Response

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# Effects of Pancreatitis and Type 2 Diabetes Mellitus on the Development of Pancreatic Cancer: A Nationwide Nested Case-Control Study (*Diabetes Metab J* 2025;49:252-63)

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We sincerely appreciate the insightful comments provided by Dr. Lai and Dr. Liao regarding our recent publication entitled, 'Effects of pancreatitis and type 2 diabetes mellitus on the development of pancreatic cancer: a nationwide nested case-control study' [1]. We also would like to thank the editor for the opportunity to further discuss our findings and address the points raised.

First, we fully agree with your interpretation that the coexistence of type 2 diabetes mellitus (T2DM) and pancreatitis may have an additive effect on the risk of pancreatic cancer. In our study, the risk of pancreatic cancer was significantly higher in patients with both T2DM and pancreatitis than in those with either condition alone. A recent review has emphasized that these two conditions independently influence pancreatic cancer development, and their coexistence may further deteriorate the pancreatic tumor microenvironment, promoting the initiation and progression of pancreatic cancer [2].

Pancreatitis induces persistent inflammation characterized by recurrent cellular injury, cytokine secretion, fibrosis, and increased proliferative activity, creating a microenvironment favorable for tumor development. Specifically, cytokines such as interleukin 6 (IL-6) and IL-8, as well as activation of transcription factors like nuclear factor-κB, are closely associated with the development and progression of pancreatic neoplasms [3]. Meanwhile, T2DM, characterized by hyperinsulinemia and insulin resistance, stimulates insulin receptor and insulin like growth factor-1 (IGF-1) receptor signaling pathways such as phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK), which may promote pancreatic cell proliferation, survival, and tumorigenesis [4].

Moreover, recent literature highlights the significance of endocrine–exocrine crosstalk in the pancreas as a critical factor influencing disease progression. The simultaneous presence of metabolic and inflammatory stressors may further deteriorate the pancreatic tumor microenvironment and facilitate carcinogenesis [2]. Therefore, we concur that patients with both pancreatitis and diabetes mellitus should be considered at high risk for pancreatic cancer and may benefit from early screening and close clinical surveillance.

Furthermore, in our study, the pancreatic cancer risk did not significantly differ between patients with diabetes mellitus followed by pancreatitis and those with post-pancreatitis diabetes mellitus. This finding indicates that the simultaneous presence of the two conditions, regardless of their temporal order, is the primary determinant of pancreatic cancer risk. We fully concur with your interpretation on this point.

We concur that the exact mechanism underlying the in-

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creased pancreatic cancer risk in insulin users remains unclear—specifically, whether it results from poor glycemic control or β-cell dysfunction induced by pancreatic cancer. Future studies based on data sources that include glycosylated hemoglobin would help clarify the relationship among glycemic status, insulin use, and cancer risk.

Regarding your point on reverse causality, in our main analyses, we applied a one-year lag period to minimize this bias, and we performed sensitivity analyses using different lag periods to evaluate the robustness and consistency of our findings. As you correctly pointed out, the association was stronger with shorter lag periods, reinforcing the clinical implication that pancreatic cancer screening may be particularly important in individuals with newly diagnosed diabetes.

Furthermore, as this study employed a nested case-control design, we acknowledge that the reported odds ratios indicate associations rather than absolute risks. We appreciate your emphasis on this methodological point, which may help readers interpret our findings with appropriate caution.

In conclusion, we sincerely thank Dr. Lai and Dr. Liao for their insightful comments and constructive suggestions. Their points have allowed us to further clarify and underscore the significance and implications of our findings. We believe our responses have adequately addressed the issues raised and provide enhanced clarity regarding the interpretation and clinical relevance of our study.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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