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ASSOCIATION BETWEEN APE1 ASP148GLU AND COLORECTAL CANCER RISK: A META-ANALYSIS

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ABSTRACT

Background: Colorectal cancer (CRC) is recognized as one of the most common cancer globally. The association between CRC and apurinic endonuclease 1 (APE1) Asp148Glu polymorphism remains unclear; thus, this meta-analysis aimed to explore whether APE1 Asp148Glu polymorphism is related to CRC risk.

Methods: Embase, PubMed, Cochrane library, CNKI and Wanfang databases were subject to a systematic search until April, 17, 2020 to evaluate the effect of APE1 Asp148Glu polymorphism on CRC risk. The associated strength was used to evaluate with odds ratios (ORs) with 95% confidence intervals (CIs) between Asp148Glu polymorphism and CRC risk. Subgroup analyses were also performed.

Results: In total, 11 articles including 8,136 subjects (3,836 cases and 4,300 controls) were included. Five genetic models were analyzed, including the additive model (G vs. T), the heterozygote comparison (TG vs. TT), the homozygote comparison (GG vs. TT), the dominant model (TG+GG vs. TT), and the recessive model (GG vs. TG+TT). In these models, T refers to thymine and G refers to guanine. The APE1 Asp148Glu polymorphism in heterozygote comparison [OR (95%CI) = 1.36 (1.05, 1.75), $P=0.019$] and dominant model [OR (95%CI) = 1.31 (1.07, 1.61), $P=0.010$] significantly increased CRC risk. No significant association was seen for the additive model [OR (95%CI) = 1.14 (1.00, 1.31), $P=0.057$], recessive model [OR (95%CI) = 0.97 (0.71, 1.31), $P=0.826$] or in homozygote comparison [OR (95%CI) = 1.15 (0.88, 1.52), $P=0.309$]. Moreover, CRC risk indicated a remarkable association with APE1 Asp148Glu polymorphism in the PCR-RFLP additive model, homozygote comparison and recessive model ($P<0.05$).

Conclusions: The APE1 Asp148Glu (T>G) may be a potential risk factor for CRC.

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INTRODUCTION

Colorectal cancer (CRC), a malignant tumor of the large intestine, is now recognized as one of the most frequently diagnosed cancers globally [1]. The incidence rate of CRC has increased consistently in many countries. Colorectal cancer is the third most common cancer (excluding skin cancer) in both men and women in the United States; the American Cancer Society estimates that in 2020 there will be over 147,000 new cases [2]. Colorectal cancer results from cumulative DNA damage, leading to the malignant transformation of colonic epithelial cells [3]. Chromosomal instability, microsatellite instability and aberrant DNA-methylation are the main causes of instability in the CRC genome [4]. The DNA stability may be influenced by endogenous (e.g., reactive oxygen spe-

cies) or environmental factors (e.g., X-rays, smoke and pesticides), which result in DNA damage [5].

Base excision repair (BER), nuclear excision repair, mismatch repair and double-stranded break repair could be used to repair DNA damage [6]. The BER pathway is the main repair pathway that repairs base damage in both the cell nucleus and mitochondria [7]. Apurinic/apyrimidinic endonuclease 1 (APE1), a multifunctional key enzyme of 35,555 Da (EC 4.2.99.18), is located on the long arm of chromosome 14 (14q11.2-q12) [8]. The N-terminal region of APE1 enzyme encodes the redox function and the C-terminal region encodes the DNA repair activity [9]. As an apurinic/apyrimidinic endonuclease, APE1 is implicated in the repair of DNA damage caused by oxidants and/or alkylating agents during the second step of

the BER pathway [10]. The APE1 hydrolyzes the 5'-phosphodiesterase bond at the apurinic/aprimidinic site to produce a single-stranded DNA intermediate containing the 3'-hydroxyl group and the 5'-deoxyribonucleoside [11]. Moreover, APE1, as a redox factor, regulates a variety of transcription factors, such as AP-1 and Myb, during the development of cancer by mediating the redox state of cysteine residues located in the DNA-binding domains or within the regulatory regions, such as the transactivation domain of the transcription factors themselves [12]. Eighteen single nucleotide polymorphisms (SNP) have been reported for APE1 [13]. Two widely studied functional SNPs are promoter -656 T>G, rs1760944 and 1349 T>G, rs1130409 on 5th exon. The change from aspartic acid to glutamic acid in exon 5 of Asp148Glu (1349 T>G) has attracted intense interest. The formation of these amino acid substitution variants may be attributed to the effects of ionizing radiation [13].

Clinical epidemiological studies have shown that SNP in APE1 may be the molecular mechanism responsible for modulating the susceptibility to malignancies [14]. Correlation of APE1 polymorphisms with the CRC risk has been assessed previously but there has been no consistent conclusion on the role of APE1 Asp148Glu in CRC. Two studies have suggested that CRC risk was associated with APE1 Asp148Glu [15, 16], while another has shown no effect [17].

However, the relatively small sample sizes and statistical power in prior studies limit the value of the results and the strength of the conclusions. A previous meta-analysis indicated that APE1 Asp148Glu polymorphism did not play a key role in CRC risk, although the majority of the subjects was Asian or Caucasian [18]. Conversely, another meta-analysis indicated the role of APE1 Asp148Glu SNP variation was involved in the malignant transformation of CRC [16]. More recent meta-analysis studies [15, 19] focused on the relationship between APE1 Asp148Glu polymorphism and the risk of CRC but this relationship was not studied systematically.

To provide a basis for the study of the association between APE1 Asp148Glu polymorphism and CRC risk, a meta-analysis was performed to evaluate the potential effects of APE1 Asp148Glu polymorphism on CRC tumorigenesis.

MATERIALS AND METHODS

Study selection

Five electronic databases, including PubMed, Embase, Trials database of the Cochrane library (<https://www.cochranelibrary.com/>), Chinese National Knowledge Infrastructure databases and Wanfang, were selected to identify articles reporting the effect of APE1 Asp148Glu

polymorphism on the risk of CRC. Selection strategies used in the manuscript were as follows: ("APE1" OR "APEX1" OR "APEX" OR "Asp148Glu" OR "D148E" OR "rs3136820") AND ("polymorphisms" OR "genetic polymorphism" OR "polymorphism" OR "variant" OR "mutant") AND ("CRC" OR "colon cancer" OR "rectal cancer" OR "colorectal neoplasms" OR "colonic neoplasms" OR "colorectal tumor" OR "rectal tumor" OR "colon tumor"), and the latest selection date was October 9, 2020. Details on the full search strategies are available from the authors. To identify additional relevant publications, reference lists of review articles were also analyzed.

Inclusion and exclusion criteria

Studies were included in the analysis if they met the following inclusion criteria: 1) CRC case-controls were included in the studies; 2) subjects in the study were human; 3) studies evaluated the association between the risk of CRC and the polymorphism of APE1 Asp148Glu; and 4) studies included genotype frequency. Studies with the following criteria were excluded: 1) family members or close family members were included in case-control studies; 2) study were reviews, comments or letters; 3) for the repeated studies or different studies involving the same data, only the study with the most complete information was selected; and 4) gene distribution that did not meet the Hardy-Weinberg equilibrium (HWE).

Data extraction and quality evaluation

Two reviewers independently extracted data from the individual studies. The information, including first author, publication year, country of origin, age, sex, total number of the case and control groups, the control group, and genotype data, were collected on a pre-designed form. After data extraction, the extraction tables were exchanged between the two reviewers. If there was inconsistent conclusion, then all authors of this paper discussed the results and came to a consensus. Assessment of the quality in the included literatures was performed using Clark et al. [20]. The form had a total of 10 entries, and each item was scored as one point. Studies that scored six points or more were defined as high quality.

Statistical analysis

A chi-squared test was used to test the genotype distribution frequency of the included controls for each study to assess compliance with the HWE. Significant imbalance occurred when $P < 0.05$. Five different genetic models were used to assess the relationship between the risk of CRC and the polymorphism of APE1 Asp148Glu. These genetic models included 1) the additive model

(G vs. T), 2) the heterozygote comparison (TG vs. TT), 3) the homozygote comparison (GG vs. TT), 4) the dominant model (TG+GG vs. TT), and 5) the recessive model (GG vs. TG+TT). In these models, T refers to thymine and G refers to guanine. Odds ratio (OR) with 95% confidence interval (CI) were chosen as the covariants for evaluating the above associations. Statistical heterogeneity among studies was calculated and evaluated by Q and I² statistics [21]. When Q statistic $P < 0.05$ and/or $I^2 > 50\%$, the random-effects model was chosen to pool data; otherwise, the fixed-effects model was used.

Subgroup analysis was stratified by the genotyping method and ethnicity. To demonstrate the stable of the results, sensitivity analyses (achieved by removing one study for each calculation) were performed. Finally, Egger's test was used to evaluate the level of publication bias for the included studies. All statistical analyses were done by Stata11.0 software (StataCorp, College Station, TX, USA).

RESULTS

Study selection

The detail of study selection was shown in Figure 1. In total, 149 articles were selected, including 36 articles from PubMed, 68 articles from Embase, three articles from Cochrane library, 31 articles from CNKI and 11

articles from Wanfang. After removal of duplicates, 115 articles remained. There were 92 obviously irrelevant articles. A total of seven papers, including four meta-analyses, two without the genes of interest and one letter, were ruled out after reviewing the abstracts. After reviewing the full texts, a total of 11 articles were included in the study [15-17, 19, 22-28].

Study characteristics

As shown in Table 1, a total of 11 articles were included and analyzed. Two case-control trails were designed and included in the publication by Berndt et al. [22]; thus, there were 12 trials. A total of 8,136 subjects (3,836 cases and 4,300 controls) were included. The published studies ranged from 2006 to 2017, and included Asian (five studies), Caucasian (six studies) and mixed population (one study). Controls from hospital-based populations in all eligible studies were analyzed. Genotype data of case and control groups and HWE test results are shown in Table 1. The genotypes in the control group were all in line with the HWE requirements. As shown in Table 2, all 11 studies had quality scores of more than six points, suggesting that all individual studies were high enough quality for the meta-analysis.

Meta-analysis of the effect of APE1 Asp148Glu polymorphism on CRC risk

The results of heterogeneity were statistically insignificant in the additive model ($P < 0.05$, $I^2 = 73.5\%$); therefore, the random effects model was utilized to pool the data in the meta-analysis. The OR for the additive model was 1.14 [95%CI (1.00, 1.31), $P = 0.057$] (Figure 2A). This indicated that APE1Asp148Glu polymorphism was associated significantly with higher CRC risk in the additive model. Since the heterogeneity result was significant in the heterozygote comparison ($P < 0.05$, $I^2 = 80.7\%$), the pooled OR was 1.36 in the heterozygote comparison [95%CI (1.05, 1.75), $P = 0.019$] using the random effects model (Figure 2B). The heterozygote comparison showed a significant relationship between APE1 Asp148Glu and CRC risk. The heterogeneity test results of the homozygote comparison were significant ($P < 0.05$, $I^2 = 69.5\%$). Using the random effects model, the pooled OR was found to be 1.15 in the homozygote comparison [95%CI (0.88, 1.52), $P = 0.309$], which showed the absence of a significant difference (Figure 2C). Moreover, the dominant model shows a significant heterogeneity test ($P < 0.05$, $I^2 = 74.1\%$); thus, the random effects model was utilized to perform the meta-analysis. The OR of the dominant

FIGURE 1.
STUDY IDENTIFICATION AND SELECTION DIAGRAM.

TABLE 1.
CHARACTERISTICS OF THE INCLUDED STUDIES.

Study, year	Country	Diagnostic method	Genotyping method	Source of controls	Ethnicity	group	n	age (years)	M/F	Genotype frequency			HWE, P value
										TT	TG	GG	
Berndt, 2007 [21]	USA	Sigmoidoscopy examination	TaqMan	HB	Caucasian (A)	Case	720	63.2±5.2	534/233	175	364	153	-
						Control	725	62.0±5.2	535/238	204	335	171	0.1480
					Mixed (B)	Case	47	-	-	11	23	13	-
						Control	48	-	-	18	22	7	0.9476
Canbay, 2011 [22]	Turkey	Surgery	PCR-RFLP	HB	Caucasian	Case	79	60.22±10.60	51/28	28	43	8	-
						Control	247	59.73±8.64	130/117	151	63	33	0.1425
Dziki, 2017 [16]	Poland	Histopathologically confirmed	Real-time PCR	HB	Caucasian	Case	312	63±8	178/134	51	237	21	-
						Control	320	63±8	NR	88	158	55	0.2774
Jelonek, 2010 [23]	Poland	Hospital record	PCR-RFLP	HB	Caucasian	Case	153	age- and sex-matched		49	59	5	-
						Control	153			38	87	28	0.0787
Kasahara, 2008 [17]	Japan	Surgery	PCR-RFLP	HB	Asian	Case	68	67.3±10.9	37/26	23	41	4	-
						Control	121	67.4±6.7	74/47	70	41	10	0.2649
Lai, 2016 [15]	Taiwan	Hospital record	Real-time PCR	HB	Asian	Case	727	60.3±12.8	410/317	236	349	130	-
						Control	736	60.7±13.0	409/327	249	361	117	0.4670
Li, 2013 [24]	China	Surgery	PCR-RFLP	HB	Asian	Case	451	59.40±11.16	263/188	123	247	81	-
						Control	631	57.00±11.21	364/267	186	335	110	0.0518
Moreno, 2006 [25]	Spain	Hospital record	Arrayed primer extension	HB	Caucasian	Case	377	NR	225/152	95	177	87	-
						Control	329	NR	175/154	99	147	66	0.4061
Pardini, 2008 [26]	Czech	Colonoscopic results	TaqMan	HB	Caucasian	Case	532	58.5±10.5	294/238	140	261	130	-
						Control	532	57.4±12.8	294/238	157	267	106	0.6961
Ye, 2010 [27]	China	Histopathologically confirmed	MassARRAY	HB	Asian	Case	123	60.9±11.1	78/45	37	86		-
						Control	158	age- and sex-matched		52	106		>0.05*
Zhang, 2014 [28]	China	Pathologically confirmed	PCR-CTPP	HB	Asian	Case	247	59.22±14.54	145/102	87	90	70	-
						Control	300	56.96±15.84	175/125	122	137	41	0.7970

Abbreviations: HB, hospital-based; HWE, Hardy–Weinberg equilibrium; NR, not reported; PCR-CTPP, polymerase chain reaction with confronting two-pair primers; PCR-RFLP, polymerase chain reaction followed by restriction fragment length polymorphism.

*Lack of complete genotype frequency distribution information, $P>0.05$ was selected from individual study.

model was 1.31 [95%CI (1.07, 1.61), $P=0.010$], indicating that APE1Asp148Glu polymorphism contributed to increased risk in the dominant model. The heterogeneity test result of the recessive model was significant ($P<0.05$, $I^2=80.9\%$); thus, the OR of the recessive model was determined to be 0.97 [95%CI (0.71, 1.31), $P=0.826$] using the random effects model (Figure 2E), suggesting that there was no significant association for CRC risk in recessive model.

Subgroup analysis

The subgroup analysis was performed mainly from two patient characteristics: genotyping method and ethnicity. When grouped by the genotyping method, the results

showed that using the polymerase chain reaction with the confronting two-pair primer method (PCR-CTPP) significantly increased the association between Asp148Glu and CRC in the additive model [OR(95%CI) =1.52 (1.19, 1.93), $P=0.001$], and homozygote comparison [OR(95%CI)=2.39 (1.49, 3.84), $P<0.001$], and recessive model [OR (95%CI)=2.50 (1.62, 3.84, $P<0.001$] (Table 3). Whereas, no significant difference was found in heterozygote comparison [OR (95%CI)=0.92 (0.63, 1.35), $P=0.674$], and dominant model [OR (95%CI)=1.26 (0.89, 1.79), $P=0.193$]. Additionally, APE1Asp148Glu polymorphism was not significantly associated in the five models using TaqMan, PCR followed by restriction fragment length polymorphism (PCR-RFLP), and real-time PCR methods and arrayed primer exten-

TABLE 2.
QUALITY ASSESSMENT OF THE INCLUDED ARTICLES.

Author	Parameter assessed										Sum of quality assessment score
	Control group	Hardy-Weinberg equilibrium	Case group	Primer	Reproducibility	Blinding	Power calculation	Statistics	Corrected statistics	Independent replication	
Berndt, 2007 [21]	1	1	1	1	1	1	0	1	0	0	7
Canbay, 2011 [22]	1	1	1	1	1	0	0	1	0	0	6
Dziki, 2017 [16]	0	1	1	1	1	1	0	1	0	0	6
Jelonek, 2010 [23]	1	1	1	1	1	0	0	1	0	0	6
Kasahara, 2008 [17]	1	1	1	1	1	0	0	1	0	0	6
Lai, 2016 [15]	1	1	1	1	1	1	1	1	0	0	8
Li, 2013 [24]	1	1	1	1	1	0	0	1	0	0	6
Moreno, 2006 [25]	0	1	1	1	1	1	1	1	0	1	8
Pardini, 2008 [30]	1	1	1	1	1	0	1	1	0	0	7
Ye, 2010 [27]	1	1	1	1	1	0	0	1	0	0	6
Zhang, 2014 [28]	1	1	1	1	1	0	0	1	0	0	6

sion (APE) ($P>0.05$). With regard to ethnicity, no remarkably relationship was found between Asp148Glu and CRC among Asian, Caucasian or mixed populations in any of the five genetic models ($P>0.05$) (Table 3).

Sensitivity analysis

Sensitivity analysis is shown in Figure 3. When the study by Jelonek et al. [23] was removed, results were significantly altered for the additive model [OR (95%CI) = 1.18 (1.07, 1.31), $P=0.001$] and the homozygote comparison [OR (95%CI) = 1.27 (1.04, 1.55), $P=0.021$]. Similarly, the OR results ranged from 1.24 [95%CI (0.98, 1.56)] to 1.46 [95%CI (1.14, 1.87)] based on the heterozygote comparison, indicating unstable results. In contract, the OR results based on the dominant model were changed from 1.23 [95%CI (1.02, 1.49)] to 1.39 [95%CI (1.17, 1.65)], and the OR results in the recessive model ranged from 0.88 [95%CI (0.66, 1.16)] to 1.10 [95%CI (0.85, 1.43)], and both dominant model and recessive model were stable.

Publication bias

No significant effect of publication bias for enrolled studies in the meta-analysis was seen using Egger's test in the additive model ($P=0.431$), codominant model ($P=0.209$), homozygote comparison ($P=0.642$), dominant model ($P=0.247$) or recessive model ($P=0.429$).

DISCUSSION

When intracellular DNA is exposed to ultraviolet irradiation, oxidation and ionizing radiation, many reactive oxygen species attack the DNA and form an apurinic/

aprimidinic site, leading to DNA hydrolysis, oxidation and fracture [29]. Abnormal expression of the APE1 gene leads to defects in DNA damage repair, promoting gene mutation and increasing an individual's susceptibility to cancers, including lung [30], breast [31] or colon cancers [32]. A previous study showed APE1 148Glu showed finite changes in DNA repair capacity in comparison with wild-type genotypes [33]; however, more recent studies have shown contrasting results. Gdowicz-Klosok et al. showed that polymorphisms in APE1 affected both DNA repair activities and cell proliferation. The APE1 Asp148Glu polymorphism revealed an obviously elevated level of DNA incisions immediately after irradiation [34]. Functional studies by Berndt et al. suggested that, following exposure to ionizing radiation, the APE1 148Glu allele changed the ability of endonuclease and DNA binding, thereby reducing communication with other base excision repair proteins and increasing the mitotic delay [22]. Meta-analyses demonstrated that APE1 Asp148Glu DNA sequence variations attenuated the risk of lung cancer [35], but not affect the risk of prostate [36], bladder [37] or urinary cancers [38]. However, a previous meta-analysis showed that the role of APE1 Asp148Glu did not exert an effect on CRC risk [18].

The results in the present study indicated that the OR were 1.15 in the homozygote comparison [95%CI (0.88, 1.52), $P=0.309$], 1.36 in the heterozygote comparison [95%CI (1.05, 1.75), $P=0.019$] and 1.31 in the dominant model [95%CI (1.07, 1.61), $P=0.010$]. These results revealed that the APE1 TG genotype may be a potential risk factor for CRC. In a previous study, Au et al. found that in lymphocytes exposed to X-ray and ultraviolet light, APE1 polymorphisms of DNA repair with the TG

FIGURE 2.
FOREST PLOT OF THE POTENTIAL EFFECT ON COLORECTAL CANCER RISK FOR PATIENTS WITH APE1 ASP148GLU POLYMORPHISM.

A, additive model; B, heterozygote comparison; C, homozygote comparison; D, dominant model; E, recessive model. Abbreviation: CRC, colorectal cancer.

genotype induced more damage though comparing the chromosome aberrations [39]. The APE1 Asp148Glu (T>G) was found to be correlated with various tumors, with an OR value of 1.08, suggesting that the variant APE1 D148E was a tumor susceptibility gene

[40]. Dziki et al. indicated that the genotyping results for Asp/Glu of polymorphism of APE1 gene could increase the CRC risk (OR 2.588, $P < 0.0001$) [16]. De Ruyck et al. found APE1 Asp148Glu polymorphism showed a close correlation with lung cancer risk

TABLE 3.
SUBGROUP ANALYSIS.

Groups	N	OR (95%CI)	PA	I2 (%)	PH
Model: G vs. T					
Overall	11	1.14 (1.00, 1.31)	0.057	73.5	<0.001
Genotyping method					
TaqMan	3	1.13 (0.95, 1.35)	0.151	46.1	0.156
PCR-RFLP	4	1.09 (0.68, 1.76)	0.714	88.5	<0.001
Real-time PCR	2	1.06 (0.93, 1.20)	0.379	0.0	0.754
APE	1	1.18 (0.95, 1.47)	0.127	-	-
PCR-CTPP	1	1.52 (1.19, 1.93)	0.001	-	-
Ethnicity					
Caucasians	6	1.05 (0.85, 1.28)	0.665	79.8	<0.001
Asian	4	1.23 (1.01, 1.49)	0.039	68.0	0.025
Mixed	1	1.75 (0.98, 3.13)	0.058	-	-
Model: TG vs. TT					
Overall	11	1.36 (1.05, 1.75)	0.019	80.7	<0.001
Genotyping method					
TaqMan	3	1.21 (1.00, 1.45)	0.047	0.0	0.577
PCR-RFLP	4	1.57 (0.71, 3.46)	0.260	90.7	<0.001
Real-time PCR	2	1.60 (0.64, 3.99)	0.312	93.6	<0.001
APE	1	1.25 (0.88, 1.79)	0.212	-	-
PCR-CTPP	1	0.92 (0.63, 1.35)	0.674	-	-
Ethnicity					
Caucasians	6	1.42 (0.95, 2.14)	0.090	86.4	<0.001
Asian	4	1.21 (0.87, 1.68)	0.261	72.6	0.012
Mixed	1	1.71 (0.66, 4.43)	0.268	-	-
Model: GG vs. TT					
Overall	11	1.15 (0.88, 1.52)	0.309	69.5	<0.001
Genotyping method					
TaqMan	3	1.28 (0.90, 1.82)	0.170	47.5	0.149
PCR-RFLP	4	0.73 (0.30, 1.81)	0.497	79.3	0.002
Real-time PCR	2	0.94 (0.54, 1.62)	0.813	63.5	0.098
APE	1	1.37 (0.90, 2.10)	0.144	-	-
PCR-CTPP	1	2.39 (1.49, 3.84)	<0.001	-	-
Ethnicity					
Caucasians	6	0.91 (0.60, 1.39)	0.676	76.0	0.001
Asian	4	1.39 (0.96, 2.02)	0.078	60.0	0.058
Mixed	1	3.04 (0.93, 9.95)	0.066	-	-

Groups	N	OR (95%CI)	PA	I2 (%)	PH
Model: TG+GG vs. TT					
Overall	12	1.31 (1.07, 1.61)	0.010	74.1	<0.001
Genotyping method					
TaqMan	3	1.21 (1.02, 1.44)	0.033	0.0	0.510
PCR-RFLP	4	1.37 (0.64, 2.91)	0.415	90.6	<0.001
Real-time PCR	2	1.46 (0.75, 2.84)	0.268	88.8	0.003
APE	1	1.29 (0.92, 1.80)	0.134	-	-
PCR-CTPP	1	1.26 (0.89, 1.79)	0.193	-	-
MassARRAY	1	1.14 (0.69, 1.90)	0.613	-	-
Ethnicity					
Caucasians	6	1.30 (0.90, 1.86)	0.162	84.6	<0.001
Asian	5	1.23 (0.99, 1.54)	0.066	50.4	0.089
Mixed	1	2.03 (0.83, 4.97)	0.121	-	-
Model: GG vs. TG+TT					
Overall	11	0.97 (0.71, 1.31)	0.826	80.9	<0.001
Genotyping method					
TaqMan	3	1.15 (0.80, 1.67)	0.447	63.8	0.063
PCR-RFLP	4	0.62 (0.31, 1.25)	0.182	68.9	0.022
Real-time PCR	2	0.63 (0.18, 2.17)	0.463	92.4	<0.001
APE	1	1.19 (0.83, 1.71)	0.343	-	-
PCR-CTPP	1	2.50 (1.62, 3.84)	<0.001	-	-
Ethnicity					
Caucasians	6	0.72 (0.46, 1.12)	0.142	83.9	<0.001
Asian	5	1.31 (0.85, 2.02)	0.216	76.0	0.006
Mixed	1	2.18 (0.78, 6.10)	0.136	-	-

Abbreviations: A, P value for test of the association; APE, arrayed primer extension; CI, confidence interval; OR, odds ratio; PCR-CTPP, polymerase chain reaction with confronting two-pair primers; PCR-RFLP, polymerase chain reaction followed by restriction fragment length polymorphism; PH, P value for between-study heterogeneity; PN, number of studies

for the Asp/Glu genotype [41]. These results support our conclusions, in the current study, that APE1 Asp148Glu (T>G) facilitated the increase of CRC risk.

The SNP genotyping included the use of PCR-RFLP, PCR-CTPP, TaqMan and Sanger sequencing techniques [42]. In the stratified analysis of this study, PCR-CTPP showed a statistically increased cancer risk, while there were no differences for the other detection techniques. The PCR-CTPP technique only requires the design of two pairs of primers; thus, it is suitable for use in a standard laboratory. In comparison with the traditional PCR-RFLP, specific restriction endonuclease sites are not required in the PCR-CTPP genotyping assay, which makes it lower cost and

FIGURE 3.
SENSITIVITY ANALYSES FOR THE POTENTIAL EFFECT ON COLORECTAL CANCER RISK FOR PATIENTS WITH APE1 ASP148GLU POLYMORPHISM.

A, additive model; B, heterozygote comparison; C, homozygote comparison; D, dominant model; E, recessive model. Abbreviation: CRC, colorectal cancer.

less time-intensive [43]. The two fluorescent probes used in TaqMan make genotyping accurate and fast but result in higher labour and material costs [44]. Due to its simplicity and reliability, the PCR-CTPP assay has

been a popular technique for assessing SNP [45] and a newly designed PCR-CTPP has been shown to be both rapid and reliable for polymorphism detection in a clinic setting [46]. A previous study indicated that the accuracy

and sensitivity of the detection of gene polymorphism varied among the various analytical methods: PCR-RFLP; TaqMan and high-resolution DNA melting analysis [48]. Thus, PCR-CTPP SNP detection methods may serve an important function in the evaluation of the role of APE1 Asp148Glu polymorphism in CRC. In the present study, the differences in CRC risk determined with different SNP detected methods may be attributed to different detection principles.

A previous study by Zhou et al. reported that APE1 Asp148Glu polymorphism indicated a significant association risk for urinary cancers in an Asian population, while CRC risk in Caucasians and African Americans was not influenced by this SNP variation [38]. Kaur et al. demonstrated that APE1 may not be key factor for diseases in a population from north-west India [47]. In this study, subgroup analysis according to ethnicity showed no correlation between the SNP variation and cancer susceptibility based on Asian, Caucasian or mixed populations. This discrepancy may be explained by possible roles of ethnic and environmental differences. Thus, it is helpful for both early detection and future prevention of disease to understanding the genotype frequency of important functional gene polymorphisms within a specific ethnic group.

The OR significance for the additive and codominant models was reversed in the sensitivity analysis after removal of the study by Jelonek et al. [24]. In Jelonek's study, results of the genotype frequency distribution were detected in 113 of 153 patients (TT, n = 49; T/G, n = 59; GG, n = 5) [24]; this may have led to the heterogeneity in our study.

The impact of polymorphism in whole-genomic and DNA repair genes for CRC risk may prove useful for diagnosis or prevention and treatment of CRC patients. Cancers are multi-factor diseases, and models with gene-gene and gene-environment were recently used to predict tumor risk using high-throughput genotyping [49]. The roles of gene-gene and gene-environment in CRC carcinogenesis need to be investigated in the future. Furthermore, chemotherapeutic agents and/or targeted therapies could be useful for personalized treatment for polymorphism of DNA repair genes in CRC patients [5].

In this study, meta-analysis was used to systematically, objectively and comprehensively evaluate and quantitatively analyze the results of multiple studies, which improved the reliability of our results about the APE1 Asp148Glu polymorphism in increasing the risk of CRC. However, the meta-analysis had some limitations. First, significant heterogeneity was calculated when we analyzed the association between patients with APE1 Asp148Glu polymorphism and the risk of CRC. In addition, the number of subgroups included was small after strat-

ification, and more high-quality, large-sample studies would be required to verify the stability of the results. Second, due to lack of complete information on patients, such as gender and age, the effect of these potential confounders on the results could not be considered in this study.

In summary, this meta-analysis demonstrated that the APE1 Asp148Glu (T>G) may be a risk factor for tumorigenesis of CRC. However, there is still a need for well-designed, large-sample, multi-center clinical studies in the future to provide more reliable evidence.

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