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Associations between CDH1 gene polymorphisms and the risk of gastric cancer

A meta-analysis based on 44 studies

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Abstract

Background: Numerous studies have investigated the association between CDH1 polymorphisms and gastric cancer (GC) risk. However, the results have been inconsistent and controversial. To further determine whether CDH1 polymorphisms increase the risk of GC, we conducted a meta-analysis by pooling the data.

Methods: Relevant case-control studies were collected from PubMed, Embase, Web of Science and Cochrane databases up to January 7, 2024. Subsequently, odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the strength of correlations. A sensitivity analysis was performed to evaluate the robustness and reliability of these included studies.

Results: A total of 25 articles including 44 studies, were included in this meta-analysis, including 26 studies on rs16260, 6 studies on rs3743674, 7 studies on rs5030625, and 5 studies on rs1801552. The pooled results showed that rs16260 was remarkably associated with an increased GC risk of GC among Caucasians. Moreover, the rs5030625 variation dramatically enhanced GC predisposition in the Asian population. However, no evident correlations between CDH1 rs3743674 and rs1801552 polymorphisms and GC risk were observed.

Conclusions: Our findings suggested that CDH1 gene polymorphisms were significantly correlated with GC risk, especially in rs16260 and rs5030625 polymorphisms.

Abbreviations: CDH1 = E-cadherin, CI = confidence interval, GC = gastric cancer, NOS = Newcastle Ottawa Scale, OR = odds ratio, SNP = single nucleotide polymorphism.

Keywords: CDH1, GC, gene polymorphism, meta-analysis, susceptibility

1. Introduction

Gastric cancer (GC) is the fifth most common malignancy and third leading cause of cancer-related deaths worldwide. According to the global statistics, there were nearly 19.3 million new cancer cases and 10 million cancer deaths, and the mortality of GC accounts for 5.6% of overall incident cases.[1] In 2024, 26,890 new GC cases and 10,880 mortalities are projected to occur in the United States.[2] Over the past years, the morbidity and mortality of GC has prominently declined, but it remains an important global public health problem owing to its complex carcinogenesis and poor prognosis.[3,4] Although the explicit pathological mechanism of gastric carcinogenesis is still unclear, the incidence of GC depends on geographic particularities, differences between young and old patients and the fact that E-cadherin plays role in epithelial-mesenchymal transition.[5,6] GC is regarded as a complex and multi-factorial disease that roots in the interaction among environmental and genetic risk factors, including *Helicobacter pylori* (*H pylori*) infection, high-salt diet, cigarette smoking, and alcohol intake.[7–9] Genome-wide association studies have demonstrated strong correlations of multiple common single nucleotide polymorphisms (SNPs), and these SNPs have been reported to associate with

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

All analyses were based on previously published studies; thus, ethical approval was not required for this systematic review.

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individual GC risk, including miR-627, interleukin and DNA methyltransferase 1.[10–12] A small percentage of the population exposed to risk factors contributes to the occurrence and development of GC, suggesting that SNPs may play an essential role in the pathogenesis of GC.[13]

E-cadherin gene (CDH1) encodes an adhesion glycoprotein with a large extracellular domain composed of single transmembrane segment and short cytoplasmic domains and 5 repeat domains.[14] As a tumor suppressor, CDH1 is located on chromosome 16q22.1, which establishes and maintains epithelial intracellular adhesion, cell polarity and tissue architecture.[15–17] Meanwhile, cell adhesion plays a crucial role in the process of tumor invasion and metastasis.[18] Aberrant expression of CDH1 is widely recognized as a pivotal step in the occurrence of human epithelial cancers, including GC and breast cancer.[19] Increasing evidence has shown that lower expression of CDH1 gene may induce dysfunction of intercellular adhesion, resulting in invasive neoplasm development and metastasis in GC.[20] The downregulated expression of CDH1 in GC patients is negatively connected with the GC progression.[21,22] It has been proposed that lower E-cadherin expression could be a miserable prognostic marker for GC.[23] Therefore, loss of E-cadherin function during tumor progression could be partially attributable to SNPs of putative susceptibility alleles.[24]

Numerous studies have proved the associations between CDH1 polymorphisms and the risk of GC in humans.[25–27] The most widely studied sites are CDH1 rs16260 (–160C > A) and rs5030625 (–347G > GA) in the promoter region, which can decrease the transcription efficiency of the gene.[28,29] As for the rs16260 polymorphism, the A-allele shows low transcription factor binding affinity and reduces the transcriptional efficiency by approximately 68%, whereas the mutant may increase the risk of GC.[30] The rs5030625 GA-allele has been found to weaken the transcriptional activity of CDH1.[31] Compared to the G-allele, it brings about CDH1 downregulation and low expression of E-cadherin.[32,33] Other CDH1 gene polymorphisms, such as rs3743674 (+54T > C) and rs1801552 (2076C > T) are further investigated in different ethnicity, facilitating the identification of haplotypes correlated with GC risk.[34] Studies on individual genetic variants may be less powerful in detecting small genetic effects and fail to capture the joint contribution from multiple genetic variants. Therefore, we performed a meta-analysis to explore the relationship between 4 CDH1 gene polymorphisms (rs16260, rs5030625, rs3743674, and rs1801552) and the risk of GC.

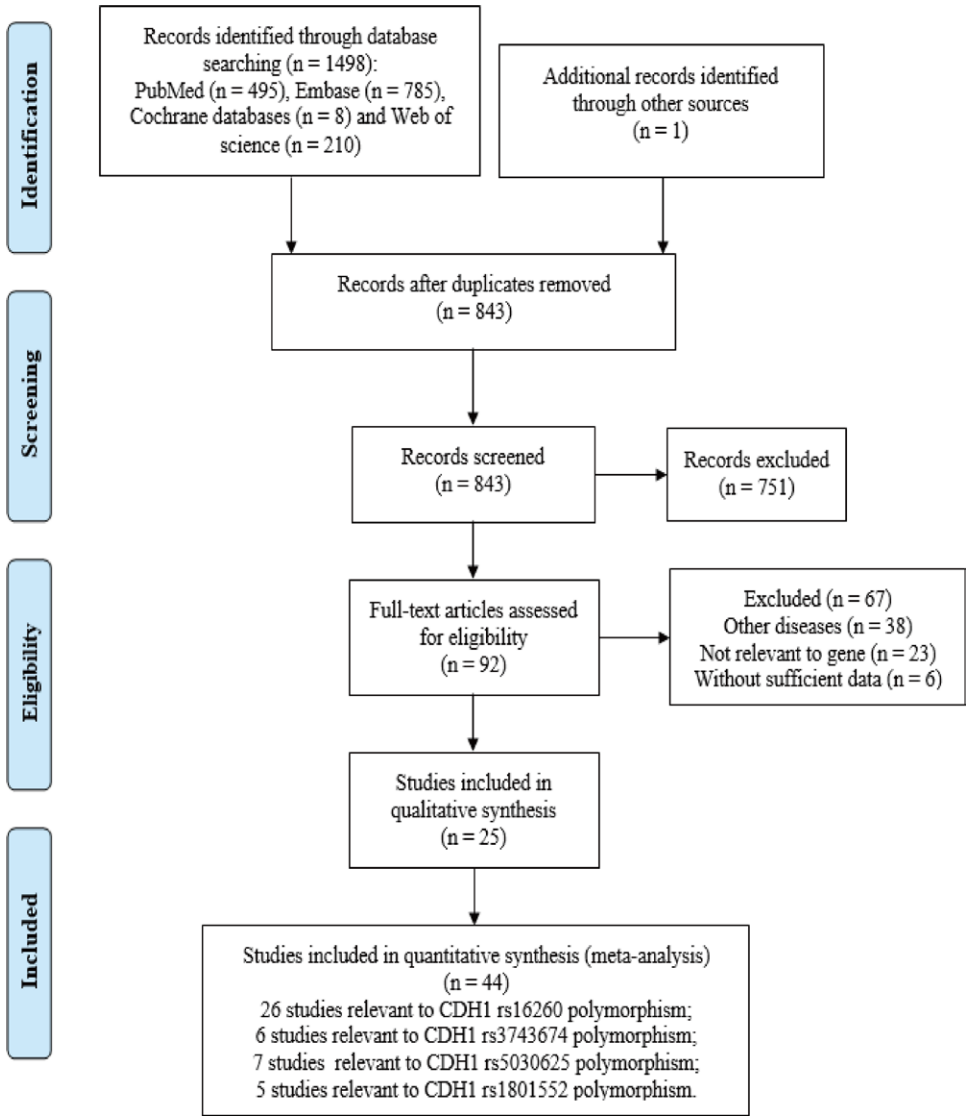

Figure 1. Flow diagram of the eligible study selection process.

2. Materials and methods

2.1. Search strategy

This meta-analysis was carried out according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[35] Relevant studies were extracted from the PubMed, Embase, Web of Science, and Cochrane databases up to January 7, 2024. The search strategy included the following keywords: "stomach neoplasm or gastric neoplasm or gastric cancer or gastric carcinoma" and "polymorphisms or SNP or genotype or variation or mutation" and "CDH1 or E-cadherin or cadherin-1." Simultaneously, we manually reviewed the relevant literature in the retrieved references.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: case-control study, evaluation of the relationship between CDH1 polymorphisms and GC susceptibility, clear description of GC diagnoses and the sources of cases, and sufficient information on genotype distribution of CDH1 polymorphisms for pooled analysis. The exclusion criteria were as follows: reviews, case reports, meta-analyses, letters, conference abstracts, and conference papers; no control; and no available data information provided.

2.3. Data extraction and quality assessment

Relevant data were extracted independently by 2 investigators (Q.J. and M.Y.) from the included articles, and any divergence could be resolved through discussion or a third analyst. The following information was collected from each included article: first author's surname, year, country, ethnicity, the number of subjects in the case and control groups, source of control, genotype detection methods, genotype frequencies, and Hardy–Weinberg equilibrium data.

The Newcastle Ottawa Scale (NOS) was adopted to assess the process in terms of queue selection (4 items, 0–4 stars), comparability of queues (1 item, 0–2 stars), and evaluation of results ascertaining of exposure or outcome (3 items, 0–3 stars).[36] Higher NOS scores showed higher literature quality, and the research with NOS scores of 6 or more was considered to be of high methodological quality.

2.4. False-positive report probability (FPRP) analysis

The probability of meaningful correlations of CDH1 gene polymorphisms and the risk of GC can be determined by conducting the FPRP analysis.[37] In order to explore the notable relationships observed in this meta-analysis, we adopted prior probabilities of 0.25, 0.1, 0.01, 0.001, and 0.0001 and computed the FPRP values as described previously. The association that reached the FPRP threshold of < 0.2 was considered significant.

2.5. Statistical analysis

The strength of the relationship between CDH1 polymorphisms and GC risk was evaluated by computing the crude odds ratios (ORs) with 95% confidence intervals (CIs).

Subsequently, we performed a heterogeneity test. Studies with P value < .05 or $I^2 \geq 50\%$ were considered to have obvious heterogeneity, and the random-effect model (REM) was applied for the analysis. Otherwise, a fixed-effect model (FEM) was used. Subgroup analyses were performed to determine the sources of heterogeneity. Furthermore, a sensitivity analysis was implemented to estimate the influence of each study on

Table 1

Characteristics of the included studies in our meta-analysis.

Author	Year	Ethnicity	Sample size case/control	Genotyping methods	Source of control	NOS	CDH1 polymorphisms
Wu MS[39]	2002	Asian	201/196	PCR-RFLP	HB	5	rs16260, rs1801552
Pharoach_C[40]	2002	Caucasian	148/93	PCR-RFLP	HB	6	rs16260
Pharoach_G[40]	2002	Caucasian	132/42	PCR-RFLP	HB	6	rs16260
Pharoach_P[40]	2002	Caucasian	153/331	PCR-RFLP	HB	6	rs16260
Humar B[41]	2002	Caucasian	53/70	PCR-RFLP	PB	8	rs16260, rs3743674
Kuraoka[42]	2003	Asian	106/90	PCR-SSCP	HB	6	rs16260
Park[43]	2003	Asian	292/146	PCR-SSCP	HB	5	rs16260
Shin Y[29]	2004	Asian	28/142	PCR-DHPLC	HB	7	rs16260, rs5030625
Lu Y[44]	2005	Asian	206/261	PCR-RFLP	PB	8	rs16260
Song CG[45]	2005	Asian	102/101	PCR-DHPLC	PB	8	rs16260
Cattaneo F[46]	2006	Caucasian	107/246	PCR-RFLP	PB	8	rs16260
Yamada H[47]	2007	Caucasian	148/292	PCR-RFLP	HB	7	rs16260, rs3743674, rs1801552
Medina F[48]	2007	Asian	39/78	PCR-SSCP	HB	6	rs16260
Zhang XF[33]	2008	Caucasian	239/343	PCR-RFLP	HB	8	rs16260, rs3743674, rs5030625
Jenab M[49]	2008	Caucasian	245/949	TaqMan	PB	9	rs16260
Zhang B[50]	2008	Caucasian	572/625	PCR-RFLP	HB	7	rs16260, rs3743674, rs5030625
Corso G[51]	2009	Asian	412/408	PCR-RFLP	PB	8	rs16260
Al-Moundhri[52]	2010	Caucasian	174/166	Sequencing	PB	7	rs16260, rs3743674
Borges N[53]	2010	Asian	58/51	Sequencing	HB	6	rs16260, rs5030625
Zhan Z[54]	2012	Caucasian	354/361	PCR-LDR	HB	7	rs16260
Menbari1[38]	2013	Asian	144/162	PCR-RFLP	HB	5	rs16260
Chu CM[55]	2014	Asian	107/134	Sequencing	HB	5	rs16260, rs3743674, rs1801552
Bustos C[56]	2016	Caucasian	45/48	Sequencing	HB	7	rs16260, rs5030625
Shekarriz[57]	2021	Caucasian	97/95	PCR-RFLP	HB	7	rs16260, rs5030625
Akcakaya[58]	2021	Caucasian	78/113	PCR-RFLP	HB	7	rs16260, rs5030625
Huang X[59]	2021	Asian	262/524	PCR-RFLP	PB	9	rs16260, rs1801552
Huang X[59]	2021	Asian	244/244	PCR-RFLP	HB	8	rs16260, rs1801552
Vishteh M[60]	2022	Caucasian	48/41	Sequencing	HB	5	rs16260

DHPLC = denaturing high performance liquid chromatography, HB = Hospital-based, HWE = Hardy-Weinberg equilibrium, LDR = ligation detection reaction, NOS = Newcastle-Ottawa Scale, PB = population-based, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphisms, SSCP = single-strand conformational polymorphism.

the overall results and prevent the existence of separate studies, leading to the reversal of the pooled results. Publication bias was assessed using the Begg's rank correlation test and Egger's linear regression test. *P* value < .05, indicating an obvious publication bias. All data analyses were conducted using Stata16.0 software (Stata Corp LP, College Station).

Table 2

Results of meta-analysis in CDH1 polymorphisms with risk of gastric cancer.

SNP	Model	OR (95% CI)	*P*	I^2 (%)	$P_{(H)}$	Effect model
CDH1 rs16260C/A	Allelic (A vs C)	1.08 (0.96, 1.21)	.192	61.1	.000	REM
	Homozygous (AA vs CC)	1.21 (0.92, 1.58)	.166	50.1	.002	REM
	Heterozygous (CA vs CC)	1.02 (0.89, 1.18)	.737	53.6	.001	REM
	Dominant (AA + CA vs CC)	1.06 (0.92, 1.22)	.450	58.9	.000	REM
	Recessive (AA vs CA + CC)	1.22 (0.95, 1.56)	.122	45.9	.006	REM
CDH1 rs3743674T/C	Allelic (C vs T)	1.13 (0.87, 1.45)	.364	73.1	.002	REM
	Homozygous (CC vs TT)	1.23 (0.62, 2.44)	.548	77.8	.000	REM
	Heterozygous (CT vs TT)	1.13 (0.82, 1.57)	.474	65.0	.014	REM
	Dominant (CC + CT vs TT)	1.15 (0.82, 1.62)	.430	71.0	.004	REM
	Recessive (CC vs CT + TT)	1.18 (0.70, 1.98)	.544	70.3	.005	REM
CDH1 rs5030625G/GA	Allelic (GA vs G)	1.05 (0.93, 1.19)	.418	6.7	.377	FEM
	Homozygous (GA/GA vs GG)	0.85 (0.62, 1.17)	.328	38.4	.136	FEM
	Heterozygous (G/GA vs GG)	1.23 (1.04, 1.44)	.013*	23.7	.247	FEM
	Dominant (GA/GA + G/GA vs GG)	1.16 (0.99, 1.35)	.062	0.0	.578	FEM
	Recessive (GA/GA vs G/GA + GG)	0.77 (0.57, 1.05)	.104	46.1	.084	FEM
CDH1 rs1801552C/T	Allelic (T vs C)	0.99 (0.86, 1.12)	.815	0.0	.377	FEM
	Homozygous (TT vs CC)	1.05 (0.80, 1.40)	.712	0.0	.720	FEM
	Heterozygous (CT vs CC)	0.87 (0.72, 1.06)	.157	0.0	.247	FEM
	Dominant (TT + CT vs CC)	0.91 (0.75, 1.09)	.299	0.0	.578	FEM
	Recessive (TT vs CT + CC)	1.14 (0.88, 1.47)	.324	0.0	.084	FEM

P: *P* value of Z test for statistical significance, P_H: *P* value of Q-test for heterogeneity test.

CDH1 = E-cadherin.

*$P < .05$.

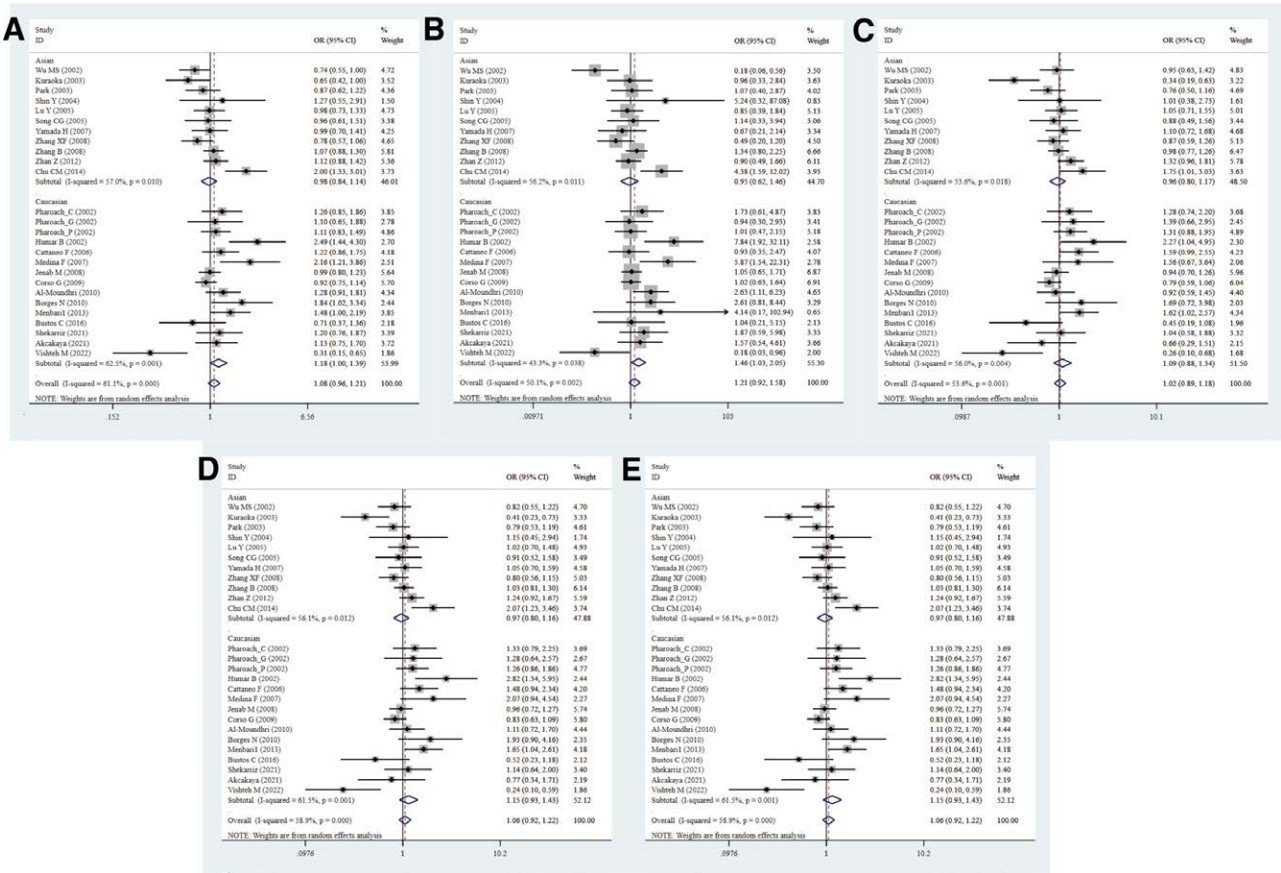

Figure 2. Association between CDH1 rs16260 gene polymorphism and GC risk in all 5 models. (A) Allele model; (B) dominant model; (C) heterozygote model; (D) homozygote model; (E) recessive model. CDH1 = E-cadherin, GC = gastric cancer.

Table 3

Stratified analyses of CDH1gene polymorphisms with the risk of gastric cancer.

		Allele		Homozygote		Heterozygote		Dominant		Recessive	
Locus	**No.**	**OR (95% CI) *P***	**I^2 (%)**	**OR (95% CI) *P***	**I^2 (%)**	**OR (95% CI) *P***	**I^2 (%)**	**OR (95% CI) *P***	**I^2 (%)**	**OR (95% CI) *P***	**I^2 (%)**
CDH1 rs16260C/A											
Caucasian	15	1.18 (0.99, 1.39) .056	62.5	1.46 (1.03, 2.05) .032*	43.3	1.09 (0.88, 1.34) .448	56.0	1.15 (0.93, 1.43) .208	61.5	1.43 (1.06, 1.93) .021*	34.0
Asian	11	0.98 (0.84, 1.14) .770	57.0	0.95 (0.62, 1.46) .816	56.2	0.97 (0.80, 1.17) .710	53.6	0.97 (0.80, 1.17) .719	56.1	0.98 (0.65, 1.48) .906	54.8
Source of control											
PB	6	1.14 (0.93, 1.40) .205	63.0	1.34 (0.84, 2.13) .221	57.5	1.06 (0.83, 1.36) .629	53.8	1.12 (0.87, 1.43) .377	59.1	1.29 (0.85, 1.96) .231	51.0
HB	20	1.05 (0.91, 1.22) .469	62.5	1.16 (0.82, 1.63) .408	50.5	1.00 (0.84, 1.20) .980	55.8	1.03 (0.86, 1.23) .770	60.9	1.18 (0.86, 1.63) .300	47.3
NOS scores											
N1	18	1.06 (0.92, 1.22) .436	56.1	1.20 (0.85, 1.69) .305	46.2	0.98 (0.82, 1.19) .859	55.8	1.02 (0.85, 1.22) .842	57.2	1.24 (0.89, 1.73) .197	46.3
N2	8	1.13 (0.91, 1.41) .258	72.6	1.24 (0.78, 1.98) .361	62.0	1.09 (0.87, 1.36) .468	54.6	1.13 (0.88, 1.45) .327	66.8	1.17 (0.95, 1.75) .434	51.3
Sample size											
S1	13	1.18 (0.90, 1.54) .239	72.4	1.82 (1.13, 2.93) .014*	45.3	0.96 (0.68, 1.36) .825	66.7	1.03 (0.92, 1.15) .624	27.1	1.88 (1.31, 2.70) .001*	17.1
S2	13	1.01 (0.92, 1.11) .795	26.2	0.96 (0.73, 1.25) .714	36.3	1.04 (0.92, 1.18) .550	32.3	1.07 (0.74, 1.53) .727	72.6	0.94 (0.72, 1.24) .681	41.4
Genotyping methods											
PCR-RFLP	14	1.07 (0.95, 1.21) .277	47.9	1.04 (0.74, 1.47) .820	47.7	1.09 (0.95, 1.26) .221	30.7	1.09 (0.94, 1.27) .236	40.3	1.03 (0.74, 1.43) .866	48.7
PCR-SSCP	3	1.03 (0.57, 1.87) .918	81.6	1.68 (0.60, 4.76) .327	60.8	0.72 (0.34, 1.49) .368	77.5	0.84 (0.39, 1.81) .652	81.5	1.91 (0.89, 4.14) .099	33.9
PCR-DHPLC	2	1.02 (0.69, 1.52) .909	0.0	1.46 (0.47, 4.55) .514	0.0	0.91 (0.55, 1.50) .714	0.0	0.96 (0.60, 1.55) .878	0.0	1.52 (0.50, 4.63) .465	0.0
TaqMan	1	0.99 (0.80, 1.23) .944	_	1.05 (0.65, 1.71) .836	_	0.94 (0.70, 1.26) .674	_	0.96 (0.72, 1.27) .770	_	1.09 (0.68, 1.73) .733	_
Sequencing	5	1.06 (0.61, 1.83) .828	83.2	1.68 (0.68, 4.19) .264	65.1	0.85 (0.45, 1.59) .609	75.4	0.94 (0.48, 1.85) .862	81.7	1.89 (0.95, 3.78) .072	43.3
	1	1.12 (0.88, 1.42) .375	_	0.90 (0.49, 1.66) .740	_	1.32 (0.96, 1.81) .083	_	1.24 (0.93, 1.67) .151	_	0.81 (0.45, 1.47) .122	_
CDH1 rs3743674T/C											
Ethnicity											
Caucasian	2	1.02 (0.62, 1.68) .946	28.3	1.17 (0.61, 2.23) .636	0.0	0.72 (0.40, 1.28) .258	0.0	0.84 (0.49, 1.44) .525	0.0	1.35 (0.87, 2.08) .177	0.0
Asian	4	1.16 (0.84, 1.62) .374	82.3	1.23 (0.48, 3.14) .672	86.6	1.27 (0.90, 1.80) .181	70.0	1.27 (0.85, 1.89) .247	79.1	1.09 (0.50, 2.36) .831	81.9
Source of control											
PB	2	1.02 (0.62, 1.68) .946	28.3	1.17 (0.61, 2.23) .636	0.0	0.72 (0.40, 1.28) .257	0.0	0.84 (0.49, 1.44) .525	0.0	1.35 (0.87, 2.08) .177	0.0
HB	4	1.16 (0.84, 1.62) .374	82.3	1.23 (0.48, 3.32) .672	86.6	1.27 (0.90, 1.80) .181	65.0	1.27 (0.82, 1.62) .247	79.1	1.09 (0.50, 2.36) .831	81.9
NOS scores											
N1	3	1.04 (0.90, 1.20) .626	0.0	0.90 (0.64, 1.28) .564	0.0	1.00 (0.71, 1.41) .985	52.1	1.07 (0.88, 1.29) .503	0.0	1.02 (0.61, 1.70) .948	62.9
N2	3	1.17 (0.65, 2.10) .610	77.0	1.59 (0.37, 6.90) .538	74.7	1.28 (0.67, 2.44) .462	67.6	1.26 (0.60, 2.65) .545	78.1	1.35 (0.43, 4.26) .607	61.8
Sample size											
S1	2	0.90 (0.60, 1.37) .629	0.0	0.66 (0.22, 2.02) .467	0.0	0.87 (0.34, 2.27) .779	55.3	0.90 (0.46, 1.74) .750	29.5	0.63 (0.21, 1.92) .420	0.0
S2	4	1.20 (0.89, 1.62) .233	81.5	1.39 (0.63, 3.09) .414	85.5	1.18 (0.80, 1.74) .408	74.2	1.24 (0.82, 1.88) .310	79.8	1.29 (0.72, 2.31) .394	79.9
Genotyping methods											
PCR-RFLP	4	1.13 (0.77, 1.65) .527	83.2	1.47 (0.54, 3.99) .452	85.3	1.15 (0.73, 1.79) .548	76.5	1.17 (0.72, 1.90) .518	81.9	1.29 (0.57, 2.90) .545	79.8
Sequencing	2	1.10 (0.85, 1.43) .485	0.0	0.99 (0.55, 1.77) .965	0.0	1.05 (0.68, 1.61) .842	0.0	1.05 (0.70, 1.58) .822	0.0	1.02 (0.45, 2.32) .964	48.6
CDH1 rs5030625G/GA											
Ethnicity											
Caucasian	4	0.97 (0.84, 1.12) .683	0.0	0.71 (0.49, 1.03) .070	9.4	1.16 (0.96, 1.40) .125	52.3	1.07 (0.89, 1.28) .467	0.0	0.65 (0.45, 0.93) .019*	40.1
Asian	3	1.30 (1.03, 1.64) .027*	0.0	1.48 (0.79, 2.78) .218	20.8	1.41 (1.04 1.90) .027*	0.0	1.42 (1.06, 1.89) .018*	0.0	1.31 (0.71, 2.43) .385	55.4
Source of control											
HB	7	1.05 (0.93, 1.19) .418	6.7	1.48 (0.79, 2.78) .328	38.4	1.23 (1.04, 1.44) .013*	23.7	1.16 (0.99, 1.35) .062	0.0	0.77 (0.57, 1.05) .104	46.1
NOS scores											
N1	6	1.01 (0.88, 1.16) .917	0.0	0.79 (0.56, 1.12) .179	40.5	1.19 (0.99, 1.43) .065	31.9	1.11 (0.93, 1.32) .246	0.0	0.72 (0.51, 1.01) .058	50.1
N2	1	1.23 (0.95, 1.61) .121	_	1.27 (0.59, 2.71) .539	_	1.37 (0.97, 1.93) .072	_	1.36 (0.98, 1.89) .071	_	1.10 (0.53, 2.32) .795	_
Sample size											
S1	5	0.99 (0.86,1.15) .937	0.0	0.75 (0.52, 1.07) .115	44.7	1.18 (0.98, 1.43) .074	45.4	1.10 (0.92, 1.31) .300	0.0	0.68 (0.48, 0.97) .034	54.1
S2	2	1.25 (0.98, 1.60) .078	0.0	1.33 (0.70, 2.56) .388	0.0	1.36 (0.98, 1.88) .063	0.0	1.36 (1.00, 1.85) .052	0.0	1.18 (0.63, 2.24) .607	0.0

(*Continued*)

Table 3

(*Continued*)

Locus	No.	Allele		Homozygote		Heterozygote		Dominant		Recessive	
		OR (95% CI) *P*	I^2 (%)	OR (95% CI) *P*	I^2 (%)	OR (95% CI) *P*	I^2 (%)	OR (95% CI) *P*	I^2 (%)	OR (95% CI) *P*	I^2 (%)
Genotyping methods											
PCR-RFLP	4	1.17 (0.95, 1.43) .134	0.0	0.99 (0.600, 1.64) .977	42.6	1.45 (1.11, 1.89) .007*	30.4	1.34 (1.04, 1.73) .022*	0.0	0.82 (0.50, 1.33) .417	59.2
PCR-DHPLC	1	1.90 (0.94, 3.85) .075	_	18.82 (0.74, 481.70) .076	_	1.82 (0.78, 4.26) .170	_	1.98 (0.86, 4.56) .108	_	15.55 (0.62, 391.63) .096	_
Sequencing	2	0.96 (0.82, 1.13) .630	0.0	0.73 (0.48, 1.11) .136	0.0	1.09 (0.88, 1.34) .441	0.0	1.03 (0.84, 1.25) .804	0.0	0.71 (0.47, 1.06) .092	0.0
CDH1 rs1801552C/T											
Ethnicity											
Caucasian	1	1.16 (0.68, 1.96) .590	_	1.33 (0.47, 3.80) .589	_	1.08 (0.44, 2.64) .869	_	1.16 (0.50, 2.68) .734	_	1.27 (0.53, 3.04) .590	_
Asian	4	0.97 (0.85, 1.11) .705	0.0	1.04 (0.77, 1.39) .816	0.0	0.86 (0.70, 1.05) .137	0.0	0.90 (0.74, 1.08) .254	0.0	1.13 (0.86, 1.47) .386	0.0
Source of control											
PB	1	1.16 (0.68, 1.96) .590	_	1.33 (0.47, 3.80) .589	_	1.08 (0.44, 2.64) .869	_	1.16 (0.50, 2.68) .734	_	1.27 (0.53, 3.04) .590	_
HB	4	0.97 (0.85, 1.11) .705	0.0	1.04 (0.77, 1.39) .816	0.0	0.86 (0.70, 1.05) .137	0.0	0.90 (0.74, 1.08) .254	0.0	1.13 (0.86, 1.47) .386	0.0
NOS scores											
N2	5	0.99 (0.86, 1.12) .815	0.0	1.05 (0.80, 1.40) .712	0.0	0.87 (0.72, 1.06) .157	0.0	0.91 (0.75, 1.09) .299	0.0	1.14 (0.88, 1.47) .324	0.0
Sample size											
S1	2	1.09 (0.80, 1.48) .593	0.0	1.32 (0.68, 2.56) .406	0.0	0.94 (0.59, 1.49) .781	0.0	1.01 (0.65, 1.57) .965	0.0	1.34 (0.74, 2.42) .331	0.0
S2	3	0.96 (0.83, 1.11) .611	0.0	1.00 (0.74, 1.37) .986	0.0	0.86 (0.69, 1.06) .152	0.0	0.89 (0.72, 1.09) .244	0.0	1.10 (0.82, 1.46) .532	0.0
Genotyping methods											
PCR-RFLP	4	0.98 (0.85, 1.12) .727	0.0	1.03 (0.76, 1.38) .684	0.0	0.87 (0.70, 1.07) .176	0.0	0.90 (0.74, 1.10) .293	0.0	1.11 (0.85, 1.46) .447	0.0
Sequencing	1	1.05 (0.72, 1.54) .786	_	1.32 (0.56, 3.08) .527	_	0.89 (0.52, 1.53) .670	_	0.96 (0.57, 1.61) .874	_	1.40 (0.63, 3.12) .410	_

CDH1 = E-cadherin, DHPLC = denaturing high performance liquid chromatography, HB = hospital-based, LDR = ligation detection reaction, N1 = quality score < 7, N2 = quality score ≥ 7, PB = Population-based, PB = Population-based, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphisms, S1 = sample size < 1000, S2 = sample size ≥ 1000, SSCP = single-strand conformational polymorphism

*$P < .05$.

Table 4

After excluding studies inconsistent with HWE, the associations between two CDH1 gene polymorphisms and GC risk under 5 genetic models.

SNP	Model	OR (95% CI)	*P*	I^2 (%)	$P_{(H)}$	Effect model
CDH1 rs16260C/A	Allelic (A vs C)	1.10 (0.98, 1.25)	.116	60.2	.000	REM
	Homozygous (AA vs CC)	1.26 (0.94, 1.68)	.129	53.8	.002	REM
	Heterozygous (CA vs CC)	1.06 (0.93, 1.21)	.379	41.0	.024	REM
	Dominant (AA + CA vs CC)	1.10 (0.95, 1.26)	.206	52.4	.002	REM
	Recessive (AA vs CC + CA)	1.21 (0.93, 1.58)	.164	47.4	.008	REM
CDH1 rs5030625G/GA	Allelic (GA vs G)	1.26 (1.02, 1.55)	.030	0.0	.756	FEM
	Homozygous (GA/GA vs GG)	1.52 (0.87, 2.67)	.144	0.0	.426	FEM
	Heterozygous (G/GA vs GG)	1.30 (1.00, 1.69)	.054	0.0	.809	FEM
	Dominant (GA/GA + G/GA vs GG)	1.33 (1.03, 1.71)	.029	0.0	.809	FEM
	Recessive (GA/GA vs G/GA + GG)	1.37 (0.79, 2.38)	.258	0.0	.424	FEM

P: *P* value of *Z* test for statistical significance, *P(H)*: *P* value of Q test for heterogeneity test.

CDH1 = E-cadherin, CI = confidence interval, GC = gastric cancer, HWE = Hardy-Weinberg equilibrium.

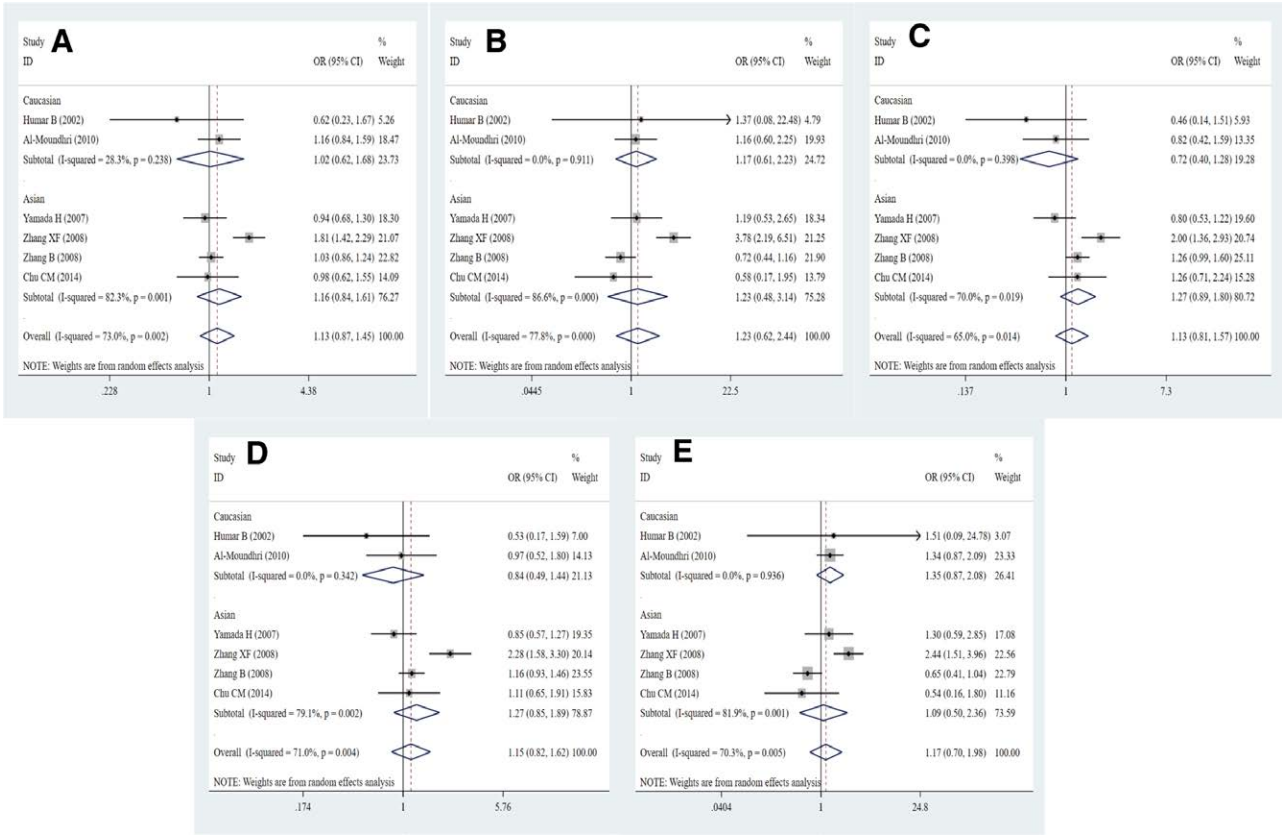

Figure 3. Association between CDH1 rs3743674 gene polymorphism and GC risk in all 5 models. (A) allele model; (B) dominant model; (C) heterozygote model; (D) homozygote model; (E) recessive model. CDH1 = E-cadherin, GC = gastric cancer.

3. Results

3.1. Literature search and screening

As shown in Figure 1, the literature search yielded 1499 initial articles through PubMed (n = 495), Embase (n = 785), Web of Science (n = 210), Cochrane databases (n = 8), and one additional record[38] was retrieved from other sources. After excluding 656 duplicate publications, 751 article were eliminated after carefully screening the abstract and title. Among these, 677 records were reviews, case reports, editorials, comments, conference abstracts, and meta-analyses, and 74 records discussed animal or in vitro experiments. After carefully reviewing the full text, 67 references were further excluded for the following reasons: 38 articles were not related to gastric cancer, 23 articles involved other genes or CDH1 SNPs, and 6 articles lacked available data. Finally, the remaining 25 eligible articles embodying 44 studies were enrolled in our study, including 26 studies on rs16260, 6 studies on rs3743674, 7 studies on rs5030625 and 5 studies on rs1801552, respectively.[29,33,38–60] Pharoah's study was conducted in 3 countries, Canada, Germany, and Portugal, so each group was separately presented for analyses.[40] The detailed characteristics and genotype distributions of the eligible studies among the 4 CDH1 sites are listed in Table 1 and Table S1, Supplemental Digital Content, http://links.lww.com/MD/M672.

3.2. Characteristics of the included studies

A total of 4787 GC cases and 6359 healthy controls were enrolled in our study. Fifteen studies focused on Caucasian populations and 13 on Asian populations. Moreover, the sources of the 8 control groups were based on the hospital, and those of the 20 control groups were based on the population. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used to examine CDH1 gene polymorphisms in 16 studies. Of the remaining studies, 5 involved the sequencing method, 3 used the polymerase chain reaction-single-strand conformational polymorphism (PCR-SSCP) method, 2 used the PCR-based denaturing high performance liquid chromatography (PCR-DHPLC) method, and 1 used the PCR-ligation detection reaction (PCR-LDR) method, respectively. Subgroup analyses were performed according to ethnicity, source of control, quality scores, sample size, and genotyping methods. The quality scores of the eligible publications ranged from 6 to 9, indicating that all included studies were of high quality (Table S2, Supplemental Digital Content, http://links.lww.com/MD/M673).

3.3. Meta-analysis of the CDH1 rs16260 and GC risk

A total of 26 studies with 4281 GC patients and 5591 controls were included to explore the association between CDH1 rs16260 polymorphism and the risk of GC. Overall, there was no significant association between rs16260 and GC risk in 5 genetic models (A vs C: OR = 1.08, 95% CI = 0.96–1.21, $P = .192$; AA vs CC: OR = 1.21, 95% CI = 0.92–1.58, $P = .166$; CA vs CC: OR = 1.02, 95% CI = 0.89–1.18, $P = .737$; AA + CA vs CC: OR = 1.06, 95% CI = 0.92–1.22, $P = .450$; AA vs CC + CA: OR = 1.22, 95% CI = 0.95–1.56, $P = .122$, Table 2; Fig. 2). The rs16260 mutation evidently increased the risk of GC among Caucasian (AA vs CC: OR = 1.46, 95% CI = 1.03–1.34, $P = .032$; AA vs CC + CA: OR = 1.43, 95% CI = 1.06–1.93, $P = .021$). Similarly, rs16260 was prominently associated with an enhanced risk of GC in

Figure 4. Association between CDH1 rs5030625 gene polymorphism and GC risk in all 5 models. (A) allele model; (B) dominant model; (C) heterozygote model; (D) homozygote model; (E) recessive model. CDH1 = E-cadherin, GC = gastric cancer.

subgroup of small sample size (AA vs CC: OR = 1.82, 95% CI = 1.13–2.93, *P* = .014; AA vs CC + CA: OR = 2.04, 95% CI = 1.47–2.84, *P* = .001). Stratification analyses by source of controls, quality scores and genotyping methods revealed no significant relationship between rs16260 and GC risk (Table 3). Heterogeneity dramatically existed in 5 genetic models, and results indicated that heterogeneity markedly decreased in subgroups of lager sample size and PCR-DHPLC genotyping method.

3.4. Meta-analysis of the CDH1 rs3743674 and GC risk

For the rs3743674 polymorphism, 6 studies with 1286 cases and 1620 controls met the inclusion criteria. The pooled results showed that the rs3743674 polymorphism was not remarkably implicated in GC susceptibility (C vs T: OR = 1.13, 95% CI = 0.87–1.45, *P* = .364; CC vs TT: OR = 1.23, 95% CI = 0.62–2.44, *P* = .548; CT vs TT: OR = 1.13, 95% CI = 0.82–1.57, *P* = .474; CC + CT vs TT: OR = 1.15, 95% CI = 0.82–1.62, *P* = .430; CC vs TT + CT: OR = 1.18, 95% CI = 0.70–1.98, *P* = .544, Table 2; Fig. 3). As shown in Table 3, subgroup analyses by ethnicity, source of control, quality scores, sample size and genotyping methods revealed no significant correlation between rs3743674 and GC risk. Interestingly, we found that heterogeneity observably diminished and disappeared in subgroups of Caucasian, PB, lower quality score, small sample size and sequencing method.

3.5. Meta-analysis of the CDH1 rs5030625 and GC risk

To determine the relationship between rs5030625 and GC risk, 7 studies with 1201 cases and 1612 controls were included in this meta-analysis. In the overall analysis, an evident association was identified in the heterozygous model (G/GA vs GG: OR = 1.23, 95% CI = 1.04–1.44, *P* = .013, Table 2). Moreover, the rs5030625 variation remarkably increased GC susceptibility in Asians (GA vs G: OR = 1.30, 95% CI = 1.03–1.64, *P* = .027; G/GA vs GG: OR = 1.41, 95% CI = 1.04–1.90, *P* = .027; GA/GA + G/GA vs GG: OR = 1.42, 95% CI = 1.06–1.89, *P* = .018), while the recessive model was notably related to a decreased risk of GC among Caucasians (GA/GA vs G/GA + GG: OR = 1.23, 95% CI = 1.04–1.44, *P* = .013, Table 3; Fig. 4), suggesting that ethnic differences in genetic backgrounds could affect CDH1 expression. In the stratified analysis by genotyping methods, a prominent correlation was observed in the PCR-RFLP subgroup (G/GA vs GG: OR = 1.45, 95% CI = 1.11–1.89, *P* = .007; GA/GA + G/GA vs GG: OR = 1.34, 95% CI = 1.04–1.73, *P* = .022). No statistically significant findings were detected in either the sample size or quality scores subgroup. The heterogeneity results indicated that there was no heterogeneity among the 5 gene models.

3.6. Meta-analysis of the CDH1 rs1801552 and GC risk

Five eligible studies with 807 patients and 1263 controls were included in this meta-analysis to determine the association between the CDH1 rs1801552 SNP and GC risk. The pooled analyses disclosed no distinct relationship between the rs1801552 and GC risk (T vs C: OR = 0.99, 95% CI = 0.86-1.12, *P* = .815; TT vs CC: OR = 1.05, 95% CI = 0.80-1.40, *P* = .712; CT vs CC: OR = 0.87, 95% CI = 0.72-1.06, *P* = .157; TT + CT vs CC: OR = 0.91, 95% CI = 0.75-1.09, *P* = .299; TT vs CT + CC: OR = 1.14, 95% CI = 0.88-1.47, *P* = .324; Table 2; Fig. 5). Further subgroup analysis by ethnicity, source of control, quality scores, sample size and genotyping method indicated no significant association (Table 3). The results of the

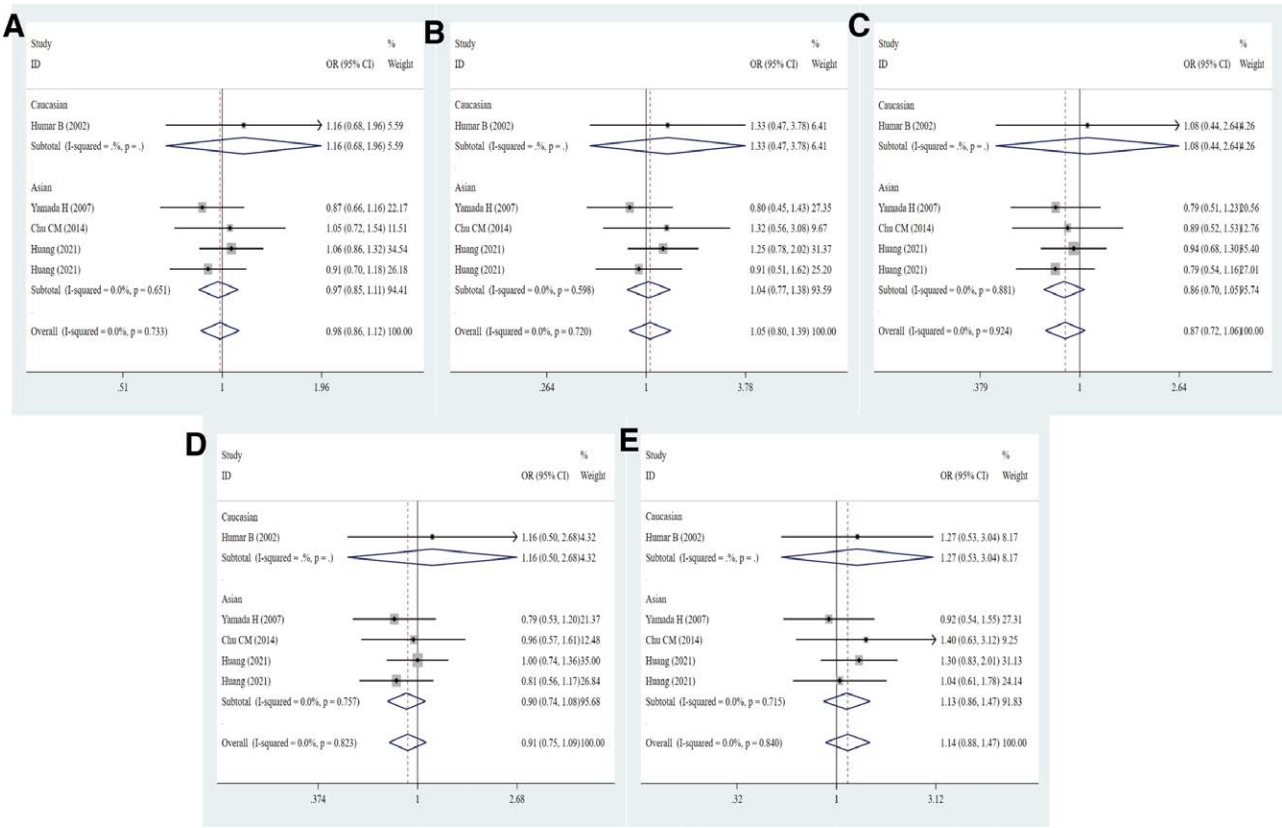

Figure 5. Association between CDH1 rs1801552 gene polymorphism and GC risk in all 5 models. (A) allele model; (B) dominant model; (C) heterozygote model; (D) homozygote model; (E) recessive model. CDH1 = E-cadherin, GC = gastric cancer.

heterogeneity test showed no significant heterogeneity in all 5 gene models; therefore, a fixed-effects model was used to examine the correlation.

3.7. Sensitivity analysis and publication bias

A sensitivity analysis was conducted by eliminating each individual study. As shown in Figure 6, the pooled OR and 95% CI did not materially change, indicating that our results were relatively robust. After removing some studies that did not comply with Hardy–Weinberg equilibrium, the heterogeneity did not dramatically change in rs16260 (A vs C: $I^2 = 60.2$, $P_{(heterogeneity)} = .000$; AA vs CC: $I^2 = 53.8$, $P_{(heterogeneity)} = .002$; CA vs CC: $I^2 = 41.0$, $P_{(heterogeneity)} = .024$; AA + CA vs CC: $I^2 = 52.4$, $P_{(heterogeneity)} = .002$; AA vs CC + CA: $I^2 = 47.4$, $P_{(heterogeneity)} = .008$). Regarding the rs5030625 polymorphism, there was no significant change in heterogeneity (GA vs G: $I^2 = 0.0$, $P_{(heterogeneity)} = .756$; GA/GA vs GG: $I^2 = 0.0$, $P_{(heterogeneity)} = .426$; G/GA vs GG: $I^2 = 0.0$, $P_{(heterogeneity)} = .809$; GA/GA + G/GA vs GG: $I^2 = 0.0$, $P_{(heterogeneity)} = .809$; GA/GA vs G/GA + GG: $I^2 = 0.0$, $P_{(heterogeneity)} = .424$; Table 4). Begg's rank correlation test and Egger's linear regression test were used to assess potential publication bias, and no publication bias was observed (Table 5; Fig. 7).

3.8. FPRP results

We investigated determinants of FPRP across a range of probabilities to determine whether a given relationship between CDH1 polymorphisms and GC risk is deserving of attention or is noteworthy. In this respect, our main results were further supported by the FPRP analysis. As shown in Table 6, with a prior probability < 0.25, CDH1 rs5030625 polymorphism was associated with the risk of GC in the heterozygote and dominant models ($P < .2$).

4. Discussion

Recently, the cancer diagnosis and treatment have significantly improved, but the exact mechanism of gastric tumorigenesis remains unknown.[3] There is convincing data that single nucleotide polymorphisms (SNPs) can predict the cancer risk and prognosis.[13,61] As a vital tumor invasion suppressor, CDH1 plays an essential role in maintaining cell adhesion and normal tissue morphology.[15–17] Abnormal expression of CDH1 is closely associated with a variety of epithelial tumors, including gastric cancer (GC), and further promotes cancer invasion and metastasis.[19] Given the contradictory and inconsistent results of previous studies, we performed a more accurate and strict screening criteria to estimate the associations between the 4 common CDH1 SNPs (rs16260, rs3743674, rs5030625, and rs1801026) and GC risk. Of these, 2 gene polymorphisms are located in the promoter region at positions −160 and −347 from the transcription start site, whereas the CDH1 promoter region can have a profound influence on transcriptional efficiency.[20,34] The putative susceptibility allele can reduce the activity and increase the risk of tumor progression, invasion and metastasis.[61]

An increasing number of studies have examined the relationship between CDH1 rs16260 polymorphism and risk of GC. For example, Wu et al first reported that carriers with the variant AA genotype in GC cases were significantly lower than that of controls.[39] In 2007, a study conducted by Medina-Franco demonstrated an increased risk of GC based on the expression of the rs16260 AA genotype.[48] In contrast, Corso et al found that the rs16260 polymorphism was not significantly associated with GC risk in the Italian population.[51] Compared with the C-allele, the transcriptional efficiency of the A-allele has been reported to decrease by 68%, implying that the variant may increase the risk of tumor invasion and metastasis.[30]

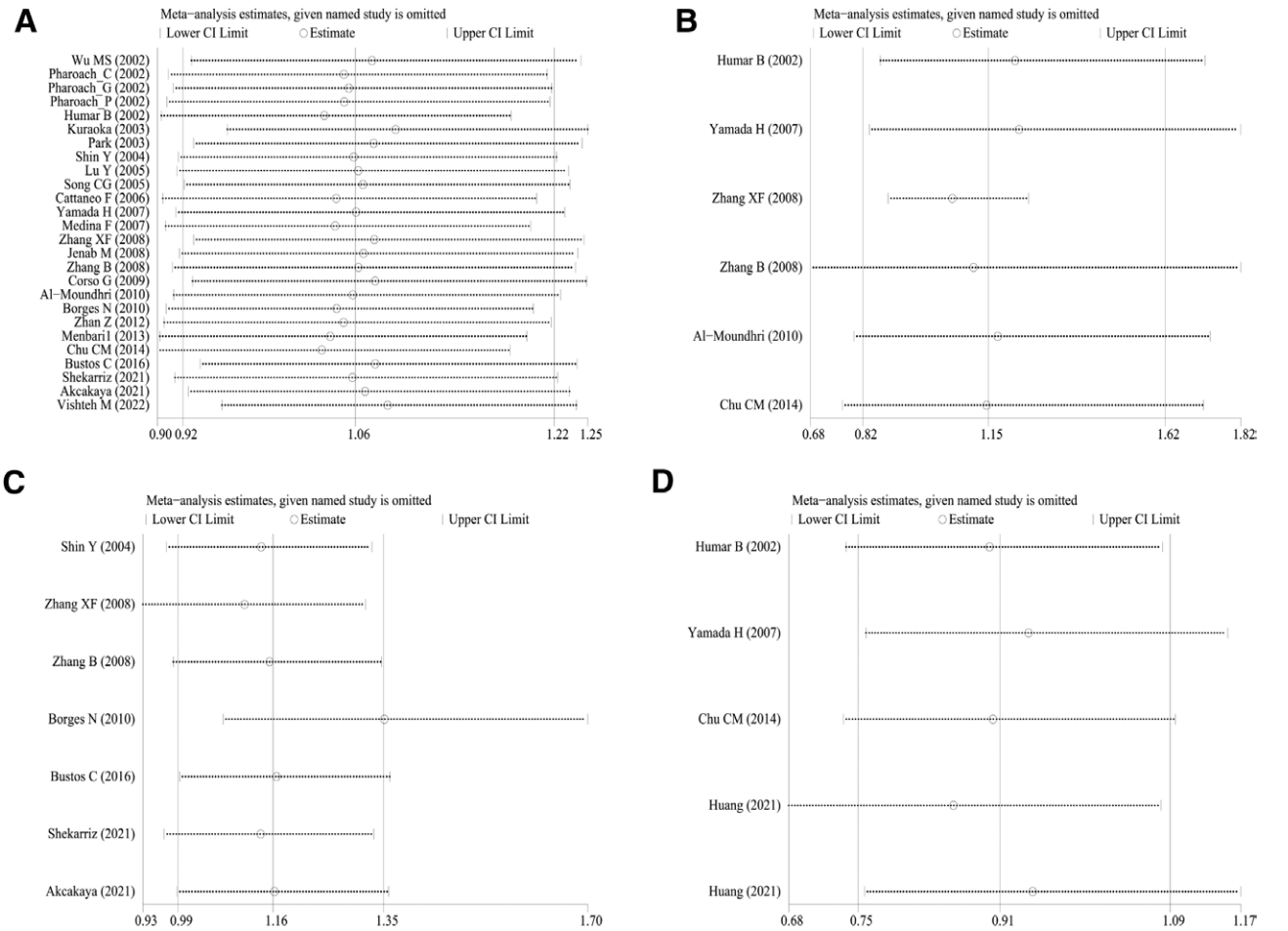

Figure 6. Sensitivity analysis through deletion of one study at a time to reflect the influence of the individual dataset to the pooled ORs in CDH1 gene polymorphisms under the dominant model. (A) the rs16260 polymorphism; (B) the rs3743674 polymorphism; (C) the rs5030625 polymorphism; (D) the rs1801552 polymorphism. CDH1 = E-cadherin, OR = odds ratio.

Table 5

Publication bias of various models for the CDH1 gene polymorphisms.

	Allelic		Homozygous		Heterozygous		Dominant		Recessive	
Variables	P_B	P_E	P_B	P_E	P_B	P_E	P_B	P_E	P_B	P_E
CDH1 rs16260C/A	.252	.340	.481	.512	.217	.347	.234	.349	.508	.524
CDH1 rs3743674T/C	.707	.775	.707	.978	1.000	.494	1.000	.482	1.000	.794
CDH1 rs5030625G/GA	.368	.172	1.000	.240	1.000	.172	.764	.164	1.000	.244
CDH1 rs1801552C/T	.806	.861	1.000	.745	.806	.930	.806	.916	.100	.695

P_B: *P* value of Begg's rank correlation test. P_E: *P* value of Egger's linear regression test.

As for the rs16260 polymorphism, there was no significant association with overall GC risk. When stratified by ethnicity, the rs16260 polymorphism was notably associated with an increased risk of GC among Caucasians, but not among Asians. Consistent with previous findings, the results showed that different genetic backgrounds and environmental exposure may contribute to tumorigenesis and cancer progression.[61] Similarly, a significant association was observed between rs16260 and GC risk in subgroup of small sample size. It is well known that other carcinogenesis factors, such as *H pylori* infection, high-salt diet, cigarette smoking, and alcohol intake, have been extensively studied in the GC development. For example, one study[49] displayed a detailed distribution of CDH1 genotypes according to smoking status, as well as one study[55] on *H pylori* infection. Given the lack of raw data on specific risk factors in most studies, certain variables for the distribution of genotypes needed to be investigated in the future.

Previous studies provided evidence that the rs3743674 C-allele (C/C or C/T) significantly increased the risk of developing GC.[33] In overall analysis, no significant association of the rs3743674 SNP and risk of GC was found. Similarly, there was no remarkable relationship between rs3743674 and GC risk in terms of sample size, source of controls, quality scores and genotyping methods. In addition, we found no significant relationship between rs1801552 and GC susceptibility. Consistent with our results, the rs5030625 was positively associated with GC risk. The rs5030625 variation notably enhanced GC risk

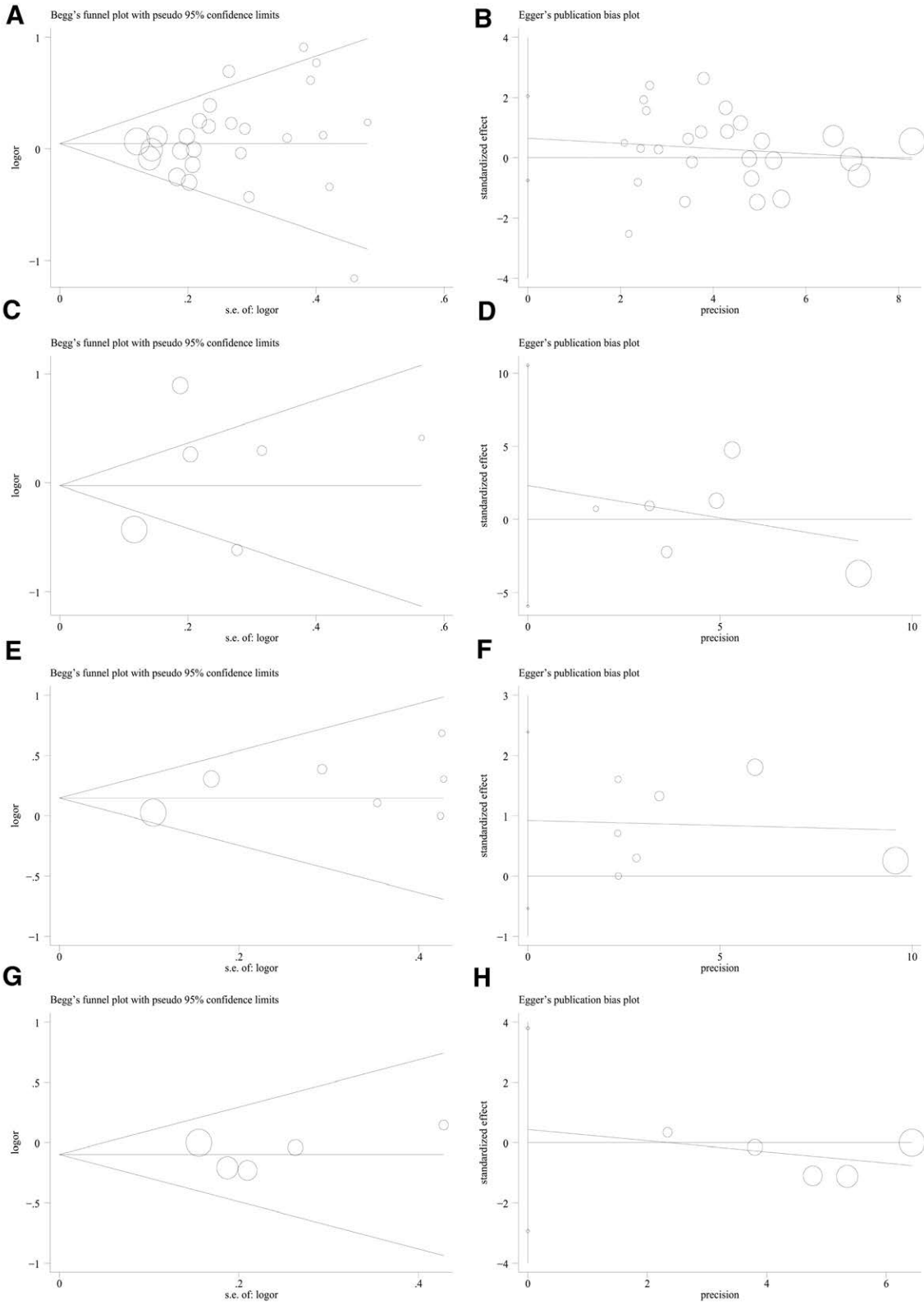

Figure 7. Begg's funnel plot and Egger's linear regression plot for detecting the publication bias through the dominant model. (A) Begg's test for rs16260 polymorphism; (B) Egger's test for rs16260 polymorphism; (C) Begg's test for rs3743674 polymorphism; (D) Egger's test for rs3743674 polymorphism; (E) Begg's test for rs5030625 polymorphism; (F) Egger's test for rs5030625 polymorphism; (G) Begg's test for rs1801552 polymorphism; (H) Egger's test for rs1801552 polymorphism.

among Asians, indicating that the GA allele variant may be a hazard factor in the Asian population. The possible mechanism is that the –347GA allele could rarely disrupt the –347G-protein binding, and then decrease the CDH1 transcriptional activity, eventually leading to downregulation of CDH1 and low expression of E-cadherin.[29,32]

Table 6

False-positive report probability analysis of the noteworthy results.

SNP	Genetic model	OR (95% CI)	*P*	Power	Prior probability				
					0.25	0.1	0.01	0.001	0.0001
CDH1 rs16260C/A	Allele	1.08 (0.96, 1.21)	.184	1.000	0.356	0.624	0.948	0.995	0.999
	Homozygote	1.21 (0.92, 1.58)	.161	1.000	0.326	0.592	0.941	0.994	0.999
	Heterozygote	1.02 (0.89, 1.18)	.790	1.000	0.703	0.877	0.987	0.999	1.000
	Dominant	1.06 (0.92, 1.22)	.417	1.000	0.555	0.789	0.976	0.998	1.000
	Recessive	1.22 (0.95, 1.56)	.113	1.000	0.253	0.504	0.918	0.991	0.999
CDH1 rs3743674T/C	Allele	1.13 (0.87, 1.45)	.337	1.000	0.503	0.752	0.971	0.997	1.000
	Homozygote	1.23 (0.62, 2.44)	.554	1.000	0.644	0.844	0.984	0.998	1.000
	Heterozygote	1.13 (0.82, 1.57)	.466	1.000	0.583	0.808	0.979	0.998	1.000
	Dominant	1.15 (0.82, 1.62)	.424	1.000	0.560	0.793	0.977	0.998	1.000
	Recessive	1.18 (0.70, 1.98)	.531	0.977	0.620	0.830	0.982	0.998	1.000
CDH1 rs5030625G/GA	Allele	1.05 (0.93, 1.19)	.445	1.000	0.572	0.800	0.978	0.998	1.000
	Homozygote	0.85 (0.62, 1.17)	.319	0.999	0.489	0.742	0.969	0.997	1.000
	Heterozygote	1.23 (1.04, 1.44)	.001	1.000	0.029*	0.083*	0.499	0.909	0.990
	Dominant	1.16 (0.99, 1.35)	.055	1.000	0.142*	0.332	0.845	0.982	0.998
	Recessive	0.77 (0.57, 1.05)	.099	0.997	0.229	0.471	0.907	0.990	0.999
CDH1 rs1801552C/T	Allele	0.99 (0.86, 1.12)	.873	1.000	0.724	0.887	0.989	0.999	1.000
	Homozygote	1.05 (0.80, 1.40)	.740	1.000	0.689	0.869	0.987	0.999	1.000
	Heterozygote	0.87 (0.72, 1.06)	.167	1.000	0.334	0.601	0.943	0.994	0.999
	Dominant	0.91 (0.75, 1.09)	.306	1.000	0.478	0.733	0.968	0.997	1.000
	Recessive	1.14 (0.88, 1.47)	.312	1.000	0.484	0.738	0.969	0.997	1.000

CDH1 = E-cadherin.

*$P < .2$.

The present meta-analysis had several limitations. First, the sample size of the included studies was relatively small, and lacked sufficient statistical capacity to explore the real association. Second, owing to insufficient data on environmental factors and lifestyle habits such as alcohol consumption, smoking status, and *H pylori* infection, we failed to analyze these potential correlative factors. Third, these studies were limited to Asians and Caucasians; however, it is unclear whether the results can be applied to other populations. Despite these shortcomings, the present meta-analysis had several advantages. The search strategy was more complete to avoid omitting included studies. Moreover, the quality of the included studies was better, based on the NOS score. Simultaneously, we emphasized the identification of potential sources of heterogeneity through subgroup analysis and sensitivity analysis and comprehensively evaluated publication bias using Begg's rank correlation test and Egger's linear regression test.

In conclusion, the rs16260 mutation was positively associated with GC risk in Caucasians. Moreover, the rs5030625 polymorphism remarkably elevated the risk of GC in the overall analysis and the Asian subgroup. Therefore, large-scale studies in different ethnic groups are needed to elucidate the exact function of CDH1 gene polymorphisms in predisposition to GC.

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