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Interaction between *ACE* insertion/deletion polymorphism and type 2 diabetes mellitus in pancreatic cancer risk: Evidence from an Algerian cohort

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Abstract: Pancreatic cancer risk was investigated in relation to the angiotensin-I-converting enzyme (ACE) insertion/deletion (I/D) polymorphism and its interaction with type 2 diabetes mellitus in an Eastern Algerian population through a hospital-based case-control study. The research involved 35 patients with confirmed pancreatic cancer and 140 matched healthy controls. Genotyping was performed to determine *ACE* I/D profiles, and statistical analysis was used to quantify risk associations. Type 2 diabetes mellitus was common, affecting more than half of the patients. The heterozygous ID genotype was associated with a 2.5-fold increased cancer risk, and this association was significant only among individuals with diabetes. Multivariable analysis suggested the ID genotype as an independent risk factor, with an approximately 8-fold higher risk after adjustments. This preliminary study suggests the *ACE* I/D polymorphism may influence pancreatic cancer risk, with type 2 diabetes acting as a critical effect modifier and identifying a potential high-risk subgroup for targeted surveillance. These exploratory findings warrant validation in larger, population-based cohorts.

Keywords: pancreatic cancer; *ACE* polymorphism; genetic risk; type 2 diabetes; Algerian population

INTRODUCTION

Pancreatic cancer (PC) remains one of the most lethal malignancies, characterized by a bleak prognosis and limited therapeutic options. Despite medical advances, its late detection and aggressive nature mean that fewer than 10% of patients survive beyond five years after diagnosis [1,2].

This poor prognosis stems largely from late diagnosis, aggressive tumor biology, and limited therapeutic advances [2,3]. The etiology of pancreatic cancer is multifactorial, involving complex interactions between genetic susceptibility and environmental risk factors, including smoking, obesity, chronic pancreatitis, and type 2 diabetes mellitus (T2DM) [3,4]. Notably, T2DM exhibits a bidirectional relationship with PC, serving as both a risk factor and consequence of the disease, which complicates etiological understanding [5]. The risk is particularly pronounced in new-onset diabetes; a diagnosis within the previous two years was associated with a significantly increased risk of pancreatic cancer (adjusted odds ratio (OR)=4.4), suggesting that recent metabolic changes may represent an early marker of occult disease [6].

Emerging research has implicated the renin-angiotensin system (RAS) in tumor development pathways. Within this system, the angiotensin-converting enzyme (ACE) catalyzes angiotensin II (Ang II) formation, a peptide signaling molecule that activates angiotensin type 1 receptors to stimulate cellular proliferation, angiogenesis, stromal remodeling, and inflammatory responses [7-9]. A commonly studied genetic variation in the *ACE* gene involves an insertion/deletion (I/D) polymorphism in intron 16 (rs4646994), which influences circulating ACE concentrations, with the D allele correlating with enhanced enzymatic activity [10].

The relationship between this polymorphism and pancreatic cancer risk, however, appears to be complex and may be significantly mediated by T2DM. The *ACE* I/D polymorphism appears to exhibit a complex interaction with T2DM that may indirectly influence pancreatic cancer risk. Multiple studies have established a link between the *ACE* D allele and an increased susceptibility to T2DM. A meta-analysis confirmed this association [11], with the DD genotype specifically shown to confer a 2.35-fold increased risk of developing type 2 diabetes mellitus [12]. This suggests that the *ACE* I/D polymorphism could indirectly influence pancreatic cancer risk by predisposing individuals to T2DM, a well-established risk factor for malignancy. It was further suggested that the *ACE* I/D polymorphism could play a role in pancreatic disease development through interaction with both genetic background and environmental factors [13]. While this polymorphism has been associated with susceptibility to various cancers, its direct relationship with PC risk has shown inconsistent patterns across different ethnic groups [14,15].

These discrepancies may stem from multiple factors, including limited statistical power in previous studies, population-specific genetic backgrounds, and inadequate consideration of critical metabolic comorbidities such as T2DM [10]. The direct causal mechanism linking the ACE polymorphism to pancreatic cancer remains unclear, and more research is needed to establish the nature of this relationship. In Algeria, where both pancreatic cancer incidence and diabetes prevalence are increasing, genetic epidemiology research remains underdeveloped.

The primary objective of this investigation was to assess the association between the *ACE* I/D polymorphism and pancreatic cancer risk in an Algerian cohort. A secondary aim was to evaluate potential effect modification by T2DM status in this relationship, specifically testing the hypothesis that the genetic risk is elevated in the presence of diabetes.

MATERIALS AND METHODS

Ethics statement

The research protocol was approved by the Ethics Board of the University Hospital in Constantine (under approval code EC/CHUC/03/02-2022, issued on June 19, 2022). All investigative procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki. All participants provided written informed consent.

Study population and design

This hospital-based, retrospective case-control investigation was carried out at the Department of Surgery A, University Hospital of Constantine, Algeria, from April 2023 to June 2025. The study population included 35 consecutive patients with histologically confirmed pancreatic adenocarcinoma. Diagnosis validation integrated radiological imaging, surgical exploration, and pathological examination findings. Individuals with previous malignant disease were excluded from participation. A control group of 140 cancer-free volunteers was recruited from the metabolic outpatient clinic of the same healthcare facility during the same timeframe. Controls were frequency-matched to cases according to age and sex distribution. Inclusion criteria for control participants required no personal history of malignancy or chronic pancreatic disease and no pancreatic cancer diagnosis among first-degree relatives.

Data collection

Demographic and clinical information was obtained through dual approaches: a comprehensive review of medical archives providing documented clinical history, laboratory data, and comorbid conditions, and structured interviews conducted by trained personnel using a standard questionnaire. This instrument included data on lifestyle habits (tobacco use), anthropometric measurements (weight, height), familial medical background, and previous health conditions. Diabetes mellitus classification followed established criteria: either fasting plasma glucose ≥126 mg/dL or previously documented clinical diagnosis [16]. Participants with type 1 diabetes or other specific diabetes variants were excluded from analysis. The body mass index was

expressed as the weight/height^2 (kg/m^2) and categorized according to WHO standards [17].

DNA extraction

Peripheral blood specimens (5-10 mL) were collected from each subject using K3EDTA anticoagulated vacuum tubes. Genomic DNA isolation was performed employing the salting-out precipitation method [18]. The extracted DNA was then assessed for purity and concentration using a NanoDrop spectrophotometer (Thermo Scientific, NanoDrop 8000) and subsequently stored at -20°C until genetic analysis.

Molecular testing

Genotyping for the *ACE* gene polymorphism (rs4646994) was done via polymerase chain reaction (PCR) methodology using these primers: forward: 5'-CTG GAG ACC ACTCCC ATC CTT TCT-3' and reverse: 5'-GAT GTG GCC ATC ACA TTC GTC AGA T-3'. PCR amplification was performed in a final reaction volume of 10 µL, consisting of 10-50 ng of template DNA, 1× PCR buffer, 1.5 mM $MgCl_2$, 0.2 mM of each dNTP, 0.4 µM of each primer, and 0.5 U of Taq DNA polymerase. Reactions were carried out on a Veriti™ 96-Well Fast Thermal Cycler (Applied Biosystems) under the following cycling conditions: initial denaturation at 95°C for 5 min; 35 cycles at 94°C for 30 s, 63°C for 45 s, and 72°C for 30 s; followed by a final extension at 72°C for 5 min. PCR products were electrophoresed on 2% agarose gels stained with ethidium bromide and visualized under UV illumination. The insertion (I) allele produced a 490 bp fragment, while the deletion (D) allele yielded a 190 bp fragment. Genotypes were therefore classified as II (490 bp), DD (190 bp), or ID (both 490 bp and 190 bp). For quality control, 10 randomly selected samples were re-genotyped in independent PCR assays, showing 100% concordance. The overall genotyping call rate was 100%. Each PCR run included a positive control (known *ACE* genotype), a negative control (no DNA template), and a molecular weight marker for fragment size verification.

Statistical methods

Statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Quantitative variables were summarized as the mean±standard deviation (SD) or median with interquartile range (IQR), depending on distribution. Qualitative variables were presented as counts and percentages. Normality of quantitative variables was assessed using the Shapiro-Wilk test and by visual inspection of histograms. Group comparisons were performed using the Student's t-test when normality assumptions were met, and the Mann-Whitney U-test otherwise. Categorical variables were compared using the χ^2 test or Fisher's exact test when expected cell counts were <5. Associations between *ACE* I/D genotypes and pancreatic cancer risk were examined using ORs with 95% confidence intervals (CIs). Crude ORs were first calculated, followed by multivariable logistic regression analyses. Given the limited sample size, multivariable models were restricted to a reduced set of covariates to minimize overfitting. Model stability was checked through evaluation of standard errors and confidence interval widths. A two-sided P value <0.05 was considered statistically significant.

RESULTS

This study evaluated the role of demographic, clinical, and genetic factors in pancreatic cancer risk in an Algerian cohort, with a specific focus on the interplay between *ACE* I/D polymorphism and type 2 diabetes mellitus.

Clinical and demographic features

Table 1 summarizes the comparative profile of pancreatic cancer patients and control subjects. The study groups demonstrated comparable age distributions, with nearly identical mean ages (62.6±9.6 years for cases versus 62.6±12.6 years for controls; P=1.00). A striking disparity emerged in T2DM prevalence, which was significantly elevated in cancer patients (54.3%) relative to controls (22.9%, P<0.001). The nutritional status patterns also differed significantly between groups. Underweight individuals were four times more prevalent among cases (14.3% vs. 3.6%, P<0.001), whereas obesity was markedly less frequent in the patient cohort (2.86% vs. 37.9%, P<0.001). No statistically significant differences were observed for sex distribution, smoking history, or hypertension prevalence between the two groups (all P>0.05).

Table 1. Clinical and demographic characteristics of the study cohort

Characteristics	Cases (N=35) N (%)	Controls (N=140) N (%)	P
Age (years), mean ±SD	62.60± 9.63	62.60±12.58	1.00
<50	3 (8.6)	12 (8.6)	0.078
50-59	9 (25.7)	43 (30.7)	
60-69	11 (31.4)	49 (35.0)	
>70	12 (34.3)	36 (25.7)	
Sex n (%)			
Male	15 (42.9)	60 (42.9)	0.573
Female	20 (57.1)	80 (57.1)	
Smoking n (%)			
Yes	5 (14.3)	25 (17.9)	0.616
No	30 (85.7)	115 (82.1)	
Body Mass Index (kg/m²) n (%)			
<18.5(Underweight)	5 (14.3)	5 (3.6)	**<0.001**
18.5-24.9 (Normal)	19 (54.3)	45 (32.1)	
25.0-29.9 (Overweight)	10 (28.6)	37 (26.4)	
>30.0 (Obese)	1 (2.9)	53 (37.9)	
Type 2 diabetes mellitus n (%)			
Yes	19 (54.3)	32 (22.9)	**<0.001**
No	16 (45.7)	108 (77.1)	
High blood pressure n (%)			
Yes	17 (48.6)	56 (40.0)	0.358
No	18 (51.4)	84 (60.0)	

N – number of individuals; SD – standard deviation. For quantitative variables, group comparisons were performed using the Student's t-test when normality assumptions were met, and the Mann–Whitney U-test otherwise. Categorical variables were compared using the χ^2 test; significance threshold: P<0.05

Table 2. Genotype and allele frequencies of the *ACE* polymorphism.

Genotype	Cases (n=35) N (%)	Controls (n=140) N (%)	OR (95% CI)	P
DD	23 (65.7)	103 (73.6)	Reference	-
ID	11 (31.4)	20 (14.3)	2.46 (1.04-5.84)	**0.036**
II	1 (2.9)	17 (12.1)	0.26 (0.033-2.08)	0.176
Allele D	57 (81.4)	226 (80.7)	Reference	-
Allele I	13 (18.6)	54 (19.3)	0.95 (0.49-1.87)	0.891

N – number of individuals; CI – confidence interval; OR – odds ratio; P was examined by the χ2 test; significance threshold: P<0.05

ACE genotype frequencies and association analysis

Table 2 presents the distribution of *ACE* genotypic patterns and their association with disease susceptibility. A markedly elevated susceptibility to PC was observed in carriers of the heterozygous ID genotype (OR=2.46; 95% CI: 1.04-5.84; P=0.036) compared with DD homozygotes. While the II genotype showed a trend toward a protective effect, this association lacked statistical significance (OR=0.26; 95% CI: 0.03-2.08; P=0.176). Allele frequency analysis revealed no significant difference between cases and controls (P=0.891). Genotype distributions in the control population exhibited deviation from the Hardy-Weinberg equilibrium (P<0.001).

Genetic inheritance model analyses

As detailed in Table 3, genetic model analyses demonstrated a non-significant increased risk within the dominant model (ID+DD versus II: OR=4.70; 95% confidence interval: 0.60-36.59; P=0.106). The recessive inheritance pattern comparing DD to combined ID/II genotypes did not show a meaningful association with cancer susceptibility (OR=1.45; 95% confidence interval: 0.66-3.21; P=0.354).

Stratified analysis by diabetes status

Subgroup analysis based on T2DM status revealed a significant interaction effect (*P*interaction = 0.042). Table 4 shows that the genotypic association of *ACE* polymorphisms with disease risk was exclusively evident among diabetic individuals. Within this subgroup, both ID (OR=5.25; 95% CI: 1.07-25.79; P=0.034) and DD (OR=3.19; 95% CI: 1.24-8.17; P=0.013) genotypes conferred significantly elevated risk compared to the II genotype. No significant genetic associations were detected in non-diabetic participants.

Multivariable regression analysis

Given the limited number of cases, multivariable logistic regression analyses were deliberately restricted to minimize overfitting. Smoking and hypertension were tested but were not retained in the final model due to a lack of statistical significance and model instability. As shown in Table 5, following adjustment for age, sex, and BMI category, both T2DM and the *ACE* ID genotype remained independently

Table 3. Dominant and recessive genetic models of *ACE* polymorphism.

Genetic Model	Genotype Groups	Cases (N=35) N (%)	Controls (N=140) n (%)	OR (95% CI)	P
Dominant model	ID+DD	34 (97.1)	123(87.9)	4.70 (0.60-36.59)	0.106
	II	1 (2.9)	17 (12.1)	Reference	-
Recessive model	DD	23 (65.7)	103 (73.6)	1.45 (0.66-3.21)	0.354
	ID+II	12 (34.3)	37 (26.4)	Reference	-

N – number of individuals; CI – confidence interval; OR – odds ratio; P was examined by the $\chi 2$ test; significance threshold: P<0.05

Table 5. Multivariable logistic regression analysis of pancreatic cancer risk

Variable	Adjusted OR (95% CI)	P
T2DM	3.14 (2.13-4.63)	**<0.001**
ACE ID genotype	8.19 (3.24-20.70)	**<0.001**

CI – confidence interval; OR – odds ratio; significance threshold: P<0.05

associated with pancreatic cancer risk. T2DM was associated with a more than three-fold increase in risk (adjusted odds ratio (aOR)=3.14; 95% CI: 2.13-4.63; P<0.001), while carriers of the ACE ID genotype had a significantly increased risk compared with DD homozygotes (aOR=8.19; 95% CI: 3.24-20.70; P<0.001).

DISCUSSION

The present investigation provides novel insights into the association between *ACE* I/D polymorphism and pancreatic cancer susceptibility in an Algerian population, with particular emphasis on the modifying effect of type 2 diabetes mellitus. Three principal observations emerge from our findings: T2DM was strongly associated with PC, the heterozygous ID genotype was strongly associated with increased disease susceptibility, and this genetic effect was exclusively evident among individuals with diabetes, highlighting a significant gene-environment interaction.

The strong link connecting T2DM and pancreatic cancer observed in our cohort aligns with global epidemiological evidence [19,6]. The substantially higher diabetes prevalence among cases (54.3%) compared to controls (22.9%) reinforces the established link between these conditions. Large prospective studies have reported a two- to three-fold elevated risk, particularly within the first years following diabetes diagnosis [6,18]. This temporal pattern reflects the complex bidirectional relationship: long-standing diabetes may contribute to tumorigenesis through hyperinsulinemia, hyperglycemia, and chronic low-grade inflammation, whereas new-onset diabetes may represent an early manifestation of occult pancreatic malignancies [20]. Given the retrospective design of the present study, we are unable to distinguish between these mechanisms. Accordingly, diabetes should be interpreted as an associated metabolic condition rather than a confirmed causal risk factor. This distinction is particularly important given that diabetes prevalence has risen substantially from 8.9% in 2003 to 14.4% in 2016-2017 [21], underscoring the need for heightened clinical vigilance in diabetic populations.

Notable differences in nutritional status were also observed between groups. Underweight status was approximately four times more prevalent among pancreatic cancer patients, a finding consistent with

Table 4. *ACE* genotypic distribution in cases versus controls, stratified by T2D

ACE genotypes	Cases(N=35) n (%)		Controls(N=140) n (%)		OR (95% CI)	P
	With T2DM (n=19)	**Without T2DM** (n=16)	**With T2DM** (n=32)	**Without T2DM** (n=108)		
DD	11 (57.9)	12 (75.0)	23 (71.9)	80 (74.1)	3.19 (1.24-8.17)	**0.013**
ID	7 (36.9)	4 (25.0)	5 (15.6)	15 (13.9)	5.25 (1.07-25.79)	**0.034**
II	1 (5.3)	0 (0.0)	4 (12.5)	13 (12.0)	-	0.097
Interaction test						*P* interaction **0.042**

N – number of individuals; CI – confidence interval; OR – odds ratio; T2DM – type 2 diabetes mellitus; significance threshold was examined by the $\chi 2$test; significance threshold: P<0.05

cancer-associated cachexia and metabolic wasting [22,23]. In contrast, obesity was less frequent among PC cases. This pattern is best explained by reverse causality, as the body mass index was assessed at the time of cancer diagnosis, when substantial involuntary weight loss is common. Indeed, more than 60% of patients with pancreatic cancer experience significant pre-diagnostic weight loss, which can obscure prior obesity status [24]. Conversely, BMI in controls reflects habitual anthropometric status measured during routine clinic visits. Therefore, BMI values between cases and controls are not directly comparable, and the observed imbalance should not be interpreted as evidence of selection bias or a protective effect of obesity. We adjusted for BMI cautiously in multivariable analyses and explicitly avoided causal interpretation of this variable. Smoking and hypertension, although recognized risk factors [25,26], were not significantly associated with pancreatic cancer in our cohort, likely reflecting limited statistical power or population-specific characteristics.

Genetic analysis revealed that heterozygous ID genotype carriers had significantly elevated pancreatic cancer risk (OR=2.46), while the II genotype showed a non-significant protective trend. The absence of allele frequency differences suggests that genotype configuration, rather than individual alleles, influences disease susceptibility. Previous studies of *ACE* polymorphisms in cancer have yielded inconsistent results across populations [10,15,27]. Our data contribute novel evidence from a previously understudied North African population, potentially explaining earlier discrepancies through ethnic-specific genetic backgrounds.

The biological plausibility of our findings is supported by genotype-dependent *ACE* expression patterns, with intermediate levels in ID heterozygotes [14,28]. This moderate enzymatic activity may create a permissive microenvironment by disrupting angiogenic balance and modulating local RAS signaling [8,9]. Similar nonlinear risk patterns have been reported in cardiovascular disorders and other cancers [29], suggesting complex *ACE*-mediated mechanisms across pathologies.

Genetic model analyses showed an elevated but non-significant risk in the dominant model, with no association under the recessive model, thereby supporting the primary role of the heterozygous genotype rather than conventional inheritance patterns. This conclusion aligns with meta-analyses in other malignancies [10,15,27]. Mechanistically, RAS activation promotes key cancer hallmarks including angiogenesis, stromal fibrosis, and inflammation [14,28,30]. In pancreatic cancer, specifically, angiotensin II stimulates vascular endothelial growth factor (VEGF) expression and activates pancreatic stellate cells, driving desmoplasia and therapy resistance [31,32].

A notable finding was the interaction between *ACE* genotype and diabetes. Stratified analyses revealed that the ID and DD genotypes conferred elevated risk exclusively in diabetic individuals, with formal interaction testing confirming T2DM as an effect modifier. This synergy is biologically plausible, as diabetic metabolic disturbances (hyperglycemia, insulin resistance, and inflammation) amplify RAS signaling pathways [30-32]. Pancreatic stellate cells, key drivers of desmoplasia, are particularly responsive to angiotensin II stimulation [8], suggesting that diabetic individuals with risk genotypes experience compounded oncogenic signaling [31].

These findings have potential clinical implications. *ACE* genotyping in diabetic patients could enhance risk stratification and enable earlier detection in high-risk subgroups. Furthermore, they raise questions about potential protective effects of RAS inhibitors (ACE inhibitors, ARBs) in genetically susceptible individuals [33,34], though current evidence remains insufficient to support clinical recommendations.

This study addresses an important research gap as the first investigation of *ACE* polymorphisms in pancreatic cancer in Algeria and North Africa. However, several limitations should be acknowledged. The modest sample size, particularly for stratified analyses, results in sparse data and reduces statistical stability, potentially inflating effect sizes. Owing to the rarity of pancreatic cancer in the region and the challenges of obtaining histologically confirmed cases, our findings should be regarded as preliminary and hypothesis-generating.

Although *ACE* genotype frequencies deviated from the Hardy-Weinberg equilibrium in the control group ($P<0.001$), extensive re-evaluation of genotyping procedures revealed no evidence of technical error. This deviation most likely reflects population-specific genetic structure, as reported in other genetically diverse populations [35,36]. To reduce the risk of overfitting, multivariable models were simplified in accordance

with events-per-variable recommendations, although residual model instability cannot be excluded. Finally, the retrospective design precluded evaluation of diabetes duration, glycemic control, or medication use.

CONCLUSIONS

Our results offer a complex picture of pancreatic carcinogenesis in which a genetic variant (*ACE* ID) acts independently and synergistically with a metabolic condition (diabetes) to increase risk. The deviation from HWE in controls and the characteristics of control recruitment warrant caution and call for validation in larger, population-based studies from the same region. Nevertheless, the strength and biological plausibility of our main findings, especially the gene-environmental interaction, remain compelling. From a translational perspective, these preliminary observations highlight a potential high-risk subgroup that could benefit from intensified surveillance. Furthermore, these findings provide a rationale for exploring therapeutic modulation of the RAS pathway, for which pharmacological inhibitors are already widely available, although the clinical implications require further investigation. These findings should be interpreted considering the study's limitations and do not imply causality; confirmation in larger, prospective, population-based studies is warranted.

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