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# Lack of association between the *CDH1* polymorphism and gastric cancer susceptibility: a meta-analysis

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**E-Cadherin (CDH1) plays a key role in cell adhesion, which is vital to the normal development and maintenance of cells. Down regulation of *CDH1*, may lead to dysfunction of the cell-cell adhesion system, resulting in increased susceptibility to tumor development and subsequent tumor cell invasion and metastasis. The *CDH1* C-160A polymorphism could decrease its transcription efficiency and may increase susceptibility to cancer development, but its relevance to gastric cancer is generally disputed. Consequently, we performed a meta-analysis of published case-control studies, including 4218 gastric cancer cases and 5461 controls. Overall, no significant association was observed between the *CDH1* C-160A polymorphism and risk of gastric cancer in all genetic models. In the stratified analysis by total sample size, a significant association was observed in the small sample size subgroup (total sample size $< 300$), but the results should be interpreted with caution. In conclusion, this meta-analysis failed to confirm the association between the *CDH1* C-160A polymorphism and risk of gastric cancer. Large-scale and well-designed studies are needed to confirm our findings.**

Gastric cancer is the second most common cancer worldwide. Although the incidence of gastric cancer has decreased in recent years, it remains a major health concern due to the high mortality and poor prognosis for this disease[1,2]. Although it is well known that environmental factors, dietary habits, tobacco smoking, alcohol consumption, and Helicobacter pylori infection are associated with the risk of gastric cancer, host genetic factors may be one of the most critical in gastric carcinogenesis[3–7].

Cell-cell adhesions play crucial roles not only in regulating morphogenesis of both normal and neoplastic tissues but also in invasion and metastasis of cancer. E-cadherin, the so-called CDH1, is a member of a family of transmembrane glycoproteins expressed in epithelial cells and is responsible for calcium-dependent cell-cell adhesion[8–10]. It plays an important role in cell adhesion, which is vital to the normal development and maintenance of cells. Dysfunction of the cell-cell adhesion system triggers neoplastic development. In humans, the *CDH1* gene is located on chromosome 16q22.1, and codifies a mature polypeptide with 728 amino acids[11]. Since CDH1 is the prime cell adhesion mediator, the gene is thought to serve as a tumor invasion suppressor. Down regulation of *CDH1*, may lead to a loss of CDH1 mediated cell-cell adhesion, resulting in increased susceptibility to tumor development and subsequent tumor cell invasion and metastasis[12].

In recent years, studies have confirmed that single-nucleotide polymorphisms (SNPs) in the promoter region of the *CDH1* gene influence its transcriptional activity and alter the expression of E-cadherin. It has been postulated in a series of studies that these SNPs may be associated with cancer development[13–15]. The most widely studied polymorphism is *CDH1* C-160A (rs16260), where the A allele decreases transcription efficiency of the *CDH1* gene and may increase susceptibility to cancer development in some populations. Recently, a considerable number of studies have been conducted to investigate the associations between the *CDH1* C-160A polymorphism and susceptibility of gastric cancer[16–35]. However the results remain controversial and ambiguous. In 2007, Medina-Franco[26] found that the AA genotype had a significantly elevated risks for gastric cancer in a Mexican population (OR = 6.5, 95% CI = 2.1–19.6). In 2010, Al-Moundhri[32] found the similar result in an Omani population (OR = 3.6, 95% CI = 1.1–11.8). In contrast, in 2002, Wu[18] observed that in a Taiwanese population the frequency of the variant AA genotype in gastric cancer cases was significantly lower than that of controls, conferring a 5-fold decrease in the risk of gastric cancer (OR = 0.20, 95% CI = 0.06–0.56) compared with the CC genotype. However, in 2009, Corso[31] reported that the *CDH1* C-160A polymorphism was not significantly

associated with gastric cancer susceptibility in an Italian population (OR = 0.7, 95% CI = 0.3–1.5). Meta-analysis is considered a powerful tool for summarizing the contradicting results from different studies with more statistical power. To solve the problem of inadequate statistical power and controversial results, we performed a meta-analysis of published case-control studies.

## Results

**Characteristics of eligible studies.** The literature search for this meta-analysis started in March 2014 and ended in August 2014. A total of 116 relevant articles were yielded by the literature search. After screening the titles, 78 articles were excluded because of obvious irrelevance. After reading the abstracts and full texts of the remaining articles, review articles (n = 12) as well as articles without controls (n = 4) and sufficient data (n = 2) were excluded. Thus, a total of 20 articles[16–35] (22 independent case-control studies) met the inclusion criteria, and included 4218 gastric cancer cases and 5461 controls. The data collected from the included studies were summarized in Table 1, and the flow chart of study selection process was shown in Fig. 1.

**Results of meta-analysis.** Overall, no significant association was observed between the *CDH1* C-160A polymorphism and risk of gastric cancer in all genetic models (AA vs. CC: OR = 1.19, 95%CI: 0.89–1.58; CA vs. CC: OR = 1.01, 95% CI: 0.88–1.15; CA+AA vs. CC: OR = 1.04, 95%CI: 0.91–1.19; AA vs. CC+CA: OR = 1.17, 95%CI: 0.90–1.52) (Fig. 2). There was heterogeneity among the studies ($P = 0.001$ for the homozygous genetic model; $P = 0.011$ for the heterozygous genetic model; $P = 0.001$ for the dominant genetic model; $P = 0.004$ for the recessive genetic model). To eliminate heterogeneity, we conducted further meta-analyses stratified according to ethnicity, source of controls, quality scores and total sample size. Similarly, in the subgroup analysis stratified by ethnicity, there was no significant association between the *CDH1* C-160A polymorphism and risk of gastric cancer in all genetic models, and so was it in the subgroup analysis stratified by source of controls and quality scores. In the stratified analysis by total sample size, a significant association was observed in the small sample size subgroup (total sample size < 300) in the homozygous genetic model (OR = 2.24, 95%CI = 1.51–3.34) and recessive genetic model (OR = 2.10, 95%CI = 1.51–3.34) (Table 2).

**Sources of heterogeneity.** There was significant heterogeneity for all genetic model comparison. The study ethnicity, source of controls, quality scores and total sample size were regarded as the potential confounding factors. Metaregression revealed that total sample size was the sources of between-study heterogeneity under homozygous ($t = -3.00$, $P = 0.007$) and recessive genetic models ($t = -2.87$, $P = 0.009$), which was consistent with subgroup analyses results in homozygous and recessive genetic models. Moreover, under the dominant genetic model, meta-regression showed that total sample size might be the sources of between-study heterogeneity ($t = -1.86$, $P = 0.077$), which was also consistent with subgroup analyses results in the dominant genetic model. Simultaneously, we found that the study ethnicity, source of controls, and quality scores did not contribute to the source of heterogeneity.

**Sensitivity analysis.** Some studies with low quality scores (quality scores < 8), or that deviated from Hardy-Weinberg equilibrium (HWE), were enrolled in this meta-analysis. Sensitivity analysis was performed to determine whether these factors had an impact on the overall estimate. The influence of a single study on the overall meta-analysis estimate was investigated by omitting one study at a time, respectively. The omission of any single study did not make a significant difference in the pooled effects, suggesting that the results were reliable and stable (Supplementary Figure 1).

**Publication bias.** Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (Fig. 3). Moreover, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results did not suggest any evidence of publication bias ($P = 0.323$ for the homozygous genetic model; $P = 0.131$ for the heterozygous genetic model; $P = 0.060$ for the dominant genetic model; $P = 0.497$ for the recessive genetic model).

Table 1 | Characteristics of eligible studies included in the meta-analysis

| | | | | | | | | cases | | | controls | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| author | year | country | ethnicity | quality scores | source of controls | sample size (case/conctrol) | HWE | CC | CA | AA | CC | CA | AA |
| Humar[16] | 2002 | Italy | Caucasian | 6 | HB | 53/70 | 0.555 | 17 | 26 | 10 | 40 | 27 | 3 |
| Pharoach-C[17] | 2002 | Canada | Caucasian | 8 | HB | 148/93 | 0.231 | 58 | 76 | 14 | 43 | 44 | 6 |
| Pharoach-G[17] | 2002 | Germany | Caucasian | 7 | HB | 132/42 | 0.345 | 61 | 58 | 13 | 22 | 15 | 5 |
| Pharoach-P[17] | 2002 | Portugal | Caucasian | 7 | HB | 153/331 | 0.223 | 62 | 80 | 11 | 153 | 151 | 27 |
| Wu[18] | 2002 | Taiwan | Asian | 9 | HB | 201/196 | 0.302 | 95 | 102 | 4 | 83 | 94 | 19 |
| Park[19] | 2003 | Korea | Asian | 5 | HB | 292/146 | 0.43 | 186 | 92 | 14 | 85 | 55 | 6 |
| Kuraoka[20] | 2003 | Japan | Asian | 4 | HB | 106/90 | 0.01 | 61 | 34 | 11 | 32 | 52 | 6 |
| Shin[21] | 2004 | Korea | Asian | 8 | HB | 28/142 | 0.454 | 21 | 6 | 1 | 110 | 31 | 1 |
| Lu[22] | 2005 | China | Asian | 9 | PB | 206/261 | 0.391 | 119 | 75 | 12 | 152 | 91 | 18 |
| Song[23] | 2005 | China | Asian | 9 | PB | 102/101 | 0.448 | 58 | 38 | 6 | 55 | 41 | 5 |
| Zhang[24] | 2005 | China | Asian | 10 | HB | 239/343 | 0.042 | 170 | 62 | 7 | 228 | 96 | 19 |
| Cattaneo[25] | 2006 | Italy | Caucasian | 10 | PB | 107/246 | 0.476 | 50 | 51 | 6 | 139 | 89 | 18 |
| Medina-Franco[26] | 2007 | Mexico | mixed | 4 | HB | 39/78 | 0.699 | 15 | 16 | 8 | 44 | 30 | 4 |
| Yamada[27] | 2007 | Japan | Asian | 6 | HB | 148/292 | 0.919 | 93 | 51 | 4 | 187 | 93 | 12 |
| Jenab[28] | 2008 | mixed | Caucasian | 10 | PB | 245/949 | 0.87 | 119 | 101 | 25 | 451 | 408 | 90 |
| Zhang B[29] | 2008 | China | Asian | 8 | HB | 668/625 | 0.453 | 418 | 211 | 39 | 403 | 194 | 28 |
| Zhang XF[30] | 2008 | China | Asian | 10 | HB | 239/343 | 0.042 | 170 | 62 | 7 | 228 | 96 | 19 |
| Corso[31] | 2009 | Italy | Caucasian | 7 | PB | 412/408 | 0.395 | 206 | 163 | 43 | 185 | 185 | 38 |
| Al-Moundhri[32] | 2010 | Omen | Caucasian | 8 | PB | 174/166 | 0.429 | 93 | 60 | 21 | 93 | 65 | 8 |
| Borges[33] | 2010 | Brazil | mixed | 6 | HB | 58/51 | 0.090 | 27 | 20 | 11 | 32 | 14 | 5 |
| Zhan[34] | 2012 | China | Asian | 10 | HB | 361/354 | 0.647 | 219 | 116 | 26 | 196 | 137 | 21 |
| Chu[35] | 2014 | Taiwan | Asian | 10 | HB | 107/134 | 0.938 | 48 | 44 | 15 | 84 | 44 | 6 |

HB, hospital-based; PB, population-based.

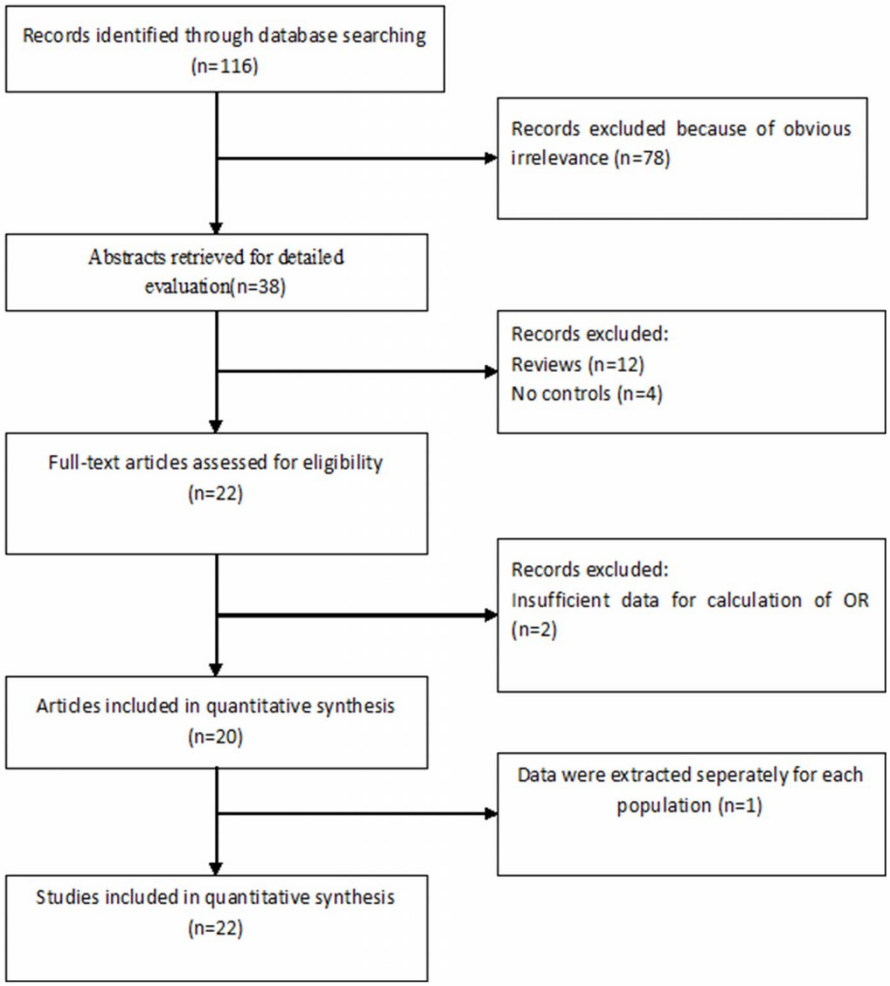


**Figure 1** | **Flow chart of study selection in the meta-analysis.**

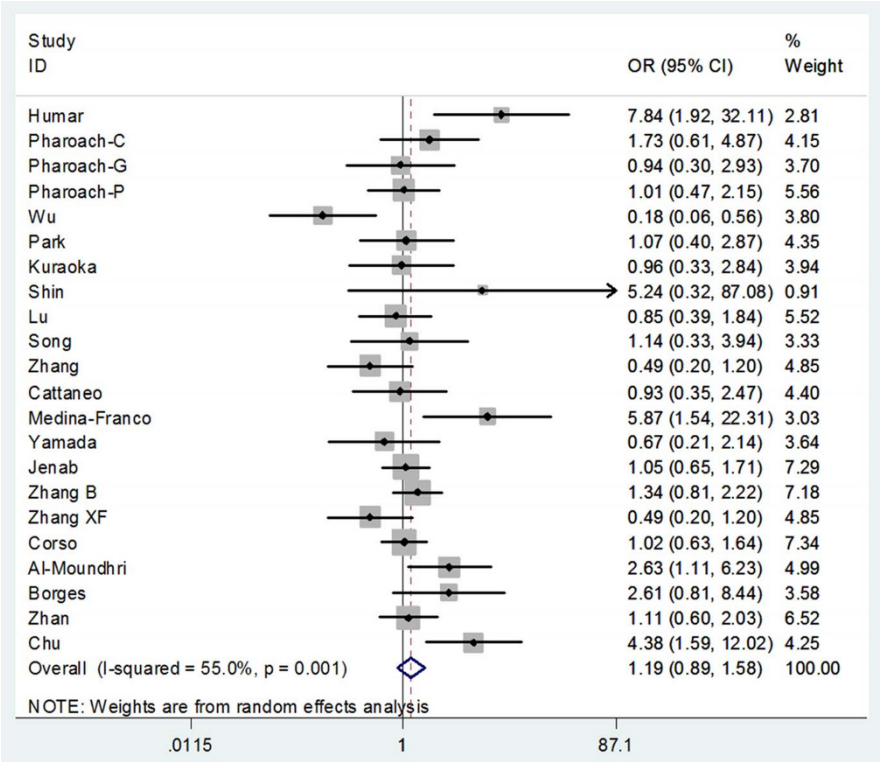


**Figure 2** | **Forest plot of the *CDH1* C-160A polymorphism and risk of gastric cancer under the homozygous genetic model (AA vs. CC).**

Table 2 | Pooled ORs and 95% CIs of the association between the *CDH1* C-160A polymorphism and risk of gastric cancer

| Variable | n[a] | Sample size (case/control) | AA vs CC | | | CA vs CC | | | CA/AA vs CC | | | AA vs CC/CA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | OR(95%CI) | P[b] | P[c] | OR(95%CI) | P[b] | P[c] | OR(95%CI) | P[b] | P[c] | OR(95%CI) | P[b] | P[c] |
| overall | 22 | 4218/5461 | 1.19(0.89-1.58) | 0.235 | 0.001 | 1.01(0.88–1.15) | 0.923 | 0.011 | 1.04(0.91–1.19) | 0.560 | 0.001 | 1.17(0.90–1.52) | 0.240 | 0.004 |
| ethnicity | | | | | | | | | | | | | | |
| Asian | 14 | 2697/3027 | 0.92(0.61–1.38) | 0.681 | 0.008 | 0.91(0.77–1.07) | 0.246 | 0.042 | 0.91(0.77–1.08) | 0.278 | 0.020 | 0.97(0.65–1.43) | 0.862 | 0.012 |
| Caucasian | 8 | 1424/2305 | 1.25(0.97–1.61) | 0.082 | 0.106 | 1.06(0.91–1.23) | 0.440 | 0.062 | 1.09(0.95–1.26) | 0.213 | 0.053 | 1.22(0.96–1.56) | 0.102 | 0.149 |
| source | | | | | | | | | | | | | | |
| HB | 16 | 2972/3330 | 1.23(0.82–1.86) | 0.315 | 0.000 | 1.03(0.86–1.22) | 0.770 | 0.006 | 1.07(0.89–1.29) | 0.487 | 0.000 | 1.19(0.82–1.73) | 0.354 | 0.001 |
| PB | 6 | 1246/2131 | 1.11(0.85–1.46) | 0.431 | 0.469 | 0.96(0.82–1.12) | 0.572 | 0.261 | 0.98(0.85–1.14) | 0.835 | 0.412 | 1.15(0.89–1.49) | 0.293 | 0.360 |
| quality scores | | | | | | | | | | | | | | |
| ≥8 | 13 | 2825/3953 | 1.07(0.73–1.55) | 0.737 | 0.003 | 0.99(0.89–1.10) | 0.882 | 0.339 | 1.00(0.90–1.11) | 0.973 | 0.103 | 1.05(0.74–1.50) | 0.779 | 0.004 |
| <8 | 9 | 1393/1508 | 1.42(0.89–2.25) | 0.140 | 0.044 | 1.04(0.76–1.42) | 0.817 | 0.001 | 1.12(0.82–1.53) | 0.488 | 0.001 | 1.29(0.98–1.71) | 0.073 | 0.123 |
| sample size | | | | | | | | | | | | | | |
| ≥300 | 13 | 3445/4660 | 0.95(0.79–1.15) | 0.625 | 0.057 | 0.95(0.86–1.05) | 0.327 | 0.335 | 0.95(0.87–1.05) | 0.317 | 0.370 | 0.93(0.71–1.23) | 0.626 | 0.037 |
| <300 | 9 | 773/801 | 2.24(1.51–3.34) | 0.000 | 0.109 | 1.19(0.80–1.76) | 0.373 | 0.003 | 1.34(0.90–2.00) | 0.149 | 0.001 | 2.10(1.42–3.09) | 0.000 | 0.331 |

[a]Number of studies
[b]P value of Z test.
[c]P value of Q-test for heterogeneity test.

## Discussion

*CDH1* is recognized as a crucial invasion suppressor gene in several human carcinomas, and inactivation or down regulation of E-cadherin has been found to be correlated with tumor aggressiveness and metastatic potential[36]. A C/A SNP exists at -160 from the transcriptional start site of the *CDH1* gene promoter and the A allele decreases transcriptional efficiency by 68% compared with the C allele *in vitro*[13], which attracted a lot of attentions to investigate the possible effects of this polymorphism on the susceptibility of gastric cancer. However, results of these studies were not consistent or even contradictory. To resolve this controversy, the present meta-analysis, including 4218 cases and 5461 controls from 22 case-control studies, explored the association between the *CDH1* C-160A polymorphism and risk of gastric cancer.

In the overall data synthesis, there was no association between the *CDH1* C-160A polymorphism and risk of gastric cancer in all genetic models. It was a negative result, but was in accordance with the results of majority studies included in this meta-analysis. Although the single included study showed significant association between certain genotype and susceptibility of gastric cancer, it could not be ruled out the existence of false positive results due to the reasons as follows. First, some studies contained a small sample size, so the results might be not reliable and stable enough. Second, the positive results of some results were contradictory. For example, Wu[18] reported that AA was a protective genotype, while Humar[16] and Chu[35] reported that AA was a susceptible genotype. Due to these inconsistent results, no significant pooled result could be obtained. Meanwhile, sensitivity analysis did not alter the results, implying that the results were robust.

In the stratification analysis of ethnicity, no significant association was observed in any of the genetic models, suggesting that ethnic differences in genetic backgrounds and environmental and social factors did not affect the association between the *CDH1* C-160A polymorphism and risk of gastric cancer. Similar results were observed in the subgroup analysis by source of controls and quality scores. In the subgroup analysis stratified by total sample size, a significant association between the *CDH1* C-160A polymorphism and risk of gastric cancer was observed in the small sample size subgroup in the homozygous genetic model and recessive genetic model. These significant results may be due to the limited sample size of studies, which had insufficient statistical power to support the association and may have generated a fluctuated risk estimate, so the findings in this subgroup should be interpreted with caution.

In order to seek out the genetic variants related to gastric cancer, much effort has been made to explore the association between gene polymorphisms via case-control study. Recently, accumulating number of genome-wide association studies (GWASs) have focused on the association between gene polymorphisms and risk of gastric cancer[37–42]. However, we have not found any data about the association between the *CDH1* C-160A polymorphism and risk of gastric cancer based on GWAS, probably due to some limitations in these studies such as small sample size. Meta-analysis is a powerful method for resolving inconsistent findings from a relatively large number of subjects, so it can obtain more reliable results than a single study. Similarly, we failed to find correlation between the *CDH1* C-160A polymorphism and risk of gastric cancer in this meta-analysis.

Our results indicated that the *CDH1* C-160A polymorphism was not associated with the risk of gastric cancer both in Asian and Caucasian populations, which were in accord with the results of the previous study by Gao[43] and inconsistent with the study by Li[44]. There were two main differences between the prior studies and ours. First, apart from ethnicity, the influence of factors such as study quality and sample size was not stated to explore the potential associations in the subtype analysis. Second, the literature searches of the two previous meta-analyses were conducted before March 2008 and November 2010, respectively. Since then, several

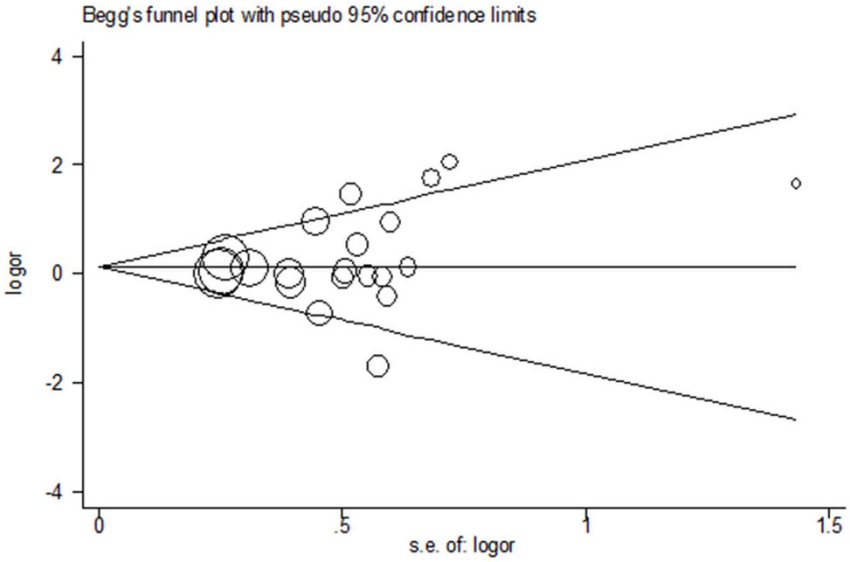


**Figure 3 | Funnel plot for studies of the association of the *CDH1* C-160A polymorphism and risk of gastric under the homozygous genetic model (AA vs. CC).**

additional studies of the *CDH1* C-160A polymorphism and risk of gastric cancer were published. Therefore, the sample was larger and the results of our meta-analysis were more reliable than those of previous studies.

All of the studies included in this meta-analysis met our inclusion criteria and the publication bias was not found. In spite of these, several limitations in this analysis should be mentioned when the results are interpreted. First, the meta-analysis was performed at the study level. For lack of sufficient data, we were unable to analyse potential correlative factors such as environmental factors and life-style habits which were important in the gastric carcinogenesis. It is also possible that the potential function of this polymorphism is diluted or covered by other genetic background or environment factors, and these important factors should not be ignored. Second, our analysis was limited to Asian and Caucasian populations, therefore, it is unknown whether these results are generalizable to other populations. Third, only published studies were included in this meta-analysis, publication bias might have inevitably occurred. Last, a relatively small number of available studies were included in our meta-analysis, which may reduce the statistical power for identifying possible associations between the *CDH1* C-160A polymorphism and risk of gastric cancer. The findings in this meta-analysis should thus be interpreted with caution.

In conclusion, this meta-analysis failed to confirm the association between the *CDH1* C-160A polymorphism and risk of gastric cancer, indicating that this polymorphism is not a biomarker for susceptibility to gastric cancer. However, large-scale studies in different ethnic groups with more detailed individual data are needed to validate our findings. Investigations of the gene-environmental interaction may lead to an improved, more comprehensive understanding of the roles of the *CDH1* C-160A polymorphism in the aetiology of gastric cancer.

## Methods

**Literature search.** Two investigators independently searched eligible studies on the associations between the *CDH1* C-160A polymorphism and gastric cancer. Published studies were identified through a computerized search of PubMed, without language limitation, up to August 2014. Electronic searches were performed by using the following search terms: (CDH1, E-cadherin or rs16260) and (gastric cancer, gastric carcinoma or stomach cancer) and polymorphism. In addition, the reference lists of retrieved articles were checked by handsearch for additional potential studies. A study reported results from more than one population was considered as separate studies. Studies included in this meta-analysis had to meet the following inclusion criteria: (a) a case-control study design, (b) evaluated the *CDH1* C-160A polymorphism and risk of gastric cancer, and (c) had detailed genotype frequency of cases and controls, or frequencies that could be calculated from the article text. Studies deviated from HWE were included and sensitivity analysis was performed to see whether this deviation can have an impact on the overall estimate.

**Data extraction and quality assessment.** Two investigators independently extracted data and reached a consensus on all of the items. The following data were extracted from the eligible studies: the first author's name, year of publication, country, ethnicity, source of controls, evidence of HWE, and numbers of cases and controls. Qualities of studies were assessed according to predefined criteria based on previous observational studies[45,46] (Supplementary Table 1). Study authors were contacted for detailed data when there was insufficient information to determine the relationship between the polymorphism and risk of gastric cancer.

**Statistical analysis.** Pooled ORs and their 95% CIs were used to assess the strength of association between the *CDH1* C-160A polymorphism and risk of gastric cancer. The significance of the pooled ORs was determined by the Z test, and $P < 0.05$ was considered statistically significant. Homozygous (AA vs. CC), heterozygous (CA vs. CC), dominant (CA+AA vs. CC), and recessive (AA vs. CC+CA) genetic models were investigated. Subgroup analysis was performed by ethnicity, quality scores, source of controls, and total sample size. HWE was tested by the Chi-square test among controls, and $P < 0.05$ was considered a departure from HWE. Between-study heterogeneity was evaluated by using the Chi-square based Q test. Heterogeneity was considered significant for $P < 0.05$, and the random-effects model was used. Otherwise, the fixed-effects model was used. Moreover, a meta-regression was used to delineate the major sources of between-study heterogeneity. Sensitivity analyses were performed to assess the stability of the results. Funnel plots and Egger's linear regression test were used to diagnose potential publication bias, and $P < 0.05$ was used as an indication for possible publication bias. All analyses were done with Stata software (version 10.0 StataCorp LP, College Station, TX). *P* values were two-sided.

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## Author contributions

B.J. and K.Z. conceived and designed the experiments. H.S. and C.B. performed the experiments. K.Z., J.O. and W.S. analyzed the data. B.J. wrote the paper.

## Additional information

**Supplementary information** accompanies this paper at http://www.nature.com/scientificreports

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