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CDH1 promoter polymorphism and stomach cancer susceptibility

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Abstract The relationship of stomach cancer susceptibility and the presence of *E-cadherin* (*CDH1*) promoter −160 C/A polymorphism had been reported with conflicting results. To further explore the association of this polymorphism with stomach cancer susceptibility, we performed an extensive search of relevant studies and carried out a meta-analysis to obtain a more precise estimate. A total of 16 studies including 2,611 cases and 3,788 controls were involved in this meta-analysis. When all studies involved, the meta-analysis results suggest no statistically significant association between *CDH1* −160 C/A polymorphism and stomach cancer risk (CA vs. CC: OR = 1.01, 95% CI: 0.85–1.19; AA vs. CC: OR = 1.05, 95% CI: 0.75–1.46; dominant model: OR = 1.02, 95% CI: 0.86–1.20; recessive model: OR = 1.04, 95% CI: 0.76–1.41). When subgroup analyses were performed by ethnicity, the A-allele carriers conferred a decreased stomach cancer risk in Asians (AA vs. CC: OR = 0.67, 95% CI: 0.47–0.96; dominant model: OR = 0.85, 95% CI: 0.72–0.99), but no statistically significant association was found in Caucasians. In conclusion, this meta-analysis suggests that *CDH1* −160 A-allele may play a protective role of stomach cancer development in Asians but not in Caucasians.

Keywords Stomach cancer · Susceptibility · *CDH1* · Polymorphism

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Introduction

Stomach cancer has become a major public health challenge. It was reported that 934,000 patients of stomach cancer occurred in 2002 and 700,000 cases die of this disease annually [1]. However, the incidence of stomach cancer varied in different ethnicities. Host genetic susceptibility has been suggested as one of the most important possible explanations for inter-individual difference in stomach cancer risk. Several genes had been identified as potential stomach cancer susceptibility genes. *E-cadherin* (*CDH1*) encodes an adhesion glycoprotein. This protein mediates cell–cell adhesion, establishes and maintains cell polarity and tissue architecture [2, 3]. Several polymorphisms and somatic mutations had been identified in *CDH1* [4, 5]. An important one was −160 C/A (rs16260) polymorphism in the promoter region, which had been reported to have an approximately 68% decreased transcriptional activity for the A allele compared with the C allele [6]. A recent meta-analysis had suggested that the *CDH1* −160A allele is a low-penetrant risk factor for developing prostate cancer [7]. Several studies had reported the role of *CDH1* −160 C/A polymorphism in stomach cancer risk [8–21], but the results were conflicting. To further explore the association of this polymorphism with stomach cancer susceptibility, we performed an extensive search of relevant studies and carried out a meta-analysis to obtain a more precise estimate.

Methods

Studies search

PubMed and Embase were searched on Nov 8, 2010 with the search terms: "*CDH1*", "*E-cadherin*", "polymorphism", "stomach cancer", and "gastric cancer". All eligible studies were retrieved. Manual searches were also performed. The reference lists of related articles were also checked for potential studies. Where there were overlapped participants among studies, the most complete and recent results were included.

Inclusion criteria

The inclusion criteria were: (a) evaluation the association of the *CDH1* −160 C/A polymorphism and stomach cancer risk, (b) case–control studies, and (c) present numbers of cases and controls with the AA, CA, and CC genotypes, respectively.

Data collection

Data was extracted independently by two authors using a standardized data extraction form including first author's surname, publication date, ethnicity, characteristics of controls, genotyping methods, total number of cases and controls, and numbers of cases and controls with the AA, CA, and CC genotypes. Any disagreement was resolved by a discussion of the two. Different ethnicity were categorized as Caucasian, Asian, African, or mixed descents.

Statistical analysis

Hardy–Weinberg equilibrium (HWE) was evaluated for each study, using the goodness-of-fit χ^2 test. $P < 0.05$ was considered representative of departure from HWE. Crude ORs with its 95% confidential intervals (CIs) were used to estimate the gene effect. Heterogeneity assumption was checked by the chi-based Q-test ($P < 0.10$ was considered representative of statistically significant heterogeneity) [22]. When $P \geq 0.10$, the fixed-effects model (the Mantel–Haenszel method) was used [23]. When $P < 0.10$, the random-effects model (the DerSimonian and Laird method) was used [24]. Subgroup analyses were performed by ethnicity. Begg's funnel plot and Egger's linear regression test were carried out to estimate of potential publication bias. $P < 0.05$ was considered representative of statistically significant publication bias [25]. All the statistical tests were performed with STATA version 9.0.

Results

Main characteristics

A total of 14 publications met the inclusion criteria [8–21]. The ORs in Pharoah's study were presented separately by three different country groups, so each group was considered separately for analyses [17]. Thus, a total of 16 studies including 2,611 cases and 3,788 controls were used in the meta-analysis. Table 1 lists the main characteristics of all studies identified. The genotypes distribution in the

Table 1 Main characteristics of all involved studies

Author	Year	Ethnicity	Characteristics of controls	Method	Cases/controls	HWE
Zhang	2007	Asian	Matched for age, gender	RFLP	239/343	N
Shin	2004	Asian	Healthy	DHPLC	28/142	Y
Wu	2002	Asian	Matched for age, gender	RFLP	201/196	Y
Kuraoka	2003	Asian	–	–	106/90	N
Park	2003	Asian	Healthy	SSCP	292/146	Y
Song	2005	Asian	Matched for age, gender	DHPLC	102/101	Y
Lu	2005	Asian	Matched for age, gender	RFLP	206/261	Y
Yamada	2007	Asian	Matched for age, gender and residence	RFLP	148/292	Y
Humar	2002	Caucasian	Matched for age, gender and residence	RFLP	53/70	Y
Pharoah-C	2002	Caucasian	Matched for age, gender	RFLP	148/93	Y
Pharoah-G	2002	Caucasian	Matched for age, gender	RFLP	132/42	Y
Pharoah-P	2002	Caucasian	Matched for age, gender	SSCP	153/331	Y
Jenab	2008	Caucasian	Matched for age, gender	SSCP	245/950	Y
Cattaneo	2006	Caucasian	Healthy	RFLP	107/246	Y
Corso	2009	Caucasian	Matched for age, gender	RFLP	412/408	Y
Medina	2007	Mixed	Matched for age, gender	SSCP	39/78	Y

HWE Hardy–Weinberg equilibrium, *RFLP* restriction fragment length polymorphism, *DHPLC* denatured high performance liquid chromatography, *SSCP* single-strand conformational polymorphism, *N* no, *Y* yes

Table 2 Main results of this meta-analysis

	CA vs. CC		AA vs. CC		Dominant model		Recessive model	
	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Total	1.01 (0.85,1.19)	0.01	1.05 (0.75,1.46)	0.01	1.02 (0.86–1.20)	0.01	1.04 (0.76–1.41)	0.03
Ethnicity								
Asian	0.87 (0.74–1.02)	0.11	0.67 (0.47–0.96)	0.19	0.85 (0.72–0.99)	0.26	0.79 (0.47–1.31)	0.09
Caucasian	1.18 (0.92–1.52)	0.04	1.16 (0.89–1.51)	0.20	1.20 (0.94–1.54)	0.03	1.13 (0.87–1.46)	0.34

P_h *P* value of Q test for heterogeneity test

controls was in agreement with HWE in all studies except for Zhang et al. and Kuraoka et al. [8, 11].

Main results

The meta-analysis results were listed in Table 2. When all studies involved, the meta-analysis results suggest no statistically significant association between *CDH1* −160 C/A polymorphism and stomach cancer risk (CA vs. CC: OR = 1.01, 95% CI: 0.85–1.19; AA vs. CC: OR = 1.05, 95% CI: 0.75–1.46; dominant model: OR = 1.02, 95% CI: 0.86–1.20; recessive model: OR = 1.04, 95% CI: 0.76–1.41). When subgroup analyses were performed by ethnicity, the A-allele carriers conferred a decreased stomach cancer risk in Asians (AA vs. CC: OR = 0.67, 95% CI: 0.47–0.96; dominant model: OR = 0.85, 95% CI: 0.72–0.99), but no statistically significant association was found in Caucasians. When the studies of Zhang et al. and Kuraoka et al. in which controls were not in agreement with HWE were deleted, the results were not materially altered (data not shown).

Publication bias test results

The shapes of the funnel plots did not reveal any evidence of obvious asymmetry in all comparison models. Also, the Egger's test results still did not suggest any evidence of publication bias ($P = 0.273$ for CA vs. CC, $P = 0.368$ for AA vs. CC, $P = 0.120$ for dominant model, and $P = 0.549$ for recessive model).

Discussion

Recently, meta-analysis was widely used to explore the association of genetics polymorphism and cancer risk [26–30]. A meta-analysis approach may assist in estimating the population-wide effects of a genetic risk factor in human disease and may provide a quantitative approach for combining the data of various studies on the same topic to explain their diversity. Growing number of studies have suggested that *CDH1* −160 C/A polymorphism was associated with the development of several kinds of cancer such as stomach cancer [8–21], urothelial cancer [31], and prostate cancer [7]. Because stomach cancer is one of the most common malignant diseases and a number of studies have reported a role of the *CDH1* −160 C/A polymorphism in stomach cancer risk with inconclusive results, we performed this meta-analysis to estimate the association specifically.

Interestingly, our results indicated that *CDH1* −160 A-allele carriers conferred a possible protective effect in Asians, but no statistically significant association was found in Caucasians, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in [32]. Furthermore, the influence of the −160A allele might be masked by the presence of other as-yet unidentified causal genes involved in stomach cancer development. In addition, it also likely that the observed ethnic differences may be due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate [33]. Considering the limited studies and subject numbers included in the subgroup, our results should be interpreted with caution. Although Africans were considered to have a high incidence of stomach cancer, we found no data regarding them.

Some limitations should be acknowledged. Firstly, the number of subjects in the subgroup analysis was relatively small, not having enough statistical power to explore the real association. Secondly, our results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for the adjustment by other co-variates.

In summary, the present analysis supports growing evidence that *CDH1* −160 A-allele may play a protective role of stomach cancer development in Asians but not in Caucasians. However, large sample and well-designed studies considering gene–gene and gene–environment interactions are warranted to confirm this finding.

Acknowledgments Conflict of interest statement None declared.

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