RESEARCH ARTICLE

Lack of Association between the CDH1 -160C>A Polymorphism and Risk of Gastrointestinal Cancer - a Meta-Analysis

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Abstract

E-cadherin (CDH1) genetic variations alter gene transcriptional activity of epithelial cells *in vitro* and may cause susceptibility to various cancers. Associations of CDH1 -160C>A polymorphism with various cancers have been widely reported. However, the results are controversial and inconsistent. To derive a more accurate estimation of the relationship, a meta-analysis was performed with regard to gastrointestinal (GI) cancer risk. Eligible studies were identified through a search of PubMed database until December 2015. Associations between the CDH1 -160C>A polymorphism and GI cancer risk was considered by odds ratios (ORs) together with their 95% confidence intervals (CIs). A total of 31 studies including 11,606 cases and 12,655 controls were involved in this meta-analysis. Overall, this meta-analysis showed no association between CDH1 -160C>A polymorphism and GI cancer risk (A vs. C: OR = 1.08, 95%CI = 0.98-1.18, P = 0.086;CA vs. CC: OR = 1.09, 95%CI = 0.97-1.22, P = 0.118; AA vs. CC: OR = 1.10, 95%CI = 0.89-1.35, P = 0.356; AA vs. CC + CA: OR = 1.06, 95%CI = 0.96-1.18, P = 0.207; CA+AA vs. CC: OR = 1.01, 95%CI = 0.84-1.22, P = 0.89). In subgroup analysis, similar results were found. In conclusion, this meta-analysis has demonstrated that there is a lack of association of the CDH1-160C>A polymorphism with GI cancer susceptibility.

Keywords: E-cadherin - polymorphism - gastrointestinal cancer - risk - meta-analysis

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Introduction

Cancer has a significant impact on public health and is the second main cause of death in developing countries (Torre et al., 2015). Gastrointestinal (GI) tract and the associated organs of digestion are responsible for more cancers and common types of GI cancer are esophageal, gastric and colorectal cancer (Siegel et al., 2012). There is considerable geographic diversity in the rates of GI cancers (Yamada T, 2009). Most gastrointestinal stromal tumors (GISTs) arise in the stomach and small intestine. GI tumors might not cause any signs unless they are in a determinate location or grow to a certain size and most of the cancers are detected at an advanced stage when prognosis is poor (Nakayama and Nakayama, 2006). Therefore, it is important to investigate the genetic and epigenetic variation in susceptibility to GI carcinogenesis and recognize the markers that will facilitate identification of individuals at risk of GI carcinogenesis.

E-cadherin gene (CDH1) is located chromosome 16q22.1, and this region of chromosome encode a 97-kDa transmembrane glycoprotein (Zou et al., 2009). This protein consists of a highly conserved cytoplasmic tail, a transmembrane region and five extracellular cadherin repeats (Shapiro and Weis, 2009). Cadherins are calcium-dependent cell adhesion proteins. They preferentially react with themselves in a homophilic interaction in connecting cells; cadherins may thus contribute to the sorting of heterogeneous cell types (Vincent et al., 2004). CDH1 is involved in mechanisms regulating cell-cell adhesions, mobility, proliferation and is necessary to the normal development and maintenance of cells (Agiostratidou et al., 2006). E-cadherin is the major member of cell adhesion molecule family expressed by epithelial cells (Breier et al., 2014).

The effects of CDH1 polymorphisms on the incidence of several human cancers have been investigated. The CDH1 - 160C>A polymorphism (rs16260) representing a C to A transversion in the -160 position of the promoter and the CDH1 -160C>A polymorphism has been associated with susceptibility to esophageal, gastric and colorectal cancer. This polymorphism in the CDH1 gene promoter was shown affect CDH1 transcription, thus suppressing CDH1 expression and may increase susceptibility to cancer development in some populations (Li et al., 2000).

In previous years, several studies have investigated the relationship between CDH1 -160C>A polymorphism and GI cancer susceptibility, but the published results

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are controversial and inconsistent. In 2006, Cattaneo found that association between the altered allele and an increased susceptibility to the colorectal and gastric tumors (1.66- and 1.81- fold, respectively) in an Italian population (Cattaneo et al., 2006). However, in 2005, Lu reported that E-cadherin gene -160C>A promoter polymorphism may not play a significant role in the risk of gastric cancer in Chinese population (OR=0.90 and 95% CI=0.42-2.01 for AA genotype) (Lu et al., 2005). In 2008, Tan concluded that CDH1 -160C>A polymorphism is not associated with the susceptibility to the colorectal cancer in the German population (OR=0.85 and 95% CI =0.50-1.47 for AA genotype) (Tan et al., 2008). We accomplished an updated meta-analysis of all available case-control literatures applying 5 genetic models to gain a more reliable conclusion. Besides, stratified analysis by ethnicity, source of controls and cancer type were also conducted for further study.

Materials and Methods

Publication selection

A systematic literature search in the PubMed database was performed to identify studies about the association between CDH1 C-160A polymorphism and digestive system cancer (up to December, 2015). The search terms and keywords used were as follows: "polymorphism", "CDH1 or E-Cadherin", "esophageal", "gastric", "colorectal" and "cancer or carcinoma". Moreover, a hand search for references cited in the eligible articles was also conducted to look for additional potential studies. An article expressed results from more than one population was considered as separate studies and some studies included several cancer types.

Inclusion and exclusion criteria

Studies included in current meta-analysis should comprise the following inclusion criteria: (a) the study was published in English, (b)case-control studies about the association of CDH1 C-160A polymorphism with risk of digestive system cancer, (c) the study provided sufficient genotype distribution data to compute odds ratios (ORs) and 95% confidence intervals (CIs). Studies such as case reports, case-only studies, duplicated studies, unpublished data, letters and review must be excluded.

Data extraction

For each eligible study, the following information were extracted: cancer location, first author's name, year of publication, country, ethnicity of the study population, source of controls, number of cases and controls with different genotypes, genotyping method and Hardy-Weinberg equilibrium (HWE) for controls.When we had different views on the results, discussions were conducted to reach an agreement.

Statistical analysis

The strength of association between the CDH1 C-160A polymorphism and risk of digestive system cancer was assessed by odds ratios (ORs) with 95% confidence intervals (CIs) under the Allelic model (A vs. C), heterozygote model (CA vs. CC), homozygote model (AA vs. CC), recessive model (AA vs. CC+CA) and dominant model (CA+AA vs. CC). The significance of the combine ORs was determined by the Z test, and $P< 0.05$ was considered statistically significant. Subgroup analyses were conducted based on ethnicity, source of controls and cancer type. The heterogeneity among the studies was evaluated by the Q-test, and the degree of

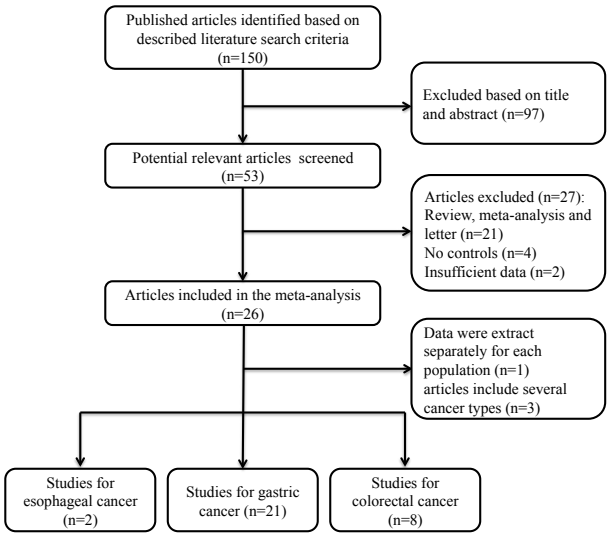

Figure 1. Selection of Reports

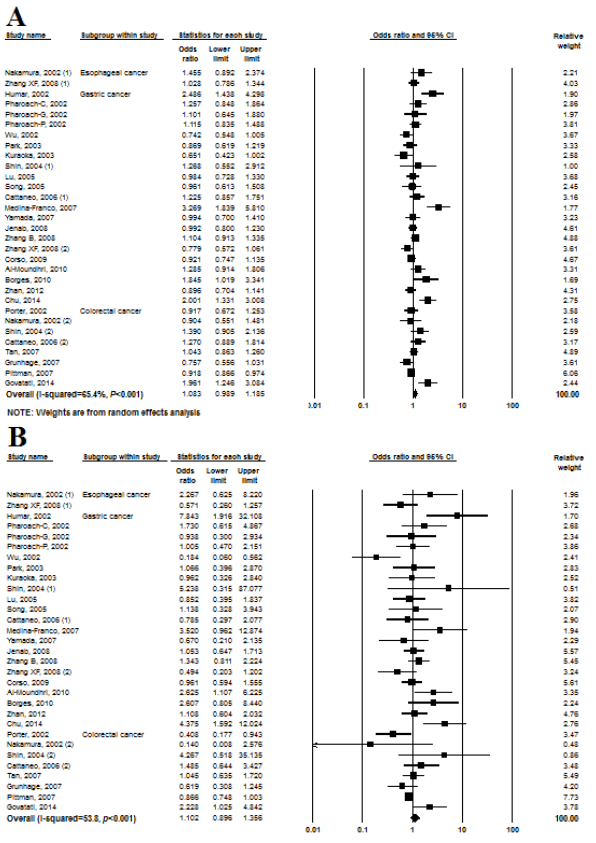

Figure 2. Forest Plot of Associations between E-cadherin -160C>A Polymorphism and GI Cancer Risk. A: Allelic genetic model (A vs. C); B: Homozygous genetic model (AA vs. CC)

heterogeneity was estimated with the I^2 statistic (Higgins and Thompson, 2002). A significant Q-statistic (P<0.10) or I^2> 40% demonstrated heterogeneity between the studies, so the pooled OR was calculated by a random-effects model (DerSimonian and Laird, 1986). Otherwise, a fixed effect model was applied. HWE was evaluated by chi-square in the control group, and a value of P>0.05 showed that the controls followed HWE balance. Publication bias was tested by using Egger's linear regression and Begg's funnel plots, and P<0.05 was used as a sign for possible publication bias (Song et al., 2002). Statistical analysis was performed using Comprehensive Meta-Analysis (version 2.2.064) with a two-sided P-value; P< 0.05 was considered significant.

Results

Characteristics of studies

A total of 150 potentially relevant publications were systematically identified through PubMed database, using different combinations of key words (Figure 1). 31 case-control studies from 26 publications including 11,606 cases and 12,655 controls were used to evaluate the association of CDH1 -160C>A polymorphism with GI cancer risk. In this meta-analysis, the role of CDH1 -160C/A polymorphism was derived from two esophageal cancer studies (Nakamura et al., 2002; Zhang et al., 2008b), 21 gastric cancer studies (Humar et al., 2002; Pharoah et al., 2002; Wu et al., 2002; Kuraoka et al., 2003; Park et al., 2003; Shin et al., 2004; Lu et al., 2005; Song et al., 2005; Cattaneo et al., 2006; Medina-Franco et al., 2007; Yamada et al., 2007; Jenab et al., 2008; Zhang et al., 2008a; Corso et al., 2009; Al-Moundhri et al., 2010; Borges Bdo et al., 2010; Zhan et al., 2012; Chu et al., 2014), and eight colorectal cancer studies (Nakamura et al., 2002; Porter et al., 2002; Shin et al., 2004; Cattaneo et al., 2006; Grunhage et al., 2008; Tan et al., 2008; Pittman et al., 2009; Govatati et al., 2014).

Four studies was not consistent with HWE balance (P<0.05). Of the 31 case control studies, 16 were conducted in Asian populations; 13 were in Caucasian populations; and 2 were in mixed populations. 12 studies were population based

(PB), and the other 19 studies were hospital-based (HB). All studies were written in English. The selected study characteristics were summarized in Table 1.

Main results

Association between the CDH1 C-160A polymorphism and GI cancer risk A total of 31 relevant studies, consisting of 11,606 patients and 12,655 controls, were examined for the association between the CDH1 C-160A polymorphism and GI cancer risk. The main results of meta-analysis and heterogeneity test were listed in Table 2. Overall,

Table 1. Details of the Studies Inclued in the Meta-Analysis

Cancer location	First author	Year	Country	Ethnicity	Source of controls	Cases	Controls	Genotyping method	HWE
Esophageal cancer	Nakamura	2002	Japan	Asian	PB	74	147	SSCP	0.66
	Zhang XF	2008	China	Asian	HB	333	343	PCR-RFLP	0.04
Gastric cancer	Humar	2002	Italy	Caucasian	HB	53	70	PCR-RFLP	0.56
	Pharoach-C	2002	Canada	Caucasian	HB	148	93	PCR-RFLP	0.23
	Pharoach-G	2002	Germany	Caucasian	HB	132	42	PCR-RFLP TaqMan	0.35
	Pharoach-P	2002	Portugal	Caucasian	HB	153	331	SSCP	0.22
	Wu	2002	Taiwan	Asian	HB	201	196	PCR-RFLP	0.3
	Park	2003	Korea	Asian	HB	292	146	SSCP	0.43
	Kuraoka	2003	Japan	Asian	HB	106	90	PCR-RFLP	0.01
	Shin	2004	Korea	Asian	HB	28	142	PCR-RFLP	0.45
	Lu	2005	China	Asian	PB	206	261	PCR-RFLP	0.39
	Song	2005	China	Asian	PB	102	101	PCR-DHPLC	0.45
	Cattaneo	2006	Italy	Caucasian	PB	107	246	PCR-RFLP	0.48
	Medina	2007	Mexico	Mixed	HB	39	78	SSCP	0.7
	Yamada	2007	Japan	Asian	HB	148	292	PCR-RFLP	0.92
	Jenab	2008	Mixed	Caucasian	PB	245	949	TaqMan	0.88
	Zhang B	2008	China	Asian	HB	668	625	PCR-RFLP	0.45
	Zhang XF	2008	China	Asian	HB	239	343	PCR-RFLP	0.04
	Corso	2009	Italy	Caucasian	PB	412	408	PCR-RFLP	0.4
	Al-Moundhri	2010	Omen	Caucasian	PB	174	166	Sequencing	0.43
	Borges	2010	Brazil	Mixed	HB	58	51	Sequencing	0.09
	Zhan	2012	China	Asian	HB	361	354	PCR-LDR	0.65
	Chu	2014	Taiwan	Asian	HB	107	134	Sequencing	0.94
Colorectal cancer	Porter	2002	UK	Caucasian	HB	290	171	PCR-RFLP	0.07
	Nakamura	2002	Japan	Asian	PB	96	147	SSCP	0.66
	Shin	2004	Korea	Asian	PB	260	147	PCR-RFLP	0.44
	Cattaneo	2006	Italy	Caucasian	PB	106	246	PCR-RFLP	0.48
	Tan	2007	Germany	Caucasian	PB	498	600	PCR-RFLP	0.36
	Grunhage	2007	Germany	Caucasian	HB	188	217	PCR-RFLP	0.29
	Pittman	2009	UK	Caucasian	HB	5679	5412	AS-PCR	0.39
	Govatati	2014	India	Asian	PB	103	107	PCR-Sequencing	<0.01

Table 2. The Association between CDH1 -160C>A Polymorphism and Gastrointestinal Cancer

	Test of association 95% CI				Test of heterogeneity	
	OR	Lower	Upper	P-value	P-value $_{Q\text{ test}}$	I^2 (%)
A vs. C						
Overall	1.08	0.98	1.18	0.086	<0.001	65.4
Asian	1.03	0.90	1.19	0.609	0.001	59.5
Caucasian	1.05	0.94	1.16	0.368	0.007	55.7
HB	1.06	0.93	1.20	0.368	<0.001	72.2
PB	1.08	0.99	1.18	0.070	0.150	30.1
Esophageal cancer	1.11	0.88	1.40	0.369	0.222	33.0
Gastric cancer	1.10	0.96	1.25	0.137	<0.001	66.3
Colorectal cancer	1.04	0.89	1.22	0.593	0.006	64.4
AA vs. CC						
Overall	1.10	0.89	1.35	0.356	<0.001	53.8
Asian	1.05	0.72	1.53	0.782	0.004	55.3
Caucasian	1.03	0.80	1.31	0.796	0.024	48.8
HB	1.03	0.76	1.38	0.844	<0.001	62.3
PB	1.18	0.95	1.46	0.131	0.284	16.2
Esophageal cancer	1.03	0.27	3.92	0.963	0.074	68.7
Gastric cancer	1.20	0.91	1.58	0.192	0.004	51.2
Colorectal cancer	0.95	0.66	1.36	0.800	0.031	54.4
CA vs. CC						
Overall	1.09	0.89	1.33	0.118	<0.001	61.3
Asian	1.09	0.88	1.34	0.403	<0.001	69.4
Caucasian	1.05	0.92	1.20	0.432	0.027	48.0
HB	1.11	0.93	1.31	0.22	<0.001	72.1
PB	1.04	0.93	1.17	0.422	0.407	3.8
Esophageal cancer	1.29	0.96	1.73	0.081	0.861	<0.001
Gastric cancer	1.20	0.91	1.58	0.286	<0.001	66.9
Colorectal cancer	0.94	0.87	1.01	0.094	0.125	38.1
CA+AA vs. CC						
Overall	1.06	0.96	1.18	0.207	<0.001	55.1
Asian	1.02	0.87	1.20	0.75	0.004	55.1
Caucasian	1.06	0.93	1.21	0.368	0.013	52.8
HB	1.03	0.90	1.19	0.621	<0.001	62.2
PB	1.08	0.97	1.20	0.158	0.209	23.8
Esophageal cancer	1.22	0.92	1.61	0.155	0.498	<0.001
Gastric cancer	1.05	0.91	1.21	0.438	0.001	55.2
Colorectal cancer	1.07	0.89	1.28	0.460	0.017	58.8
AA vs. CC+CA						
Overall	1.09	0.89	1.33	0.365	0.001	51.5
Asian	1.07	0.74	1.54	0.689	0.005	53.8
Caucasian	1.00	0.81	1.25	0.937	0.600	41.1
HB	1.01	0.76	1.34	0.105	<0.001	60.2
PB	1.20	0.97	1.48	0.085	0.326	12.5
Esophageal cancer	0.94	0.25	3.54	0.935	0.074	68.6
Gastric cancer	1.20	0.92	1.56	0.167	0.008	48.2
Colorectal cancer	0.91	0.87	1.04	0.184	0.041	52.0

no significant association was found between CDH1 C-160A polymorphism and risk of GI cancer under all five genetic models (A *vs.* C: OR=1.08, 95%CI=0.98-1.18, P=0.086; CA *vs.* CC: OR=1.09, 95%CI=0.97-1.22, P=0.118; AA *vs.* CC: OR=1.10, 95%CI=0.89-1.35, P=0.356; AA *vs.* CC + CA: OR=1.06, 95%CI=0.96-1.18, P=0.207; CA+AA *vs.* CC: OR=1.01, 95%CI=0.84-1.22, P=0.89). To eliminate heterogeneity, we performed further meta-analyses stratified according to ethnicity, source of controls and cancer type. The similar results were observed in the stratified analyses by ethnicity, source of controls (population-based), and cancer type. The detail results of the heterogeneity test and meta-analysis were listed in Table 2 and Figure 2, 3.

Test of heterogeneity

Significant heterogeneity revealed among overall literatures for the CDH1 C-160A polymorphism and GI cancer risk (allelic: P<0.001, I^2=65.4%; homozygous: P<0.001, I^2=53.8%; heterozygous: P<0.001, I^2=61.39%, dominant and allele: P<0.001, I^2=55.1% and recessive: P=0.000, I^2=51.5%). Hence, random-effect model was applied to generate CIs for these genetics models comparison (P<0.05). Otherwise, fixed-effect model was used.

Publication bias

Publication bias of literatures was performed to assess by Begg's funnel plot and Egger's test. The shape of the funnel plot did not demonstrate significant asymmetry in CDH1 C-160A polymorphism (Figure 5 A, B). In addition, egger's test was used to provide statistical evidence of

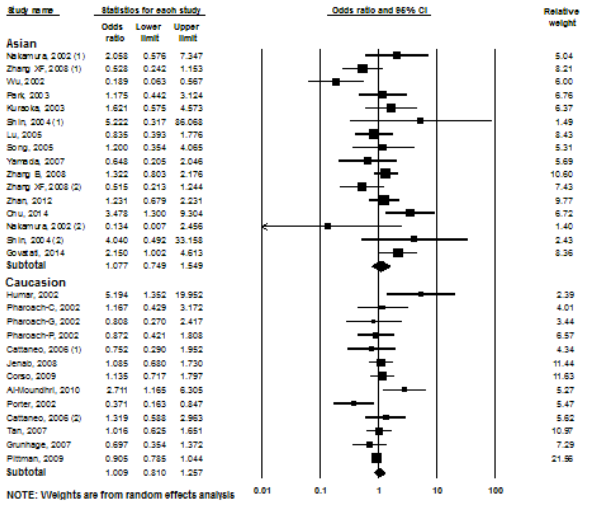

Figure 3. Forest Plot of Subgroup Analysis by Ethnicity on the Association between CDH1 -160C>A Polymorphism and GI Cancer Risk. Recessive model AA vs. CC+CA

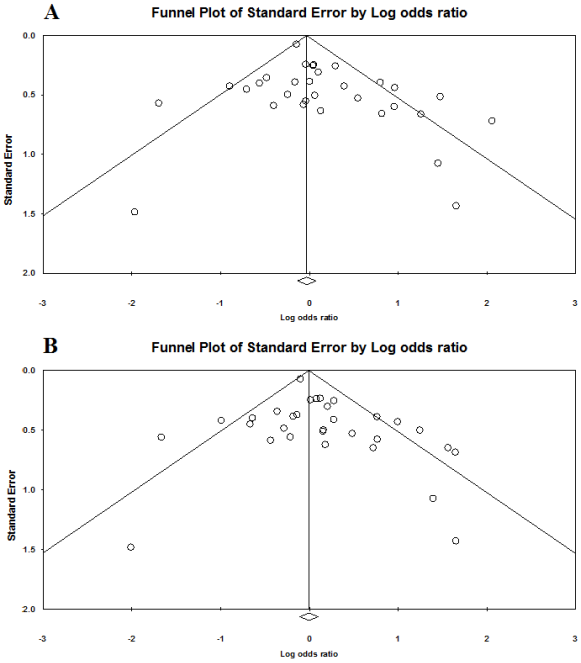

Figure 5. Forest Plot of Association between E-cadherin -160C>A Polymorphism and GI Cancer Risk. A: Allelic genetic model (A vs. C); B: Homozygous genetic model (AA vs. CC)

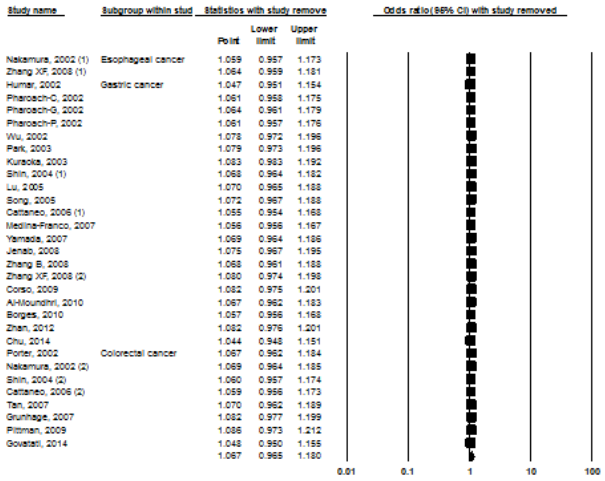

Figure 4. Forest Plot of ORs with 95% CI for GI Cancer Risk Associated with the CDH1 -160C>A Polymorphism (random effects) after Exclusion of the Study Contributing to Substantial Heterogeneity

funnel plot asymmetry. The Egger's test results and Begg's funnel plot suggested no evidence of publication bias in the meta-analysis of CDH1 -160C>A for homozygous genetic model (p=0.079) and recessive genetic model (p=0.153), although possible publication bias was suggested for allelic model (p=0.003), heterozygous model (p=0.009), dominant model (p=0.0.003).

Sensitivity analysis

A sensitivity analysis was performed to evaluate the stability of the overall results through the sequential omission of each individual study. The results show that no single study could affect the overall results, which indicated the reliability of our results (Figure 4).

Discussion

E-cadherin has fundamental role in epithelial cell-cell adhesion, tissue formation, and suppression of cancer (Vasioukhin, 2012). Dysfunctions of the cell-cell adhesions play vital roles in invasion and metastasis of cancer. CDH1 is a tumor invasion suppressor and down regulation of CDH1 may direct to a deficiency of CDH1 mediated cell-cell adhesion, resulting in increased risk of tumor development and further tumor cell invasion and metastasis (Xiong et al., 2012).

The transversion of C to A in the -160 promoter of CDH1 gene causes decreasing of transcriptional efficiency compared with the C allele *in vitro* (Li et al., 2000). Several studies performed to investigate the association between CDH1 -160 C/A polymorphism and esophageal, gastric and colorectal cancer risk, although controversial results have been published. In order to make more clear of this controversy, the present meta-analysis, including 12655 controls and 11606 cases from 31 case-control studies, assessed the association between CDH1 -160C/A polymorphism and GI cancer. The finding polymorphism associated with cancer risk may be effective for providing personalized diagnosis and therapy of certain cancers.

The overall results demonstrate no association between the CDH1 C-160A polymorphism and risk of GI cancer in all genetic models. Four studies of current meta-analysis deviated from HWE and two independent analyses including or excluding Hardy-Weinberg disequilibrium studies showed the same result (data not shown). The overall results were in accordance with the results of majority studies included in this meta-analysis. We further conducted subgroup analysis according to ethnicity and significant association was discover in neither Asian nor Caucasian populations. This result suggest that the genetic background or environment they live in may not influence the CDH1 -160C>Apolymorphism on GI

cancer susceptibility. Similar results were observed in the subgroup analysis by source of controls and cancer type.

Some includedstudies showed significant association between this polymorphism and susceptibility of GI cancer. There may be positive results due to reasons as follows. First, some studies comprised a small sample size and the study with small sample sizes may have inexpressive statistical power to discover a slight effect. Second, most data of cases were not stratified by tobacco use, alcohol consumption, diet and other environmental factors. It is well demonstrated that the carcinogenesis of GI cancer is a result of the interaction between genetic backgroundand environmental factors. Besides the role of genetic variants, smoking behavior represents an important effect on the GI susceptibility. It has been reported that smoking inhanced CRC risk threefold (Hansen et al., 2007). In addition, the other environmental factors such as alcohol consumption, diet and so on increase the susceptibility to cancer. Third, the family history of GI cancer patients have not considered in most included studies. Record of family history, either positive or negative, is more likely to be up-to-date for GI cancer screening compared to those with no record of family history (Carney et al., 2013). Meanwhile, sensitivity analysis did not shift the results, implying that the results were robust.

There may be some limitations in this meta-analysis. First, in the stratified analyses, only two studies conducted in esophageal cancer. The subjects were too small to have enough statistical power to find the real association. Second, the controls were not uniformly defined. Therefore, the control groups may have different risks of developing GI cancer.

Non-differential misclassification bias was possible. Third, studies published in languages other than English were not considered for inclusion. Therefore, our results should be interpreted with caution.

Despite these limitations, current meta-analysis still had some advantages. First, a systematic review of the association of CDH1 -160C>A polymorphism with GI cancer risk is statistically more powerful than any single study. This study is a new meta-analysis that investigated the association of CDH1 -160C>A with GI cancer risk.

In summary, our meta-analysis provides information that there is a lack of association of the CDH1 -160C>A polymorphisms with GI cancer. However, the consideration of gene- environment and gene-gene interactions are required to further evaluate the interaction of CDH1 -160C>A polymorphism with GI cancer susceptibility. There may be the CDH1 -160C>A polymorphism not associated with susceptibility to GI cancer, but we propose investigating the role of this polymorphism in development and progression of GI cancer in future studies.

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