RESEARCH ARTICLE

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

Qi-Wen Deng[1&], Bang-Shun He[1&], Yu-Qin Pan[1], Hui-Ling Sun[2], Ye-Qiong Xu[1], Tian-Yi Gao[1], Rui Li[2], Guo-Qi Song[1], Shu-Kui Wang[1]*

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

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 (rs5030625) 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.

*[1]Central Laboratory, Nanjing First Hospital, Nanjing Medical University, [2]Department of Life Sciences, Nanjing Normal University, Nanjing, China &Equal contributors *For correspondence: shukwang@163.com*

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_h) > 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
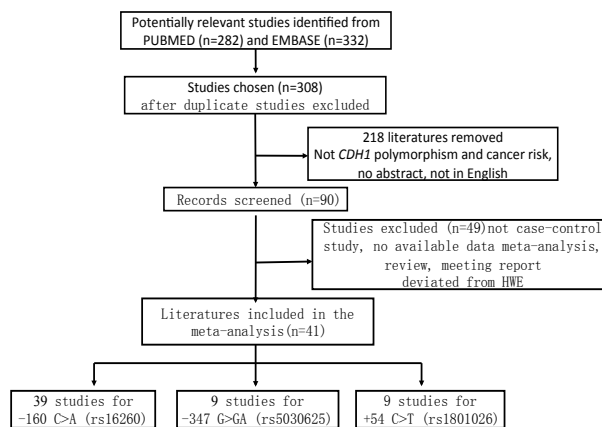
Figure 1. Flow Chart of Studies Identified According to Inclusion and Exclusion Criteria

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-Moundhri, 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).

Table 1. Characteristics of Studies Included in the Meta-analysis

Cancer	First author	Year	Country	Ethnicity	Source	Genotyping method	Polymorphism site	Case/Control	HWE
breast cancer	Lei	2002	Sweden	Caucasian	HB	SSCP	CDH1 -160 C>A	576/348	0.58
	Sarrio	2003	Spain	Caucasian	HB	PCR-RFLP	CDH1 -160 C>A	45/20	0.57
	Cattaneo	2006	Italy	Caucasian	PB	PCR-RFLP	CDH1 -160 C>A	99/246	0.48
	Tipirisetti	2013	India	Asian	HB	Sequencing and PCR-RFLP	CDH1 -347 G>GA	202/250	0.52
colorectal cancer	Porter	2002	U.K.	Caucasian	HB	PCR-RFLP	CDH1 -160 C>A	290/171	0.07
	Nakamura	2002	Japan	Asian	PB	SSCP	CDH1 -160 C>A, -347 G>GA	96/147	0.66, 0.25
	Shin	2004	Korea	Asian	PB	PCR-RFLP	CDH1 -160 C>A, -347 G>GA	260/147	0.44, 0.05
	Cattaneo	2006	Italy	Caucasian	PB	PCR-RFLP	CDH1 -160 C>A	106/246	0.48
	Tan	2007	Germany	Caucasian	PB	PCR-RFLP	CDH1 -160 C>A	498/600	0.36
	Grunhage	2007	Germany	Caucasian	HB	PCR-RFLP	CDH1 -160 C>A	188/217	0.29
	de Lima	2009	Brazil	Caucasian	HB	PCR-RFLP	CDH1 -160 C>A	103/105	0.84
	Pittman	2009	U.K.	Caucasian	HB	AS-PCR	CDH1 -160 C>A	5679/5412	0.39
Esophageal cancer	Nakamura	2002	Japan	Asian	PB	SSCP	CDH1 -160 C>A, -347 G>GA	74/147	0.66, 0.25
	Zhang	2007	China	Asian	HB	PCR-RFLP	CDH1 -347 G>GA, +54 C>T	333/343	0.36, 0.06
	Li	2011	China	Asian	HB	PCR-RFLP	CDH1 +54 C>T	310/310	0.51
gastric cancer	Wu	2001	Taiwan	Asian	HB	PCR-RFLP	CDH1 -160 C>A	201/196	0.3
	Humar	2002	Italy	Caucasian	HB	PCR-RFLP	CDH1 -160 C>A	53/70	0.56
	Pharoah	2002	Canada	Caucasian	HB	Mixed	CDH1 -160 C>A	433/466	0.2
	Park	2003	Korea	Asian	HB	SSCP	CDH1 -160 C>A	292/146	0.43
	Lu	2005	China	Asian	PB	PCR-RFLP	CDH1 -160 C>A	206/261	0.39
	Medina-Franco	2006	Mexico	Cacausian	HB	SSCP	CDH1 -160 C>A	39/78	0.7
	Cattaneo	2006	Italy	Caucasian	PB	PCR-RFLP	CDH1 -160 C>A	107/246	0.48
	Yamada	2007	Japan	Asian	HB	PCR-RFLP	CDH1 -160 C>A	148/292	0.92
	Zhang	2007	China	Asian	HB	PCR-RFLP	CDH1 -347 G>GA, +54 C>T	239/343	0.36, 0.06
	Jenab	2008	France	Caucasian	HB	TaqMan	CDH1 -160 C>A	245/949	0.87
	Corso	2009	Italy	Caucasian	PB	PCR-RFLP	CDH1 -160 C>A	412/408	0.39
	Borges	2010	Brazil	Caucasian	HB	Sequencing	CDH1 -160 C>A	58/51	0.09
	AI-Moundhri	2010	Sultanate	Asian	HB	Sequencing of Oman	CDH1 -160 C>A, +54 C>T	174/166, 174/157	0.43,0.85
	Li	2011	China	Asian	HB	PCR-RFLP	CDH1 +54 C>T	230/230	0.87
	Zhan	2012	China	Asian	HB	PCR-LDR	CDH1 -160 C>A	354/361	0.06
prostate cancer	Tsukino	2003	Japan	Asian	HB	PCR-RFLP	CDH1 -160 C>A	219/219	0.66
	Hajdinjak	2004	Slovenia	Caucasian	HB	TaqMan	CDH1 -160 C>A	183/198	0.48
	Lindstrom	2005	Sweden	Caucasian	PB	DASH	CDH1 -160 C>A	199/506	0.15
	Kamoto	2005	Japan	Asian	HB	PCR-RFLP	CDH1 -160 C>A	236/348	0.25
	Pookot	2005	USA	African	HB	PCR-RFLP	CDH1 -160 C>A	49/117	0.92
	Bonilla	2006	USA	African	HB	PCR-RFLP	CDH1 -160 C>A	208/235	0.23
	Goto	2007	Japan	Asian	HB	PCR-RFLP	CDH1 -160 C>A	200/159	0.25
Other cancers	Kiemeney	2006	Netherland	Caucasian	PB	PCR-RFLP	CDH1 -160 C>A, -347 G>GA	194/341, 185/326	0.94, 0.15
	Cattaneo	2006	Italy	Caucasian	PB	PCR-RFLP	CDH1 -160 C>A	101/246	0.48
	Li	2011	China	Asian	HB	PCR-RFLP	CDH1 +54 C>T	280/330	0.49
	Cattaneo	2006	Italy	Caucasian	PB	PCR-RFLP	CDH1 -160 C>A	92//246	0.48
	Govatati	2011	India	Asian	HB	PCR-RFLP	CDH1 -347 G>GA	715/500	0.16
	Chien	2011	Taiwan	Asian	HB	PCR-RFLP	CDH1 -160 C>A	131/347	0.84
	Li	2011	China	Asian	HB	PCR-RFLP	CDH1 +54 C>T	261/261	0.86
	Chien	2011	Taiwan	Asian	HB	PCR-RFLP	CDH1 -160 C>A	251/347	0.84
	Wang	2012	China	Asian	HB	PCR-RFLP	CDH1-160C>A, -347G>GA, +54C>T	92/169, 97/165, 95/163	0.13, 0.05, 0.14
	Jacobs	2011	Germany	Caucasian	HB	TaqMan	CDH1 -160 C >A, +54 C>T	56/361, 56/355	0.92, 0.50

PB, population based; HB, hospital based; PCR, polymerase chain reaction; PCR-RFLP, restriction fragment length polymorphism; AS-PCR, allele-specific PCR; SSCP, single-strand conformation polymorphism; DASH, dynamic allele-specific hybridization; HWE, Hardy-Weinberg equilibrium

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_h =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	No.	Homozygous			Heterozygous			Allele	
		OR (95% CI)	Phet	I² (%)	OR (95% CI)	Phet	I² (%)	OR (95% CI)	Phet
For -160 C >A		A/A vs. C/C			C/A vs. C/C			A vs. C	
All[1]	12,858/13,730	1.17 (0.96-1.43)	0.000	60.6	**1.13 (1.02-1.24)**	0.000	57.0	1.11 (1.02-1.20)	0.000	68.8
Cancer type									
Breast	720/614	1.09 (0.71-1.68)	0.847	0.0	1.11 (0.88-1.41)	0.681	0.0	1.08 (0.90-1.29)	0.918	0.0
Gastric	2,722/3,690	1.20 (0.84-1.72)	0.002	61.5	1.07 (0.96-1.19)	0.089	36.8	1.11 (0.97-1.27)	0.003	60.1
Colorectal	7,220/7,045	0.88 (0.77-1.00)	0.09	45.2	1.05 (0.87-1.27)	0.043	53.9	**0.93 (0.88-0.98)**	0.125	40.0
Prostate	1,205/1,659	1.90 (1.33-2.71)	0.39	4.8	1.17 (0.88-1.56)	0.01	64.4	1.24 (0.98-1.57)	0.007	66.0
Others	991/1,607	1.08 (0.61-1.91)	0.000	72.9	1.19 (0.90-1.58)	0.002	67.1	**1.11 (1.02-1.20)**	0.000	78.7
Ethnicity									
Asian	2,934/2,958	1.03 (0.67-1.60)	0.000	67	1.10 (0.94-1.29)	0.004	56.6	1.10 (0.93-1.30)	0.000	73.5
Caucasian	9,717/10,465	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
African	168/229	0.56 (0.17-1.87)	0.528	0.0	0.59 (0.20-1.78)	0.027	79.5	0.67 (0.29-1.53)	0.041	76.0
Mixed	39/78	**5.87 (1.54-22.31)**	-	-	1.56 (0.67-3.64)	-	-	**2.16 (1.21-3.86)**	-	-
Source of control									
HB	10,414/11,074	1.09 (0.85-1.41)	0.000	65.2	1.09 (0.96-1.23)	0.000	61.5	1.07 (0.96-1.19)	0.000	72.9
PB	2,444/2,656	**1.31 (1.06-1.62)**	0.206	23.5	**1.16 (1.04-1.30)**	0.192	24.9	**1.16 (1.06-1.26)**	0.193	24.8
For -347 G >GA		GA/GA vs. G/G			G/GA vs. G/G			GA vs. G	
All	2,202/1,878	**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)	0.001	68.9
Cancer type									
Esophageal	408/490	1.38 (0.77-2.48)	0.205	37.8	0.90 (0.68-1.19)	0.086	66.1	0.88 (0.50-1.58)	0.037	77.1
Colorectal	356/294	**2.99 (1.11-8.06)**	0.062	71.3	1.23 (0.88-1.73)	0.103	62.4	1.32 (0.72-2.43)	0.035	77.6
Others	1,438/1,584	1.39 (0.99-1.97)	0.084	51.2	0.84 (0.61-1.16)	0.006	72.2	0.95 (0.74-1.22)	0.008	70.9
Ethnicity									
Asian	2,017/1,552	1.49 (1.12-1.98)	0.078	45.2	0.88 (0.68-1.15)	0.002	69.2	1.00 (0.80-1.24)	0.001	72.7
Caucasian	185/326	1.77 (0.25-12.67)	-	-	0.99 (0.64-1.52)	-	-	1.03 (0.70-1.52)	-	-
Source of control									
HB	1,586/1,258	**1.44 (1.06-1.96)**	0.081	51.8	0.85 (0.63-1.16)	0.005	73.0	0.98 (0.77-1.24)	0.006	72.1
PB	616/620	1.84 (0.89-3.80)	0.169	40.5	1.01 (0.79-1.28)	0.057	60.1	1.05 (0.69-1.58)	0.010	73.3
For +54 C >T		T/T vs. C/C			C/T vs. C/C			T vs. C	
All	1,978/2,149	0.76 (0.46-1.25)	0.000	74.6	**0.70 (0.60-0.82)**	0.673	0.0	**0.81 (0.68-0.97)**	0.002	67.4
Cancer type									
Gastric	643/730	0.62 (0.23-1.64)	0.002	84.2	**0.58 (0.44-0.77)**	0.511	0.0	0.75 (0.48-1.16)	0.001	85.1
Esophageal	643/653	0.87 (0.48-1.60)	0.159	49.6	0.85 (0.64-1.13)	0.607	0.0	0.86 (0.72-1.02)	0.326	0.0
Others	692/1,109	0.83 (0.28-2.50)	0.003	78.8	**0.70 (0.55-0.88)**	0.907	0.0	**0.78 (0.66-0.93)**	0.053	60.9
Ethnicity									
Asian	1,922/1,794	0.64 (0.41-1.01)	0.003	67.2	**0.70 (0.60-0.81)**	0.583	0.0	**0.78 (0.66-0.93)**	0.005	65.4
Caucasian	56/355	4.60 (1.39-15.21)	-	-	0.80 (0.40-1.58)	-	-	1.32 (0.79-2.19)	-	-

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
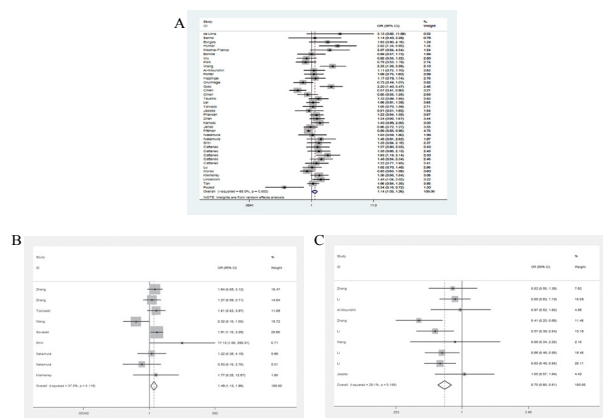

Figure 2. A: Forest Plots of Effect Estimates for CDH1 –160 C>A Polymorphism (AA+CA vs. CC). For each of the studies, the estimation of OR and its 95% CI is plotted with a box and a horizontal line, filled diamond pooled OR and its 95% CI. B: Forest plots of effect estimates for CDH1 –347 G>GA polymorphism (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

population-based controls (homozygous: OR=1.31, 95% CI=1.06-1.62, P_h=0.206; heterozygous: OR=1.16, 95% CI=1.04-1.30, P_h=0.192; allele: OR=1.16, 95% CI=1.06-1.26, P_h=0.193; recessive: OR=1.24, 95% CI=1.02-1.52, P_h=0.234 and dominant: OR=1.19, 95% CI=1.07-1.32, P_h=0.185).

-347 G>GA. The over results for the -347 G>GA polymorphism and cancer risk are shown in Tables 2 and 3. Results of the pooled analysis indicated significantly increased risk was found between -347 G>GA polymorphism and overall cancer risk (homozygous: OR=1.49, 95% CI=1.13-1.98 (Figure 2B), P_h=0.119 and recessive: OR=1.55, 95% CI=1.17-2.05, P_h=0.175). In the subgroup analysis, a statistically significant association was found for colorectal cancer (homozygous: OR=2.99, 95% CI=1.11-8.06, P_h=0.062 and recessive: OR=2.91, 95% CI=1.08-7.85, P_h=0.54), Asian (homozygous: OR=1.49, 95% CI=1.12-1.98, P_h=0.078 and recessive: OR=1.55, 95% CI=1.17-2.05, P_h=0.119) and hospital-based controls (homozygous: OR=1.44, 95% CI=1.06-1.96, P_h=0.081 and recessive: OR=1.50, 95% CI=1.11-2.03, P_h=0.098).

+54 C>T. The over results for the +54 C>T polymorphism and cancer risk are shown in Tables 2

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	Recessive			Dominant		
			OR (95% CI)	P^{het}	I² (%)	OR (95% CI)	P^{het}	I² (%)
For –160 C >A			A/A vs. (C/C+C/A)			(A/A+C/A) vs. C/C		
All[1]	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	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)	0.708	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			GA/GA vs. (G/G+G/GA)			(GA/GA+G/GA) vs. G/G		
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			T/T vs. (C/C+C/T)			(T/T+C/T) vs. C/C		
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_h=0.186) showed in Figure 2C and allele model (OR=0.81, 95% CI=0.68-0.97, P_h=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_h=0.511 and dominant: OR=0.57, 95% CI=0.44-0.75, P_h=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 =0.000), -347 G>GA (homozygous: P =0.119; heterozygous: P =0.004, dominant and allele: P =0.000) and +54 C>T (homozygous: P =0.000; recessive: P =0.000 and allele: P =0.000). Hence, random-effect model was applied to generate CIs for these genetics models comparison (P_h

<0.05). Otherwise, fixed-effect model was used.

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_h=0.056). 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_h=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.
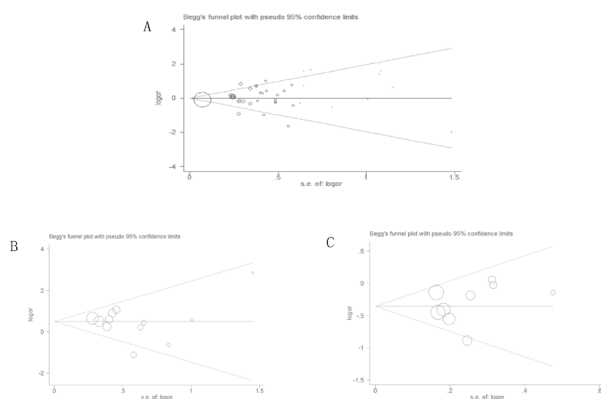
Figure 3. Begg's Funnel Plot of Egger's Test for Publication Bias for Three Polymorphisms. Each circle represents as an independent study for the indicated association. Log[OR], natural logarithm of OR. Horizontal lines mean effect size. A: Begg's funnel plot of publication bias test for CDH1 –160 C>A polymorphism. B: Begg's funnel plot of publication bias test for –347 G>GA polymorphism. C: Begg's funnel plot of publication bias test for CDH1 +54 C>T polymorphism

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.

Acknowledgements

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