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Association between the epithelial cadherin -160C/A gene polymorphism and diffuse gastric cancer risk: a meta-analysis

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ABSTRACT. Several previous studies have investigated whether the -160C/A epithelial cadherin promoter polymorphism confers an increased risk of diffuse gastric cancer (DGC), but conflicting results have been reported. To explore further the association of this polymorphism with DGC susceptibility, we performed an extensive search of relevant studies and conducted a meta-analysis to obtain a more precise estimate. We conducted a systematic literature search using the databases EMBASE, PubMed, and Web of Knowledge for reports published before August 2012 that met certain criteria. Information was carefully and independently extracted from all eligible publications by 2 of the authors. Twelve distinct data sets from 10 case-control studies were analyzed. They included 1115 cases of DGC and 2965 controls. Although none of the genotypes was associated with DGC risk, a slight trend of increased risk was found among A allele carriers [odds ratio (OR) = 1.237, 95% confidence interval (95%CI), 0.940-1.627], CA heterozygotes (OR = 1.229, 95%CI = 0.938-1.610), and AA homozygotes (OR = 1.146,

95%CI = 0.684-1.918). However, when the cases were stratified by ethnicity, a diverging trend occurred in AA homozygotes between the Asian group (OR = 0.710, 95%CI = 0.328-1.536) and its Caucasian counterpart (OR = 1.434, 95%CI = 0.657-3.131). Taken together, the summarized analyses of these case-control studies demonstrated that the -160A of the epithelial cadherin gene exhibited no significant association with susceptibility for DGC; however, the results suggested that it is a potential genetic risk factor in both Asians and Caucasians. Additional large-scale, well-designed studies are necessary to confirm whether AA homozygosity is a protective factor in Asians.

Key words: Diffuse gastric cancer; Epithelial cadherin; Polymorphism; Meta-analysis; Genetic susceptibility

INTRODUCTION

In 1965, gastric adenocarcinoma was initially classified into two histological types - intestinal and diffuse - according to the morphological features of tumors (Lauren, 1965). In contrast to the worldwide decline in the incidence of gastric carcinoma (Kelley and Duggan, 2003), the incidence of diffuse gastric carcinoma (DGC), particularly that of the signet ring type, has been increasing (Henson et al., 2004). Several studies have shown that DGC is comparatively frequent in young women (Lauren, 1965; Lauren and Nevalainen, 1993; Zheng, et al., 2007), and Zheng et al. (2007) have suggested that this characteristic indicates a contribution of genetic factors more than environmental factors to DGC. Histologically, cell cohesion is less apparent or absent in DGC compared with its intestinal counterpart, and cancer cells spread diffusely in the gastric wall as poorly differentiated adenocarcinoma, signet ring type, and undifferentiated carcinoma. Among the various molecules regulating cell-to-cell cohesion, epithelial cadherin (E-cadherin; CDH1) plays a critical role. It is a member of a family of transmembrane glycoproteins involved in calcium-dependent cell-to-cell adhesion, and it appears to play a role in organogenesis and morphogenesis (Takeichi, 1991). Moreover, E-cadherin is frequently inactivated in DGC but not in other types of gastric carcinoma (Becker et al., 1994). Thus, identification of predisposing genetic factors and molecular pathways underlying DGC susceptibility is fundamental to the development of effective prevention, early diagnosis, and therapeutic strategies. Several polymorphisms have been identified in the coding geographic distributions of the CDH1 gene. Of these, the most commonly known is in the -160C/A (promoter geographic distribution; rs16260), which has demonstrated 70% reduced A allele transcriptional activity compared with that of the C allele (Li et al., 2000). Recently, several studies have investigated whether the -160C/A CDH1 promoter polymorphism confers an increased risk for DGC development, but the results are conflicting (Humar et al., 2002; Pharoah et al., 2002; Wu et al., 2002; Park et al., 2003; Medina-Franco et al., 2007; Jenab et al., 2008; Zhang et al., 2008; Corso et al., 2009; Borges et al., 2010; Zhan et al., 2012). To explore further the association of this polymorphism with DGC susceptibility, we performed an extensive search of relevant studies and conducted a meta-analysis to obtain a more precise estimate.

MATERIAL AND METHODS

Search strategy

We conducted a systematic literature search using the databases EMBASE, PubMed, and Web of Knowledge for reports published before August 2012. We used the keywords CDH1, E-cadherin, and polymorphism in combination with stomach neoplasm or gastric carcinoma or gastric cancer. The full texts of the candidate reports were examined carefully to determine whether they contained sufficient information concerning the -160C/A polymorphism and DGC risk. Furthermore, their reference lists were reviewed to identify relevant studies.

Inclusion criteria

Included articles were published in English, contained genotype frequency in various histological types of gastric cancer, tested for rs16260 SNPs, presented the number of cases and control participants, and provided the odds ratio (OR) with confidence intervals (CIs) or data sufficient to compute these values. Several studies reported consortium results with multiple independent populations; these populations were listed as separate data sets. Excluded studies reported neither the exact number of DGC patients nor the genotype frequency.

Data extraction

Information was carefully and independently extracted from all eligible publications by 2 of the authors (X.W. Chen and J.X. Sun) according to the inclusion criteria listed above. Any disagreements that arose were resolved through discussion between the 2 authors. The following data were collected from each study: first author's surname, publication date, country in which the study was performed, ethnicity of participants, genotyping methods, components of cases, characteristics of controls, Hardy-Weinberg equilibrium (HWE), number of total cases and controls, and respective counterparts of different genotypes. Ethnicities were categorized as Asian, Caucasian, and African. When studies included patients from more than 1 region, genotype data were extracted separately according to ethnicity for subgroup analyses. In some countries, the population consists of various ethnicities, particularly the region of South America; we classified this population as an independent group named after the particular country. We did not define a minimum number of patients to include in this meta-analysis.

Statistical methods

HWE was evaluated for each study using the goodness-of-fit chi-square test. A P value of <0.05 was considered representative of departure from HWE. Summary ORs and corresponding 95%CIs were derived and summarized using random-effects modeling weighted by the total variance of each data set (Borenstein et al., 2007). Subgroup differences were compared using the Q test for heterogeneity for each covariate separately. Begg's funnel plot and Egger's linear regression test were conducted to estimate the potential publication bias. A P value of <0.05 was considered representative of statistically significant publication bias (Egger et al., 1997). All the statistical tests were performed with STATA version 11.0 (StataCorp, College Station, Texas).

Score of cumulative evidence

Assessment of cumulative evidence was based on a consensus evaluation guideline (Venice criteria) specific to gene-disease association studies and focused on the amount of evidence, replication of the evidence, and protection from bias. Cumulative evidence was strong, moderate, and weak (Ioannidis et al., 2008).

RESULTS

Of the 195 abstracts retrieved through the search criteria, 169 were irrelevant, 7 were excluded because they were meta-analyses, and 9 articles had not stratified gastric cancer based on histological type. Regarding irrelevant articles, 29 studies were excluded because they investigated genes other than E-cadherin, 15 studies did not explore CDH1 polymorphism, 64 had been performed on cancers other than gastric cancer, and 61 pertained to different positions that did not contain the -160C/A polymorphism. As a result, 10 articles containing 12 data sets were eligible for this meta-analysis (Figure 1). They included 1115 cases with diffuse gastric cancer and 2965 controls. The characteristics of the eligible articles are presented in detail in Table 1.

Regarding ethnicity, 4 studies (Wu et al., 2002; Park et al., 2003; Zhang et al., 2008; Zhan et al., 2012) were performed on Asian populations and included 622 cases and 1524 controls; 7 data sets from 5 studies (Humar et al., 2002; Pharoah et al., 2002; Medina-Franco et al., 2007; Jenab et al., 2008; Corso et al., 2009) were performed on Caucasian subjects and included 468 cases and 1390 controls; and 1 study (Borges et al., 2010) was performed on Brazilian populations and included 25 cases and 51 controls. Concerning the characteristics of the controls, 7 data sets from 5 studies (Humar et al., 2002; Pharoah et al., 2002; Wu et al., 2002; Medina-Franco et al., 2007; Jenab et al., 2008) were based on gender- and sex-matched controls and included 433 cases and 1178 controls, whereas 5 studies (Park et al., 2003; Zhang et al., 2008; Corso et al., 2009; Borges et al., 2010; Zhan et al., 2012) were not matched by gender and included 682 cases and 1787 controls. All studies included were consistent with HWE.

The pooled ORs of all genotypes along with their 95%CIs are presented in Table 2. Although none of the genotypes was associated with DGC risk (Figure 2), we observed a slight trend of increasing risk among A allele carriers (OR = 1.237, 95%CI = 0.940-1.627), CA heterozygotes (OR = 1.229, 95%CI = 0.938-1.610), and AA homozygotes (OR = 1.146, 95%CI = 0.684-1.918). A stratified analysis was conducted to identify the source of heterogeneity, and 2 types of covariates were introduced, including ethnicity and characteristics of controls (Table 3).

The stratified analysis of DGC confirmed the null associations that were demonstrated with overall analysis. Both methods exhibited no statistically significant association, yet the same trend in subgroup analysis was observed. However, AA homozygotes presented a confounding trend between the Asian group (OR = 0.710, 95%CI = 0.328-1.536) and its Caucasian counterpart (OR = 1.434, 95%CI = 0.657-3.131), suggesting that AA heterozygosity has a protective role in the Asian population, whereas AA homozygosity is related to an increased risk of DGC among Caucasians (Figure 3). Similarly, AA homozygotes exhibited a difference in comparison with the unmatched control group (OR = 0.991, 95%CI = 0.658-1.494) and matched counterparts (OR = 1.146, 95%CI = 0.684-1.918; Figure 4).

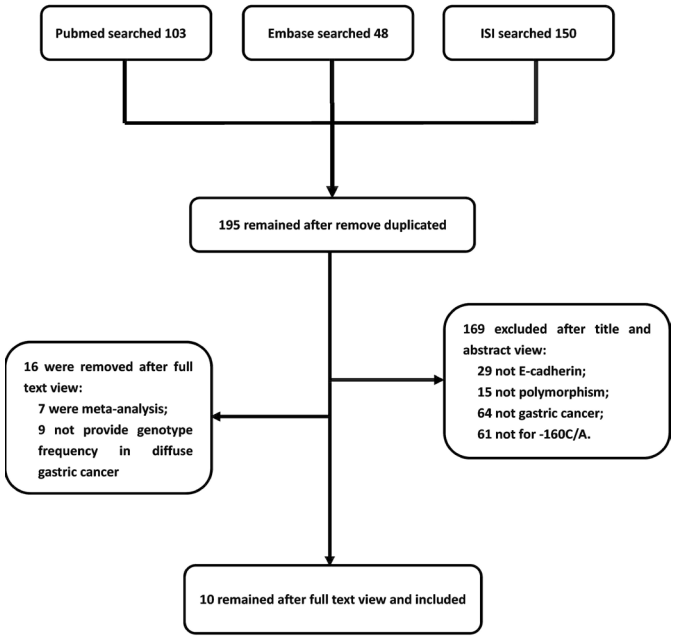

Figure 1. Flowchart of the studies selected.

Table 1. Characteristics of all eligible studies.

First author	Year	Country	Ethnicity	Genotyping method	Case	Control	Source	Matched	HWE
Zhan	2012	China	Asian	PCR-LDR	GC	Healthy	Hospital	No matched	P > 0.05
Borges	2010	Brazil	Brazilian	PCR	GC	Cancer-free	Hospital	No matched	P > 0.05
Corso	2009	Italy	Caucasian	PCR-RFLP	GC	Healthy	Hospital	No matched	P > 0.05
Zhang	2008	China	Asian	PCR-RFLP	GC	CAG	Hospital	No matched	P > 0.05
Jenab	2008	Europe	Caucasian	PCR-Taqman	GC	Cancer-free	Population	Gender, age	P > 0.05
Medina-Franco	2007	Mexico	Caucasian	PCR-SSCP	DGC	Healthy	Hospital	Gender, age	P > 0.05
Park	2003	Korea	Asian	PCR-SSCP	GC	Healthy	Hospital	No matched	P > 0.05
Wu	2002	Taiwan	Asian	PCR-RFLP	GC	Healthy	Hospital	Gender, age	P > 0.05
Pharoah	2002	Canada	Caucasian	PCR-RFLP	GC	Healthy	Hospital	Gender, age	P > 0.05
Pharoah	2002	Germany	Caucasian	PCR-RFLP	GC	Healthy	Hospital	Gender, age	P > 0.05
Pharoah	2002	Portugal	Caucasian	PCR-SSCP	GC	Healthy	Hospital	Gender, age	P > 0.05
Humar	2002	Italy	Caucasian	PCR-RFLP	DGC	Healthy	Hospital	Gender, age	P > 0.05

HWE = Hardy-Weinberg equilibrium; PCR = polymerase chain reaction; LDR = ligation detection reaction; RFLP = restriction fragment length polymorphism; SSCP = Single-Strand Conformation Polymorphism; GC = gastric cancer; DGC = diffuse gastric cancer; CAG= chronic atrophic gastritis.

Table 2. Stratified analysis of the epithelial cadherin -160C/A polymorphism and diffuse gastric cancer risk.

Stratified type	No. of data sets	No. of cases	No. of controls	CA+AA		CA heterozygotes		AA homozygotes	
				OR	95%CI	OR	95%CI	OR	95%CI
Ethnicity									
Asian	4	622	1524	1.127	0.768, 1.656	1.209	0.782, 1.871	0.710	0.328, 1.536
Brazilian	1	25	51	2.994	1.107, 8.095	3.048	1.047, 8.870	2.844	0.629, 12.857
Caucasian	7	468	1390	1.239	0.814, 1.884	1.163	0.799, 1.695	1.434	0.657, 3.131
Controls									
Unmatched	5	682	1787	1.184	0.743, 1.887	1.220	0.734, 2.030	0.991	0.658, 1.494
Matched	7	433	1178	1.296	0.920, 1.826	1.221	0.944, 1.578	1.288	0.502, 3.308
Overall	12	1115	2965	1.237	0.940, 1.627	1.229	0.938, 1.610	1.146	0.684, 1.918

OR = odds ratio; 95%CI = 95% confidence interval.

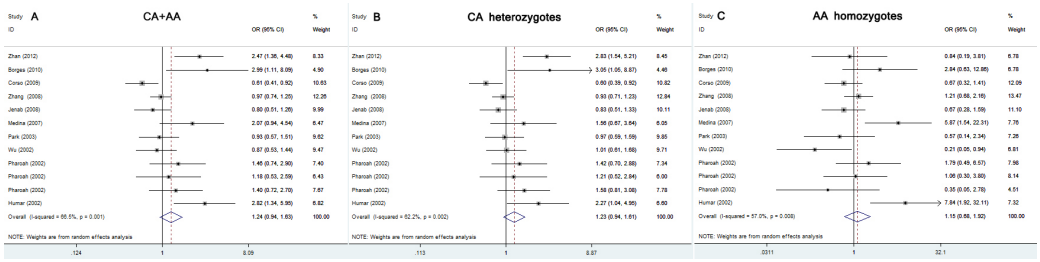

Figure 2. Forest plots for all genotypes of epithelial cadherin (CDH1) polymorphism associated with diffuse gastric cancer (DGC). **A.** Forest plots for CA and AA genotypes. **B.** Forest plots for CA heterozygotes. **C.** Forest plots for AA homozygotes.

Table 3. Heterogeneity test for studies of each genotype in different stratification types with Cochrane's Q-test and the quantity I^2.

Stratified type	No. of data sets	CA+AA			CA heterozygotes			AA homozygotes		
		Q value	P value	I^2 (%)	Q value	P value	I^2 (%)	Q value	P value	I^2 (%)
Ethnicity										
Asian	4	9.02	0.029	66.7	11.00	0.012	72.7	5.22	0.156	42.5
Brazilian	1	0.00	-	-	0.00	-		0.00	-	-
Caucasian	7	19.57	0.003	69.3	14.25	0.027	57.9	18.10	0.006	66.9
Controls										
Unmatched	5	19.27	0.001	79.2	21.11	0.000	81.0	4.07	0.396	1.8
Matched	7	12.08	0.060	50.3	6.57	0.363	8.6	21.10	0.002	71.6
Overall	12	32.82	0.001	66.5	29.11	0.002	62.2	25.57	0.008	57.0

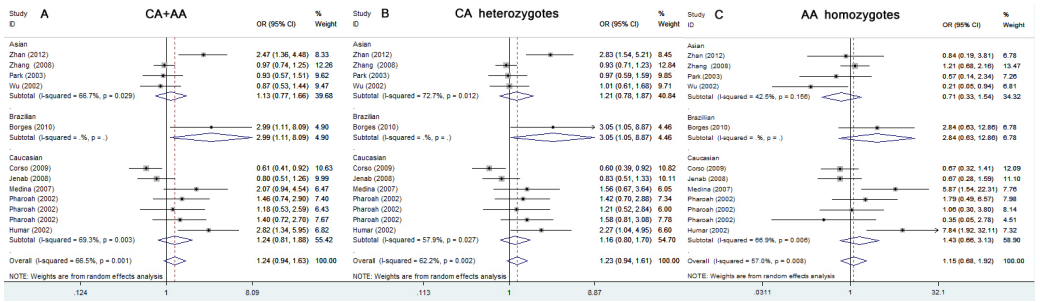

Figure 3. Stratified analysis based on ethnicity. **A.** Forest plots for CA and AA genotypes associated with DGC risk among Asians, Brazilians, and Caucasians. **B.** Forest plots for CA heterozygotes associated with DGC risk among Asians, Brazilians, and Caucasians. **C.** Forest plots for AA homozygotes associated with DGC risk among Asians, Brazilians, and Caucasians.

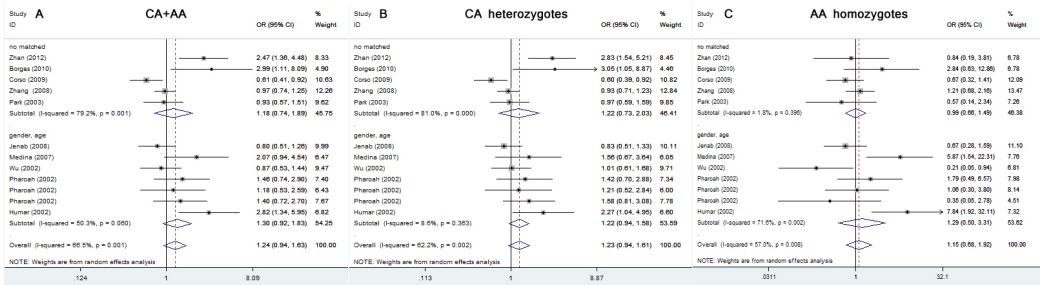

Figure 4. Stratified analysis based on control characteristics.

DISCUSSION

The Lauren classification of DGC is analogous to the World Health Organization classification of DGC of the signet ring cell type. Pathology reports describing undifferentiated, mucinous adenocarcinoma or poorly differentiated adenocarcinomas also raise the possibility of DGC. DGC typically exhibits decreased or absent immunohistochemical staining for E-cadherin, consistent with its disorganized architecture. CDH1 encodes E-cadherin, which is a cell surface, transmembrane glycoprotein critical for the adhesion of epithelial cells to one another. Loss of expression of E-cadherin has been associated with the invasiveness of cancer cells. The majority of sporadic and hereditary cases of DGC do not express E-cadherin, implying that mutation, loss, or methylation occurs in normal CDH1 alleles (Schrader and Huntsman, 2010). Decreased E-cadherin expression is a feature of many poorly differentiated epithelial cancers (Gamallo et al., 1993; Mayer et al., 1993; Kadowaki et al., 1994; Winter et al., 2008). In particular, E-cadherin expression is downregulated in sporadic DGC (Mayer et al., 1993). As highlighted above, molecular genetic differences exist between intestinal gastric carcinoma and DGC, but overall, the loss of E-cadherin expression remains the major discriminator between the two subtypes. A CDH1 promoter polymorphism at -160 C/A has been shown *in vitro* to play a role in transcriptional regulation, whereas the A allele has been shown to exhibit decreased transcriptional efficiency and weaker transcription factor binding affinity (Li et al., 2000).

Four meta-analyses by Wang et al. (2008), Gao et al. (2008), Cui et al. (2011), and Wang et al. (Wang et al., 2011) have recently been conducted on the association between the CDH1 -160 C/A polymorphism and gastric cancer risk. Although all of them found that the polymorphism was unassociated with gastric cancer risk, a consistent pattern was observed in gastric cancer regarding a decreased risk in Asians and an increased risk in Europeans. However, in the meta-analysis by Li et al. (2012), the A allele 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, suggesting that the CDH1 -160 A allele potentially plays a protective role in the development of stomach cancer only in Asians.

To our knowledge, the present meta-analysis is the first general overview of the associations between E-cadherin -160C/A and susceptibility to DGC. We summarized several conflicting reports and achieved certain results in concordance with previous studies. Our synthesized data demonstrated no significant associations and exhibited a reciprocal trend between Asian and Caucasian AA homozygotes.

Although the summarized results in both present and previous meta-analyses have demonstrated that the CDH1 -160C/A polymorphism plays a role in the risk of either gastric cancer or DGC, conflicting results also arose. In two Italian studies, Corso et al. (2009) observed a decreasing trend in A allele carrier, CA heterozygote, and AA homozygote distribution, which contrasted with the results of a study by Humar et al. (2002). To explain these conflicting results, we highlight several common factors that may have contributed to the genetic association studies. Different genotyping methods may have given rise to differences in sensitivity and detectability. Moreover, some study design factors also made differences, particularly the selection of controls: whether they matched with cases regarding gender or age; whether they were hospital based or population based; and whether they were in HWE. The total OR in the Caucasian subgroup was yielded with the study conducted by Humar et al. (2002), which might

indicate that selecting matched controls is recommended for future studies.

Of particular interest, the Asian group, after omitting the study by Wu et al. (2002), exhibited an altered result in which AA homozygosity changed from a protective factor to a risk factor for DGC. Conversely, this alteration potentially resulted from selection bias owing to the small sample size, particularly hospital-based, case-control studies. As a positive association, a public bias may be present; thus, we need a greater number of large-scale studies to confirm this result.

Another obvious association was presented in the only Brazilian study (Borges et al., 2010), in which the ethnic composition consisted of Caucasians, Mestizos, and blacks. Because the region has high rates of gastric cancer, numerous gastric cancer patients are living in Brazil, including those with DGC. An epidemiological study has suggested that the non-Caucasian races constitute a higher percentage of gastric cancer patients (Nishimoto et al., 2002). Many risk factors, including low socioeconomic status, cigarette smoking, and low consumption of fruits and vegetables, potentially interact with a polymorphism of susceptibility to gastric cancer; thus, additional large-scale studies are warranted to elucidate underlying mechanisms.

The opposing trends demonstrated in stratified analyses of the characteristics of controls have indicated that different design factors (Kim-Cohen et al., 2006; Tang, 2006; Pereira et al., 2009), even different genotyping platforms or different genotyping errors (Zaitlen and Eskin, 2010), potentially hinder the confirmation of the study (Han and Eskin, 2012). Ideal controls are composed of a general group of subjects without the disease of interest from which qualified cases arise once diagnosed. This general group does not exclude those with other diseases, whereas no relationship should be expected between the healthy status of the control and the investigated "risk factor" because the correlation may exaggerate or underestimate the overall estimated OR (Wang et al., 2012).

Certain limitations of this study should be noted. First, the sources of controls were almost all hospital based rather than population based. Second, many studies used unmatched controls, potentially introducing confounding factors such as age and gender. Likewise, because most of the studies included in this meta-analysis were conducted a decade ago, the genotyping technologies potentially exhibit differences in sensitivity and specificity compared with those of the more sophisticated genotyping technologies that have emerged recently. Moreover, many studies were excluded because they did not report the stratified information of genotype frequencies of polymorphism at the histological level.

Although the summarized analysis of these case-control studies demonstrated that -160A of the E-cadherin gene exhibited no significant association with susceptibility to DGC, a slight trend was observed toward a genetic risk factor in both the Asian and the Caucasian groups. These results in DGC appear to conflict with previous conclusions in gastric cancer, particularly in the Asian subgroup. However, large-scale, well-designed studies are warranted to determine whether AA homozygosity trends toward being a protective factor in Asians.

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