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Diabetes and Pancreatic Cystic Neoplasms—Dangerous Liaisons

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Cho et al[1] offer an important perspective on whether diabetes is associated with an increased risk of pancreatic cystic neoplasms (PCNs). Using a cohort of more than 3.8 million Korean adults followed up for more than 10 years, the authors report a stepwise increase in PCN incidence across worsening glycemic categories, with the highest risk observed in individuals with diabetes of 5 or more years of duration. The risk increases in younger individuals, men, and current smokers. These findings contribute meaningfully to the evolving understanding of metabolic influences in pancreatic disease. Yet, for clinicians interpreting these data in clinical practice, several methodologic and diagnostic limitations require careful contextualization.

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Interpreting PCNs: Strengths and Fragilities

The study relies on *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* codes to identify pancreatic cysts. While claims-based methods allow for unprecedented population coverage, they inherently lack the diagnostic precision needed in pancreatic cytology because *ICD-10* codes do not distinguish (1) serous cystadenomas from mucinous cysts; (2) branch duct intraductal papillary mucinous neoplasms (IPMNs) from main duct IPMNs; (3) small indeterminate cysts from clinically significant lesions; and (4) imaging-based incidental findings from symptomatic cysts.

In addition, although the authors excluded codes associated with pancreatitis and pseudocysts, residual diagnostic overlap is likely. In routine clinical practice, small incidental cysts—common in magnetic resonance imaging series—may never generate an *ICD* code. Conversely, some *ICD*-coded cysts may reflect provisional or inconsistent labeling.

Thus, while the finding of an association is compelling, the absolute incidence and the cyst phenotype captured in this study remain uncertain. This limitation does not limit the epidemiologic value but should temper clinical extrapolation.

Population-Specific Considerations: East Asian Genetic and Metabolic Background

An additional factor to consider is that the entire cohort derives from a relatively homogeneous population. Individuals of East Asian ancestry have distinct metabolic characteristics—such as a higher propensity for type 2 diabetes at lower body mass index, different patterns of visceral adiposity, and potential differences in pancreatic fat distribution and β-cell vulnerability—that may modulate the interaction between glycemic dysfunction and pancreatic epithelial injury.[2] Therefore, while the association observed by Cho et al[1] is likely generalizable in direction, the magnitude of risk reported in this study may not be fully generalizable to other populations.

Diabetes Exposure: Binary Categories Without Therapeutic Granularity

The classification of glycemic status (normoglycemia, impaired fasting glucose, diabetes <5 or ≥5 years) is consistent with a prior study.[3] However, for a disease landscape increasingly shaped by therapeutic heterogeneity, the absence of medication-specific data is a crucial limitation.

ICD-10 and claims data capture prescriptions but not disease phenotypes (type 1 vs type 2), degrees of insulin resistance, metabolic control, or the intensity of glucose lowering. Importantly, the dataset does not reliably capture (1) treatment classes (glucagon-like peptide-1 [GLP-1] receptor agonists, sodium-glucose cotransporter 2 [SGLT2] inhibitors, dipeptidyl peptidase-4 [DPP-4] inhibitors); (2) cumulative exposure; (30 treatment sequence or step-up therapy; (4) time-varying medication patterns; or (5) the degree of glycemic control (eg, hemoglobin A_{1c} [HbA_{1c}] trajectories).

This is a key gap because modern antidiabetic therapies exert pharmacologic effects on the exocrine pancreas that are still incompletely understood. Studies have evaluated associations between incretin-based therapies and pancreatitis or pancreatic cancer, with still debated results. Whether GLP-1 receptor agonists or DPP-4 inhibitors influence cyst initiation is entirely unknown.[4]

Similarly, the increasing use of SGLT2 inhibitors—agents with strong metabolic, anti-inflammatory, and weight-modifying effects—might theoretically alter pancreatic microenvironmental stress.[5] Conversely, chronic insulin therapy may reflect more advanced or long-standing diabetes, potentially confounding associations between insulin exposure and cyst risk.

Cho et al[1] report an exploratory subgroup suggesting a higher cyst risk among individuals who use insulin. While intriguing, this likely reflects disease severity rather than causal exposure. In clinical practice, insulin-treated patients often have a longer disease duration, worse metabolic control, and higher prevalence of comorbidities—all factors that may influence pancreatic epithelial vulnerability. Without medication-level granularity and glycemic control measures, these patterns remain hypothesis-generating rather than definitive.

Clinical Interpretation: Modest Relative Risks but Low Absolute Incidence

From a clinician standpoint, the most important message is that although diabetes is associated with increased PCN incidence, the absolute risk remains very low. The overall rate was 0.82 per 1000 person-years, increasing to 1.82 per 1000 person-years in individuals with 5 or more years of diabetes.[1] In other words, even after a decade of follow-up, PCNs remain uncommon in all glycemic categories.

This observation is essential when discussing screening or surveillance implications. No current guideline recommends imaging solely on the basis of diabetes. The data presented here do not justify changing that recommendation. Instead, these findings support a more tailored clinical awareness. In a patient with diabetes—particularly a younger male or an active smoker—an incidental cyst may merit more attentive evaluation or shorter initial follow-up intervals. Routine cyst surveillance based solely on glycemic status remains unwarranted, given the low absolute incidence. Diabetes should be considered a modifying factor, not a primary driver, in clinical decision-making about cyst follow-up. Smoking cessation should be recommended in patients with diabetes with newly diagnosed pancreatic cysts.

Mechanistic Plausibility With Metabolic Stress and Ductal Vulnerability

The findings also align with biological models of pancreatic injury. Chronic metabolic stress in diabetes is associated with oxidative stress, low-grade inflammation, and epithelial remodeling. Experimental work has demonstrated that hyperglycemia may amplify oncogenic pathways in *KRAS*-variant or *GNAS*-variant ductal cells—aberrations central to IPMN biology.[6] Although speculative, this mechanism could explain the findings in younger individuals, whose baseline cyst prevalence is low but whose epithelial susceptibility may be more influenced by metabolic factors.

The synergistic effect observed with smoking—another promoter of pancreatic inflammation—strengthens the argument for a microenvironmental model where metabolic and lifestyle stressors jointly modulate ductal vulnerability. Of note, smoking is a risk factor associated with the occurrence of IPMN and with the progression of low-risk IPMN to clinically relevant lesions with high-risk features for malignant tumors.[7]

What Clinicians Still Need to Know

The results of Cho et al[1] raise 4 important questions for future clinical research. The first is "Does the degree of glycemic control modify cyst risk?" HbA_{1c} trajectories or markers of insulin resistance are missing. The second is "Do specific antidiabetic drug classes influence cyst initiation or progression?" Modern incretin-based therapies may have pancreas-relevant biological actions, but this study cannot evaluate that. The third is "Are cysts detected in diabetes more likely to be mucinous, multifocal, or progressive?" The inability to distinguish IPMN from sickle cell anemia or pseudocysts remains a major limitation of claims-based analysis. The final question is "Does diabetes accelerate cyst progression toward high-risk stigmata or cancer?" Although 4.1% of patients with cysts in this cohort developed pancreatic cancer, the temporal and causal relationship cannot be evaluated.

Conclusions

Cho et al[1] provide valuable epidemiologic evidence that diabetes—particularly long-standing diabetes—is associated with an increased likelihood of a newly diagnosed pancreatic cyst. For clinicians, the message is one of contextualized vigilance: diabetes should not trigger pancreatic imaging in the absence of symptoms or other risk factors, but it may inform diagnostic interpretation once a cyst is identified. The study's reliance on *ICD-10* definitions and lack of therapeutic or glycemic-detail limits granularity, and the genetic and metabolic specificity of this East Asian cohort may influence generalizability. Nonetheless, the overall consistency, biological plausibility, and subgroup interactions make this an important contribution that advances the clinical conversation on metabolic risk and pancreatic cystic disease.

ARTICLE INFORMATION

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REFERENCES

1. Cho IR, Chang SH, Lee SH, et al. Pancreatic cystic neoplasm risk among individuals with diabetes. *JAMA Netw Open*. 2026;9(2):e2556951. doi:10.1001/jamanetworkopen.2025.56951

2. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann N Y Acad Sci*. 2013;1281(1):64-91. doi:10.1111/nyas.12098

3. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(suppl 1):S20-S42. doi:10.2337/dc24-S002

4. Valencia-Rincón E, Rai R, Chandra V, Wellberg EA. GLP-1 receptor agonists and cancer: current clinical evidence and translational opportunities for preclinical research. *J Clin Invest*. 2025;135(21):e194743. doi:10.1172/JCI194743

5. Cho YK, Kim S, Kim MJ, Lee WJ, Kim YJ, Jung CH. New users of sodium-glucose cotransporter 2 inhibitors are at low risk of incident pancreatic cancer: a nationwide population-based cohort study. *Diabetes Metab*. 2025;51(2):101605. doi:10.1016/j.diabet.2025.101605

6. Liu YH, Hu CM, Hsu YS, Lee WH. Interplays of glucose metabolism and KRAS mutation in pancreatic ductal adenocarcinoma. *Cell Death Dis*. 2022;13(9):817. doi:10.1038/s41419-022-05259-w

7. Crippa S, Marchegiani G, Belfiori G, et al. Impact of age, comorbidities and relevant changes on surveillance strategy of intraductal papillary mucinous neoplasms: a competing risk analysis. *Gut*. 2024;73(8):1336-1342. doi:10.1136/gutjnl-2023-329961