caucasian | 1.04 | 0.77-1.41 | 0.81 | 72% | 0.0003 | Random |
| Asian | 1.58 | 1.05-2.38 | 0.03[1] | 76% | 0.002 | Random |
| Colorectal cancer | 1.12 | 0.79-1.59 | 0.51 | 79% | < 0.00001 | Random |
| Gastric cancer | 1.77 | 1.11-2.84 | 0.02[1] | 63% | 0.04 | Random |
| Esophageal cancer | 1.02 | 0.77-1.35 | 0.90 | 0% | 0.34 | Fixed |
| TG *vs* TT | 1.28 | 1.08-1.52 | 0.004[1] | 68% | < 0.0001 | Random |
| Caucasian | 1.26 | 0.98-1.63 | 0.07 | 76% | <0.0001 | Random |
| Asian | 1.30 | 1.01-1.67 | 0.04[1] | 63% | 0.01 | Random |
| Colorectal cancer | 1.23 | 0.98-1.54 | 0.08 | 73% | < 0.0001 | Random |
| Gastric cancer | 1.66 | 1.20-2.31 | 0.002[1] | 51% | < 0.0001 | Random |
| Esophageal cancer | 1.04 | 0.83-1.31 | 0.72 | 0% | 0.41 | Fixed |
| GG+TG *vs* TT | 1.32 | 1.10-1.57 | 0.002[1] | 73% | < 0.00001 | Random |
| Caucasian | 1.24 | 0.95-1.61 | 0.11 | 80% | < 0.00001 | Random |
| Asian | 1.38 | 1.07-1.78 | 0.01[1] | 66% | 0.007 | Random |
| Colorectal cancer | 1.23 | 0.98-1.55 | 0.08 | 75% | < 0.0001 | Random |
| Gastric cancer | 1.77 | 1.40-2.24 | < 0.0001[1] | 19% | 0.29 | Fixed |
| Esophageal cancer | 1.02 | 0.81-1.29 | 0.84 | 9% | 0.29 | Fixed |
| GG *vs* TT+TG | 1.10 | 0.90-1.34 | 0.33 | 70% | < 0.0001 | Random |
| Caucasian | 0.95 | 0.75-1.20 | 0.66 | 64% | 0.004 | Random |
| Asian | 1.36 | 0.95-1.95 | 0.10 | 77% | 0.002 | Random |
| Colorectal cancer | 1.05 | 0.77-1.43 | 0.76 | 79% | < 0.00001 | Random |
| Gastric cancer | 1.25 | 0.99-1.56 | 0.06 | 33% | 0.21 | Fixed |
| Esophageal cancer | 0.96 | 0.75-1.21 | 0.71 | 0% | 0.38 | Fixed |

[1]Represent a significant association between APE1 Asp148Glu polymorphism and GI cancer risk in three genetic models in the overall population.

1.23, 95%CI = 0.98-1.55, *P* = 0.08; and the recessive model: OR = 1.05, 95%CI = 0.77-1.43, *P* = 0.76).

There were four studies including 1052 cases and 1498 controls used to evaluate the relationship between APE1 Asp148Glu polymorphism and GC risk. As shown in Table 3 and Figure 3, Asp148Glu polymorphism was significantly associated with an increased risk of GC under all genetic models (allele contrast genetic model: OR = 1.41, 95%CI = 1.09-1.83, *P* = 0.009; homozygote comparison: OR = 1.77, 95%CI = 1.11-2.84, *P* = 0.02; heterozygote comparison: OR = 1.66, 95%CI = 1.20-2.31, *P* = 0.002; and the dominant model: OR = 1.77, 95%CI = 1.40-2.24, *P* < 0.0001).

There were only two EC studies included in this meta-analysis. As shown in Table 3 and Figure 3, no significant association was detected between Asp148Glu polymorphism and EC risk.

### *Sensitivity analysis and publication bias*

The influence of any single study on the overall estimate was analyzed by excluding one study at a time. No significant difference was observed when any of the studies was excluded. Therefore, our results were statistically reliable.

Funnel plot and Egger's test were performed to evaluate the publication bias. As shown in Figure 4, the funnel plots failed to detect any obvious asymmetry in all genotypes in the overall population, and the Egger's test revealed no publication bias (*P* > 0.05). Therefore, no significant publication bias was found in this meta-analysis.

## DISCUSSION

The present meta-analysis, including 4856 cases and 6136 case-free controls from 17 case-control studies, was conducted to evaluate the association between APE1 Asp148Glu polymorphism and GI cancer risk. Our results indicated that the variant genotypes were associated with an increased risk of GI cancers, especially GC.

APE1 is a key multifunctional gene involved in the base excision repair pathway. It was reported that APE1 is associated with aggressive tumor biology and has an impact on survival of GC patients[27]. The Asp148Glu polymorphism is a common non-synonymous APE1 coding region variant. Previous studies on the association between the APE1 Asp148Glu polymorphism and GI cancer risk have shown controversial results[12-26].

In a previous meta-analysis, Gu *et al*[28] suggested that the APE1 Asp148Glu polymorphism may contribute

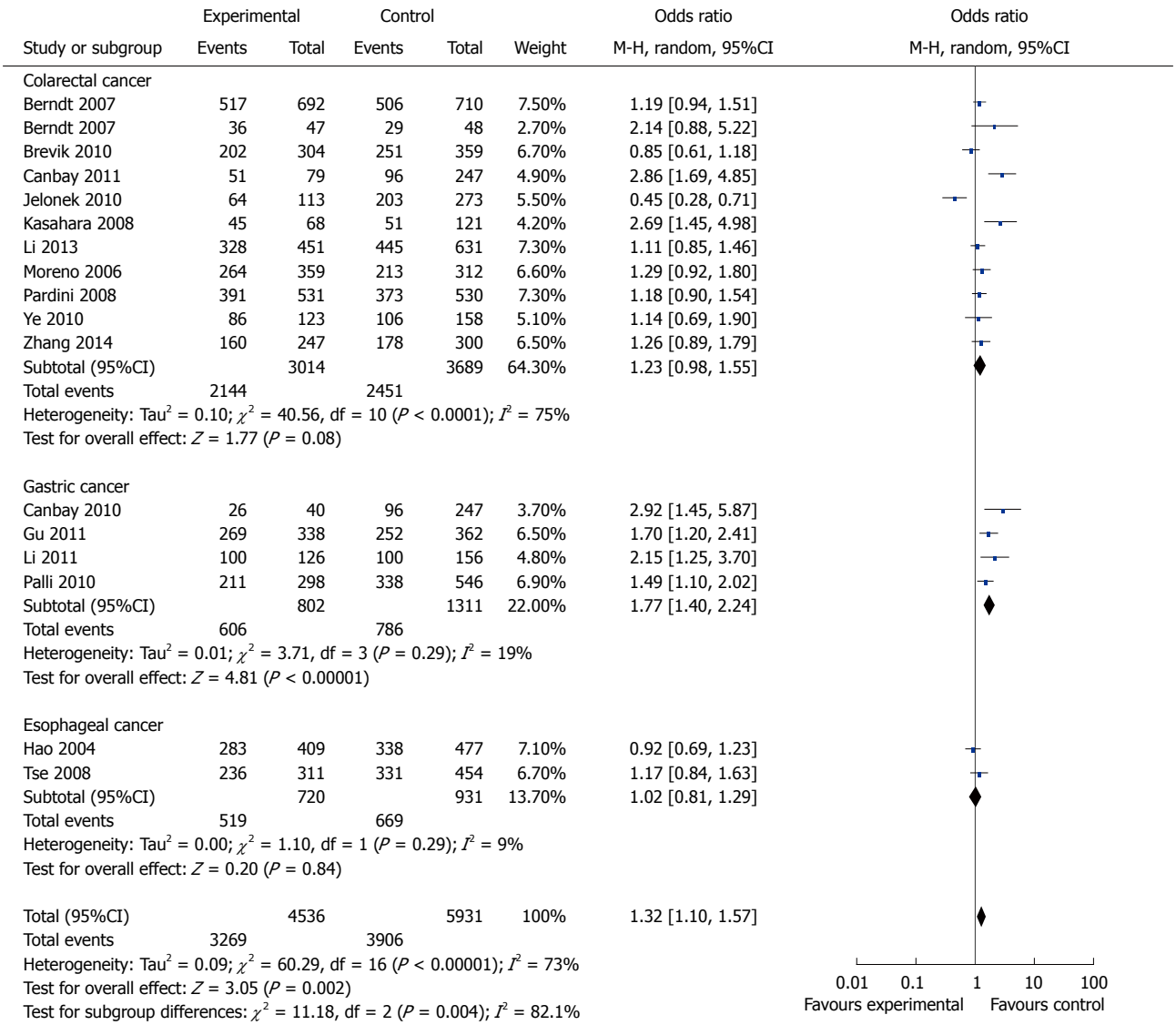


**Figure 3 Forest plot of association of apurinic endonuclease 1 Asp148Glu polymorphism with GI cancer risk stratified by cancer type (TG + GG *vs* TT).**

to genetic susceptibility to cancers, especially CRC. However, a recent meta-analysis by Shen *et al*[29] failed to detect an association between APE1 Asp148Glu polymorphism and CRC risk. We found several worthwhile queries in Shen's study. First, the ethnicity of Canbay's study was identified as Asian in Shen's meta-analysis[29]. While in the original article, the cases and controls were both based on Caucasians but not Asians[13]. Second, the study by Berndt *et al*[24] was carried out in Caucasians and a mixed non-Caucasian population, and therefore should probably be divided into two studies. Third, non-English literature database such as the CNKI should also be considered for the search of eligible case-control studies. We have found one eligible study published in Chinese and included it in this study[20].

In our study, 17 case-control studies were included. There was a significant association between APE1 Asp148Glu polymorphism and GI cancers risk in four genetic models in the overall population. Stratified analysis by ethnicity revealed that there was a statistically increased GI cancers risk in Asians. Further subgroup analysis by cancer type indicated that APE1 Asp148Glu polymorphism may contribute to GC risk.

There are some limitations of this meta-analysis that should be noted. First, this meta-analysis was based on pooled data while no individual data were available; thus, we could not assess the risk of cancer based on environmental factors, age, and other risk factors for GI cancers. Second, the small study effect, where the effects reported in small studies are larger, could not be avoided in some studies of a relative small size (< 200). Third, there was no significant association between Asp148Glu polymorphism and EC risk in this meta-analysis. Since only two EC studies with different pathological types[23,26] were included, this negative finding may result from a lack of statistical power. Larger scale multicenter studies are warranted to further validate the association between APE1 Asp148Glu polymorphism and GI cancer risk.

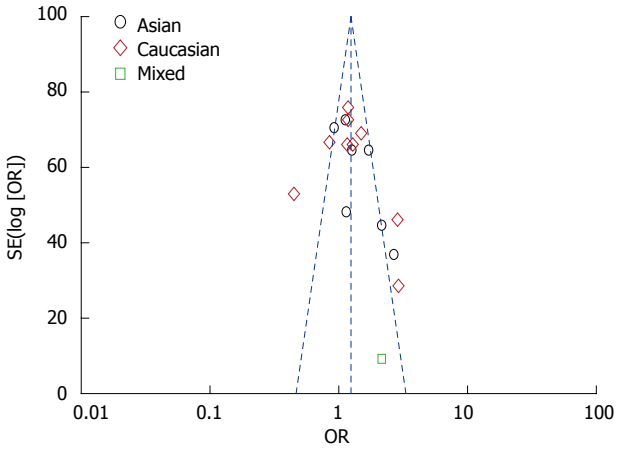


**Figure 4 Funnel plot for publication bias.**

In conclusion, our present meta-analysis provides evidence for the association between the APE1 Asp148Glu polymorphism and GI cancer risk. Results suggest that the APE1 Asp148Glu G allele was associated with an increased GI cancer risk among Asian subjects. Furthermore, the APE1 Asp148Glu polymorphism was associated with an increased risk GC. Further large-population based studies are needed to confirm the association between APE1 Asp148Glu polymorphism and EC risk.

## COMMENTS

### *Background*

Epidemiological studies have suggested that Asp148Glu polymorphism in the apurinic endonuclease 1 (APE1) gene is associated with gastrointestinal (GI) cancer risk. However, the results are still controversial.

### *Research frontiers*

APE1 plays an important role in the DNA repair system and therefore has been implicated in human carcinogenesis. Epidemiologic studies suggested that single nucleotide polymorphisms (SNP) in APE1 may confer individuals' susceptibility to cancer. Recently, numerous studies have evaluated the association between APE Asp148Glu polymorphism and cancer risk. However, the results remain inconclusive.

### *Innovations and breakthroughs*

The present meta-analysis was performed on all eligible case-control studies to estimate the association of the APE1 Asp148Glu polymorphism with GI cancer risk.

### *Applications*

The present meta-analysis showed that the APE1 Asp148Glu G allele was associated with an increased GI cancer risk among Asian subjects. Furthermore, APE1 Asp148Glu polymorphism was associated with an increased risk of GC.

### *Terminology*

SNP is DNA sequence variation occurring when a single nucleotide in the genome differs between members of a biological species or paired chromosomes. SNP in some genes may cause an increase or decrease in risk for some certain diseases.

### *Peer-review*

This meta-analysis showed that the G allele of APE1 Asp148Glu polymorphism was associated with a higher gastrointestinal tract cancer risk. However, larger scale studies are warranted to further validate the association between this polymorphism and GI cancer risk.

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**P- Reviewer**: Jiang ZY **S- Editor**: Yu J **L- Editor**: Wang TQ
**E- Editor**: Zhang DN

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ISSN 1007-9327