

Association between cadherin-17 expression and pathological characteristics of gastric cancer: A meta-analysis

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Abstract

AIM: To construct a meta-analysis in order to examine the relationship between cadherin-17 (CDH17) and

gastric cancer (GC).

METHODS: Related articles were selected by searching the following English or Chinese electronic databases: CINAHL, MEDLINE, Science Citation Index, the Chinese Journal Full-Text, and the Weipu Journal. Newcastle-Ottawa Scale (NOS) criteria were used to ensure consistency in reviewing and reporting results. Statistical analyses were conducted with Version 12.0 STATA statistical software.

RESULTS: Ultimately, 11 articles, with a total of 2,120 GC patients, were found to be eligible for study inclusion. In comparisons of GC patients by TNM stage (III-IV vs I-II: OR = 2.35, 95%CI: 1.15-4.825, $P = 0.019$), histologic grade (3-4 vs 1-2: OR = 3.48, 95%CI: 1.36-8.92, $P = 0.009$), invasion grade (T3-4 vs T1-2: OR = 2.86; 95%CI: 1.69-4.83; $P = 0.000$), and lymph node metastasis (positive vs negative: OR = 2.64; 95%CI: 1.33-5.27; $P = 0.006$), it was found that CDH17 showed more positive expressions in each of the more severe cases. Country-stratified analyses from all four experimental subgroups showed that high CDH17 expression levels may be related to GC among Chinese and Korean populations (all $P < 0.05$), with the exception of the invasion grade T3-4 vs T1-2 comparison, where the relation only held among the Chinese population (OR = 2.86, 95%CI: 1.69-4.83, $P = 0.000$).

CONCLUSION: Collectively, the data reflects the capacity of CDH17 in tumor proliferation and metastasis among GC patients.

Key words: Cadherin 17; Protein expression; Gastric cancer; Meta-analysis

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Core tip: This meta-analysis conducted in order to examine the relationship between cadherin-17 (CDH17) and gastric cancer (GC), with the data reflecting the capacity of CDH17 in tumor proliferation and metastasis in GC patients.

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INTRODUCTION

Gastric cancer (GC) is a malignant disease arising from gastric tissue. More than 90% of GCs are adenocarcinomas, with the remainder being lymphomas or emerging from gastrointestinal stromal tissue (sarcomas)^[1]. GC is the fourth most common cancer in the world and the second leading cause of cancer-related death globally^[2]. Although the last decade has witnessed a dramatic decrease in the prevalence of GC in some developed countries, approximately one million newly diagnosed cases, along with 800000 GC-related deaths, occur each year worldwide^[3]. In fact, it has been reported that two-thirds of GC cases occur in developing countries, with particularly high incidences in areas such as Japan, China, Central America, and South America^[4]. Generally, gastric carcinogenesis is a multifactorial process involving the participation of both environmental and epigenetic factors^[1,5]. A variety of factors that are related to the occurrence and progression of GC have been confirmed, including *Helicobacter pylori* infection, low fruit intake, consumption of foods high in salt, smoking, and consumption of preserved foods and nitrites^[4,6,7]. Recently, adhesion molecules such as cadherin-17 (CDH17), which is reported to be implicated in tumor invasion and metastasis, have been shown to be correlated with GC pathogenesis^[8].

CDH17, also known as liver-intestine cadherin or human peptide transporter-1, consists of seven homologous repeated domains, and while it belongs to the cadherin superfamily responsible for intercellular junction, its structure is distinct from that of classic cadherin family members^[9]. CDH17 possesses the ability to modulate Ca²⁺-dependent homophilic cell-cell adhesion without depending on cytoskeleton interaction, suggesting that it may play a central role in tumor metastasis^[10,11]. In addition, CDH17 has been shown to both act as a peptide transporter and participate in the development of the embryonic gastrointestinal tract^[12]. In recent studies, CDH17 expression was observed to be upregulated in GC patients, implying that CDH17 expression is related to

GC development^[5,9]. In general, CDH17 is expressed on the basolateral surface of enterocytes and goblet cells in the small and large intestines in a selective manner, and is seldom detected in the healthy adult stomach or liver^[10,13]. Cadherins, including CDH17, are single-pass transmembrane proteins that function mainly in cell-cell adhesion and may be implicated in tumorigenesis^[14]. It has been reported that CDH17 knockdown may result in the inactivation of Wnt signaling, which could in turn inhibit the activity of cancer cell invasion^[12]. More importantly, there is evidence indicating that loss of CDH17 may lead to an increased expression of placental growth factor and metal-responsive transcription factor-1, which is believed to increase tumor aggression, thus modulating angiogenesis in human carcinoma^[15]. Additionally, by activating the NFκB signaling pathway, CDH17 can also induce lymph node (LN) metastasis, as well as the formation of tumors in GC^[16]. With this in mind, it is possible that CDH17 expression may be involved in the pathogenesis and progression of GC. Several clinical studies have documented that high expression levels of CDH17 were positively connected with histological stage, tumor invasion, and LN metastasis of GC, revealing that CDH17 expression might be a valuable indicator for predicting the progression and prognosis of GC^[8,17]. However, other researchers have failed to find evidence to support the correlation of CDH17 expression with pathological characteristics of GC^[5,9]. With such an inconsistency in previous reported findings in mind, we performed the current meta-analysis with the available data in order to clarify the connection between CDH17 expression and the pathological features of GC.

MATERIALS AND METHODS

Literature search

The following computerized bibliographic databases were reviewed, without restrictions with respect to language or data collection, to identify relevant articles relating to the association of CDH17 expression and GC susceptibility: PubMed, Embase, CINAHL, Science Citation Index, the Cochrane Library, Current Contents Index, Chinese Biomedical, the Chinese Journal Full-Text, and the Weipu Journal. The search terms "stomach neoplasms" or "gastric cancer" or "stomach cancer" or "gastric neoplasms" or "gastric carcinomas" or "stomach carcinomas" or "carcinoma ventriculi" or "stomach neoplasms" and "CDH17 protein, human" or "CDH17" or "liver-intestine-cadherin" or "cadherin-17" were entered in the databases searches as medical subject heading terms and text words, within a highly sensitive search strategy. Manual searches were used to screen other eligible studies.

Study selection

After reading the abstract, full texts were retrieved and assessed for their suitability based on the following

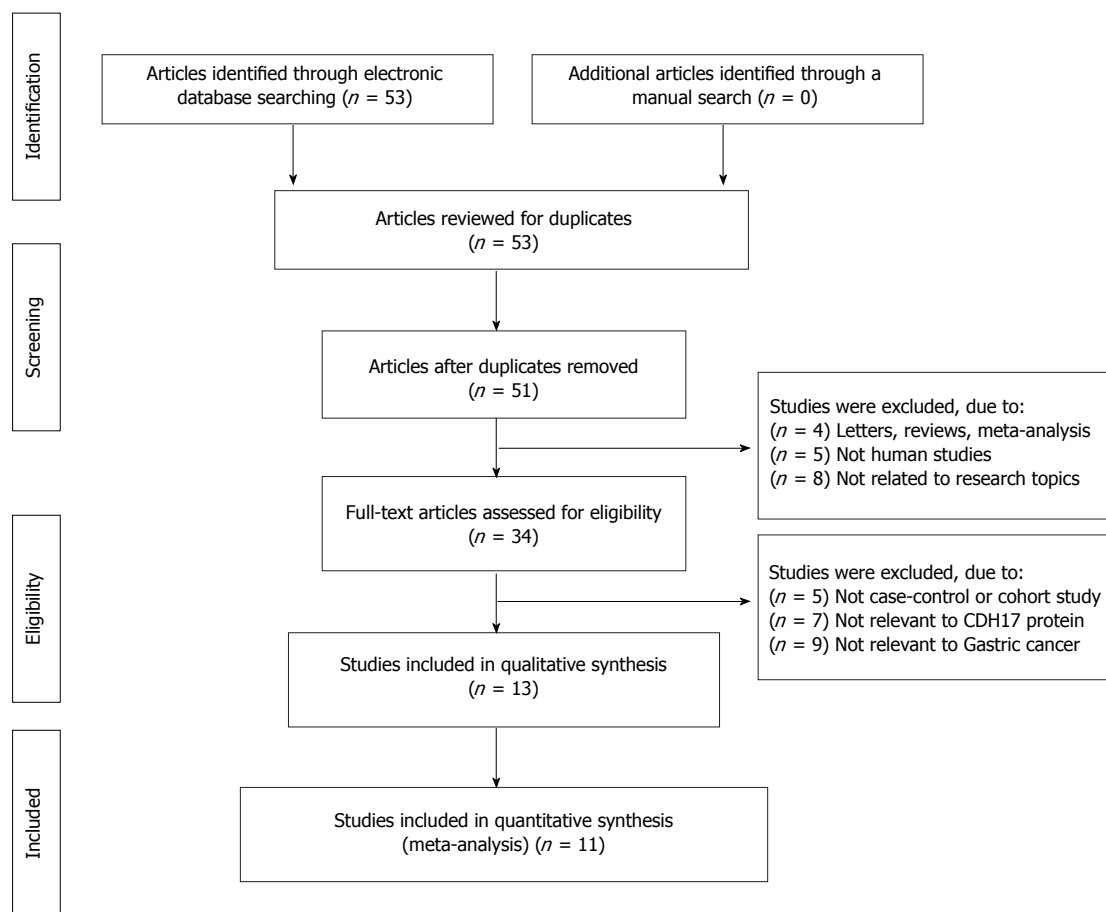


Figure 1 Flow chart showing study selection procedure. Eleven final case-controlled studies were included in this meta-analysis.

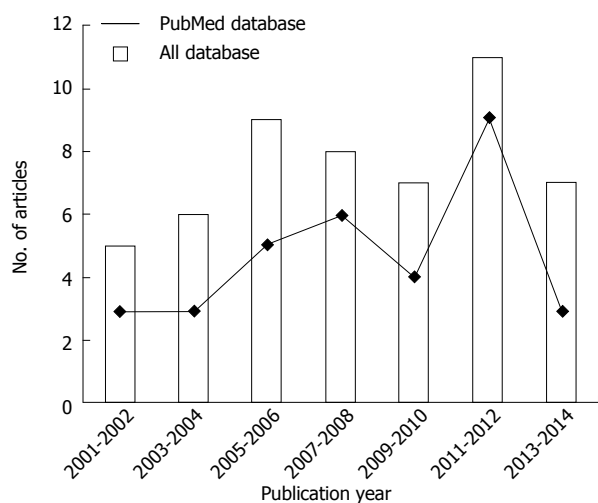


Figure 2 Distribution of topic-related literature in the electronic database over the last decade.

inclusion criteria: (1) clinical studies had to examine the association between CDH17 expression and the pathological features of GC within a human population; (2) tumor specimens were drawn from all patients confirmed to have GC *via* histological examination, and the pathological staging for each GC sample was classified in accordance with the TNM system^[18]; (3) the article must be published in a peer-reviewed journal

and provide original data; and (4) the article must supply sufficient information on CDH17 expression. The major exclusion criteria were: (1) article did not satisfy the inclusion criteria designed in the current study; (2) studies turned out to be abstracts, reviews, case report, letters, meta-analyses, or proceedings; (3) duplication publications or studies with overlapping data; and (4) subgroup analysis of the included trials.

Data extraction and quality assessment

A standard reporting form was used to extract data from each included study, with the collected descriptive information including: first author surname and initials, year of submission, country, racial descent, study design, number of cases and controls, demographic variables, CDH17 detection method, CDH17 expression, and confirmation of diagnosis. Two reviewers independently assessed the methodological quality of the included trials using the Newcastle-Ottawa Scale (NOS) criteria to ensure consistency in reviewing and reporting results^[19]. Three aspects were considered in the NOS criteria: (1) subject selection: 0-4; (2) subject comparability: 0-2; and (3) clinical outcome: 0-3. NOS scores range from 0 to 9; a score ≥ 7 indicated that the study was of good quality. Disagreement on the inclusion of a single study was settled either by discussion or after consultation with a third investigator.

Table 1 Characteristics of included studies focusing on protein expression of cadherin-17

Ref.	Year	Country	Sample	Gender (M/F)	Age (yr)	Sample	Method	NOS score
Lin <i>et al</i> ^[17]	2014	China	216	150/66	65 (32-84)	Tissue	EnVision	8
Qiu <i>et al</i> ^[9]	2013	China	156	103/53	57 (27-78)	Tissue	EnVision	7
Wang <i>et al</i> ^[16]	2012	China	191	117/74	-	Tissue	Non-EnVision	8
Sakamoto <i>et al</i> ^[5]	2012	Japan	152	-	-	Tissue	Non-EnVision	7
Wang <i>et al</i> ^[30]	2011	China	264	157/107	-	Tissue	EnVision	8
Liu <i>et al</i> ^[29]	2011	China	46	37/9	-	Tissue	EnVision	6
Lee <i>et al</i> ^[28]	2010	United States	440	-	-	Tissue	Non-EnVision	8
Xu <i>et al</i> ^[27]	2009	China	215	169/46	57 (24-82)	Tissue	Non-EnVision	8
Ge <i>et al</i> ^[35]	2008	China	166	109/57	52.2 ± 10.2	Tissue	EnVision	7
Tian <i>et al</i> ^[25]	2007	China	66	32/34	53 (29-91)	Tissue	Non-EnVision	6
Park <i>et al</i> ^[8]	2007	South Korea	208	135/73	-	Tissue	Non-EnVision	8

NOS: Newcastle-Ottawa Scale.

Statistical analysis

The association between CDH17 expression and the pathological features of GC was estimated by the odds ratio (OR) and a 95% confidence interval. We used Cochran's *Q*-statistic ($P < 0.05$ was considered significant) and I^2 tests to quantify heterogeneity^[20]. In order to calculate the pooled ORs, fixed/random effects models were used; a random effects model was applied in the event of significant heterogeneity ($P < 0.05$ or I^2 test exhibited $> 50\%$), while ORs were pooled *via* the fixed-effects model^[21,22]. In the event of significant heterogeneity, subgroup analysis was performed to find potential explanatory variables for the differences. In addition, we employed sensitivity analyses to evaluate whether a single study had the weight to impact the overall estimate. The effect of publication bias was determined *via* Egger's linear regression test ($P < 0.05$ was considered significant), which can be used to evaluate funnel plot asymmetry; an asymmetric plot reveals possible publication bias^[23,24]. Statistical analyses were conducted with STATA statistical software (Version 12.0, Stata Corporation, College Station, TX, United States).

RESULTS

Selection of eligible studies

Figure 1 shows the flow chart of identified publications and the main reason for exclusion. Initially, 53 potential articles emerged from the electronic databases. Of the 53 articles, 2 studies were duplicates and thus removed. After title/abstract screening, 17 irrelevant studies were also removed. A further 21 studies were excluded after detailed readings during full text assessment, thereby leaving 13 remaining studies for qualitative analysis. Based on this analysis, 2 additional studies were removed. This left 11 case-controlled studies published between 2007 and 2014 for the meta-analysis^[5,8,9,17,25-31] (Figure 2).

Demographic variables

The 13 include studies consisted of 2,120 total GC patients with sample sizes ranging from 46 to 440.

Sample sizes > 200 were considered "large". Of the 11 included studies, only one operated within a Caucasian population [United States (Lee HJ)]; the remaining 10 studies were conducted in Asian populations [China (Lin Z, Qiu HB, Wang J, Wang B, Liu SQ, Xu XY, Ge J, and Tian MM), Japan (Sakamoto N), and Korea (Park SS)]. Two studies (Lee HJ and Sakamoto N) did not provide gender information, while six studies (Wang J, Sakamoto N, Wang B, Liu SQ, Lee HJ, and Park SS) failed to obtain age information. There was only one non-Asian study, though it had a large sample size. The detection of CDH17 expression was divided into EnVision and non-EnVision groups (PV, LSAB, SP, and ABC). CDH17 expression in different pathological stages (TNM stage, histologic grade, invasive grade, and LN metastasis) and baseline characteristics for the 11 individual studies are summarized in Table 1.

Meta-analysis of the MMP-3 levels with GC risk

In the meta-analysis, the relationship between CDH17 expression and the pathological features of GC was assessed *via* the random effect model for observed heterogeneity (TNM III-IV vs I-II: $I^2 = 88.4\%$, $P = 0.000$; histologic grade 3-4 vs 1-2: $I^2 = 91.1\%$, $P = 0.000$; invasive grade: T3-4 vs T1-2: $I^2 = 59.7\%$, $P = 0.030$; LN metastasis: $I^2 = 85.2\%$, $P = 0.000$). Results showed that CDH17 exhibited more positive expression in patients with TNM III-IV staging GC than in those with III-IV staging GC based on the ORs from the combined results of all the included studies (OR = 2.35; 95%CI: 1.15-4.82; $P = 0.019$). We also examined the role of CDH17 expression in the histologic grade of GC progression, and found that GC tissues from histologic grades 3-4 had higher CDH17 expression than those with histologic grades 1-2 (OR = 3.48; 95%CI: 1.36-8.92; $P = 0.009$). As for the invasive grade, we found that CDH17 expression was significantly higher in GC tumors with an invasion depth of T3-4 when compared with the T1-2 (OR = 2.86; 95%CI: 1.69-4.83; $P = 0.000$). Meanwhile, GC tissues with LN metastases had higher CDH17 expression than those with no detectable LN metastases (OR = 2.64; 95%CI: 1.33-5.27; $P = 0.006$) (Figure 3).

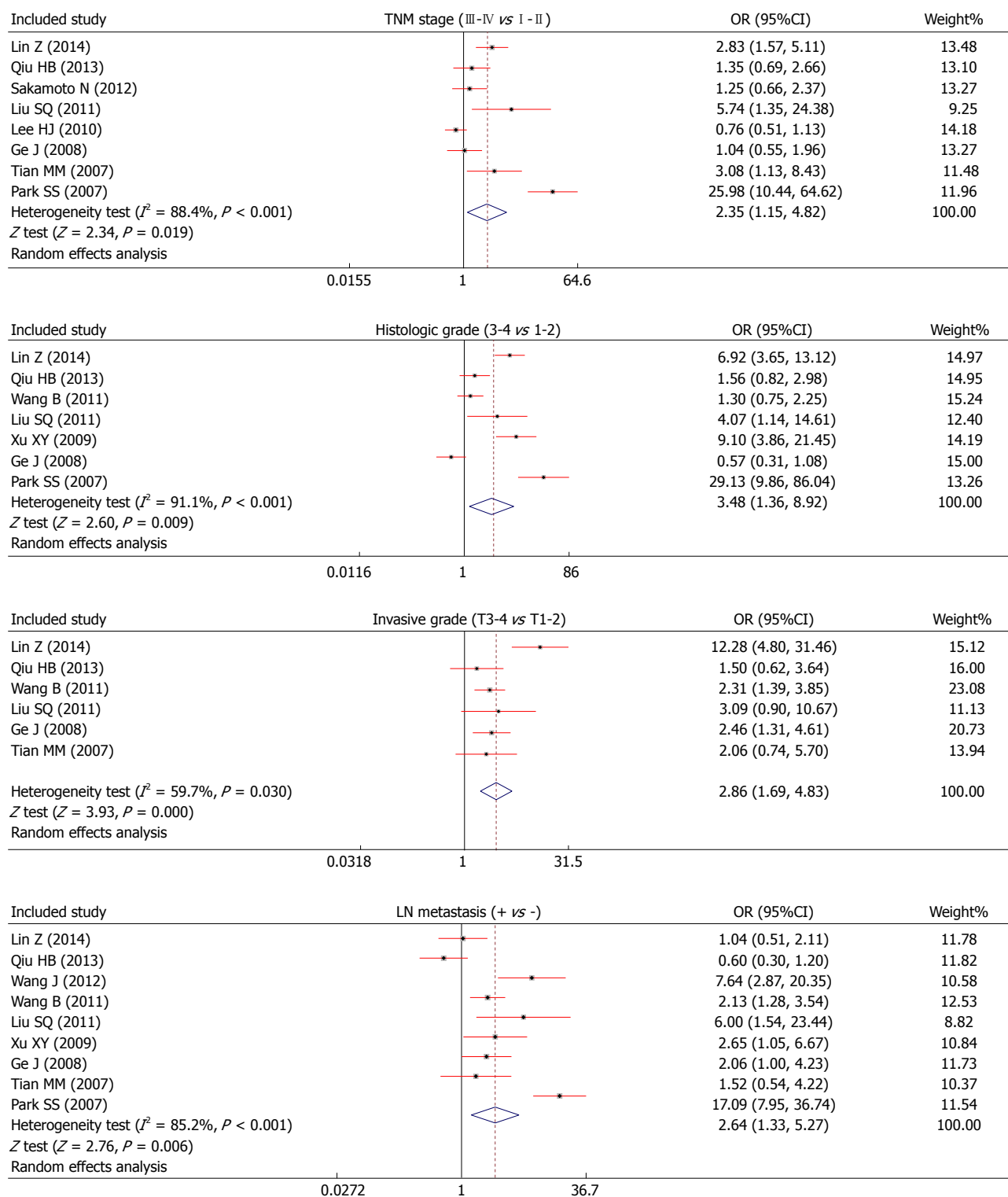
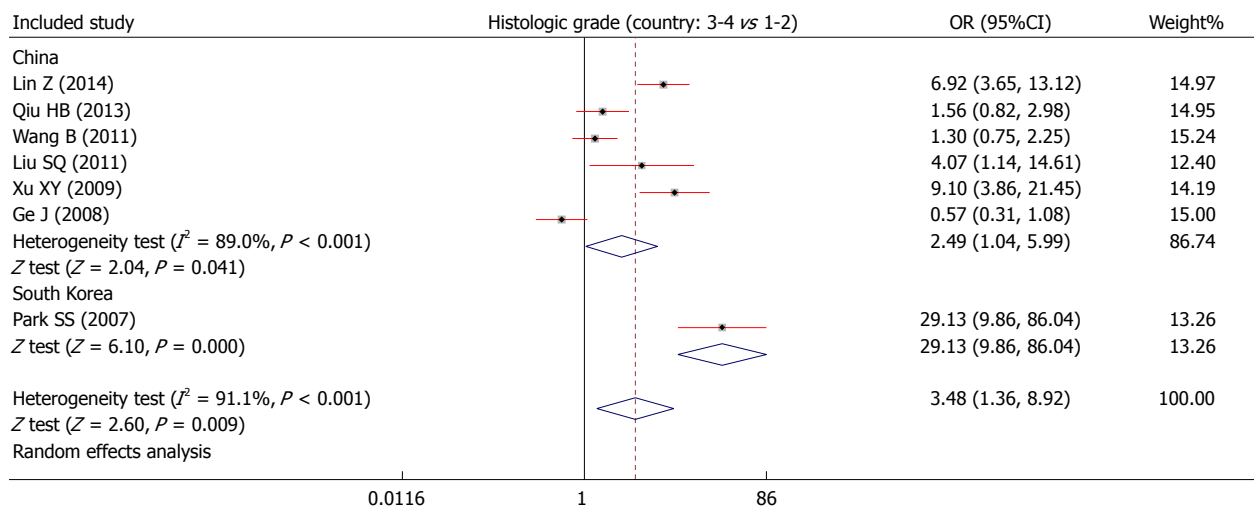
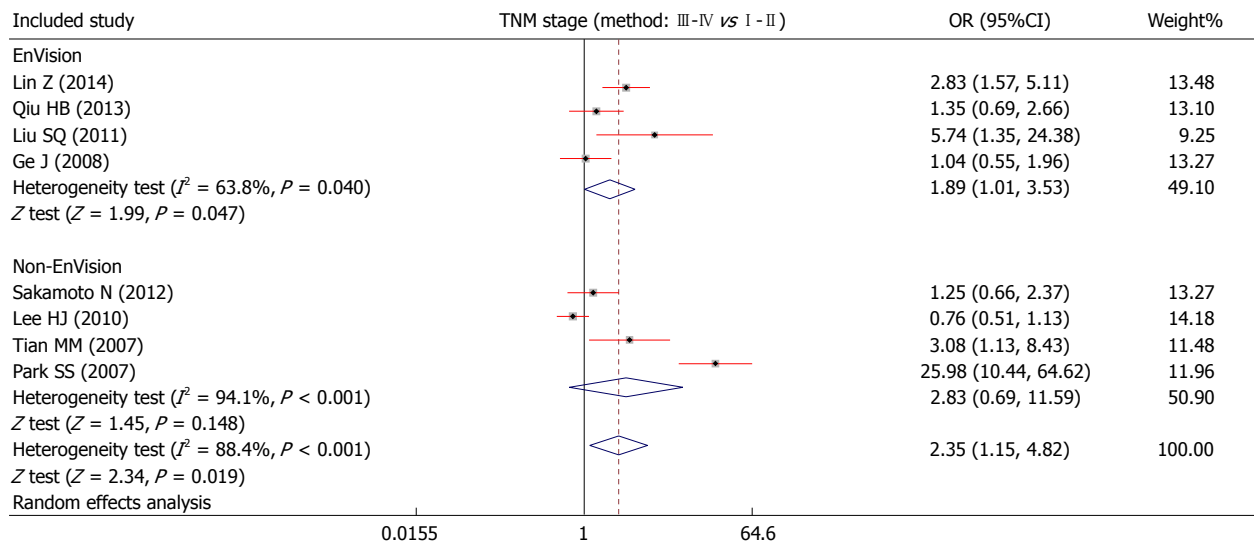
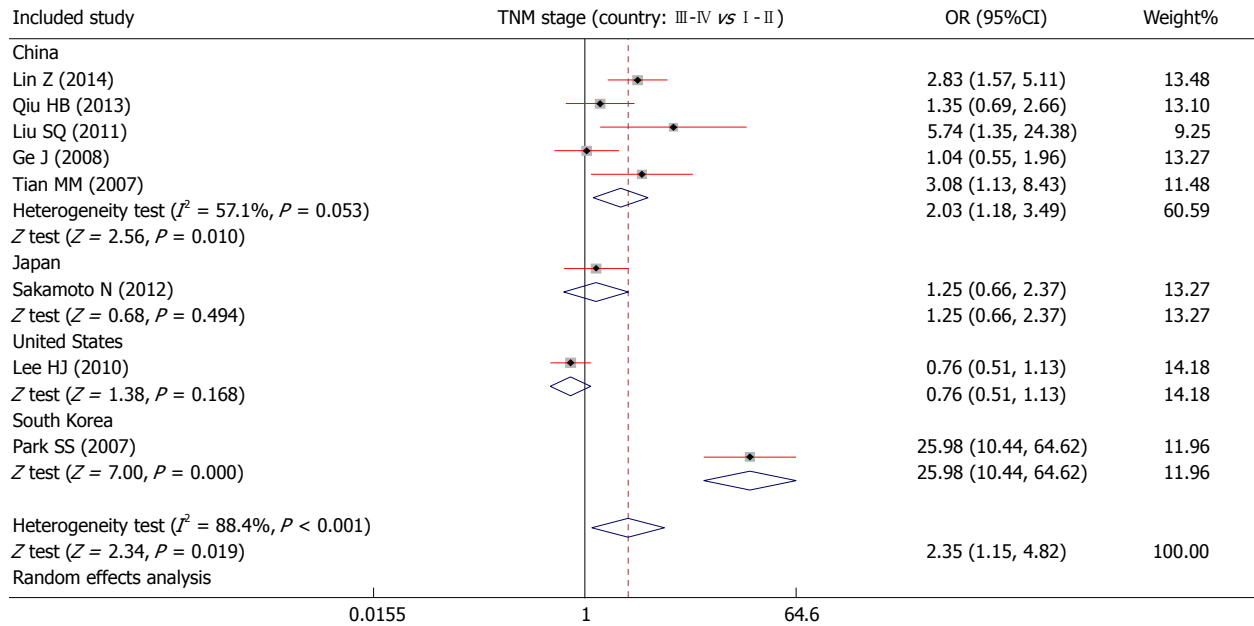


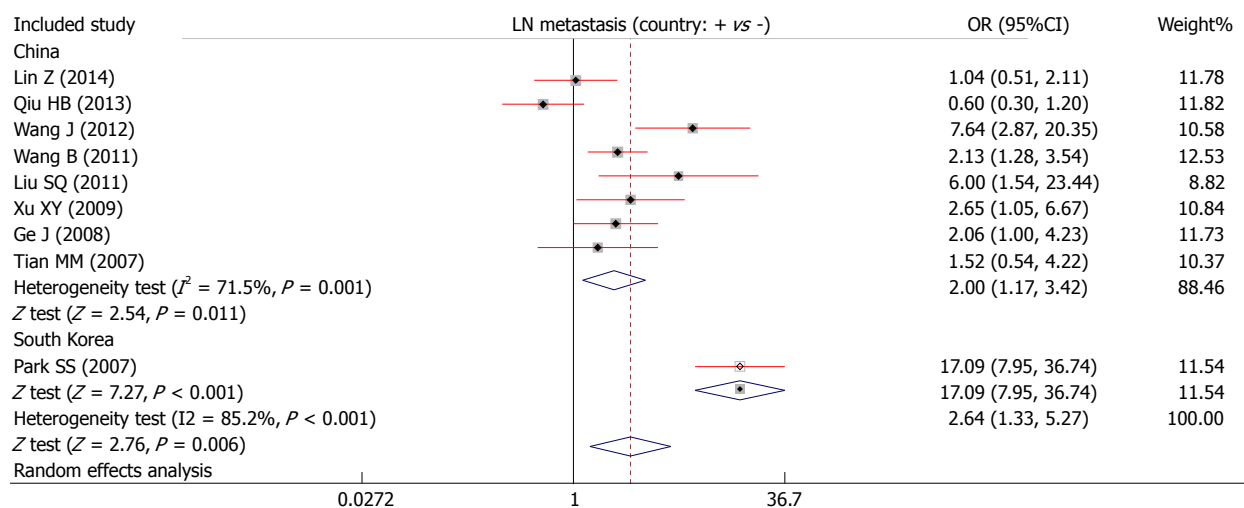
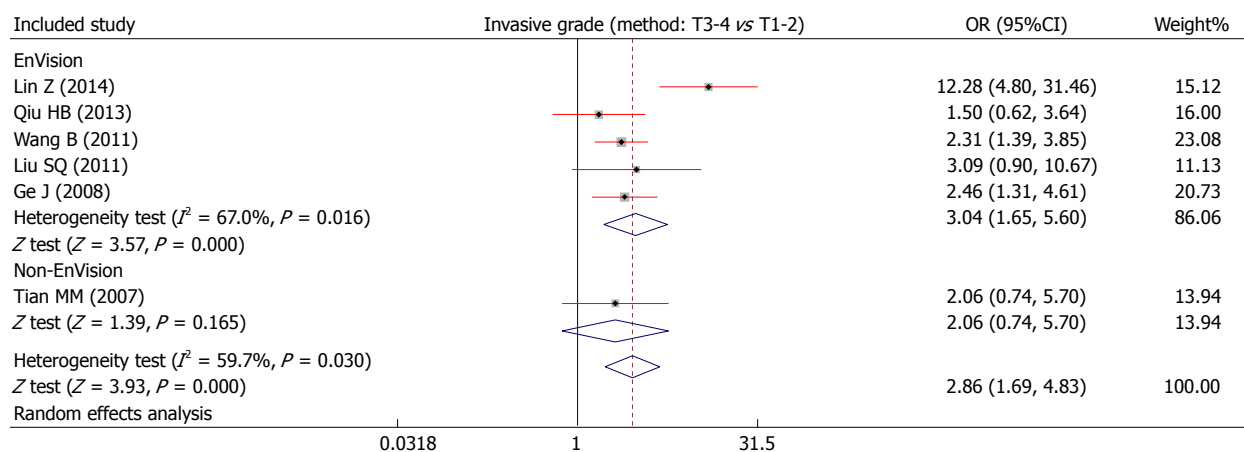
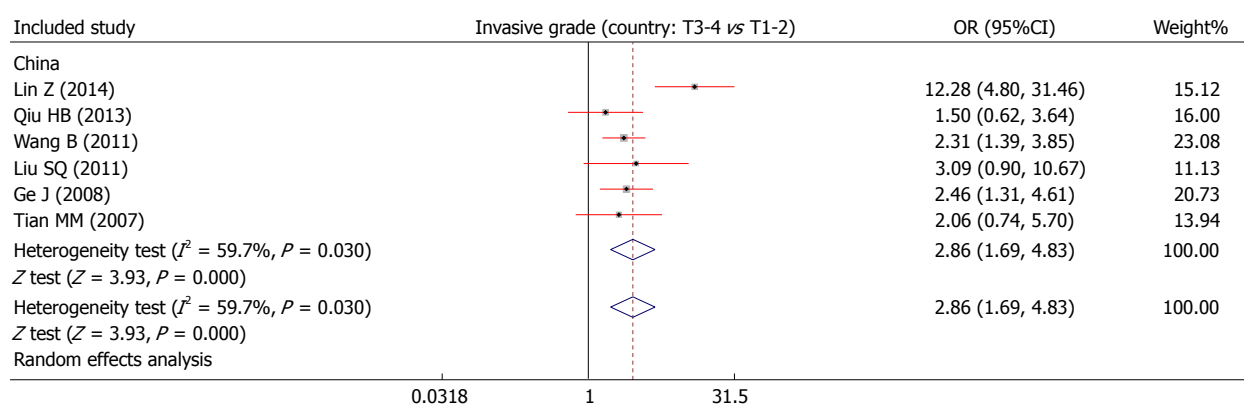
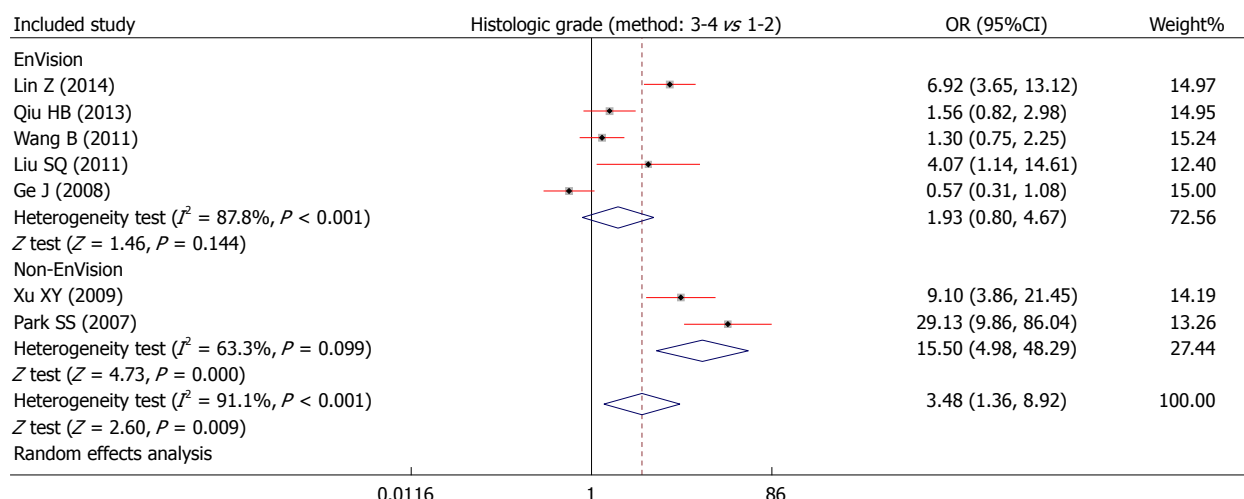
Figure 3 Forest plots for the relationships between cadherin-17 protein expression and the pathological characteristics of gastric cancer.

Subgroup analysis

Since heterogeneity was found, the relationship between CDH17 expression and the pathological features of GC were evaluated for subgroups of different explanatory variables. We found that CDH17 expression occurred more frequently in TNM III-IV staging GC than those with I-II staging GC in the China (OR = 2.03; 95%CI: 1.18-3.49; $P = 0.010$) and Korea subgroups (OR = 25.98; 95%CI: 10.44-64.62;

$P = 0.000$), but not in the Japan (OR = 1.25; 95%CI: 0.66-2.37; $P = 0.494$) or United States subgroups (OR = 0.76; 95%CI: 0.51-1.13; $P = 0.168$). In addition, we found positive associations between CDH17 expression and histologic grade of GC in the China (OR = 2.49; 95%CI: 1.04-5.99; $P = 0.041$) and Korea subgroups (OR = 29.13; 95%CI: 9.86-86.04; $P = 0.000$). Significant differences in CDH17 expression were also observed between samples with T3-4 grade





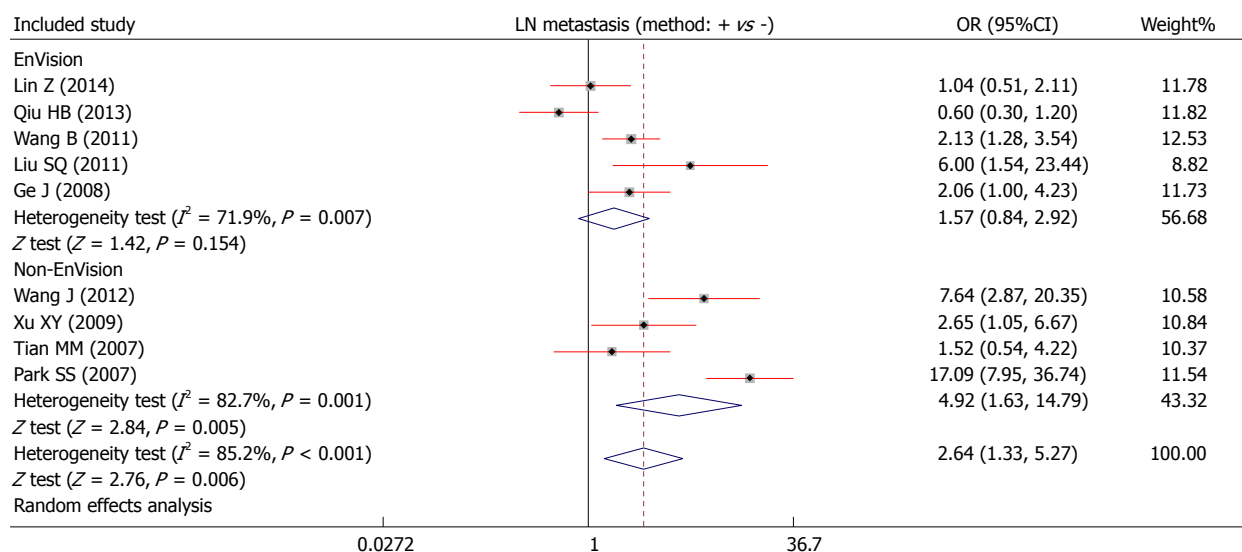


Figure 4 Subgroup analyses of the relationship between cadherin-17 protein expression and the pathological characteristics of gastric cancer.

GC and T1-2 grade GC in the China subgroup (OR = 2.86; 95%CI: 1.69-4.83; $P = 0.000$). In addition, the results showed significant difference in CDH17 expression between LN metastasis-positive samples and LN metastasis-negative GC samples in both the China (OR = 2.00; 95%CI: 1.17-3.42; $P = 0.011$) and Korea subgroups (OR = 17.09; 95%CI: 7.95-36.74; $P = 0.000$).

In the method-classified subgroup analysis, we revealed significant differences in CDH17 expression in GC patients with TNM stage III-IV when compared with those with TNM stage I-II in the EnVision subgroup (OR = 1.89; 95%CI: 1.01-3.53; $P = 0.047$), but not in the non-EnVision subgroup (OR = 2.83; 95%CI: 0.69-11.59; $P = 0.148$). Meanwhile, evidence suggested that GC patients with overexpressed CDH17 were associated with a higher histologic grade in the non-EnVision subgroup (OR = 15.50; 95%CI: 4.98-48.29; $P = 0.000$), but not in the EnVision subgroup (OR = 1.93; 95%CI: 0.80-4.67; $P = 0.144$). Additionally, the results also indicated that CDH17 expression occurred more frequently in GC patients with a higher invasive grade in the EnVision subgroup (OR = 3.04; 95%CI: 1.65-5.60; $P = 0.000$), but a similar association was not found in the non-EnVision subgroup (OR = 2.06; 95%CI: 0.74-5.70; $P = 0.165$). Furthermore, we observed increased CDH17 expression in GC patients with LN-positive metastasis relative to those with LN-negative metastasis in the non-EnVision subgroup (OR = 4.92; 95%CI: 1.63-14.79; $P = 0.005$), but not in the EnVision subgroup (OR = 1.57; 95%CI: 0.84-2.92; $P = 0.154$) (Figure 4).

Sensitivity analysis and publication bias

Sensitivity analyses were performed, with the results showing that no single study had the weight to impact the overall estimate of the association between

CDH17 expression and the pathological features of GC (Figure 5). We did not observe any obvious asymmetry from the shapes of the funnel plots, and the Egger's regression test suggested the absence of publication bias, with the exception of the association between CDH17 expression and TNM stage ($t = 2.49$; $P = 0.047$); thus, no significant publication bias was detected in the association of CDH17 expression with histologic grade ($t = 1.72$; $P = 0.146$), invasive grade ($t = 0.58$; $P = 0.594$), or LN metastasis ($t = 0.83$; $P = 0.435$) in our systematic reviews (Figure 6).

DISCUSSION

In this meta-analysis, the relationship between high CDH17 expression and pathological features of GC was observed. From the results, we can conclude there is a significant connection between CDH17 and TNM stages, histologic grade, invasive grade, and LN metastasis of GC. Single-pass transmembrane cadherins are a type of cell adhesion molecule that can regulate adhesion to adjacent cells depending on Ca^{2+} , thereby contributing to homophilic cell adhesion and tumor development^[32]. CDH17, a member of the cadherin superfamily that is expressed exclusively on enterocyte basolateral surfaces and intestine goblet cells (but not liver or stomach cells), differs from classic cadherins in structure and function^[33]. Different from classic cadherins such as E-, P-, and N-cadherins, CDH17 consists of seven cadherin type repeats without the His-Ala-Val motif of the N-terminal domain, has only 20 amino acid residues for its CDH17 cytoplasmic portion, has a short COOH-terminal for possible cell adhesion function, and displays no homology to classical cadherins which have the highly conserved 150-160 amino acid residues^[8]. The independent adhesion function from the cytoskeletal anchorage of CDH17 has no connection with catenins, actins, or

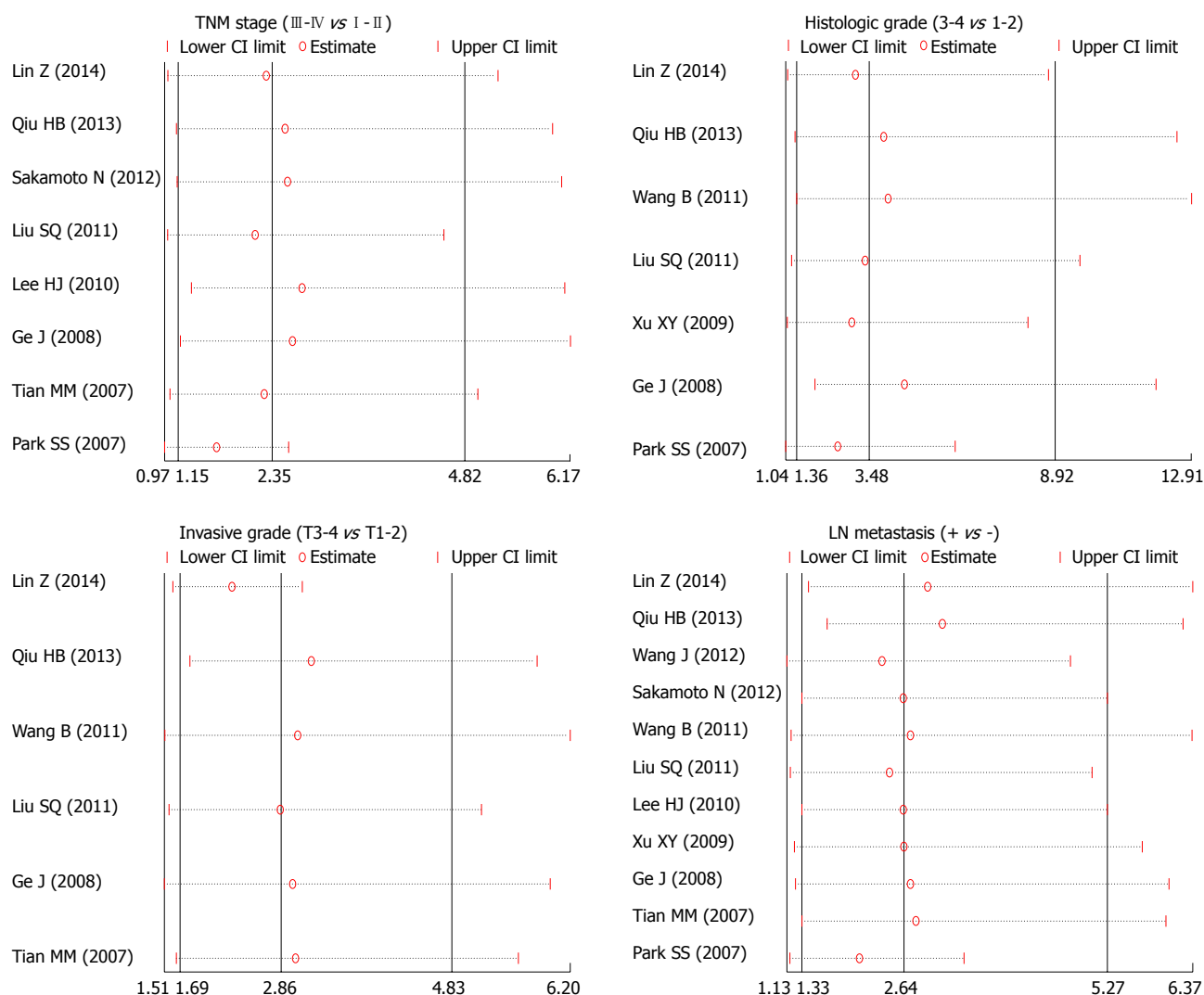


Figure 5 Sensitivity analysis of the summary odds ratio coefficients on the association between cadherin-17 protein expression and the pathological characteristics of gastric cancer.

other cytoplasmic components; this is vastly different from classical cadherins, suggesting a complementary classical cadherin adhesion function^[34]. It has been reported that the high expression of CDH17, as opposed to the low levels of other classical cadherins, is related to gastric cancer, colorectal cancer, liver cancer, pancreatic cancer, and cholangiocarcinoma, suggesting that CDH17 might play an important part in tumor progression^[33]. A series of studies have shown that the high expression of CDH17 is linked with the stage of the tumor, histological grade, invasive depth of the tumor, and lymph node metastasis of GC^[5,31]. The reason for high CDH17 expression levels in this capacity may be related to the activation of the NFκB signaling pathway, which impacts processes such as p50/p65 heterodimer regulation of the transcription of responsive genes and differentiation of lymphatic endothelium into VEGFs. Relatedly, increased nuclear translocation of p65 in GC has a close relationship with tumor invasion depth and tumor metastases^[16]. Another mechanism may involve the Wnt/β-catenin

pathway. It was found that the knockdown of CDH17 had the ability to decrease phosphorylation of GSK-3b and β-catenin related with the reduction transactivation activity of TCF/LEF, thus decreasing the expression of cyclin-D1, which is of great importance in promoting cell proliferation and inhibiting cell apoptosis^[9,35]. Furthermore, CDH17 over-expression can activate the Ras/Raf/MEK/ERK MAPK signaling pathway, which may regulate cell proliferation, apoptosis, metabolism, and differentiation, which are all processes important in tumor biology^[17]. From the above analysis, we may draw the conclusion that the high expression of CDH17 is largely related to the pathological features of GC through three signaling pathways in the cells: the NFκB signaling pathway, the Wnt/β-catenin pathway, and the Ras/Raf/MEK/ERK MAPK signaling pathway. In agreement with our conclusion, Ge *et al.*^[26] also found that the expression of CDH17 may play an important part in the development of GC, suggesting a suitable marker for the prognosis of GC.

Given the fact that several factors may affect the

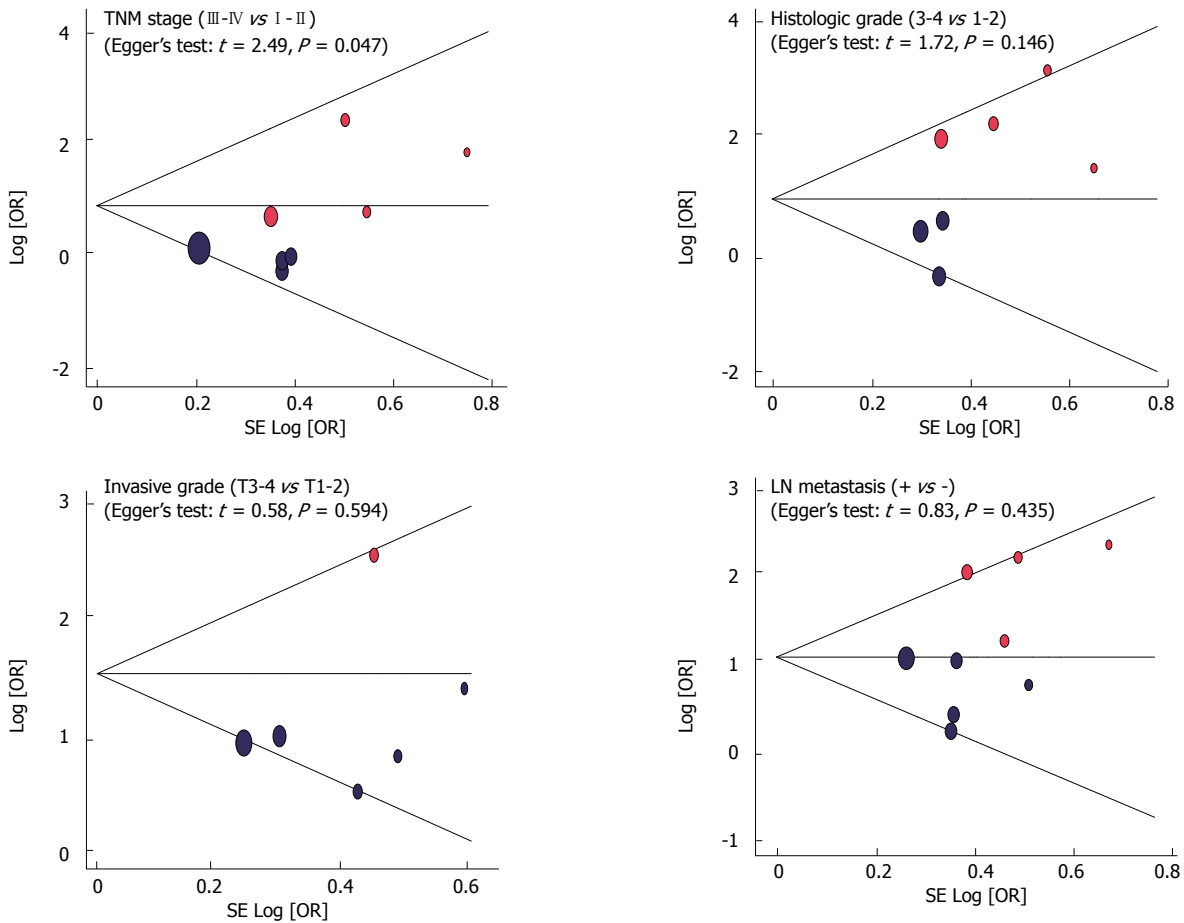


Figure 6 Funnel plot of publication biases on the association between cadherin-17 protein expression and the pathological characteristics of gastric cancer.

linkage between CDH17 expression and pathological features of GC patients, a stratified analysis based on country and detection method was conducted. From the country-stratified analysis, we found no obvious influence in either Chinese or Korean populations in TNM stages, histologic grade, invasive grade, or LN metastasis of GC. In Japan and the United States, however, the relationship was not as obvious. This can be explained by the differences in the environmental backgrounds and gene pools of these different populations. In conclusion, our results are partly in accordance with previous studies that hold that high expression of CDH17 has a typical connection with the pathological features of GC patients.

Our study does have some limitations that merit additional investigation. Firstly, our study is observational research that is cross-sectionally designed. Secondly, the sample sizes in more than half of the total involved articles were relatively small, and the number of patients in some groups was low. In particular, the small patient numbers in the stratified analyses of country and method may detract from the study results. Thirdly, there was a difference in the high/low cut-off values of CDH17 expression levels in the various included studies. The different cut-off values of

CDH17 between studies may influence the final results and be responsible for a few inconclusive outcomes. Finally, the existence of heterogeneity may also harm the integrity of results. A large number of the included studies were designed with small sample sizes, six studies lacked complete gender and age information, and the CDH17 expression detection methods were different from each other (EnVision, PV, LSAB, SP, and ABC). In this regard, differences in age, sex, and detection methods may be largely responsible for heterogeneity. Additionally, there was only one non-Asian study, and although it had a large sample size, this might have influenced the scope of our results. Considering the limitations listed above, the results, as well as the analysis, must be interpreted with caution.

In conclusion, the present study identified that CDH17 is an actual oncogene that plays an important role in cell proliferation, tumor growth, invasion, and metastasis in GC. This data may present a novel therapeutic approach in treating GC by targeting CDH17. Our conclusions, however, need to be confirmed due to the aforementioned limitations, *via* a combination of more and larger sample size publications, which use a consistent definition for cut-off values.

COMMENTS

Background

Cadherin-17 (CDH17) was detected to be overexpressed in gastric cancer (GC) and related to tumor occurrence and recurrence, invasion and metastasis, advanced tumor stage, and poor survival in GC patients. To date, the cellular function and signaling mechanisms of CDH17 in GC remain inconsistent.

Research frontiers

The cellular function and signaling mechanisms of CDH17 in GC remain inconsistent.

Innovations and breakthroughs

The present study identified that CDH17 is an actual oncogene that plays an important role in cell proliferation, tumor growth, invasion, and metastasis in GC.

Applications

These data may present a novel therapeutic approach against GC by targeting CDH17.

Terminology

Odds ratio (OR) and a 95% confidence interval (95%CI) were used to evaluate specified relationships. The Cochran's Q-statistic and I^2 test were used to evaluate potential heterogeneity among studies.

Peer-review

The review is well written and deals with an important topic. This study found that the cadherin 17 protein is associated with the growth and metastasis of gastric cancer, suggesting a potential of targeted therapy against the protein. The analysis is interesting and important.

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