MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 2456-2466
DOI: 10.12659/MSM.893954

Received: 2015.02.25
Accepted: 2015.04.22
Published: 2015.08.21

Association of APE1 Gene Asp148Glu Variant with Digestive Cancer: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BC 1 He Li*
BC 2 Jing Zou*
AEG 3 Jia Mi*
CD 3 Xiaodan Wei
CD 4 Dongmei Zhao
DF 5 Shuping Zhang
AEG 3 Geng Tian

1 Department of Gastric and Intestine, Yantai Affiliated Hospital of Binzhou Medical University, Yantai, Shandong, P.R. China
2 Department of Radiology, Yantai Affiliated Hospital of Binzhou Medical University, Yantai, Shandong, P.R. China
3 Medicine and Pharmacy Research Center, Binzhou Medical University, Yantai, Shandong, P.R. China
4 Institute of Anatomy, Binzhou Medical University, Yantai, Shandong, P.R. China
5 Institute of Pharmacology, Binzhou Medical University, Yantai, Shandong, P.R. China

* Shared first authors

Corresponding Author: Geng Tian, e-mail: tiangengshandong@yeah.net or Shuping Zhang, e-mail: spchang11725@126.com

Source of support: This work was financially supported by Taishan Scholars Construction Engineering; National Natural Science Foundation of China (81400771 and 81171303), Shandong Provincial Natural Science Foundation (ZR2014HL028 and ZR2010HM091), A Project of Shandong Province Higher Educational Science and Technology Program (J14LE01) and Binzhou Medical University Scientific Research Funds (BY2013KYQD17 and BY2013KYQD18)

Background: Apurinic/apyrimidinic endonuclease-1 (APE1) is a rate-limiting enzyme in DNA base excision repair and has been implicated in carcinogenesis. In this study, we summarize available data to examine the susceptibility of APE1 gene Asp148Glu variant to digestive cancer via a meta-analysis.

Material/Methods: Study selection and data abstraction were conducted independently by 2 authors. Random-effects model was utilized to pool effect estimates. Heterogeneity and publication bias were addressed.

Results: Sixteen articles involving 4916 digestive cancer patients and 7748 controls were qualified for this meta-analysis. Overall association showed an indicative association between Asp148Glu variant and digestive cancer under allelic (odds ratio or OR=1.11; 95% confidence interval or CI: 0.99–1.25; P=0.074) and dominant (OR=1.18; 95% CI: 1.00–1.40; P=0.056) models, with strong evidence of heterogeneity. Deviation from Hardy-Weinberg equilibrium was an obvious source of heterogeneity. In subgroup analyses by cancer sites, this variant was significantly associated with the increased risk for hepatocellular cancer under allelic (OR=1.50; 95% CI: 1.25–1.80; P<0.001) and homozygous genotypic (OR=1.55; 95% CI: 1.02–2.29; P=0.028) models. There were low probabilities of publication bias for the above comparisons.

Conclusions: The results of this meta-analysis collectively suggest that APE1 gene Asp148Glu variant is not a risk-conferring factor for digestive cancer. Further large and well-designed studies are required.

MeSH Keywords: Digestive System Neoplasms • Genetic Association Studies • Meta-Analysis

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/893954

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Background

DNA damage refers to an alteration in the chemical structure of DNA, and usually gives rise to mutations and epimutations [1,2]. In the body, damaged DNA or inappropriate bases can be identified and properly repaired by some enzymes, such as apurinic/apyrimidinic endonuclease-1 (APE1) [3]. APE1 is a rate-limiting enzyme in DNA base excision repair and is increasingly recognized to play an important role in cancer cell growth and tumorigenicity [4]. For example, in pancreatic cancer, APE1 has been implicated in anticancer properties via inhibiting pancreatic tumor growth, as well as cancer cell migration and invasion [5,6]. Moreover, APE1 was observed to be implicated in sustaining cell variability and proliferation of colon cancer and breast cancer cells [7]. It is therefore reasonable to conjecture that APE1 might play a contributory role in unraveling the molecular mechanisms of cancer.

The gene encoding APE1 is mapped on chromosome 14q11.2–14q12 and consists of 5 exons spanning approximate 2.21 kb. APE1 has a DNA-repairing domain and a redox domain, and its carboxy-terminus contains the endonuclease activity required for DNA repair [8]. A non-synonymous exonic variant, Asp148Glu (rs1130409), that resides in the carboxy-terminus of APE1 has attracted special attention in genetic cancer research. Many association studies have examined the relationship between APE1 gene Asp148Glu variant and cancer [9–11]; however, the results of most studies remain inconclusive, with no consensus on their implications, possibly due to the insufficient power of individual studies, the genetic diversity of ethnic populations, and the potentially uncontrolled confounding effects [12]. To systematically address this uncertainty, we undertook a meta-analysis by summarizing available data on the association between Asp148Glu variant and digestive cancer risk. Digestive cancer is a family of malignancies that originate from digestive organs, such as the stomach, colon, and liver, and has a strong inherited basis. For example, family members who have a mutation in a mismatch repair gene are observed to have a much higher rate of colorectal cancer than those who do not have the mutation [13].

Material and Methods

Article search

An attempt to find all original articles on the association between APE1 gene Asp148Glu variant and digestive cancer risk was conducted in the electronic databases PubMed and Embase up to December 2014. The following medical subject headings and key words were used: "apurinic/apyrimidinic or APE1 or APEX1", "gastric or stomach or colorectal or colon or rectal or esophageal or liver or hepatic or hepatocellular or pancreatic or gallbladder or biliary", "cancer or carcinoma or tumor or sarcoma or leiomyoma", along with "polymorphism or genetic or variant or mutation or allele or genotype". The bibliographies of primarily retrieved articles and previous meta-analyses were manually searched to identify citations that were not identified initially.

Study selection

The eligibility of all retrieved articles was independently ascertained by 2 of us (He Li and Jing Zou) according to the predefined criteria through scanning the titles and abstracts. As a prerequisite, only articles written in English and performed in humans were considered. Inclusion criteria for selection were: (1) all eligible articles should be original investigations; (2) clinical endpoints should be digestive cancer, including esophageal cancer, gastric cancer, colorectal cancer, hepatocellular carcinoma, biliary tract cancer and pancreatic cancer; (3) all studies should be retrospective or nested case-control studies; and (4) the genotype counts of APE1 gene Asp148Glu variant should be provided in both digestive cancer patients and controls. Abstracts and conference posters or proceedings were not included in this meta-analysis due to insufficient information of interest. All eligible articles were reported to have received approval from the local Institutional Review Board (IRB) committees.

Data abstraction

The 2 authors who were responsible for study selection independently abstracted data from each qualified article according to a standardized collection form, including the first author's last name, year of publication, ethnicity of study population, type of digestive cancer, study design, genotyping platform, matched condition, sample size, and the genotype counts of APE1 gene Asp148Glu variant between digestive cancer patients and controls, as well as the average levels of study characteristics, if available, including age, sex (the percentage of males), body mass index (BMI), and the percentages of smoking, drinking, and family history of cancer between the 2 groups. Discrepancies in data abstraction were resolved by consensus through discussion with other investigators of the present meta-analysis or through reference to the original or indexed articles. Study authors were contacted if necessary for additional information.

Statistical analysis

For the association of APE1 gene Asp148Glu variant with digestive cancer risk, 3 genetic models of inheritance including allelic (148Glu versus 148Asp), homozygous genotypic (148Glu/Glu versus 148Asp/Asp), and dominant (148Glu/Glu plus 148Asp/Glu versus 148Asp/Asp) models were calculated, and the risk effects were expressed as odds ratio (OR) and its

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corresponding 95% confidence interval (95% CI). Assessment of Hardy-Weinberg equilibrium for Asp148Glu variant was conducted only among controls using the chi-squared test at a significance level of 5%.

Heterogeneity among studies was examined for risk effects using the I^2 statistic, a transformation of the Q statistic (I^2=100%×(Q-df)/Q, where DF denotes degrees of freedom) that estimates the percentage of the variation in effect sizes that is due to heterogeneity rather than due to chance. The I^2 statistic takes values between 0 and 100% with higher values (>50%) indicating the existence of heterogeneity.

In the absence of between-study heterogeneity, fixed- and random-effects models yielded similar estimates, while in view of significant heterogeneity for several comparisons, only results from the random-effects model using the DerSimonian & Laird method [14] are presented in the present meta-analysis.

To seek potential sources of heterogeneity, both subgroup analyses and meta-regression analyses were conducted. Subgroup analyses were predefined according to the test results of Hardy-Weinberg equilibrium, different sites of digestive cancer, ethnicities, study designs, genotyping platforms, matched conditions and sample sizes. Continuous variables including age, gender, body mass index (BMI), and the percentages of smoking, drinking, family history of cancer were incorporated into a meta-regression model. The probability of publication bias was inspected by the visual Begg's funnel plots and was quantified by both Begg's and Egger's tests at a significance level of 10% [15]. In addition, the trim and fill method was adopted to estimate the number and outcomes of potentially missing studies resulting from publication bias. Statistical calculations were completed by the STATA software (StataCorp, Texas, USA, version 12.0 for Windows).

Results

Description of studies

Initial search yielded 294 potentially relevant articles according to the predefined subject headings and key words. After reviewing these articles, 278 articles were excluded with specified reasons and a total of 16 qualified articles involving 4916 digestive cancer patients and 7748 controls were left for final analysis [10,16–30].

Tables 1 and 2 show the baseline characteristics of study populations and the genotype distributions of APE1 gene Asp148Glu variant of each qualified study. Out of 16 eligible studies, 8 studies analyzed the association of this variant with colorectal cancer, 3 studies with gastric cancer, 2 studies for pancreatic cancer, and 1 study respectively for cancer of esophageal, gallbladder and hepatocellular. Eight studies involved populations of Caucasian descent, 6 studies of Asian descent and 2 studies of mixed descents. Nine studies enrolled controls from hospitals and 7 from general populations. Age or gender was reported to be matched in thirteen studies, unavailable in 2 studies, and unmatched in only 1 study. For the genotype distributions of Asp148Glu variant, Hardy-Weinberg equilibrium was satisfied in 13 studies and was not in 3 studies. Seven studies had genotypes determined by restriction fragment length polymorphism (RFLP) method, and the other 9 studies by Taqman or array method. There were twelve of 16 studies with total sample size of less than 1000. The average frequency of 148Glu allele was 45.35% in digestive cancer patients and 42.57% in controls.

APE1 gene Asp148Glu variant and digestive cancer risk

When all qualified studies were analyzed together, significance was indicative for the association between Asp148Glu variant and digestive cancer risk under allelic (OR=1.11; 95% CI: 0.99–1.25; P=0.074) and dominant (OR=1.18; 95% CI: 1.00–1.40; P=0.056) models (Figure 1). There was strong evidence of heterogeneity for all 3 genetic models (I^2=76.3%, 61.5% and 74.3% for allelic, homozygous genotypic and dominant models, respectively), while low probabilities of publication bias were observed (Figure 2). In addition, as reflected by the trim and fill method, 1 study for allelic model and 2 studies for dominant model were required to make filled funnel plots symmetrical (Supplementary Figure 1). Adjusting for the missing studies still failed to attain statistical significance for both genetic models of inheritance (data not shown).

After grouping studies by the degree of Hardy-Weinberg equilibrium test at a significance level of 5%, it was of interest to note that the corresponding effect estimates were exceedingly overestimated in studies with Asp148Glu genotypes deviating from Hardy-Weinberg equilibrium across 3 genetic models, especially under dominant model (OR=2.82; 95% CI: 1.99–3.99; P<0.001), without heterogeneity. In contrast, conformity to Hardy-Weinberg equilibrium greatly attenuated the risk estimates, yet with significant heterogeneity. In view of this divergence and to avoid biased estimates, the following subgroup analyses were restricted to the studies with Asp148Glu genotypes in Hardy-Weinberg equilibrium (Table 3).

By digestive cancer sites, significance was only observed for hepatocellular cancer under allelic (OR=1.50; 95% CI: 1.25–1.80; P<0.001) and homozygous genotypic (OR=1.55; 95% CI: 1.02–2.29; P=0.028) models, although this finding was based on 1 eligible study. Moreover, considering the magnitude of risk estimates, albeit nonsignificant, for different sites of digestive cancer, it is suggestive of heterogeneous carcinogenic mechanisms.

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Table 1. Baseline characteristics of the study populations in this meta-analysis.

Author (year)	Cancer type	Ethnicity	Design	Matched	Geno-typing	Sample size		Age (years)		Male		BMI (kg/m²)		Smoking	
						Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Moreno V. et al. (2006)	Colorectal	Caucasian	Hospital	NA	Array	359	312	NA	NA	NA	NA	NA	NA	NA	NA
Jiao L. et al. (2006)	Pancreatic	Mixed	Hospital	YES	PCR-ASG	367	330	NA	NA	0.557	0.515	NA	NA	0.612	0.535
Berndt S. et al. (2007)	Colorectal	Mixed	Population	YES	TaqMan	739	757	NA	NA	0.696	0.692	NA	NA	0.663	0.595
Tse D. et al. (2008)	Esophageal	Caucasian	Hospital	YES	TaqMan	311	454	64.0	64.0	0.894	0.874	23.00	22.00	0.800	0.683
Pardini B. et al. (2008)	Colorectal	Caucasian	Hospital	YES	PCR-RFLP	531	530	58.5	57.4	0.553	0.553	NA	NA	0.268	0.283
Kasahara M. et al. (2008)	Colorectal	Asian	Hospital	YES	PCR-RFLP	68	121	67.3	67.4	0.544	0.612	NA	NA	0.471	0.545
Huang W.Y. et al. (2008)	Gallbladder	Asian	Population	YES	Array	236	734	NA	NA	0.274	0.388	NA	NA	0.271	0.302
Palli D. et al. (2010)	Gastric	Caucasian	Population	YES	TaqMan	298	546	68.8	55.5	0.564	0.493	NA	NA	0.558	0.586
Jelonek K. et al. (2010)	Colorectal	Caucasian	Hospital	YES	PCR-RFLP	113	153	NA	NA	NA	NA	NA	NA	NA	NA
Brevik A. et al. (2010)	Colorectal	Caucasian	Population	NA	TaqMan	304	359	NA	NA	NA	NA	NA	NA	NA	NA
Canbay E. et al. (2010)	Gastric	Caucasian	Population	YES	PCR-RFLP	40	247	60.1	52.8	NA	NA	NA	NA	0.625	0.368
Gu D. et al. (2011)	Gastric	Asian	Hospital	YES	PCR-RFLP	338	362	61.8	62.5	0.657	0.660	NA	NA	0.461	0.362
Canbay E. et al. (2011)	Colorectal	Caucasian	Population	YES	PCR-RFLP	79	247	60.2	59.7	0.646	0.526	28.50	27.70	0.380	0.368
Nakao M. et al. (2012)	Pancreatic	Asian	Population	YES	TaqMan	185	1465	NA	NA	0.687	0.749	NA	NA	NA	NA
Zeng X. et al. (2012)	Hepatocellular	Asian	Hospital	YES	TaqMan	497	500	NA	NA	0.787	0.742	NA	NA	0.328	0.096
Li Y. et al. (2013)	Colorectal	Asian	Hospital	NO	PCR-RFLP	451	631	59.4	57.0	0.583	0.577	22.92	23.58	0.419	0.475

BMI – body mass index; ASG – allele-specific genotyping; PCR – polymerase chain reaction; RCLP – restriction fragment length polymorphism; NA ,– not available.

Further stratifying studies according to ethnicity, study design, matched status, sample size (at a cutoff of 1000) and genotyping platform failed to identify any significance between Asp148Glu variant and digestive cancer risk. Given the limited sample sizes in some strata, it is, however, premature to negate the potential confounding effects of these characteristics in interpreting significant heterogeneity. For example, genetic susceptibility of Asp148Glu variant to digestive cancer was ethnicity-specific, as 148Glu/Glu genotype carriers were 1.21 times (OR=1.21; 95% CI: 0.89-1.64; P=0.232) more likely to develop digestive cancer when compared to those with 148Asp/Asp genotype in Asian populations, yet this genotype seemed to be a protective or neutral factor in Caucasians (OR=0.96; 95% CI: 0.66–1.38; P=0.809).

Meta-regression analysis

To further seek other sources of heterogeneity resulting from continuous covariates, a meta-regression model was constructed by incorporating age (P=0.338), gender (P=0.485), BMI (P=0.279), smoking (P=0.431), drinking (P=0.450) and family history of cancer (P=0.721), and still all regression coefficients did not differ significantly from zero.

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Table 2. Baseline characteristics of the study populations in this meta-analysis.

Author (year)	Drinking		Family cancer history		Cases			Controls			P for HWE
	Cases	Controls	Cases	Controls	148Asp/ Asp	148Asp/ Glu	148Glu/ Glu	148Asp/ asp	148Arg/ Glu	148Glu/ Glu	
Moreno V. et al. (2006)	NA	NA	NA	NA	95	177	87	99	147	66	0.406
Jiao L. et al. (2006)	NA	NA	NA	NA	108	180	79	85	174	71	0.305
Berndt S. et al. (2007)	NA	NA	NA	NA	186	387	166	222	357	178	0.140
Tse D. et al. (2008)	0.890	0.820	NA	NA	75	162	74	123	228	103	0.892
Pardini B. et al. (2008)	NA	NA	NA	NA	140	261	130	157	267	106	0.696
Kasahara M. et al. (2008)	NA	NA	NA	NA	23	45	0	70	51	0	0.003
Huang W.Y. et al. (2008)	0.152	0.206	NA	NA	76	118	42	221	358	155	0.653
Palli D. et al. (2010)	NA	NA	0.166	0.089	103	147	48	208	243	95	0.102
Jelonek K. et al. (2010)	NA	NA	NA	NA	49	59	5	38	87	28	0.079
Brevik A. et al. (2010)	NA	NA	NA	NA	102	137	65	108	167	84	0.215
Canbay E. et al. (2010)	0.675	0.146	NA	NA	14	18	8	151	63	33	0.000
Gu D. et al. (2011)	0.373	0.287	NA	NA	69	185	84	110	183	69	0.645
Canbay E. et al. (2011)	0.241	0.146	NA	NA	28	43	8	151	63	33	0.000
Nakao M. et al. (2012)	0.694	0.663	0.043	0.040	77	75	33	542	681	242	0.257
Zeng X. et al. (2012)	0.396	0.116	0.095	0.006	66	198	440	56	203	241	0.186
Li Y. et al. (2013)	NA	NA	0.183	0.154	123	247	81	186	335	110	0.052

HWE – Hardy-Weinberg equilibrium; NA – not available.

Discussion

In this study, we aimed to summarize available data on the association between APE1 gene Asp148Glu variant and digestive cancer risk through a comprehensive meta-analysis involving 16 articles and 12664 subjects. Our findings suggested that APE1 gene Asp148Glu variant might not be a risk-conferring factor for digestive cancer. Moreover, conformity to Hardy-Weinberg equilibrium was identified as a potential source of significant overall heterogeneity.

Several possible limitations must be recognized prior to interpreting our findings. First, this meta-analysis is based on the summaries of retrospective case-control studies, which rarely establish causal relationship, and it is encouraging to incorporate the concept of Mendelian randomization into observational association studies [31]. Second, only 1 variant Asp148Glu in APE1 gene was covered in this study, which might not be sufficient to address the complex genetic architecture of digestive cancer. Third, only published articles written in English language were retrieved for inclusion and some unpublished small and/or negative articles might be missing, leading to

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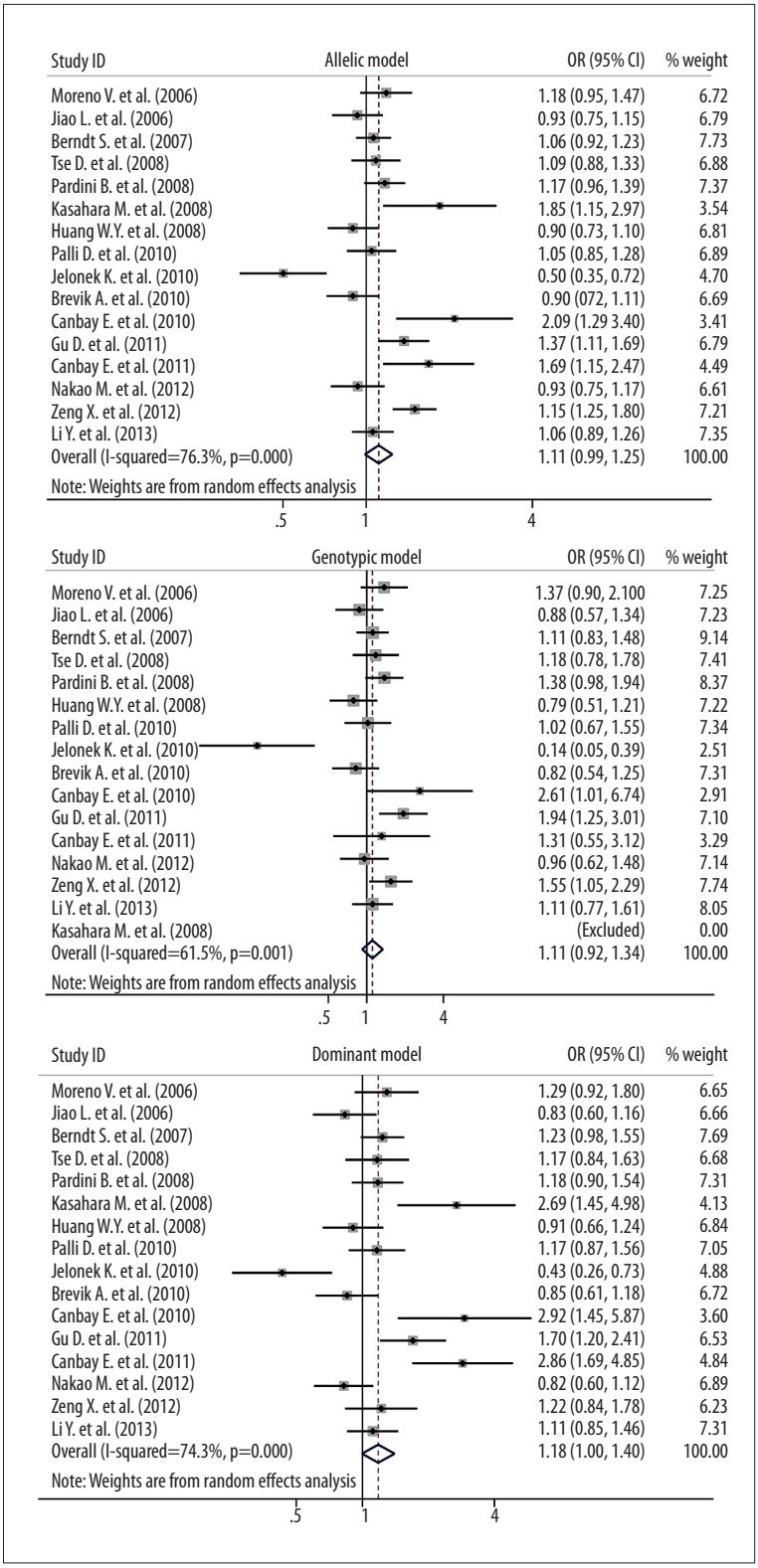

Figure 1. Forest plots of APE1 gene Asp148Glu variant for digestive cancer risk under 3 genetic models.

the potential existence of publication bias. Fourth, it is essential to examine gene-environment and gene-gene interactions at the level of both individual studies and meta-analysis. To achieve this goal, one usually needs to perform a meta-analysis of individual participant data, which is not always practical for the majority of published meta-analyses. Five, although

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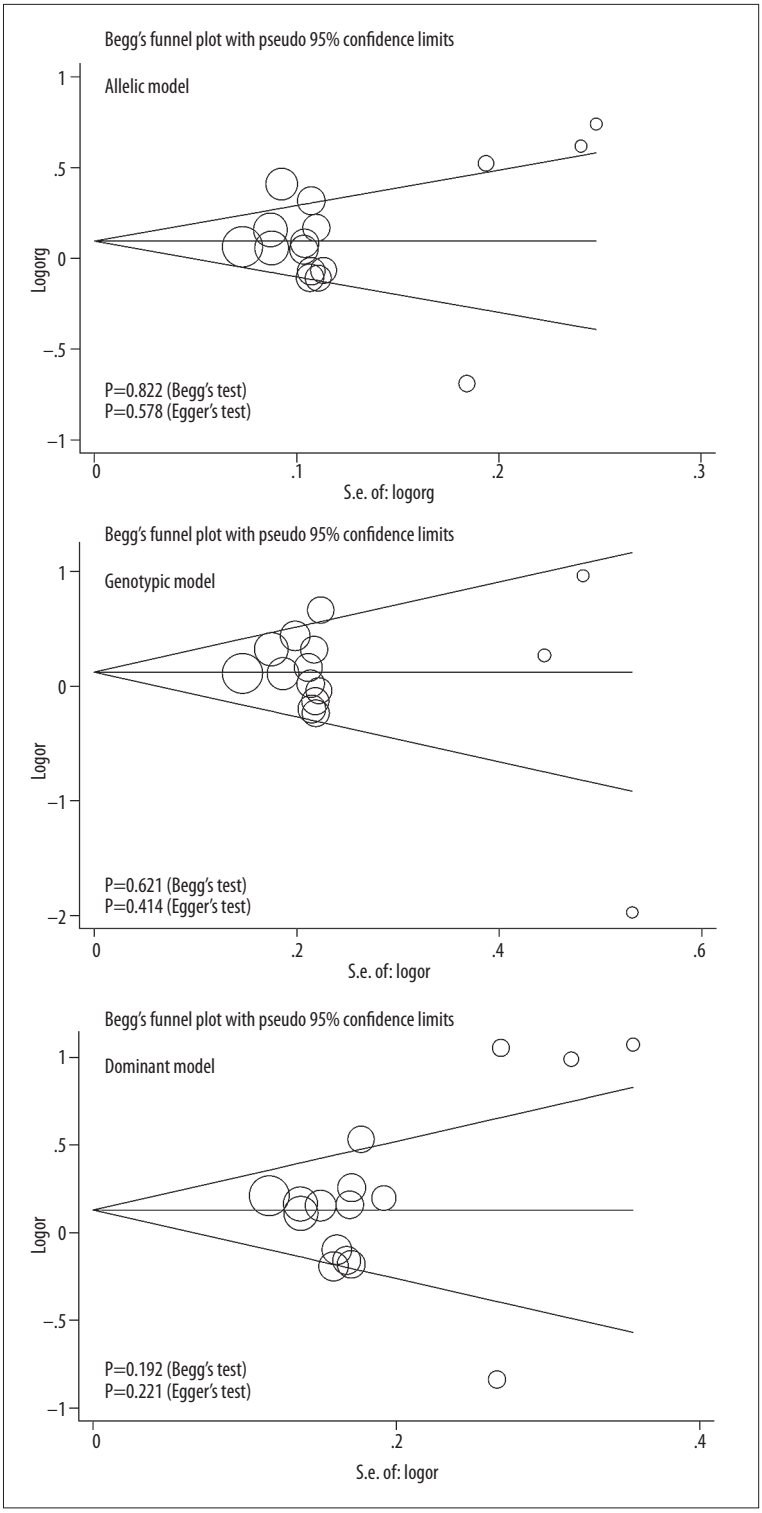

Figure 2. Begg's funnel plots of APX1 gene Asp148Glu variant with digestive cancer risk under 3 genetic models.

both subgroup and meta-regression analyses were undertaken to explore the potential sources of heterogeneity, it is still obsessing a majority of comparisons in this meta-analysis. Nevertheless, considering that residual confounding by incompletely considered physiologic covariates might exist in our findings, it seems unlikely that the effect estimates could be explained by confounding.

Despite these limitations, our stratified findings suggest that APE1 gene Asp148Glu variant might be a susceptible locus for

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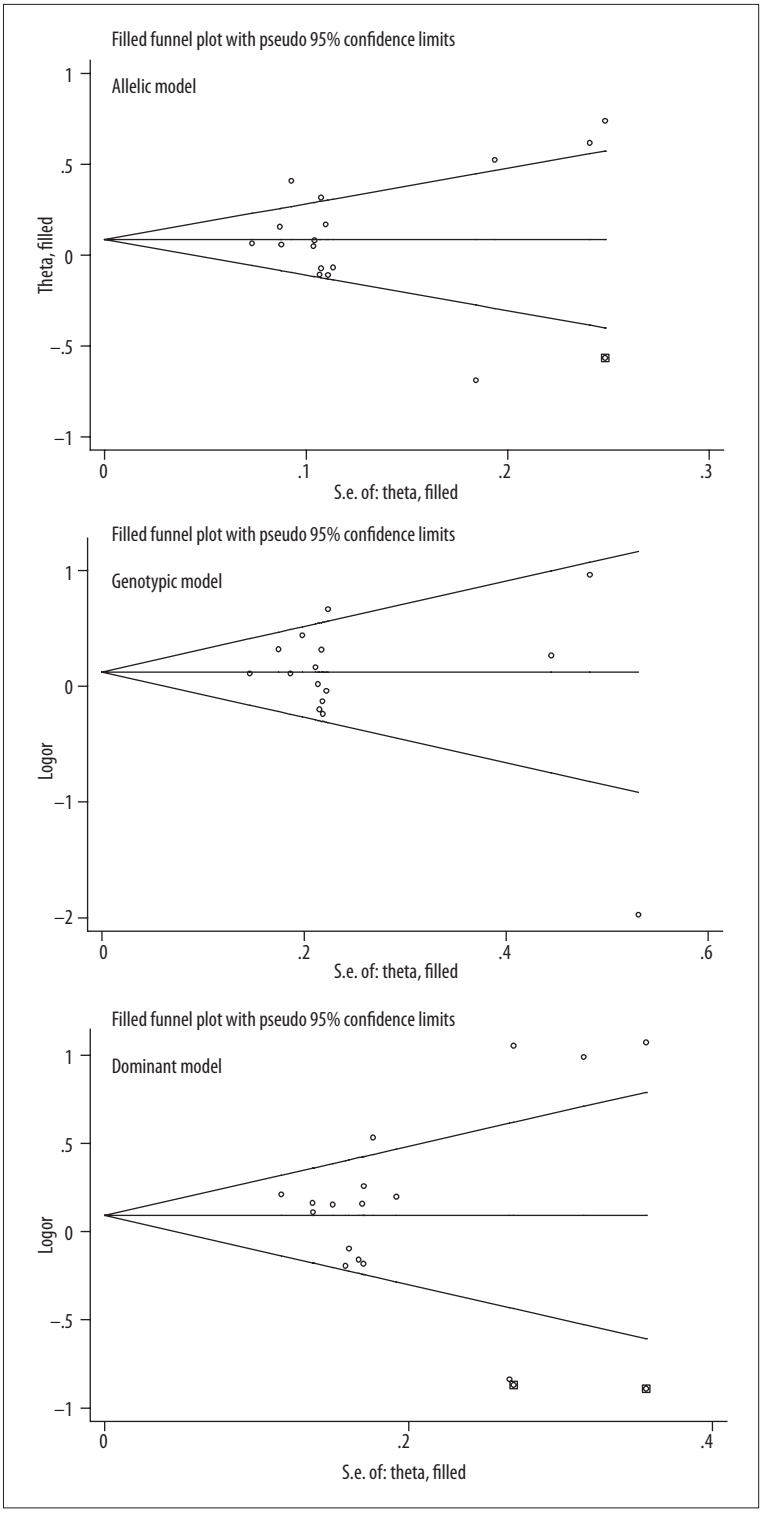

Supplementary Figure 1. Filled funnel plots of APX1 gene Asp148Glu variant with digestive cancer risk under 3 genetic models.

the development of hepatocellular cancer, suggesting that digestive cancer is characterized by marked genetic heterogeneity. This genetic heterogeneity is not surprising in light of the heterogeneous pathogenesis for different sites of cancer [32], necessitating the construction of a database of candidate genes and variants responsible for different sites of cancer. As stated by Burrell et al., there is extensive genetic diversity both between and within cancer, which poses a significant challenge to personalized cancer medicine [33]. Moreover, the effect of Asp148Glu variant on cancer susceptibility has strong

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Table 3. Subgroup analyses of all qualified studies under 3 genetic models.

Subgroups	No. of studies (cases/controls), n (n/n)	Allelic model		Genotypic model		Dominant model	
		OR; 95% CI; P	I^2 (P)	OR; 95% CI; P	I^2 (P)	OR; 95% CI; P	I^2 (P)
HWE test							
Yes	13 (4729/7133)	1.04; 0.94–1.16; 0.449	74.0% (<0.001)	1.08; 0.89–1.30; 0.450	63.8% (0.001)	1.05; 0.92–1.21; 0.472	60.8% (0.002)
No	3 (187/615)	1.84; 1.43–2.36; <0.001	0.0% (0.791)	1.80; 0.91–3.55; 0.089	10.6% (0.290)	2.82; 1.99–3.99; <0.001	0.0% (0.982)
Cancer site (HWE=YES)							
Colorectal cancer	6 (2497/2742)	0.99; 0.84–1.16; 0.858	76.0% (0.001)	0.98; 0.70–1.37; 0.909	74.8% (0.001)	1.02; 0.81–1.28; 0.891	70.0% (0.005)
Pancreatic cancer	2 (552/1795)	0.93; 0.80–1.09; 0.359	0.0% (0.980)	0.92; 0.68–1.24; 0.574	0.0% (0.768)	0.83; 0.66–1.04; 0.103	0.0% (0.965)
Gastric cancer	2 (636/908)	1.20; 0.92–1.56; 0.182	69.3% (0.071)	1.40; 0.75–2.63; 0.292	76.8% (0.038)	1.39; 0.96–2.02; 0.080	62.5% (0.103)
Esophageal cancer	1 (311/454)	1.09; 0.89–1.33; 0.433	NA	1.18; 0.78–1.78; 0.438	NA	1.17; 0.84–1.63; 0.356	NA
Gallbladder cancer	1 (236/734)	0.90; 0.73–1.11; 0.304	NA	0.79; 0.51–1.21; 0.276	NA	0.91; 0.66–1.24; 0.544	NA
Hepatocellular cancer	1 (497/500)	1.50; 1.25–1.80; <0.001	NA	1.55; 1.05–2.29; 0.028	NA	1.22; 0.84–1.78; 0.302	NA
Ethnicity (HWE=YES)							
Caucasian	6 (1916/2354)	0.98; 0.82–1.18; 0.823	76.0% (0.001)	0.96; 0.66–1.38; 0.809	75.0% (0.001)	1.00; 0.79–1.28; 0.972	68.2% (0.008)
Asian	5 (1707/3692)	1.13; 0.92–1.38; 0.232	80.8% (<0.001)	1.21; 0.89–1.64; 0.232	64.1% (0.025)	1.11; 0.87–1.41; 0.410	64.1% (0.025)
Mixed	2 (1106/1087)	1.02; 0.90–1.15; 0.788	8.2% (0.297)	1.03; 0.81–1.31; 0.789	0.0% (0.362)	1.03; 0.70–1.52; 0.868	72.6% (0.056)
Study design (HWE=YES)							
Hospital	8 (2967/3272)	1.09; 0.92–1.28; 0.331	80.8% (<0.001)	1.15; 0.86–1.55; 0.342	72.9% (0.001)	1.09; 0.88–1.35; 0.442	68.9% (0.002)
Population	5 (1762/3861)	0.99; 0.90–1.07; 0.724	0.0% (0.520)	0.97; 0.81–1.15; 0.682	0.0% (0.654)	1.00; 0.84–1.19; 0.975	42.5% (0.138)
Matched status (HWE=YES)							
Yes	10 (3615/5831)	1.04; 0.91–1.20; 0.581	78.9% (<0.001)	1.06; 0.84–1.36; 0.615	70.2% (<0.001)	1.04; 0.87–1.24; 0.645	67.2% (0.001)
No	1 (451/631)	1.06; 0.89–1.26; 0.529	NA	1.11; 0.77–1.61; 0.565	NA	1.12; 0.85–1.46; 0.429	NA
NA	2 (663/671)	1.03; 0.78–1.35; 0.836	68.6% (0.074)	1.06; 0.64–1.76; 0.822	64.9% (0.091)	1.05; 0.70–1.58; 0.823	67.0% (0.082)
Sample size (HWE=YES)							
Total sample size ≥1000	4 (1906/3383)	1.07; 0.98–1.16; 0.139	0.0% (0.476)	1.15; 0.97–1.37; 0.119	0.0% (0.618)	1.10; 0.93–1.29; 0.274	33.8% (0.209)
Total sample size <1000	9 (2823/3750)	1.03; 0.87–1.22; 0.759	81.7% (<0.001)	1.02; 0.76–1.37; 0.911	74.4% (<0.001)	1.03; 0.84–1.27; 0.790	69.0% (0.001)
Genotyping (HWE=YES)							
Non-RFLP	9 (3296/5457)	1.05; 0.94–1.18; 0.379	64.9% (0.004)	1.06; 0.92–1.23; 0.417	17.4% (0.288)	1.05; 0.92–1.18; 0.489	30.3% (0.176)
RFLP	4 (1433/1676)	1.24; 0.96–1.61; 0.100	83.9% (<0.001)	0.97; 0.52–1.81; 0.925	86.3% (<0.001)	1.04; 0.69–1.56; 0.869	83.8% (<0.001)

HWE – Hardy-Weinberg equilibrium; OR – odds ratio; 95% CI – 95% confidence interval; NA – not available, RFLP – restriction fragment length polymorphism.

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biological plausibility since this variant resides in the carboxy-terminus region of APE1 gene, the region containing the endonuclease activity required for DNA repair [34]. Functional investigations showed that individuals carrying APE1 gene 148Glu allele had higher levels of APE1 mRNA expression when compared with those with the 148Asp/Asp genotype [35]. At present, the mechanism linking APE1 gene Asp148Glu variant and hepatocellular cancer is not clear, and thus if involved, this variant might, by affecting DNA repair activity or gene function via altering the stability of mRNA, be implicated in the pathogenesis of hepatocellular cancer. In addition, we cannot rule out the possible involvement of APE1 gene Asp148Glu variant or others in strong linkage disequilibrium in other sites of cancer, considering the sample size involved in this meta-analysis. Nevertheless, considering the limited studies with inadequate sample sizes for most subgroups, our stratified findings should be considered preliminary and be viewed as hypothesis-generating for future large and well-designed studies.

Deviation from Hardy-Weinberg equilibrium was identified as a potential source of heterogeneity in our subgroup analyses. In reality, conformity to Hardy-Weinberg equilibrium weakened the association between Asp148Glu variant and digestive cancer risk. In the evaluation of case-control studies, assessment of Hardy-Weinberg equilibrium for a given genetic locus among controls is considered an important criterion [36]. Generally, deviation from Hardy-Weinberg equilibrium should imply some potential biases in the selection of controls or genotyping misclassifications, which tend to inflate the change of a false-positive association [37]. In view of this fact, all following subgroup and meta-regression analyses that sought to explore the potentially sources of heterogeneity were undertaken in studies with Asp148Glu genotypes in Hardy-Weinberg equilibrium. Unfortunately, none of the other confounding factors can explain significant heterogeneity of Asp148Glu in susceptibility to digestive cancer. Meta-regression *per se* is analogous to simple regression where an outcome variable is predicted according to the values of 1 or more explanatory variables. However, it is of importance to acknowledge that meta-regression, albeit enabling coverage of various continuous covariates, does not have the methodological rigor of a properly designed study that is intended to test the effect of these covariates formally [38]. We therefore must regard our findings as preliminary, which should be viewed as hypothesis-generating and call for validation in future large and well-design studies.

Conclusions

The results of this meta-analysis collectively suggest that APE1 gene Asp148Glu variant is not a risk-conferring factor for digestive cancer. For practical reasons, we hope that this study will not remain just another endpoint of research, but instead serve as a beginning to establish background data to unravel the contributory role of APE1 gene and its genetic alterations in the development of digestive cancer and other solid tumors.

Conflicts of interest statement

None of the authors have any conflict of interest to disclose.

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