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A pilot case-control study exploring the association of the *XPC* Lys939Gln (rs2228001) polymorphism and metabolic risk factors with pancreatic cancer in an Algerian cohort

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Abstract: The role of DNA repair gene polymorphisms in pancreatic cancer susceptibility remains insufficiently characterized, particularly in North African populations. This study investigated the association between the *XPC* Lys939Gln (rs2228001) polymorphism and pancreatic cancer risk in an Algerian cohort, alongside key metabolic risk factors. This exploratory hospital-based case-control study included 40 patients with histologically confirmed pancreatic cancer and 120 age- and sex-matched controls. Genotyping was performed using PCR-RFLP. Associations were evaluated using logistic regression models adjusted for demographic and metabolic variables. Given the limited sample size, the study was not powered to detect modest genetic effects. No statistically significant association was observed between *XPC* rs2228001 and pancreatic cancer risk under dominant, recessive, or allelic models (adjusted OR=1.22, 95% CI: 0.27-5.52; P=0.801). Type 2 diabetes mellitus was more frequent among cases and was associated with increased risk (OR=3.48, 95% CI: 1.24-9.77; P=0.018), although this finding should be interpreted with caution due to the exploratory design and limited sample size. The lower BMI observed in cases likely reflects disease-related weight loss. Under the constraints of this exploratory pilot investigation, no statistically detectable association was observed for the *XPC* rs2228001 variant. These findings are preliminary and should be considered hypothesis-generating. Larger, well-designed studies are required to clarify the interplay between genetic variation and metabolic factors in pancreatic cancer susceptibility.

Keywords: pancreatic cancer; *XPC* rs2228001; DNA repair; type 2 diabetes mellitus; Algerian population

INTRODUCTION

Pancreatic cancer remains one of the most lethal malignancies worldwide, characterised by late diagnosis, rapid progression, and a five-year survival rate rarely exceeding 10% [1-3]. Despite advances in imaging and therapeutic strategies, its incidence and mortality continue to rise, reflecting both demographic changes and persistently unclear etiological mechanisms. The disease is widely recognised as multifactorial, arising from a complex interplay between genetic susceptibility, metabolic disturbances, and environmental exposures [4-6].

Genomic instability is a central hallmark of carcinogenesis and is partly driven by defects in DNA repair pathways. The nucleotide excision repair (NER) pathway plays a critical role in maintaining genomic integrity by removing bulky DNA lesions induced by endogenous metabolic processes and environmental carcinogens [7]. Disruption of this pathway may contribute to the accumulation of mutations and subsequent malignant transformation.

The X-ray repair cross-complementing group C (*XPC*) gene encodes a key damage-recognition protein that initiates global genome NER [7,8]. Functional variation in *XPC* may influence susceptibility to cancer by modulating DNA repair capacity. In particular, the non-synonymous Lys939Gln (rs2228001) polymorphism has been extensively studied, but reported

associations vary across tumor types and populations [7,9,10]. These inconsistencies suggest a modest, context-dependent effect. Evidence in pancreatic cancer remains limited and inconclusive [7,13].

In parallel, pancreatic cancer is associated with metabolic risk factors, particularly type 2 diabetes mellitus (T2DM) and obesity, which may interact with genetic susceptibility [4-6,14]. However, these relationships are complex and may reflect reverse causation, as metabolic alterations can also represent early manifestations of the disease.

North African populations, including Algeria, remain underrepresented in molecular epidemiology studies. Investigating genetic and clinical determinants in these populations may provide valuable insights into population-specific risk profiles.

In this context, the present study aimed to explore the potential association between the *XPC* Lys939Gln (rs2228001) polymorphism and pancreatic cancer susceptibility in an Algerian population. We also assessed key clinical and metabolic factors in an exploratory pilot case-control framework. Given its exploratory design, the findings are intended to generate hypotheses rather than establish definitive associations.

MATERIALS AND METHODS

Ethics statement

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Approval was obtained from the Ethics Committee of the University Hospital of Constantine, Algeria (Approval No. EC/CHUC/03/02-2022; June 19, 2022). All participants were informed about the study objectives and study procedures, and written informed consent was obtained before inclusion. Participant confidentiality and data anonymity were strictly maintained throughout the study.

Study population

This case-control study was conducted at the University Hospital of Constantine, Algeria, between April 2023 and June 2025. The study included 40 consecutive patients with histologically confirmed pancreatic adenocarcinoma recruited from the Department of Surgery. Diagnosis was established through clinical evaluation, imaging findings, and histopathological confirmation. Patients with a prior history of malignancy were excluded. All patients were newly diagnosed and had not received chemotherapy or radiotherapy. The control group consisted of 120 cancer-free individuals recruited during the same period from outpatient clinics at the same institution. Controls were individually matched to cases by age and sex. Eligibility criteria for controls included the absence of any personal history of cancer, no known chronic pancreatic disease, and no first-degree relatives diagnosed with pancreatic cancer. All participants were of Algerian origin and unrelated.

Data collection procedures

Demographic, clinical, and lifestyle data were collected using a combination of medical record review and structured interviews conducted by trained research staff. Information obtained included age, sex, smoking status, medical history, anthropometric measurements, and family history of pancreatic or other cancers.

The body mass index (BMI) was calculated as weight in kg divided by height in m^2 (kg/m^2) and classified according to World Health Organisation criteria [15]. Underweight was defined as BMI<18.5 kg/m^2, normal weight as 18.5-24.9 kg/m^2, overweight as 25-29.9 kg/m^2, and obesity as ≥30 kg/m^2.

Type 2 diabetes mellitus (T2DM) was defined according to standard diagnostic guidelines: fasting plasma glucose ≥126 mg/dL or a prior physician-documented diagnosis [16]. Participants with type 1 diabetes or other specific subtypes were excluded from the study.

Additional lifestyle factors, including smoking history, were assessed via structured interviews. Smoking status was categorised as never, former, or current. Blood pressure readings and a history of hypertension were obtained from medical records. All data were systematically entered into a secure database for subsequent analysis.

To ensure data quality, the study employed standardised data collection instruments, and all research staff received training in anthropometric measurement and interview procedures. Any missing or ambiguous information in the medical records was clarified during participant interviews.

DNA extraction

Peripheral blood samples (5-10 mL) were collected in K3-EDTA anticoagulated tubes from all participants. Genomic DNA was extracted using the salting-out method [17], and DNA quality and concentration were assessed spectrophotometrically using a NanoDrop 8000 (Thermo Scientific, Waltham, MA, USA). DNA samples were stored at -20°C until analysis.

Molecular testing

Genotyping of the *XPC* Lys939Gln (rs2228001) polymorphism was performed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The target DNA fragment (218 bp) was amplified using the following primers: forward: 5'-TTC CCT TCA GTC AGT ATC AG-3' and reverse: 5'-GGA AAG AAA TAG AAA TAG AAG-3'. PCR reactions were carried out in a 20 µL volume containing 10-50 ng genomic 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. Amplification was performed using a Veriti™ 96-Well Fast Thermal Cycler (Applied Biosystems) as follows: initial denaturation at 94°C for 12 min; followed by 35 cycles of 95°C for 30 s, annealing at 60°C for 30s, and extension at 72°C for 30 s; with a final extension step at 72°C for 5 min.

PCR products were digested with the PvuII restriction enzyme at 37°C for 1 h following the manufacturer's protocol. The presence of the C allele introduces a restriction site, producing fragments of 150 bp and 68 bp, whereas the A allele remains undigested at 218 bp. Digested fragments were separated on 3% agarose gel in 1X TBE buffer and visualised under ultraviolet illumination after ethidium bromide staining. For quality control, 10% of samples were randomly re-genotyped in independent PCR-RFLP assays, achieving 100% concordance. Each PCR run included positive and negative controls to verify genotyping accuracy. The genotyping success rate was 100%, and all assays were performed blinded to case-control status.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics software (version 25.0; IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean±standard deviation (SD), and categorical variables as frequencies and percentages.

Comparisons between cases and controls were conducted using the independent samples t-test for continuous variables and the chi-square (χ^2) test or Fisher's exact test, as appropriate, for categorical variables.

Associations between the *XPC* rs2228001 polymorphism and pancreatic cancer risk were evaluated under dominant (AC+CC vs. AA), recessive (CC vs. AA+AC), and allelic (C vs. A) genetic models. Crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

To account for potential confounding, multivariate logistic regression was performed, adjusting for age, sex, BMI, T2DM, smoking status, and hypertension. Given the matched design, these variables were retained in the model to ensure appropriate adjustment. Results are reported as adjusted ORs with 95% CIs.

Hardy-Weinberg equilibrium (HWE) was assessed in the control group using a χ^2 goodness-of-fit test. Any observed deviation from HWE was considered a potential limitation and interpreted with caution.

No correction for multiple testing was applied due to the exploratory nature of this pilot study. Accordingly, all findings should be considered hypothesis-generating rather than confirmatory. A two-sided $P<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

The demographic and clinical characteristics of the study population are summarised in Table 1. No statistically significant differences were observed between cases and controls with respect to age and sex ($P>0.05$), indicating appropriate comparability between groups. Type 2 diabetes mellitus (T2DM) was significantly more frequent among cases compared to controls (53% vs. 23%, $P<0.001$). A higher proportion of underweight individuals was observed among cases (15% vs. 4%, $P<0.001$), most likely reflecting disease-related weight loss rather than a pre-existing etiological factor. No statistically significant differences were identified for smoking status or hypertension ($P>0.05$).

Table 1. Demographic and clinical characteristics of the study population

Characteristic	*Cases (N=40) n(%)*	*Controls (N=120) n (%)*	*P*
Age (years), mean ±SD	62.6±12.7	62.7±11.3	0.980
Sex n (%)			0.571
Male	16 (40)	48 (40)	
Female	24 (60)	72 (60)	
Smoking n (%)			0.411
Yes	5 (12)	19 (16)	
No	35 (88)	101 (84)	
Body Mass Index (kg/m²) n (%)			***<0.001***
<18.5(Underweight)	6 (15)	5 (4)	
18.5-24.9 (Normal)	21 (52.5)	40 (33)	
25.0-29.9 (Overweight)	12 (30)	32 (27)	
>30.0 (Obese)	1 (2.5)	43 (36)	
Type 2 diabetes, n (%)	21 (53)	28 (23)	***<0.001***
Hypertension, n (%)	17 (43)	46 (38)	0.640

n – number of individuals; SD – standard deviation. [1]Chi-square test for categorical variables; t-test for continuous variables. Significance threshold set up P<0.05

Table 2. Clinical and pathological features of pancreatic cancer cases (n=40)

Clinical presentation		
Symptom		***n (%)***
Abdominal pain		32 (80)
Jaundice		25 (62.5)
Weight loss		13 (32.5)
Pruritus		8 (20)
Tumor characteristics		
Feature		***n (%)***
Location	Head	33 (82.5)
	Body	5 (12.5)
	Tail	2 (5)
Histology	Adenocarcinoma	37 (92.5)
	Papillary tumour	3 (7.5)
Staging		
Stage		***n (%)***
T stage		
T1		2 (5)
T2		10 (25)
T3		21 (52.5)
T4		7 (17.5)
N stage		
N0		30 (75)
N1		8 (20)
N2		2 (5)
M stage		
M0		35 (87.5)
M1		5 (12.5)

Genotypic and allelic distribution of XPC rs2228001

Genotype and allele distributions of the *XPC* rs2228001 polymorphism are presented in Table 3. The heterozygous AC genotype was the most frequent in both cases (65%) and controls (58%), followed by the AA genotype (27.5% in cases vs. 32% in controls) and the CC genotype (7.5% vs. 10%, respectively). Allele frequencies were comparable between cases and controls (A: 60% vs. 61%; C: 40% vs. 39%), and no statistically significant differences were observed (P>0.05). Genotype distributions in the control group deviated from the HWE (P<0.05). This deviation represents a methodological limitation that may affect the interpretability of the genetic findings and should be considered when interpreting the results.

Association analysis

The association between *XPC* rs2228001 and pancreatic cancer risk was evaluated under dominant, recessive, and allelic genetic models. No statistically significant associations were identified under any of the tested models (Table 3). Under the dominant model (AC+CC vs. AA), the adjusted odds ratio was 1.22 (95% CI: 0.27-5.52; P=0.801). Similar non-significant estimates were observed under the recessive and allelic models. However, given the small sample size and limited statistical power, the study may be underpowered to detect modest genetic effects. These findings should therefore be interpreted as inconclusive rather than indicative of no association.

Multivariate analysis

Multivariate logistic regression analysis adjusted for age, sex, BMI, T2DM, smoking, and hypertension is shown in Table 4. Type 2 diabetes mellitus was independently associated with pancreatic cancer risk (OR=3.48, 95% CI: 1.24-9.77; P=0.018). Nevertheless, this association should be interpreted with caution, as the study design does not allow distinction between causal relationships and potential reverse causation. Obesity (BMI≥30) was not significantly associated with pancreatic cancer risk (OR=1.17, 95% CI: 0.13-10.1; P=0.800). Similarly, smoking and hypertension were not significantly associated with disease risk (P>0.05).

Table 3. Genotypic and allelic distribution of *XPC* rs2228001

Genotype	*Cases (N=40) n (%)*	*Controls (N=120) n (%)*	*OR (95% CI)*	*P*
AA	11 (27.5)	38 (32)	Reference	-
AC	26 (65)	70 (58)	1.28 (0.57-2.88)	0.544
CC	3 (7.5)	12 (10)	0.86 (0.21-3.62)	0.840
Allele frequency				
A	48 (60)	146 (61)	Reference	-
C	32 (40)	94 (39)	1.04 (0.62-1.74)	0.894
Dominant model				
AC+CC vs AA	29 (72.5)	82 (68)	1.22 (0.55-2.70)	0.62
Recessive model				
CC vs AA+AC	3 (7.5) vs 37 (92.5)	12 (10) vs 108 (90)	0.73 (0.20-2.73)	0.638

n – number of individuals; CI – confidence interval; OR – odds ratio; P was examined by the χ^2 test; Significance threshold set at P<0.05. Genotype frequencies in controls deviated from Hardy-Weinberg equilibrium (P<0.05)

Table 4. Multivariate logistic regression analysis of pancreatic cancer risk factors

Variable	*Adjusted OR (95% CI)*	*P*
XPC rs2228001 (AC+CC vs AA)	1.22 (0.27-5.52)	0.801
Type 2 diabetes	3.48 (1.24-9.77)	***0.018***
BMI ≥30 (Obese vs Normal)	1.17 (0.13-10.10)	0.800
Hypertension	0.89 (0.34-2.28)	0.789
Smoking	1.34 (0.28-6.45)	0.719

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

DISCUSSION

The present study was designed and conducted as an exploratory pilot investigation. Its primary aim was to investigate the potential relevance of the *XPC* rs2228001 (Lys939Gln) variant in pancreatic cancer susceptibility in an Algerian cohort, while simultaneously cataloguing prevalent metabolic traits. It should be emphasized that the genetic analysis yielded inconclusive results, with no significant association observed for rs2228001 under any tested inheritance model. This null finding should not be interpreted as definitive evidence against the variant's involvement; rather, it likely reflects limited power to detect a modest effect, potentially influenced by environmental or population-specific modifiers.

In the context of the broader molecular epidemiological literature, the absence of a detectable association is not unexpected. A large meta-analysis by He et al., including over 25,000 cases and 30,000 controls, reported a modest overall association for the Gln/Gln genotype (OR = 1.16) [7]. Notably, stratified analyses in the same report indicated that the observed risk increase was largely driven by lung and bladder cancers and by cohorts of Asian ancestry [7]. The association appeared attenuated when analyses were restricted to digestive tract cancers. Indeed, meta-analysis concerning colorectal cancer risk ultimately converged on a null association once heterogeneity and confounding factors were addressed [18]. The absence of an observable effect in this North African subgroup is consistent with the prevailing view that the functional impact of Lys939Gln is unlikely to act independently; rather, it may depend on a permissive genetic background or specific, unmeasured environmental exposures to manifest clinically.

One of the important methodological limitations encountered in this dataset pertains to the departure from HWE observed in the control group. While considerable care was taken to ensure technical fidelity during genotyping, including the use of blinded duplicates and rigorous quality control metrics, the deviation remains. This is more plausibly explained as a statistical fluctuation arising from the modest size of the hospital-based control group rather than a laboratory artifact. It is a limitation that cannot be resolved or fully explained away by post-hoc sensitivity analyses. As noted in methodological appraisals of small-scale genetic studies, such deviations are not infrequent and can introduce a layer of statistical noise that obscures case-control contrasts [19]. The observed deviation from HWE represents a key limitation, constraining confidence in the estimated allele frequencies and necessitating cautious interpretation of the findings.

With respect to metabolic covariates, T2DM showed a clear association in the multivariate model. This aligns with extensive epidemiological evidence indicating an approximately two-fold or greater increase in pancreatic cancer risk among individuals with diabetes [4,20]. However, the cross-sectional design of this pilot study precludes inference about directionality. Reverse causation is a recognized confounder, as new-onset diabetes may represent an early paraneoplastic manifestation of occult pancreatic adenocarcinoma rather than a long-term etiological factor [21-23]. In the absence of reliable data on the duration of diabetes prior to cancer diagnosis, distinguishing causal from

consequential relationships would be methodologically unsound and is therefore not attempted.

A similar interpretive challenge applies to BMI. The lower BMI observed among cases likely reflects the catabolic effects of cancer cachexia and pre-diagnostic weight loss, which are characteristic of advanced pancreatic malignancy [24-26]. This reverse causation bias is a recognized limitation of retrospective case–control studies of this disease and precludes reliable assessment of the etiological role of obesity or leanness based on a single cross-sectional anthropometric measure [24,26].

Furthermore, the absence of significant associations for smoking and hypertension in the adjusted models should be interpreted with caution. Smoking was assessed using a binary measure, lacking the quantitative detail (e.g., pack-years) needed to evaluate dose–response relationships or adequately control for this important confounder [6,27]. Similarly, the null finding for hypertension may reflect unmeasured heterogeneity in antihypertensive treatment, which can influence risk estimates in pharmacoepidemiological analyses [28,29].

This study has several strengths, including a rigorous case definition with histological confirmation and the provision of novel allele frequency data from a North African population, a region underrepresented in pancreatic cancer genetic research. However, its limitations are substantial and should be clearly acknowledged. The relatively small sample size substantially limits statistical power, restricting stratified and gene–environment interaction analyses and increasing the risk of type II error. The use of hospital-based controls introduces potential selection bias, while the absence of detailed, quantitative exposure data, particularly for tobacco, allows for residual confounding. Finally, focusing on a single nucleotide polymorphism in the *XPC* gene provides only a limited view of DNA repair capacity, which is shaped by complex polygenic interactions.

CONCLUSIONS

This exploratory pilot study does not provide definitive evidence for an association between the *XPC* rs2228001 polymorphism and pancreatic cancer susceptibility in the studied Algerian population. Given the limited statistical power, deviation from the Hardy-Weinberg equilibrium, and potential selection bias, the genetic findings should be considered inconclusive. The observed association with type 2 diabetes mellitus is consistent with existing epidemiological evidence but cannot be interpreted as causal within the constraints of this study design. The present work demonstrates the feasibility of conducting molecular epidemiological investigations in this population and provides preliminary data to inform future research. Larger, prospectively designed studies incorporating detailed exposure assessment and multivariant genetic analysis are required to better elucidate the contribution of DNA repair pathways and metabolic factors to pancreatic cancer risk.

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Conflict of interest disclosure: The authors declare no conflicts of interest.

Data availability: The data supporting this article are available in the online dataset: https://www.serbiosoc.org.rs/NewUploads/Uploads/Hamiouda%20et%20al_Dataset.pdf

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