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Original Article

Angiotensin-converting enzyme insertion/deletion polymorphism and gastric cancer: a systematic review and meta-analysis

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Abstract: Previous case-control studies on the association of the angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism with gastric cancer were controversial. A meta-analysis was conducted to further evaluate the association between polymorphism in the ACE gene I/D and gastric cancer. We searched MEDLINE (PubMed), EMBASE, Web of Science, and CBM without language restrictions to Nov 20, 2014. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association. Eight studies involving 1480 gastric cancer cases and 3773 cancer-free controls were included. Overall, no significant association between *ACE* I/D polymorphism and gastric cancer risk was observed (OR = 1.15; 95% CI 0.90-1.46, *P* = 0.26). The subgroup analysis on the basis of H. Pylori status showed the decreased gastric cancer risk in H. Pylori negative subgroup (OR = 0.40; 95% CI: 0.27-0.59; P < 0.00001) rather than in H. Pylori positive subgroup (OR = 1.82, 95% CI: 0.87-3.82, P = 0.11). Subgroup analysis was performed according to ethnicity (Caucasian and Asian). The results showed no genetic effects between *ACE* I/D polymorphism and gastric cancer risk. This meta-analysis suggested that the ACE gene I/D polymorphism was associated gastric cancer risk in H. Pylori negative subjects.

Keywords: Gastric cancer, ACE, gene polymorphism, meta-analysis

Introduction

Gastric cancer has remained one of the most severe malignancies worldwide recently, ranking the 2nd for mortality and the 4th for incidence [1]. Currently, it is recognized that gastric cancer is a complex disease that results from interactions between multiple genetic and environmental factors [2, 3]. Numerous studies have begun the search for the association between genetic variants and gastric cancer risk, and angiotensin-converting enzyme (ACE) gene has been extensively analyzed.

ACE, a key enzyme in the renin-angiotensin system (RAS), is a zinc metallopeptidase whose main function is keep blood pressure and electrolyte homeostasis. ACE cleaves angiotensin I to generate angiotensin II, a powerful vasoconstrictor and stimulator of aldosterone secretion [4]. An insertion/deletion (I/D) polymorphism of the human *ACE* gene on chromosome 17q23 comprising the presence or absence of a 287 base pair (bp) insert in intron 16 was described [5]. This polymorphism has a role in the regulation of serum ACE concentration [6]. Mean ACE activity levels in DD carriers were approximately twice that found in II genotype individuals. Subjects with the ID genotype had intermediate levels [5].

So far, some studies have investigated the association of *ACE* I/D polymorphism with gastric cancer [6-14]. Unfortunately, these epidemiological studies performed in different countries have yielded conflicting results from strong links to no association. The inconsistency of these studies may be explained by the relatively small sample size and difference in population background. Considering a single study may lack the power to provide reliable conclusion, we carried out a quantitative metaanalysis to investigate the precise relationship between the *ACE* gene variant and gastric cancer risk.

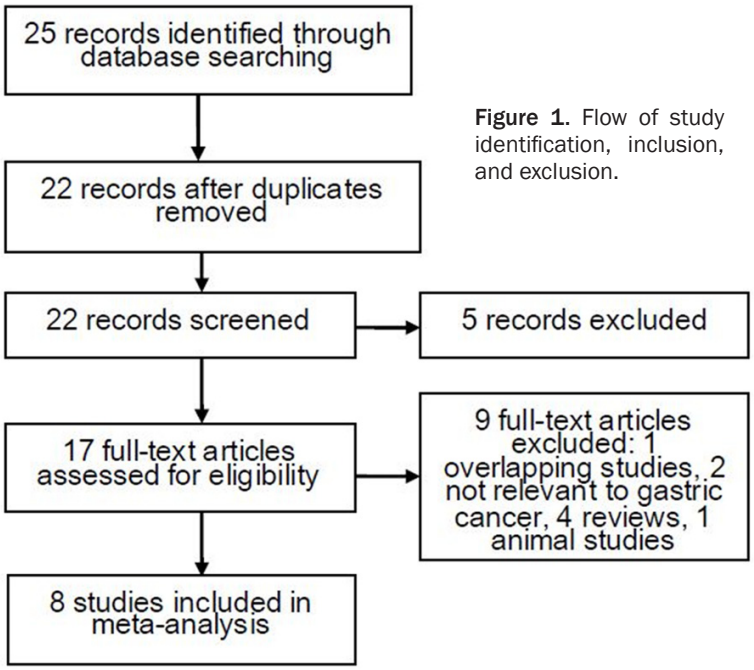

Figure 1. Flow of study identification, inclusion, and exclusion.

Methods

Publication search strategy

We searched MEDLINE (PubMed), EMBASE, Web of Science, and CBM without language restrictions to Nov 20, 2014. The following search algorithms were used: ("angiotensin converting enzyme" or ACE) AND ("gastric neoplasms" OR "gastric cancer" OR "gastric carcinoma") AND (polymorphism or mutation or variant). Reference lists of relevant articles were also reviewed to identify potential eligible studies.

Selection criteria

We included studies that (i) evaluated *ACE* I/D polymorphism and gastric cancer susceptibility, (ii) were case-control studies or cohort studies, and (iii) reported *ACE* genotype as II vs. ID vs. DD. The major exclusion criteria included: (i) reviews, case-only studies, or familial studies, (ii) lack of sufficient data for calculation of odds ratio (ORs) with 95% confidence intervals (CIs), and (iii) duplication of previous publications or replicated samples.

Data extraction and quality assessment

From each study, the following information was extracted: first author's surname, year of publication, ethnicity of the patients, study design, sample size, H. pylori status, Hardy-Weinberg equilibrium (HWE) of controls, and frequency of various genotypes in cases and controls. Study quality was assessed using the 10-point scoring scale for quality of genetic association studies.

Statistical analysis

The strength of the associations between the *ACE* I/D polymorphism and risk of gastric cancer was measured by OR with 95% CI. OR1, OR2, and OR3 were assessed for genotypes DD versus II, ID versus II, and DD versus ID, respectively. These pairwise differences were used to indicate the most appropriate genetic model as following: if OR1 = OR3 ≠ 1 and OR2 = 1, then a recessive model was suggested; if OR1 = OR2 ≠ 1 and OR3 = 1, then a dominant model was suggested; if OR2 = 1/OR3 ≠ 1 and OR1 = 1, then a complete over-dominant model was suggested; if OR1 > OR2 > 1 and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1), then a codominant model was suggested. Once the best genetic model was identified, this model was used to collapse the three genotypes into two groups (except in the case of a codominant model) and to pool the results again. The significance of the pooled OR was determined by the Z-test, and two-tailed $P < 0.05$ was considered as statistically significant.

A Q-test was performed to test for heterogeneity. A fixed-effect model was used when there was no heterogeneity ($P \geq 0.10$), otherwise a random-effect model was used. Subgroup analyses were performed based on ethnicity and H. pylori status. Sensitivity analyses were performed to assess the stability of the results, namely, a single study was deleted each time to reflect the influence of the individual data set on the pooled ORs. Funnel plots and Egger's tests were used to assess the publication bias. HWE in the control group was assessed using a Chi-square test. Statistical analyses were conducted using Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark) and

Table 1. Characteristic of the studies included in meta-analysis

First author	Year	Ethnicity	Studydesign	Case (n)	Control (n)	H. Pylori	Quality score
Ebert	2005	Caucasian	Case-control	88	145	Yes	8
Goto	2005	Asian	Case-control	202	454	Yes	8
Hibi	2011	Asian	Case-control	583	1742	Yes	8
Kupciinkas	2011	Caucasian	Case-control	114	460	No	8
Rochen	2005	Caucasian	Case-control	113	189	No	8
Shi	2013	Asian	Case-control	181	198	No	8
Su	2013	Asian	Case-control	81	61	No	7
Sugimoto	2006	Asian	Case-control	119	524	Yes	8

Table 2. Distribution of ACE I/D polymorphism genotype among gastric cancer cases and controls

	Gastric cancer			Control			HWE
First author	II	ID	DD	II	ID	DD	(*P* value)
Ebert	2	46	36	32	72	40	0.97
Goto	76	98	28	207	189	56	0.21
Hibi	252	255	75	745	791	204	0.79
Kupciinkas	27	59	28	124	218	118	0.26
Rochen	24	57	32	41	95	53	0.90
Shi	53	99	29	66	100	32	0.57
Su	20	34	27	17	19	27	0.002
Sugimoto	54	53	12	192	260	72	0.28

HWE: Hardy-Weinberg equilibrium.

STATA 11.0 (StataCorp LP, College Station, TX, USA).

Results

Characteristics of the studies

The process of selection of studies in the meta-analysis is summarized in a flow diagram (**Figure 1**). Database search revealed 25 potentially relevant publications. Eventually, 8 studies were eligible based on the inclusion/exclusion criteria. The main characteristics of included studies are shown in **Table 1**. The distribution of genotypes in the controls was consistent with HWE all studies except the study performed by Su et al (**Table 2**).

Meta-analysis

Results of this meta-analysis are showed in **Table 3**. In the overall analysis of 1480 gastric cancer cases and 3773 controls, the estimated OR1, OR2 and OR3 were 1.14, 1.16, and 1.00, respectively. These estimates suggested a dominant genetic model. The pooled OR was 1.15 (95% CI 0.90-1.46, *P* = 0.26), suggesting no association between *ACE* I/D polymorphism and gastric cancer risk (**Figure 2**). Significant between-study heterogeneity was detected.

Subgroup analysis

The subgroup analysis on the basis of H. Pylori status showed the decreased gastric cancer risk in H. Pylori negative subgroup (OR = 0.40; 95% CI: 0.27-0.59; P < 0.00001) rather than in H. Pylori positive subgroup (OR = 1.82, 95% CI: 0.87-3.82, P = 0.11). Subgroup analysis was performed according to ethnicity (Caucasian and Asian). The results showed no genetic effects between *ACE* I/D polymorphism and gastric cancer risk.

Sensitivity analysis

One cohort was excluded at each time to investigate the influence of the individual data set on the overall results. The association remained insignificant when any single study was excluded, confirming the stability of the results (data not shown). Notably, the removal of the study performed by Ebert et al. could reduce heterogeneity significantly (*P* from 0.02 to 0.19).

Publication bias

Both funnel plots and Egger's test were conducted to assess publication bias. The funnel plot was symmetrical, and no publication bias was observed by Egger's test (*P* = 0.576) (**Figure 3**).

Discussion

Gastric cancer is a genetically complex disease caused by multiple genetic and environmental factors and is the result of the interaction of multiple genetic and environmental factors [15-17]. ACE has a wide tissue and cellular distribution, and is expressed on the luminal mem-

Table 3. Results of this meta-analysis

Comparison	No. of studies	Sample size		Test of association		Heterogeneity		
		Case	Control	OR (95% CI)	*P*	*P*	I^2 (%)	Model
DD vs. II	8	779	2029	1.14 (0.85, 1.53)	0.38	0.06	47	R
ID vs. II	8	701	1744	1.16 (0.92, 1.46)	0.22	0.04	52	R
DD vs. ID	8	968	2343	1.00 (0.84, 1.19)	0.99	0.66	0	F
DD + ID vs. II								
Overall	8	1480	3773	1.15 (0.90, 1.46)	0.26	0.02	59	R
Ethnicity								
Asian	5	1165	2979	1.05 (0.83, 1.34)	0.68	0.08	52	R
Caucasion	3	258	596	1.54 (0.79, 2.98)	0.21	0.04	70	R
H. Pylori								
Positive	4	592	489	1.82 (0.87, 3.82)	0.11	< 0.00001	90	R
Negative	3	158	413	0.40 (0.27, 0.49)	< 0.00001	0.11	54	F

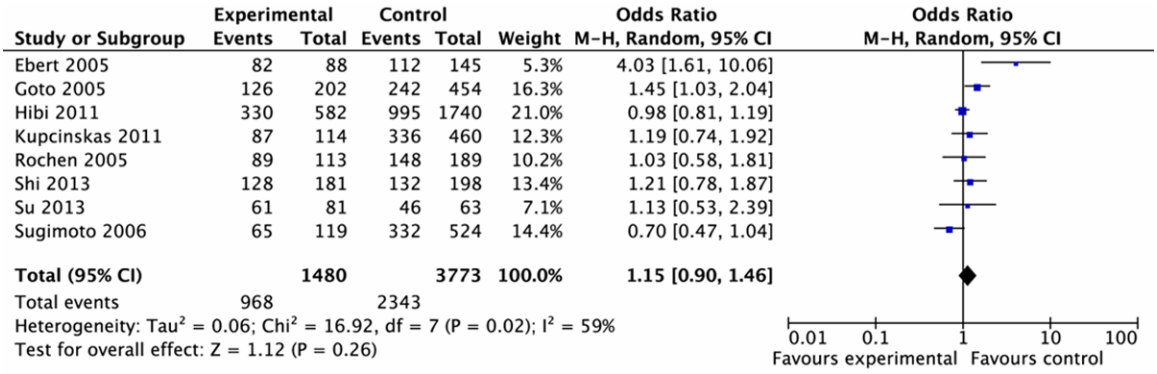

Figure 2. Meta-analysis for the association between gastric cancer risk and the *ACE* I/D polymorphism.

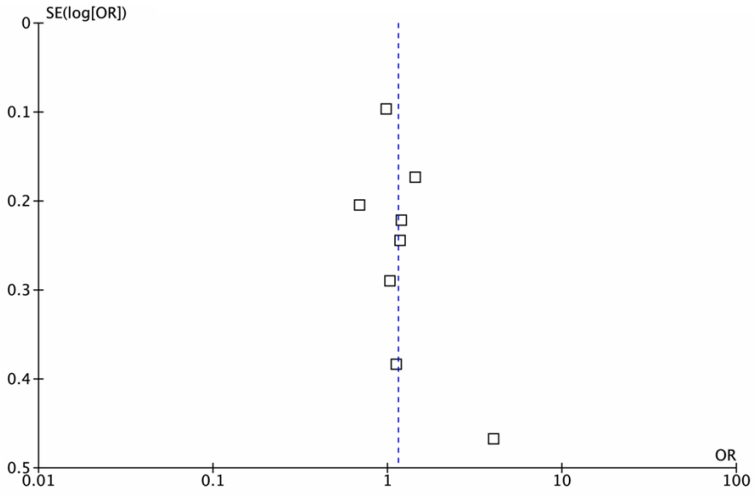

Figure 3. Funnel plot for gastric cancer risk and *ACE* I/D polymorphism.

brane of vascular endothelial cells, including of the stomach. Therefore, different levels of ACE may be associated with increased gastric cancer risk. Previous studies indicated that ACE activity might have some prognostic value in gastric cancer patients [18].

This current meta-analysis of 8 studies including 1480 cases and 3773 controls systematically evaluated the association between *ACE* I/D polymorphism and gastric cancer risk. The results indicated that *ACE* I/D polymorphism was not a risk factor for developing gastric cancer in the overall study populations. In the subgroup analysis by ethnicity, no significant association was found in Caucasians and Asians. However, in the subgroup analysis by H. Pylori status, subjects with this polymorphism showed decreased risk in H.

Pylori negative subgroup. The mechanism of this issue was still unclear. More studies are warranted to further validate this result.

The present meta-analysis had several limitations that must be taken into account. First, the heterogeneity was a major concern because obvious heterogeneity was detected in the overall analyses. Second, our meta-analysis was performed based on unadjusted ORs, and some potential confounding factors, such as age, tobacco smoking and alcohol drinking could not be assessed due to insufficient data. Third, the sample sizes were relatively small, especially in some subgroup analyses. Finally, the controls for one study included in this meta-analysis were not in HWE. However, the result was not changed after omitting this study.

In conclusion, this meta-analysis suggested that *ACE* I/D polymorphism may be not associated with the risk of gastric cancer. However, this polymorphism was significantly associated with decreased risk of gastric cancer in H. Pylori negative subjects. Large case-control studies with more ethnic groups should be performed to verify the conclusions of this meta-analysis.

Disclosure of confict of interest

None.

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References

[1] Herszényi L, Tulassay Z. Epidemiology of gastrointestinal and liver tumors. Eur Rev Med Pharmacol Sci 2010; 14: 249-58.

[2] Guo W, Dong Z, Bai Y, Guo Y, Shen S, Kuang G, Xu J. Associations between polymorphisms of HOTAIR and risk of gastric cardia adenocarcinoma in a population of north China. Tumour Biol 2014; [Epub ahead of print].

[3] Canyilmaz E, Soydemir G, Serdar L, Uslu GH, Sahbaz A, Colak F, Kandaz M, Bahat Z, Yoney A. Evaluation of prognostic factors and survival results in gastric carcinoma: single center experience from Northeast Turkey. Int J Clin Exp Med 2014; 7: 2656-66.

[4] Baudin B. New aspects on angiotensin-converting enzyme: from gene to disease. Clin Chem Lab Med 2002; 40: 256-265.

[5] Rigat B, Hubert C, Alhenc-Gelas F. An insertion/deletion polymorphism in the angiotensin I-converting enzyme gene accounting for half the variance of serum enzyme levels. J Clin Invest 1990; 86: 1343.

[6] Cambien F, Alhenc-Gelas F, Herbeth B. Familial resemblance of plasma angiotensin-converting enzyme level: the Nancy Study. Am J Hum Genet 1988; 43: 774.

[7] Röcken C, Lendeckel U, Dierkes J, Westphal S, Carl-McGrath S, Peters B, Krüger S, Malfertheiner P, Roessner A, Ebert MP. The number of lymph node metastases in gastric cancer correlates with the angiotensin I-converting enzyme gene insertion/deletion polymorphism. Clin Cancer Res 2005; 11: 2526-30.

[8] Ebert MP, Lendeckel U, Westphal S, Dierkes J, Glas J, Folwaczny C, Roessner A, Stolte M, Malfertheiner P, Röcken C. The angiotensin I-converting enzyme gene insertion/deletion polymorphism is linked to early gastric cancer. Cancer Epidemiol Biomarkers Prev 2005; 14: 2987-9.

[9] Goto Y, Ando T, Nishio K, Ishida Y, Kawai S, Goto H, Hamajima N. The ACE gene polymorphism is associated with the incidence of gastric cancer among H. pylori seropositive subjects with atrophic gastritis. Asian Pac J Cancer Prev 2005; 6: 464-7.

[10] Sugimoto M, Furuta T, Shirai N, Ikuma M, Sugimura H, Hishida A. Influences of chymase and angiotensin I-converting enzyme gene polymorphisms on gastric cancer risks in Japan. Cancer Epidemiol Biomarkers Prev 2006; 15: 1929-34.

[11] Kupcinskas J, Wex T, Bornschein J, Selgrad M, Leja M, Juozaityte E, Kiudelis G, Jonaitis L, Malfertheiner P. Lack of association between gene polymorphisms of Angiotensin converting enzyme, Nod-like receptor 1, Toll-like receptor 4, FAS/FASL and the presence of Helicobacter pylori-induced premalignant gastric lesions and gastric cancer in Caucasians. BMC Med Genet 2011; 12: 112.

[12] Hibi S, Goto Y, Ando T, Matsuo K, Wakai K, Tajima K, Goto H, Hamajima N. No association between angiotensin I converting enzyme (ACE) I/D polymorphism and gastric cancer risk among Japanese. Nagoya J Med Sci 2011; 73: 169-75.

[13] Shi ML, Shao H, Lu HH, Zhang JB. The association betweenACE polymorphism and risk of gastric cancer. Chin J Gerontol 2011; 31: 3526-8.

[14] Su ZH, Wang RH, Yang SX, Gu Y, Ma HY, Kong FH. Study of genepolymorphism and disease susceptibility in Hui-Chinese gas-tric cancer in QingHai province. J QingHai Med Coll 2013; 34: 1-6.

[15] Shen X, Zhang J, Yan Y, Yang Y, Fu G, Pu Y. Analysis and estimates of the attributable risk for environmental and genetic risk factors in gastric cancer in a Chinese population. J Toxicol Environ Health A 2009; 72: 759-66.
[16] McColl KE, Watabe H, Derakhshan MH. Sporadic gastric cancer; a complex interaction of genetic and environmental risk factors. Am J Gastroenterol 2007; 102: 1893-5.
[17] Rocco A, Staibano S, Ottini L, Mezza E, Somma P, Mariani-Costantini R, Budillon G, Nardone G. Is there a link between environmental factors and a genetic predisposition to cancer? A lesson from a familial cluster of gastric cancers. Eur J Cancer.2003; 39: 1619-24.
[18] Gard PR. Implications of the angiotensin converting enzyme gene insertion/deletion polymorphism in health and disease: a snapshot review. Int J Mol Epidemiol Genet 2010; 1: 145-57.