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Angiotensin-Converting Enzyme Gene Deletion Polymorphism is Associated with Lymph Node Metastasis in Colorectal Cancer Patients in a Chinese Population

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Background: The purpose of this study was to assess the effect of angiotensin-converting enzyme (*ACE*) gene insertion/deletion (I/D) polymorphism on the risk of lymph node metastasis (LNM) in colorectal cancer (CRC) patients.

Material/Methods: We enrolled 146 CRC patients and 106 healthy controls in this study. *ACE* gene I/D polymorphism was genotyped by polymerase chain reaction (PCR). Hardy-Weinberg equilibrium (HWE) was used to assess the goodness of fit of the genotypes. χ^2 test was used to calculate the differences of genotype and allele distributions. Odds ratios (ORs) with corresponding 95% confidence intervals (95% CIs) were used to analyze the association between *ACE* I/D polymorphism and LNM in CRC patients.

Results: Insertion/deletion (ID) and deletion/deletion (DD) genotypes were frequently observed in CRC patients, but only DD genotype and D allele were related to the susceptibility of CRC (*P*=0.038, OR=2.158, 95%CI=1.039–4.480; *P*=0.026, OR=1.501, 95%CI=1.048–2.150). DD genotype and D allele also increased the risk of LNM in CRC patients (*P*=0.028, OR=2.844, 95%CI=1.107–7.038; *P*=0.026, OR=1.692, 95%CI=1.063–2.693).

Conclusions: DD genotype and D allele of *ACE* gene I/D polymorphism might increase the risk of LNM in CRC patients.

MeSH Keywords: Cetirizine • Colorectal Neoplasms • Lymphatic Abnormalities • Polymorphism, Single-Stranded Conformational

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Background

Colorectal cancer (CRC) is one of the most common alimentary canal cancers. Although the incidence rate of CRC has decreased, the mortality of this cancer is still very high, accounting for more than one-third of all deaths in the USA [1]. However, it is reported that the morbidity and mortality of CRC have recently increased in China [2]. CRC has a poor prognosis due to the high risk of metastasis in CRC patients. It is believed that lymph node metastasis (LNM) is the main metastatic mode of CRC. LNM is the leading cause of postoperative recurrence and death for CRC patients and may influence the effectiveness of therapy. Exploration of the relative factors of LNM in CRC may contribute to the improvement of CRC therapy and increase the survival rate of CRC patients. CRC development is affected by multiple factors and steps [3,4]. Thus, the metastasis of CRC might be affected by similar factors, such as diet, lifestyle, genetic, and environmental factors [5,6]. Among these factors, the key factor for CRC progression is genetic polymorphisms [3,7–9].

Evidence indicates that angiotensin-converting enzyme (*ACE*) gene polymorphism may be significantly associated with tumor development [10–13]. ACE, a zinc metallopeptidase in the cell surface, is an enzyme of the renin-angiotensin system (RAS). ACE may promote tumor cell proliferation, migration, angiogenesis, and metastatic behavior [14–16]. Epidemiological studies show an up-regulation of ACE in different tumors [17], and a strong association was also detected between ACE inhibitors and cancer risk [18,19]; therefore, it is important to explore the association between ACE and CRC risk to find efficient treatment methods for CRC. Polymorphisms in *ACE* gene may alter the ACE function, thereby contributing to the occurrence of CRC. Insertion (I)/deletion (D) polymorphism of *ACE* gene may regulate *ACE* expression level and activity [20], as well as the cancer risk [21].

Therefore, in this study we aimed to demonstrate the association between *ACE* insertion/deletion (I/D) polymorphism and the risk of LNM in Chinese CRC patients.

Material and Methods

Subject features

We enrolled 146 CRC patients who were diagnosed by biopsy and pathology in Qilu Hospital of Shandong University in this study. None of the patients had received any therapy before sample collection. Demographics and clinical features were assessed and recorded, including age, sex, primary location, LNM, and drinking and smoking status (Table 1). Alcohol drinkers were defined as someone who drank more than once per day for at least 3 months. Smoking more than 1 cigarette per day for at least 1 year was considered as smoking. The LNM group included CRC patients who had more than 1 LNM. CRC

Table 1. Clinical characteristics of study objects.

Characteristics	Cases n=146 (%)	Controls n=106 (%)	*P* value
Age	56.36±8.75	58.17±9.11	0.563
Gender			0.987
Male	88 (60.27)	64 (60.38)	
Female	58 (39.73)	42 (39.62)	
Primary location			
Colon	68 (46.58)	–	
Rectum	78 (53.42)	–	
LNM			
Yes	66 (45.21)	–	
No	80 (54.79)	–	
Alcohol drinker			0.101
Yes	66 (45.20)	37 (34.91)	
No	80 (54.78)	69 (65.09)	
Tobacco user			0.144
Yes	70 (47.95)	41 (38.68)	
No	76 (52.05)	65 (61.32)	

LNM – lymph node metastasis.

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Table 2. Genotype and allele frequencies *ACE* I/D porlymorphism in patients with CRC.

SNP	CRC n=146 (%)	Control n=106 (%)	OR (95% CI)	*P* value
Genotype				
II	38 (26.03)	41 (38.68)	–	–
ID	74 (50.68)	48 (45.28)	1.663 (0.939–2.946)	0.080
DD	34 (23.29)	17 (16.04)	2.158 (1.039–4.480)	0.038
Alleles				
I	150 (51.37)	130 (61.32)	–	–
D	142 (48.63)	82 (38.68)	1.501 (1.048–2.150)	0.026

CRC – colorectal cancer; SNP – single nucleotide polymorphism; II – insertion/insertion; ID – insertion/deletion; DD – deletion/deletion; I – insertion; D – deletion.

patients without LNM were enrolled into the non-LNM group. Individuals without any cancers, family history of cancers, and colorectal disease were recruited from a health check-up center of the same hospital as controls. Controls were matched with cases for age, sex, and drinking and smoking status.

This study was approved by Ethics Committee of Qilu Hospital of Shandong University, and every patient signed written consent before blood specimens were collected. All subjects were of Chinese Han ethnicity and had no blood relationship with any other enrolled subject.

Specimens collection and DNA extraction

We collected 2-mL peripheral blood specimens from each patient after a 12-h fast. Blood samples were anticoagulated by EDTA. Genome DNA was extracted using the QIAamp kit (Qiagen, Germany) according to the manufacturer's instructions. DNA samples were stored at –20°C until use.

Determination of *ACE* genotype

PCR primers for *ACE* amplification were synthesized according to the previous description [22]. Primer sequences were as follows: forward, 5'-CTG GAG ACC ACT CCC ATC CTT TCT-3'; reverse, 5'-GAT GTG GCC ATC ACA TTC GTC AGA T-3'. PCR reaction was performed in a 20-μL system, containing 10 μL 2×PCR Master Mix, 1.2 μL $MgCl_2$, 0.5 μL each primer, 1.6 μL of genomic DNA, and 6.2 μL redistilled water. The program for PCR amplification was as follows: initial predenaturation 94°C for 4 min, followed by 35 cycles of 94°C for 30 s, 64°C for 90 s, and 72°C for 90 s, and a final extension at 72°C for 10 min. PCR products were detected by 1.5% agarose gel electrophoresis. There were 3 possible patterns: a 490-bp band (insertion/insertion genotype, II genotype), a 190-bp band (deletion/deletion genotype, DD genotype), and both 490-bp and 190-bp bands (insertion/deletion genotype, ID genotype).

Statistical analysis

All data analyses were performed in SPSS 18.0 software and $P<0.05$ was considered as statistically significant. Hardy-Weinberg equilibrium (HWE) was used to assess the representativeness of the participants. Direct calculation was utilized to get the genotype and allele frequencies of *ACE* gene I/D polymorphism. Genotype and allele distributions differences between LNM and non-LNM groups were calculated by χ^2 test. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to evaluate the strength of association between *ACE* gene polymorphism and LNM in CRC patients.

Results

Clinical characteristics of study objects

After diagnosis, there were 80 non-LNM CRC patients, 66 LNM CRC patients, and 106 healthy controls. Clinical characteristics are listed in Table 1. None of the clinical characteristics were significantly different between case and control groups ($P>0.05$).

Association between *ACE* gene I/D polymorphism and LNM in CRC patients

Genotype distributions of *ACE* gene I/D polymorphism did not deviate from HWE in CRC patients and healthy controls.

Frequency distributions of I/D polymorphism in CRC patients were different from healthy controls (Table 2). DD genotype was more frequently observed in CRC patients than in healthy controls, indicating a significant association with CRC risk ($P=0.038$, OR=2.158, 95%CI=1.039–4.480). ID genotype frequency was also higher in LNM CRC patients than in healthy controls, but the difference was not significant ($P>0.05$). D allele frequency showed a significantly increased trend in the

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Table 3. The effect of *ACE* polymorphism on lymph node metastasis in CRC patients.

SNP	LNM n=66 (%)	Non-LNM n=80 (%)	OR (95% CI)	*P* value
Genotype				
II	12 (18.18)	26 (32.50)	–	–
ID	33 (50.00)	38 (47.50)	1.882 (0.822–4.306)	0.132
DD	21 (31.82)	16 (20.00)	2.844 (1.107–7.038)	0.028
Alleles				
I	57 (43.18)	90 (56.25)	–	–
D	75 (56.82)	70 (43.75)	1.692 (1.063–2.693)	0.026

LNM – lymph node metastasis; SNP – single nucleotide polymorphism; II – insertion/insertion; ID – insertion/deletion; DD – deletion/deletion; I – insertion; D – deletion.

CRC patients group, and D allele significantly increased the CRC susceptibility (*P*=0.026, OR=1.501, 95%CI=1.048–2.150).

Compared with the non-LNM CRC patient group (Table 3), DD genotype frequency was obviously higher in the LNM group, which demonstrated that DD genotype might increase the risk of LNM in CRC patients (*P*=0.028, OR=2.844, 95%CI=1.107–7.038). D allele frequency also was significantly increased in the case group, and had a positive association with susceptibility to LNM in CRC patients (*P*=0.026, OR=1.692, 95%CI=1.063–2.693).

Discussion

ACE enzyme can catalyze the conversion of angiotensin I into angiotensin II, which is a potent vasoconstrictor influencing cancer progression [23]. A number of studies have reported that the mRNA and protein levels of ACE in tumor cells or tissues were different from that in normal cells or tissues [24–26]. Abnormal expression level of *ACE* gene leads to aberrant levels of angiotensin II, thus influencing tumor progression, and ACE can promote angiogenesis [27]. Angiotensin II can activate the production of transforming growth factor β (TGF β), and up-regulate the vascular endothelial growth factor (VEGF) receptor. The 2 cytokines can up-regulate angiogenesis. Some studies have reported that ACE affects the proliferation, metastasis, and recurrence of cancer [23,28,29]. Additionally, ACE inhibitors decrease the risk of CRC [19]. Therefore, we speculate that ACE relates the metastasis of CRC. The association of ACE with CRC metastasis is not conclusive. Further studies are needed to explore this possible association. LNM is the most common mode of metastasis. Thus, in this study we detected the distribution of the ACE genotypes in CRC with LNM compared to non-LNM cancer and healthy controls.

CRC, one of the most common digestive system neoplasms, has a high morbidity and mortality, and the mortality has been gradually increasing in China. When it is diagnosed, CRC patients rapidly progress to advanced stages, by which time it is too late to perform radical surgery. Distant metastasis and local recurrence are common in CRC. All of the above lead to the poor prognosis and high death rate of CRC. It would be of great significance to improve CRC therapy methods. Better understanding of the pathogenesis of CRC could provide a theoretical basis for improved diagnosis and treatment of this disease. Pathology researches have suggested that onset and development of CRC, as well as the metastasis of CRC, may be affected by various factors [30–32]. As the most common symptom of CRC, metastasis would be influenced by the same factors.

Some individuals exposed to cancerogenic substances develop tumors, and individual susceptibility may play a role in the occurrence and symptoms of cancer. This individual susceptibility may be determined by small changes in genes. Previous studies reported that *ACE* gene I/D polymorphism was associated with different cancer risk [33,34]. I/D polymorphism is an insertion or deletion polymorphism with -287bp in *ACE* gene. Based on the above, we evaluated the relationship between *ACE* gene I/D polymorphism and LNM in CRC patients.

In this study, we demonstrated that DD genotype and D allele of *ACE* I/D polymorphism were significantly related to the susceptibility of CRC occurrence. Although the frequency of ID genotype of this polymorphism was higher in CRC patients, this genotype had no association with the onset of CRC. No significant relationship between *ACE* I/D polymorphism and risk of CRC was detected in other populations [13,35]. To explore the association of *ACE* gene I/D polymorphism with the appearance of LNM in CRC patients, we compared the genotype and allele frequency distributions between LNM and non-LNM groups in CRC patients. The results demonstrated that DD genotype and D allele of *ACE* gene I/D polymorphism increased risk of LNM by 2.844-fold and 1.692-fold, respectively, in CRC patients. Although has been no previous study focused

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on LNM in CRC patients, DD genotype has been discovered to be positively associated with LNM in gastric cancer [36]. A meta-analysis indicated that I allele of *ACE* I/D polymorphism is significantly associated with cancers risk in people of white ethnicity [37]. Zha et al. reported that *ACE* DD genotype contributes to prediction of hepatocellular carcinoma [38].

These inconsistent conclusions might be due to the differences in genetic traits. Although the representativeness of the participants was good in the present study it has some limitations. Our study had a relatively small sample size, which may lead to less precise estimation of the association between the *ACE* I/D polymorphism and LNM development in patients with CRC. In addition, environmental factors might also contribute to the occurrence of LNM with *ACE* I/D polymorphism in CRC patients. However, we did not consider the epigenetic factors. To accurately analyze the relationship between *ACE* polymorphism and LNM in CRC patients, well-designed investigations with large numbers of participators are needed.

Conclusions

Our data indicate that DD genotype and D allele of *ACE* gene are significantly associated with increased susceptibility to CRC, and the DD genotype and D allele might increase the risk of LNM in patients with CRC.

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