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# Angiotensin-Converting Enzyme Gene Insertion/Deletion Polymorphism in Patients with Chronic Pancreatitis and Pancreatic Cancer

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Biljana Milicic<sup>e</sup> Dragica Dinic<sup>b</sup> Dragica Radojkovic<sup>b</sup><sup>a</sup>Clinic for Gastroenterology, Clinical Center of Serbia, <sup>b</sup>Institute of Molecular Genetics and Genetic Engineering,<sup>c</sup>School of Medicine, University of Belgrade, <sup>d</sup>First Surgical Clinic, Clinical Center of Serbia, and <sup>e</sup>Institute for Medical Informatics, School of Dentistry, University of Belgrade, Belgrade, Serbia**Key Words**Chronic pancreatitis · Pancreatic cancer ·  
Angiotensin-converting enzyme**Abstract**

The purpose of this study was to determine the frequency of angiotensin-converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism and to investigate its role as a potential risk factor in patients with chronic pancreatitis and pancreatic cancer. Deletion polymorphism of the 287-bp fragment of intron 16 of the ACE gene results in higher levels of circulating enzyme and therefore may represent a risk factor for disease development. The study included 55 patients with chronic pancreatitis, 45 patients with pancreatic cancer and 128 healthy subjects. The presence of I and D variants in the ACE gene was analyzed by a polymerase chain reaction (PCR) method. Distribution of ACE ID genotypes was analyzed by means of logistic regression. When chronic pancreatitis and pancreatic cancer groups were compared in the univariate analysis, the following factors were identified as statistically significant predictors of pancreatic disease: age, gender, smoking, fat intake, ACE II genotype and ACE DD genotype. However, in the multivariate analysis, only age, gender and smoking were singled out as predictors for the occurrence of pancreatic disease. Our findings indicate that

the ACE I/D polymorphism could play a role in the development of chronic pancreatitis and pancreatic cancer through interaction with other genetic and environmental factors.

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**Introduction**

Chronic pancreatitis and pancreatic cancer are diseases with complex and insufficiently explained etiology and pathogenesis. The origin of pancreatic disease involves numerous environmental and genetic factors and the role of genetic factors has not been clearly defined so far. Several epidemiological studies have shown that increasing age, male gender, fat intake and smoking represent risk factors for pancreatic cancer, while alcohol consumption is the main etiological factor for the occurrence of chronic pancreatitis [1–9].

Angiotensin-converting enzyme (ACE) is a key enzyme of the renin-angiotensin system, which is an enzyme circulatory cascade system and plays a primary role in the regulation of blood pressure and serum electrolytes homeostasis [10, 11]. ACE converts inactive pro-hormone angiotensin I to the active peptide hormone and potent vasoconstrictor angiotensin II. Recent studies have indicated the existence of a local renin-angiotensin system of

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the endocrine and exocrine pancreas. This system is essential for maintaining pancreatic homeostasis as it is involved in the processes of cell proliferation, differentiation, inflammation, apoptosis and fibrosis [12]. Thus, the ACE gene may have a role in the occurrence of chronic pancreatitis and pancreatic cancer.

The ACE gene insertion/deletion (I/D) polymorphism was first detected in 1990. Deletion polymorphism of the 287-bp fragment of intron 16 of the ACE gene results in higher levels of circulating enzyme [13]. It has been shown that the ACE deletion (DD) genotype results in a 1.3-fold increased risk of myocardial infarction [14].

Recent studies on experimental animals have revealed the ACE effect on pancreatic fibrogenesis [15]. It has also been proven that ACE inhibitors reduce the levels of inflammation and pancreatic fibrosis in rats [16]. Thus it has been shown that the renin-ACE-angiotensin system is directly involved in the process of inducing pancreatic inflammation and developing chronic pancreatitis. Recent studies have also revealed increased expression of the ACE gene in pancreatic cancer [17]. The role of the ACE-angiotensinogen system in the pathogenesis of pancreatic cancer is reflected in its involvement in the processes of cell growth, metastasis and angiogenesis [18, 19]. However, further studies are needed to examine the frequency of ACE gene polymorphism in and its contribution to the development of pancreatic diseases.

Epidemiologic studies involving hypertensive patients have suggested that blocking angiotensin II may decrease cancer risk [20, 21]. Angiotensin II has been shown to increase vascular endothelial growth factor (VEGF) production in cancer [22]. Pancreatic cancer expresses a high level of VEGF, a crucial component of angiogenesis in pancreatic cancer [23]. ACE inhibitors are widely used in clinical practice and may thus represent a potential novel and promising strategy for controlling angiogenesis and prevention of metastasis in patients with pancreatic cancer.

The purpose of this study was to determine the frequency of the ACE gene I/D polymorphism and to investigate its role as a potential risk factor in patients with chronic pancreatitis and pancreatic cancer.

## Patients and Methods

### Patients

The study included 55 patients with chronic pancreatitis, 45 patients with pancreatic cancer and 128 healthy subjects in the control group. The study was carried out at the Gastroenterology and Hepatology Clinic and the First Surgical Clinic, while genetic testing

was performed in the Laboratory for Molecular Biology at the Institute of Molecular Genetics and Genetic Engineering in Belgrade.

The following demographic data were analyzed for all patients: age, gender, information regarding animal fat intake, smoking and alcohol consumption. The subjects who smoked more than 20 cigarettes a day were defined as heavy smokers and the subjects who consumed more than 60 g of alcohol per day were defined as heavy drinkers. Information about fat intake was obtained by way of a questionnaire which was filled in by each subject. The questionnaire included questions about how often the subjects used pork, lard, fatty cheeses and eggs in their daily diet.

Chronic pancreatitis was diagnosed based on clinical and laboratory data about the presence of exocrine and endocrine pancreatic insufficiency, and the results of morphological tests – calcification of the pancreas diagnosed by abdominal ultrasound examination and abdominal CT or NMR scans; morphological changes of the pancreatic canalicular system, diagnosed by endoscopic retrograde cholangiopancreatography (ERCP); morphological changes of pancreas, diagnosed by endoscopic ultrasound.

The diagnosis of pancreatic adenocarcinoma was established using clinical data (pain, obstructive icterus and weight loss), laboratory test results (value of tumor marker CA19-9) and results of different diagnostic procedures (abdominal ultrasonography, abdominal CT or NMR scans, pancreatic endoscopic ultrasonography). Pathohistological tests conducted during the surgical procedures confirmed the diagnosis in all patients with pancreatic adenocarcinoma.

### Genotyping

The genotyping for ACE I/D polymorphism was performed on the DNA extracted from whole blood samples by QIAamp DNA Blood Mini Kit (Qiagen). The presence of I and D variants in the ACE gene was analyzed by a polymerase chain reaction (PCR) method using oligonucleotide primers flanking the respective fragment of the intron 16 of the human ACE gene. The PCR products were separated on 2% agarose gels stained with ethidium bromide. The amplification of the 490-bp-long fragment indicates presence of the I allele, while the amplification of the 190-bp-long fragment indicates presence of the D allele [24].

### Statistical Analysis

Descriptive statistics were performed with percentages for qualitative data, and with mean and SD for quantitative data. Categorical data were compared using Pearson's  $\chi^2$  test. Continuous variables were compared with the use of one-way ANOVA. Data were analyzed by logistic regression. The ORs evaluated by the logistic regression together with their 95% CIs were also reported. All reported p values were two-sided; differences were considered significant when p was <0.05.

## Results

The study included 45 patients with pancreatic cancer and 55 patients with chronic pancreatitis, while the control group included 128 healthy subjects. Male gender was significantly more represented in all 3 groups, with the highest frequency of male subjects noted in the chronic

**Table 1.** Characteristics of the analyzed groups

Parameters	Groups			p value
	pancreatic cancer	chronic pancreatitis	healthy subjects	
Total number	45	55	128	
Gender (M/F)	27/18	46/9	93/35	0.030 <sup>*, a</sup> 0.008 <sup>*, b</sup> 0.113 <sup>c</sup> 0.111 <sup>d</sup>
Mean age ± SD	60.9 ± 10.6	53.1 ± 12.5	40.1 ± 10.5	0.000 <sup>*, a</sup> 0.001 <sup>*, b</sup> 0.000 <sup>*, c</sup> 0.000 <sup>*, d</sup>
Smoking, n	29 (64.4)	23 (42.6)	–	0.030 <sup>*, b</sup>
Alcohol, n	25 (55.6)	40 (72.7)	–	0.073 <sup>b</sup>
Fatty food intake, n	31 (68.9)	27 (49.1)	–	0.046 <sup>*, b</sup>
ACE, n				
ID	17 (37.8)	22 (40.0)	72 (56.3)	0.000 <sup>*, a</sup>
DD	4 (8.9)	18 (32.7)	26 (20.3)	0.005 <sup>*, b</sup>
II	24 (53.3)	15 (27.3)	30 (23.4)	0.001 <sup>*, c</sup> 0.097 <sup>d</sup>

Figures in parentheses are percentages.

\* Statistically significant: <sup>a</sup> between all 3 groups; <sup>b</sup> between pancreatic cancer and chronic pancreatitis; <sup>c</sup> between pancreatic cancer and healthy subjects; <sup>d</sup> between chronic pancreatitis and healthy subjects.

pancreatitis group (table 1). Female subjects were significantly more represented in the pancreatic cancer group in comparison to the chronic pancreatitis group. Subjects with pancreatic cancer were significantly the oldest, while the control group subjects were the youngest. Compared with pancreatic cancer patients, a higher number of chronic pancreatitis patients consumed alcohol, although the difference was not statistically significant. The highest frequency of subjects characterized by fat intake was observed in the pancreatic cancer group.

The analysis of the distribution of ACE genotypes has revealed statistically significant difference between pancreatic cancer and chronic pancreatitis groups and between pancreatic cancer and healthy subjects groups, while the difference between chronic pancreatitis and healthy subjects groups was not statistically significant. Each ACE genotype was analyzed as a risk factor for pancreatic cancer and chronic pancreatitis by means of

logistic regression analysis. When pancreatic cancer and chronic pancreatitis groups were compared, in the univariate analysis the following factors were identified as statistically significant: age, gender, smoking, fat intake, ACE II genotype and ACE DD genotype. However, in the multivariate analysis only age, gender and smoking were singled out as predictors for the occurrence of a pancreatic disease (table 2). Through analysis of single predictors it was observed that females have 4 times higher risk of pancreatic cancer occurrence, that each year of life increases risk of pancreatic cancer for 6% and that smokers are at 3 times higher risk of pancreatic cancer occurrence.

## Discussion

The origin of pancreatic disease involves many environmental and genetic factors, and their roles have not yet been clearly defined. This study is the first to investigate the frequency of ACE I/D polymorphism in patients with pancreatic cancer and one of a few analyzing this polymorphism in chronic pancreatitis patients.

The only confirmed etiological factors in pancreatic cancer and chronic pancreatitis development are smoking and alcohol consumption, respectively. The findings of this study are in correlation with previous findings which indicate that age, gender, smoking, alcohol and fat intake increase risk of pancreatic disease [25–31].

In this study, there were more men than women in the groups of patients with pancreatic cancer and chronic pancreatitis, but also in the control group. In patients with pancreatic cancer, the men:women ratio was 1.5:1, which indicates that the number of women who develop pancreatic cancer is increasing [25].

While most studies report average age of over 65 years in patients with pancreatic cancer, in this study pancreatic cancer patients were 60.9 years old. The average age of patients with chronic pancreatitis was 53.1 years, which correlates with findings of other studies [26].

Smoking is considered to be the only proven risk factor for pancreatic cancer [27, 28]. In this study, distribution of smokers differed significantly between the groups. They were more frequent in pancreatic cancer patients (64.4%) than in chronic pancreatitis patients (42.6%).

The only confirmed etiological factor in chronic pancreatitis development is alcohol consumption [9]. In this study, the vast majority of chronic pancreatitis patients (73.3%) were found to be alcohol consumers, which is in correlation with findings of other studies [9]. Alcohol consumption was more frequent in patients with chronic

**Table 2.** Logistic regression analysis for pancreatic cancer and chronic pancreatitis

Parameters	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
Gender	0.293 (0.116–0.744)	0.010*	0.250 (0.078–0.806)	0.020*
Age	0.941 (0.905–0.979)	0.002*	0.940 (0.899–0.984)	0.007*
Smoking	2.443 (1.082–5.517)	0.032*	3.154 (1.109–8.972)	0.031*
Alcohol	0.469 (0.203–1.081)	0.075	–	–
Fatty food intake	2.296 (1.008–5.231)	0.048*	1.310 (0.473–3.628)	0.604
ACE: ID vs. DD+II	0.911 (0.406–2.045)	0.821	–	–
ACE: II vs. ID+DD	3.048 (1.324–7.015)	0.009*	1.666 (0.598–4.641)	0.329
ACE: DD vs. II+ID	0.201 (0.062–0.647)	0.007*	0.358 (0.084–1.526)	0.165

\* Statistically significant.

pancreatitis than in patients with pancreatic cancer, but the difference was not statistically significant.

The highest frequency of subjects who consumed fatty food was observed in pancreatic cancer patients and this study indicated that fat intake represents a risk factor for pancreatic cancer, which is in correlation with results of other studies [29–31].

Results of this study indicate association between ACE I/D polymorphism and pancreatic diseases. The ID genotype was most frequent in healthy individuals group, and statistical analysis indicates that carriers of the ID genotype are at the lowest risk of developing analyzed pancreatic diseases.

The DD genotype of the ACE I/D polymorphism was significantly more frequent in chronic pancreatitis (32.7%) than in pancreatic cancer (8.9%), which indicates that in carriers of the DD genotype the risk of chronic pancreatitis is higher than the risk of pancreatic cancer. The ACE II genotype was associated with pancreatic cancer, while the ACE DD genotype was associated with chronic pancreatitis. Results of other studies have not indicated a correlation between ACE I/D polymorphism and pathogenesis and progression of chronic pancreatitis. Oruc et al. [32] have found similar frequencies of the ACE DD genotype in groups of patients with sporadic and familial pancreatitis and healthy individuals. Also, Hucl et al. [33] have not found any significant differences in ACE DD genotype frequency in acute and chronic pancreatitis in comparison to the control group. Similar findings were reported by Indian authors who investigated the role of the ACE I/D polymorphism in tropical calcifying pancreatitis [34]. The frequency of the ACE II genotype was highest in the group of patients with pancreatic cancer and subjects with this

genotype were found to be at higher risk of developing pancreatic cancer. However, the ACE DD genotype was identified as risk factor only in univariate regression analysis, but not in multivariate regression analysis. Such finding indicates that the influence of the ACE genotype on pancreatic disease development is not independent and may be associated with other risk factors.

Having in mind the importance of the role of ACE in pancreatic diseases, numerous studies have researched the potential roles of ACE inhibitors as protective factors in angiogenesis control in pancreatic cancer. Thus, the Arafat et al. [17] study has shown that blocking endogenous angiotensin II by captopril or losartan significantly suppressed cell proliferation in human pancreatic cancer. The study by German authors from 2010 proved enalapril and aspirin to be effective chemopreventive agents by delaying the progression of pancreatic intraepithelial neoplasia and cancer formation in a genetically engineered mouse model of pancreatic cancer [35].

Based on the findings of the aforesaid studies and the results of this study, we propose further research attempts to investigate possibility of prophylactic admission of small doses of ACE inhibitors in older female patients with chronic pancreatitis who are smokers and carriers of the ACE II genotype, for the purpose of pancreatic cancer prevention [17, 35].

Logistic regression analysis has identified the ACE genotype as a statistically significant predictor of pancreatic disease in the univariate analysis. However, it has not singled it out as predictor for the occurrence of pancreatic disease in the multivariate analysis. This finding can be explained by the fact that chronic pancreatitis and pancreatic cancer are multifactorial diseases with com-



plex etiology, for which interplay of various genetic and non-genetic factors is characteristic. It is possible that the ACE I/D polymorphism plays a role in the development of chronic pancreatitis and pancreatic cancer through interaction with other genetic and environmental factors.

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