Roles of E-Cadherin (CDH1) Genetic Variations in Cancer Risk: a Meta-analysis

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Abstract

E-Cadherin (CDH1) genetic variations may be involved in invasion and metastasis of various cancers by altering gene transcriptional activity of epithelial cells. However, published studies on the association of CDH1 gene polymorphisms and cancer risk remain contradictory, owing to differences in living habits and genetic backgrounds. To derive a more better and comprehensive conclusion, the present meta-analysis was performed including 57 eligible studies of the association between polymorphisms of CDH1 gene promoter -160 C>A, -347 G>GA and 3'-UTR +54 C>T and cancer risk. Results showed that these three polymorphisms of CDH1 were significantly associated with cancer risk. For -160 C>A polymorphism, -160A allele carriers (CA and CA+AA) had an increased risk of cancer compared with the homozygotes (CC), and the similar result was discovered for the -160A allele in the overall analyses. In the subgroup analyses, obvious elevated risk was found with -160A allele carriers (AA, CA, CA+AA and A allele) for prostate cancer, while a decreased colorectal cancer risk was shown with the AA genotype. For the -347 G>GA polymorphism, the GAGA genotype was associated with increased cancer risk in the overall analysis with homozygous and recessive models. In addition, results of subgroup analysis indicated that the elevated risks were observed in colorectal cancer and Asian descendants. For +54 C>T polymorphism, a decreased risk of cancer was found in heterozygous, dominant and allele models. Moreover, +54T allele carriers (CT, CT+TT genotype and T allele) showed a potential protective factor in gastric cancer and Asian descendants.

Keywords: E-cadherin (CDH1) polymorphism - invasion - metastasis - cancer risk - meta-analysis

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Introduction

Cancer is one of serious diseases threatening public health, and is becoming more prevalent worldwide, due to the aging and growth of the population. According to the GLOBOCAN 2008, about 12.7 million cases were diagnosed and 7.6 million patients died from cancer in 2008 (Jemal et al., 2011). It is likely that gene-environment interactions are involved in tumorigenesis and development (Lichtenstein et al., 2000). Evidence from epidemiological and genetic studies provides more focus on the inherited susceptibility to cancer. Among these genetic factors, the E-cadherin (CDH1) gene, consists of a large extracellular domain composed of smaller transmembrane and cytoplasmic domains and five repeat domains (Ringwald et al., 1987). CDH1, located on chromosome 16q22.1, is one of the most important tumor suppressor genes encoding an adhesion glycoprotein (Kangelaris et al., 2007; Tamgue et al., 2013), which plays important roles in such aspects of establishment and maintenance of cell polarity and tissue architecture and intracellular adhesion (Takeichi, 1991; Pecina-Slaus, 2003). Therefore, abnormal expression of CDH1 is often occurred in a number of human epithelial cancers (Ghadimi et al., 1999). Recently, the promoter region and 3'-UTR of CDH1 have been reported to be highly polymorphic, which the polymorphisms of CDH1 are -160 C>A (rs16260), -347 G>GA and 3'-UTR +54 C>T in the promoter region and +54 C>T (rs1801026) in 3'-UTR. The emerging numbers of studies showed that three genetic variations within E-Cadherin gene have been proven to be involved in oncogenesis and development (Li et al., 2000; Shin et al., 2004; Li et al., 2011).

A number of studies had investigated the roles of CDH1 gene polymorphisms in human cancers risk, but the results were not consistent. Therefore, we performed a search of relevant literatures and carried out a meta-analysis to obtain a more accurate evaluation of the association between CDH1 genetic polymorphisms and cancer risk.
Materials and Methods

Publication selection

Studies were identified via an electronic search of PubMed and EMBASE using the following terms: “CDH1”, “E-Cadherin”, “polymorphism”, “cancer”, “tumor” or “carcinomas”. We also manually searched the references of these publications in order to retrieve additional studies. Only those published as full-text articles were included as candidates. The search updated on December 2013.

Inclusion and exclusion criteria

Studies estimating the association between CDH1 genetic polymorphisms and cancer risk had to meet all of the following criteria: 1) published in English; 2) they were original epidemiological studies on the correlation between CDH1 genetic polymorphisms and cancer susceptibility; 3) case-control studies; 4) sufficient information provided to estimate odds ratios (ORs) with 95% confidence intervals (CIs). However, duplicated studies, case-only studies, case reports, unpublished data, letters, comments, review, and studies deviated from HWE must be excluded.

Data extraction

For each eligible study, two investigators (Qiwen Deng and Bangshun He) using a standardized data extraction collected carefully information regarding the first author’s last name, year of publication, country of origin, ethnicity of the study population, cancer type, the source of control, genotyping method, polymorphism site and the numbers of cases and controls. All disagreements about eligibility were resolved by discussion after data collection and got consensus meeting with another reviewer.

Statistical methods

Each eligible study was evaluated by Hardy-Weinberg equilibrium (HWE) using the goodness-of-fit \( \chi^2 \) test. If the control of study population was existed \( P < 0.05 \), it was considered to disobey HWE which must be removed. ORs with the corresponding 95% CIs were used to estimate the strength of association between CDH1 –160 C>A, -347 G>GA and +54 C>T polymorphisms and cancer risk. The pooled ORs were also assessed for –160 C>A by homozygous (A/A vs. C/C), heterozygous (C/A vs. C/C), recessive [A/A vs. (C/A + C/C)] and dominant models [ (C/A + A/A) vs. C/C] as well as allele comparison (A vs. C) and so were -347 G>GA and +54 C>T. Stratified analyses were also performed by cancer type, ethnicity and source of control subsequently. (If one of cancer type contained less than two individual studies, it would have been combined into the “other cancers” group).

The heterogeneity across the studies was assessed by Chi square-based Q-test (Handoll, 2006). A fixed-effect model (Mantel-Haenszel method) was chose if \( p \) heterogeneity \( (P_q) > 0.05 \) for the Q test (Mantel et al., 1959). Otherwise, the random-effects model (the DerSimonian and Laird method) was chose (R DerSimonian et al. 1986). Additionally, the stability of results was used to be assessed by excluding each study individually and recalculating the ORs with the corresponding 95% CIs for the remaining ones in the sensitivity analysis. The publication bias was performed by Funnel plots and Egger’s linear regression test (Egger et al., 1997). All statistical tests were performed with STATA version 11.0 for this meta-analysis. All the \( p \) values were two-sided and \( p < 0.05 \) were considered significant.

Results

Characteristics of studies

As is depicted in Figure 1, based on the inclusion criteria, 38 eligible papers were enrolled in this meta-analysis. For –160 C>A, only 39 studies with available data were enrolled in the pooled analysis, which two papers with two cancer types presented two separate studies individually (Nakamura et al., 2002; Zhang et al., 2007) and a publication with five cancer types provided five independent studies (Cattaneo et al., 2006). Breast cancer (3 studies), gastric cancer (13 studies), colorectal cancer (7 studies), prostate cancer (7 studies) and the others were included in the pooled analysis. In addition, of the 39 studies, ethnic descendent of population were divided into three ethnic groups (Asian, Caucasian and African). However, Pookot et al study about Caucasian (Pookot et al., 2006) and Bonilla et al study about European Americans (Bonilla et al., 2006) were not enrolled, since they deviated from HWE (Table 1).

For CDH1 –347 G>GA polymorphism, seven publications with nine studies were chose for eligibility, which were classified into esophageal cancer (Nakamura et al., 2002; Zhang et al., 2007), colorectal cancer (Nakamura et al., 2002; Shin et al. 2004) and the others in the Asian and Caucasian population. In addition, the controls of five studies were hospital-based and only four were population-based (Table 1).

For +54 C>T polymorphism, 9 studies provided case-control studies with available data, which consisted of China (7 studies), other countries (2 studies) related to gastric cancer (Al-Moundhi, 2010; Li et al., 2011; Zhang et al., 2007), esophageal cancer (Zhang et al., 2007; Li et al., 2011) and other cancers in the Asian and Caucasian population. Moreover, the controls of all studies were hospital-based (Table 1).
Main results

-160 C>A. The over results for the -160 C>A polymorphism and cancer risk are shown in Tables 2 and 3. Results of the pooled analysis indicated significantly increased risk was found between -160 C>A polymorphism and overall cancer risk (heterozygous: OR=1.13, 95% CI=1.02-1.24, \(P_h =0.000\); dominant: OR=1.14, 95% CI=1.03-1.26 (Figure 2A), \(P_h =0.000\) and allele: OR=1.11, 95% CI=1.02-1.20, \(P_a =0.000\)). In a stratified analysis by cancer type, a statistically significant association was observed for prostate cancer (homozygous: OR=1.90, 95% CI=1.33-2.71, \(P_h =0.390\) and recessive: OR=1.81, 95% CI=1.28-2.56, \(P_h =0.652\)), but we found that there was a significant decreased risk between –C160A polymorphism and colorectal cancer risk (homozygous: OR=0.88, 95% CI=0.77-1.00, \(Z=1.97, P=0.048\), \(P_h =0.090\) and allele: OR=0.93, 95% CI=0.88-0.98, \(P_h =0.125\)). Ethnicity subgroup analysis revealed that rs16260 A allele was related with increased risk of cancer in Caucasian (heterozygous: OR=1.13, 95% CI=1.00-1.27, \(Z=2.02, P=0.044\), \(P_h =0.002\); dominant: OR=1.16, 95% CI=1.02-1.31, \(P_h =0.000\) and allele: OR=1.12, 95% CI=1.02-1.23, \(P_h =0.000\)). Moreover, source of controls subgroup analysis indicated increased cancer risk for
Table 2. Meta-analysis of the Association Between CDH1 -160 C>A, -347 G>GA and +54 C>T Polymorphisms and Cancer Risk

| Variables | OR (95% CI) | Phet | I² (%) | OR (95% CI) | Phet | I² (%) | OR (95% CI) | Phet |
|-----------|-------------|------|--------|-------------|------|--------|-------------|------|
| For -160 C>A All | 1.13 (1.02-1.24) | 0.000 | 57.0 | 1.11 (1.02-1.20) | 0.000 | 68.8 |
| Cancer type | | | | | | | | |
| Breast | 1.07 (0.96-1.19) | 0.089 | 36.8 | 1.11 (0.97-1.27) | 0.003 | 60.1 |
| Gastric | 1.07 (0.96-1.27) | 0.043 | 53.9 | 0.93 (0.88-0.98) | 0.125 | 40.0 |
| Colorectal | 1.05 (0.87-1.27) | 0.043 | 53.9 | 0.93 (0.88-0.98) | 0.125 | 40.0 |
| Prostate | 1.17 (0.88-1.56) | 0.01 | 64.4 | 1.24 (0.98-1.57) | 0.007 | 66.0 |
| Others | 1.19 (0.90-1.58) | 0.002 | 67.1 | 1.11 (1.02-1.20) | 0.000 | 78.7 |
| Ethnicity | | | | | | | | |
| Asian | 1.10 (0.94-1.29) | 0.004 | 56.6 | 1.10 (0.93-1.30) | 0.000 | 73.5 |
| Caucasian | 1.13 (1.00-1.27) | 0.002 | 54.2 | 1.12 (1.02-1.23) | 0.000 | 63.5 |
| African | 0.59 (0.20-1.76) | 0.027 | 79.5 | 0.67 (0.29-1.53) | 0.041 | 76.0 |
| Mixed | 1.56 (0.67-3.64) | - | - | 2.16 (1.21-3.86) | - | - |
| Source of control | | | | | | | | |
| HB | 1.07 (0.96-1.19) | 0.000 | 72.9 |
| PB | 1.17 (1.06-1.30) | 0.193 | 24.8 |

For -347 G>GA All | 1.16 (1.04-1.30) | 0.193 | 24.8 |
| Cancer type | | | | | | | | |
| Eosphageal | 1.23 (0.99-1.53) | 0.001 | 55.9 | 1.13 (1.00-1.27) | 0.002 | 54.2 | 1.12 (1.02-1.23) | 0.000 | 63.5 |
| Colorectal | 1.13 (1.00-1.27) | 0.002 | 54.2 | 1.12 (1.02-1.23) | 0.000 | 63.5 |
| Others | 1.39 (0.99-1.87) | 0.094 | 51.1 | 0.84 (0.61-1.16) | 0.006 | 72.2 | 0.95 (0.74-1.22) | 0.008 | 70.9 |
| Ethnicity | | | | | | | | |
| Asian | 1.07 (0.96-1.19) | 0.000 | 72.9 |
| Caucasian | 1.17 (0.92-1.50) | 0.000 | 68.1 |
| Mixed | 1.49 (1.13-1.98) | 0.119 | 37.5 | 0.90 (0.72-1.13) | 0.004 | 64.9 | 1.01 (0.83-1.22) | 0.000 | 68.9 |

For +54 C>T All | 1.07 (0.96-1.19) | 0.000 | 72.9 |
| Cancer type | | | | | | | | |
| Gastric | 1.07 (0.96-1.27) | 0.043 | 53.9 | 0.93 (0.88-0.98) | 0.125 | 40.0 |
| Colorectal | 1.05 (0.87-1.27) | 0.043 | 53.9 | 0.93 (0.88-0.98) | 0.125 | 40.0 |
| Prostate | 1.17 (0.88-1.56) | 0.01 | 64.4 | 1.24 (0.98-1.57) | 0.007 | 66.0 |
| Others | 1.19 (0.90-1.58) | 0.002 | 67.1 | 1.11 (1.02-1.20) | 0.000 | 78.7 |
| Ethnicity | | | | | | | | |
| Asian | 1.10 (0.94-1.29) | 0.004 | 56.6 | 1.10 (0.93-1.30) | 0.000 | 73.5 |
| Caucasian | 1.13 (1.00-1.27) | 0.002 | 54.2 | 1.12 (1.02-1.23) | 0.000 | 63.5 |
| African | 0.59 (0.20-1.76) | 0.027 | 79.5 | 0.67 (0.29-1.53) | 0.041 | 76.0 |
| Mixed | 1.56 (0.67-3.64) | - | - | 2.16 (1.21-3.86) | - | - |

Source of control | | | | | | | | |
| HB | 1.07 (0.96-1.19) | 0.000 | 72.9 |
| PB | 1.17 (1.06-1.30) | 0.193 | 24.8 |

Figure 2. A: Forest Plots of Effect Estimates for CDH1 -160 C>A Polymorphism (AA+CA vs. CC). For each of the studies, the estimation of OR and its 95% CI is plotted with a box and a horizontal line, filled diamond pooled OR and its 95% CI. B: Forest plots of effect estimates for CDH1 -347 G>GA polymorphism (GAGA vs. GG). For each of the studies, the estimate of OR and its 95% CI is plotted with a box and a horizontal line, filled diamond pooled OR and its 95% CI. C: Forest plots of effect estimates for CDH1 +54 C>T polymorphism (TT+CT vs. CC). For each of the studies, the estimate of OR and its 95% CI is plotted with a box and a horizontal line, filled diamond pooled OR and its 95% CI.
Table 3. Meta-analysis of the Association Between CDH1 -160C>A, -347 G>GA and +54 C>T Polymorphisms and Cancer Risk by Recessive and Dominant Models

| Variables | No. of studies | No. of individuals | OR (95% CI) | P<sub>het</sub> | F (%) | OR (95% CI) | P<sub>het</sub> | F (%) |
|-----------|----------------|--------------------|-------------|----------------|-------|-------------|----------------|-------|
| For -160 C>A |                |                    | A/A vs. (C/C+C/A) | | | (A/A+C/A) vs. C/C | | |
| All<sup>1</sup> | 39 | 12,858/13,730 | 1.08 (0.92-1.28) | 0.000 | 51.5 | 1.14 (1.03-1.26) | 0.000 | 65 |
| Cancer type | | | | | | | | |
| Breast | 3 | 720/614 | 1.05 (0.69-1.59) | 0.768 | 0.0 | 1.11 (0.88-1.39) | 0.792 | 0.0 |
| Gastric | 13 | 2,722/3,690 | 1.14 (0.82-1.60) | 0.004 | 58.4 | 1.11 (0.95-1.30) | 0.026 | 48.3 |
| Colorectal | 7 | 7,220/7,045 | 0.89 (0.79-1.01) | 0.231 | 26 | 1.03 (0.86-1.23) | 0.044 | 53.6 |
| Prostate | 7 | 1,205/1,659 | 1.81 (1.28-2.56) | 0.652 | 0.0 | 1.22 (0.91-1.64) | 0.004 | 68.2 |
| Others | 9 | 991/1,607 | 1.01 (0.63-1.60) | 0.006 | 62.6 | 1.18 (0.87-1.60) | 0.0 | 75.3 |
| Ethnicity | | | | | | | | |
| Asian | 15 | 2,934/2,958 | 0.98 (0.67-1.44) | 0.002 | 59.6 | 1.14 (0.94-1.37) | 0.000 | 67.4 |
| Caucasian | 21 | 9,717/10,465 | 1.12 (0.94-1.35) | 0.014 | 44.9 | 1.16 (1.02-1.31) | 0.000 | 61.3 |
| African | 2 | 168/229 | 0.69 (0.20-2.34) | 0.700 | 0.0 | 0.60 (0.21-1.72) | 0.025 | 80.1 |
| Mixed | 1 | 39/78 | 4.77 (1.34-17.02) | - | - | 2.07 (0.94-4.54) | - | - |
| Source of control | | | | | | | | |
| HB | 26 | 10,414/11,074 | 1.01 (0.82-1.25) | 0.000 | 55.7 | 1.09 (0.96-1.25) | 0.000 | 69.3 |
| PB | 13 | 2,444/2,656 | 1.24 (1.02-1.52) | 0.234 | 20.7 | 1.19 (1.07-1.32) | 0.185 | 25.7 |
| For -347 G>GA | | | | | | | | |
| All | 9 | 2,202/1,878 | 1.55 (1.17-2.05) | 0.175 | 30.4 | 0.95 (0.75-1.19) | 0.001 | 68.5 |
| Cancer type | | | | | | | | |
| Esophageal | 2 | 408/490 | 1.43 (0.80-2.54) | 0.298 | 7.7 | 0.82 (0.43-1.58) | 0.047 | 74.8 |
| Colorectal | 2 | 356/294 | 2.91 (1.08-7.85) | 0.084 | 66.5 | 1.34 (0.96-1.86) | 0.055 | 72.8 |
| Others | 5 | 1,438/1,584 | 1.47 (1.05-2.06) | 0.099 | 48.7 | 0.88 (0.65-1.21) | 0.006 | 72.2 |
| Ethnicity | | | | | | | | |
| Asian | 8 | 2,017/1,552 | 1.55 (1.17-2.05) | 0.119 | 39 | 0.93 (0.72-1.21) | 0.001 | 72.4 |
| Caucasian | 1 | 185/326 | 1.77 (0.25-12.67) | - | - | 1.01 (0.66-1.54) | - | - |
| Source of control | | | | | | | | |
| HB | 5 | 1,586/1,258 | 1.50 (1.11-2.03) | 0.098 | 48.9 | 0.91 (0.68-1.22) | 0.005 | 73.4 |
| PB | 4 | 616/620 | 1.90 (0.91-3.95) | 0.249 | 27.1 | 1.00 (0.64-1.56) | 0.018 | 70.1 |
| For +54 C>T | | | | | | | | |
| All | 9 | 1,978/2,149 | 0.89 (0.60-1.32) | 0.000 | 76.3 | 0.70 (0.60-0.81) | 0.186 | 29.1 |
| Cancer type | | | | | | | | |
| Gastric | 3 | 643/730 | 0.82 (0.37-1.84) | 0.000 | 87 | 0.57 (0.44-0.75) | 0.097 | 57.1 |
| Esophageal | 2 | 643/653 | 0.78 (0.59-1.03) | 0.079 | 67.6 | 0.85 (0.65-1.12) | 0.873 | 0.0 |
| Others | 4 | 692/1,109 | 0.95 (0.38-2.41) | 0.003 | 78.5 | 0.70 (0.56-0.87) | 0.505 | 0.0 |
| Ethnicity | | | | | | | | |
| Asian | 8 | 1,922/1,794 | 0.79 (0.55-1.14) | 0.001 | 71.4 | 0.68 (0.59-0.79) | 0.221 | 26 |
| Caucasian | 1 | 56/355 | 4.87 (1.49-15.94) | - | - | 1.05 (0.57-1.94) | - | - |

HB, Hospital based; PB, Population based; 1 The control numbers was only calculated once if the same controls were used. Statistically significant results were in bold.

and 3. Decreased risk association was observed in the overall pooled analysis for the comparison of dominant model (OR=0.70, 95% CI=0.60-0.81, P<sub>het</sub>=0.186) showed in Figure 2C and allele model (OR=0.81, 95% CI=0.68-0.97, P<sub>het</sub>=0.002). In the subgroup analysis by cancer type, rs1801026 T allele was significantly associated with decreased risk of gastric cancer (heterozygous: OR=0.58, 95% CI=0.44-0.77, P<sub>het</sub>=0.511 and dominant: OR=0.57, 95% CI=0.44-0.75, P<sub>het</sub>=0.097).

Test of heterogeneity

There was significant heterogeneity revealed among overall studies for the –160 C>A polymorphism and cancer risk (homozygous, heterozygous, recessive, dominant and allele: P<sub>het</sub>=0.000). For +54 C>T polymorphism, the results indicated that Zhang et al. (2007) and Jacobs et al. (2011) were the main origin of heterogeneity. By removed these two studies, the heterogeneity was decreased (CT+TT vs. CC: P<sub>het</sub>=0.067). However, the results were stable for –347 G>GA polymorphism by sensitivity analysis. In addition, no other single study was found to influence the pooled ORs by sensitivity analysis.

Sensitivity analysis

Sensitivity analysis was conducted to assess the stability of the results and the source of heterogeneity by sequential removal of each eligible study. For –160 C>A polymorphism, six studies (Wu et al., 2002; Pookot et al., 2006; Grünhage et al., 2007; Pittman et al., 2009; Chien et al., 2011; Corso et al., 2012) were the main origin of heterogeneity, which the heterogeneity was obviously decreased after exclusion of these studies (CA+AA vs. CC: P<sub>het</sub>=0.056). For +54 C>T polymorphism, the results were stable for –347 G>GA polymorphism by sensitivity analysis. In addition, no other single study was found to influence the pooled ORs by sensitivity analysis.
Publication bias

Publication bias of studies was conducted to assess by Begg’s funnel plot and Egger’s test. The shape of the funnel plot did not show significant asymmetry in three polymorphisms of CDH1 (Figure 3 A, B, C). In addition, egger’s test was used to provide statistical evidence of funnel plot asymmetry. We observed no obvious publication bias for −160 C>A, −347 G>GA and +54 C>T. Hence, there was no publication bias revealed in the current meta-analysis.

Discussion

As we all know, the association between CDH1 polymorphisms and cancer risk had been investigated in many studies. However, for different cancers, the results remained to be inconsistent. Moreover, the results were contradictory for the same cancer from many studies. In the current case-control study, associations of three CDH1 polymorphisms (−160 C>A, rs16260; −347 G>GA, rs5030625; +54 C>T, rs1801026) and cancer risk were estimated. The polymorphisms of CDH1 may play a critical role in the tumorigenesis, development and prognosis of sever kinds of cancer, such as colorectal cancer, gastric cancer, prostate cancer, breast cancer and esophageal cancer (Lei et al., 2002; Jonsson et al., 2004; Medina-Franco et al., 2007; Zhang et al., 2007; Li et al., 2011). Therefore, we performed this meta-analysis to estimate the associations between CDH1 polymorphisms and cancer risk.

We concluded that rs16260 A allele was obviously associated with increased cancer risk based on 12858 cases and 13730 controls in overall pooled results from 39 studies. A stratified analysis by cancer type indicated that rs16260 AA genotype increased risk of prostate cancer, which was consistent with results for the previous study (Qiu et al., 2008), but no significant associations were observed in breast cancer and gastric cancer, which revealed that rs16260 polymorphism might have different effects on distinct cancers. Otherwise, results appeared in gastric cancer were inconsistent with previous studies (Cui et al., 2011; Corso et al., 2012; Li et al., 2012), which might be caused by limited studies enrolled in the present meta-analysis. Different inclusion and exclusion criteria should also be considered to influence the final pooled results. However, for colorectal cancer based on 7220 cases and 7045 controls, rs16260 A allele was a protective factor, which was contradictory with the hypothesis that the rs16260 A allele was associated with reduced CDH1 transcription (Li et al., 2000; Nakamura et al., 2002; Shin et al., 2004). The discrepancy may result from different mechanisms of carcinogenesis. For example, for gastric cancer and colorectal cancer, the risk factors have bad dietary habit (eating high-fat, high-protein and processed food frequently that was rich in nitrate, fungus, aromatic hydrocarbon and methylcholanthrene in faeces contributing to tumorigenesis), helicobacter pylori infection, smoking and drinking respectively. Moreover, men, whose family had a history of gastric and colorectal cancer, would be at increased risk of the condition according the epidemiology reports, while for prostate cancer, sexual activity, fat intake, race and family history were main source of risk factors. The varied mechanisms may have different effects on the −160 C>A polymorphism leading to the different results. Subsequently stratified analysis by country indicated borderline increased cancer risk was found only in Caucasian population, which might be related with genetic background and the environment exposure, but no significant association among Asian and African population was discovered, maybe due to the small sample size (2934 cases and 2958 controls in Asian; 168 cases and 229 controls in African) or the different frequency of rs16260 A allele variant in this study. Finally, the results, for a stratified analysis by source of controls, indicated that different sources of controls played different roles in cancer risk by the stratified analysis. A significant association with increased cancer risk was discovered for population-based controls, which was inconsistent with the previous study (Qiu et al., 2008; Wang et al., 2011). As population-based controls usually represented the healthy population, but there were the sick people in the hospital-based controls, a proper and representative population-based controls should enrolled in the further studies to make the results more dependable.

Several studies showed that CDH1 −347GA/GA genotype was obvious association with the increased cancer risk (Zhang et al., 2007; Li et al., 2008; Chien et al., 2011; Chien et al., 2012) Our results showed that −347GA allele were a risk factor in the overall pooled ORs for homozygous and recessive models based on 2202 cases and 1878 controls, which were similar results with the previous study on the basis of 822 cases and 803 controls (Wang et al., 2011). However, similar results were discovered by different genetic models, which inadequate amount of studies and selection bias lead to the condition. Cancer type by subgroup analysis indicated that an increased cancer risk was found in colorectal cancer, which was consistent with Wang et al. study. Moreover, the similar results were observed in Asian descendants but not in Caucasian descendants. As described above, the genetic background and frequencies of −347GA allele in different
races contributed to these results. However, there were only nine studies enrolled in present study. Well-designed, unbiased, large case-control studies should be performed to acquire a more precisely association between CDH1 -374 G>GA polymorphism and cancer risk due to the small size of population for the two ethnicities.

As for CDH1 +54 C>T polymorphism, there has been no meta-analysis concerning the association between the CDH1 +54 C>T polymorphism and cancer risk up to now. Our results indicated +54 T allele and C/T genotype were significant association with decreased cancer risk between CDH1 +54 C>T polymorphism and cancer risk. And subgroup analysis by ethnicity and cancer type revealed that +54T allele and C/T genotype were a protective factor in Asian and gastric cancer respectively. Meanwhile, a similar association with decreased cancer risk was also observed for comparison of TT+CT vs. CC in gastric cancer and Asian. The results suggested different cancer types and races might lead to distinct effects of +54 C>T polymorphism. These conditions may be explained by the possible mechanism that +54 C/C genotype was associated with the down-regulation of E-cadherin expression by modulating the mRNA stability (Keirsebilck et al., 1998) and the C allele decreased the transcriptional efficiency by 2-fold compared with the T allele by a dual luciferase reporter assay, so this polymorphism could increase the risk of certain cancers by decreasing the expression of E-cadherin (Li et al., 2011). However, the study showed that +54T allele significantly increased breast cancer risk in south Indian women (Tipirisetti et al., 2013), the contradictory conclusion might resulted from genetic and ethnic variability among populations, deviated from HWE in the controls and also the different selection criteria chosen by investigators. In addition, only nine studies were enrolled in the analysis, which could affect the results due to small amount of studies. To acquire a more accurate conclusion, more related and well-designed studies were needed to further clarify the association of +54 C>T polymorphism and cancer risk.

Some limitations of this meta-analysis should be acknowledged. Firstly, all eligible studies were limited to English papers. So some studies were missed due to not in English, but corresponded with the inclusion criteria. Secondly, while publication bias was not detected in three polymorphisms of CDH1, publication bias which we did not detect might also exist in other polymorphisms owing to small amount of studies. Thirdly, controls were not uniformly defined. Although the healthy populations were the main source of the controls, some of them might be patients. Fourthly, in the subgroup analysis, the number of cases and controls was relatively small in different cancers, races and source of controls, not having sufficient statistical power to achieve the real association. At last, our results had to interpret with caution owing to basing on unadjusted estimates so that further studies were conducted to confirm our unadjusted estimates.

In conclusion, we performed this meta-analysis to evaluate the association between three CDH1 polymorphisms and cancer risk. Despite these above limitations, our results showed that -160 C>A was associated with an increased risk, especially for prostate cancer which was contrary with colorectal cancer, Caucasian descendants and population-based controls. Meanwhile, -347GA/GA genotype was significant associated with increased risk of cancer, especially in colorectal cancer, Asian descendants and hospital-based controls. In addition, +54T allele and C/T genotype were the protective factor in the overall pooled analysis, especially in Asian descendants and gastric cancer. However, it was essential to conduct more large trials using standardized unbiased design, homogeneous cancer patients and well-matched controls. Moreover, gene-environment and gene-gene interactions should also be taken into account in the analysis so that eventually lead to our better and comprehensive estimates of the three CDH1 polymorphisms and cancer risk.

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