The Relationship of Acute Pancreatitis and Pancreatic Cancer

To the Editor:

We read with great interest the article by Phillips et al[1] that suggests a remote history of acute pancreatitis (AP) may accelerate carcinogenesis with pancreatic cancer diagnosed 4.7 years earlier than patients without a history of pancreatitis. It is a large, prospectively collected, retrospectively analyzed case-control study of pancreatic adenocarcinoma (PC) patients. However, the accuracy of this study could be improved.

First, the authors used only parenchymal calcifications as the diagnostic criteria for definitive evidence of chronic pancreatitis (CP), which may underestimate the prevalence of CP, a well-established risk factor for the development of PC.[2]

In the present study, the PC patients were stratified based on patients' history of pancreatitis, less than 2 years, 2 years or more, and unknown before PC diagnosis. Only patients with pancreatitis for 2 years or more was significantly associated with the earlier diagnosis of PC, which contradicted prior cohort studies suggesting that the risk of PC was highest in the first 2 years following AP diagnosis.[3–5]

The study also did not report the details of etiology, number of prior episodes, length of follow-up, and severity of AP, which will have a crucial impact on the development of PC and/or CP. As reported by Sadr-Azodi et al,[5] non–gallstone-related AP had a higher risk of PC than those with gallstone-related AP, and the long-term (>10 years) association between non–gallstone-related AP and PC may be mediated through recurrent AP or CP. Besides, it is reported that after a first episode of AP 17% of patients would develop recurrent pancreatitis, and almost 8% of patients progress to CP within 5 years,[4] and increasing number of recurrent episodes of AP was associated with increased risk of PC.[5] The severity of AP determined the risk of new-onset diabetes; latter is also an important risk factor of PC.[6]

The causal relationship of AP and PC is controversial, because a significant number of patients with PC initially present with AP.[4] The authors considered acute/severe inflammation as the underlying mechanism of AP to PC, but we don't think the inflammatory course of AP could be persistent more than 5 or even 10 years. Although a first episode of AP may be related to PC, this risk is mainly present in patients who progress to CP.[7] Of course, it is a question for further analysis.

In conclusion, we appreciate the authors' finding of the potential impact of AP on PC. However, the definition of CP, point of time to evaluate the relationship of AP and the risk of PC, and the details of etiology, number of prior episodes, length of follow-up, and severity of AP need to be improved.

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REFERENCES

1. Phillips AE, Shah N, Borhani AA, et al. Prior history of pancreatitis accelerates the development of pancreatic adenocarcinoma. *Pancreas*. 2018;47:1262–1266.
2. Kirkegård J, Mortensen FV, Cronin-Fenton D. Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. *Am J Gastroenterol*. 2017;112:1366–1372.
3. Kirkegård J, Cronin-Fenton D, Heide-Jørgensen U, et al. Acute pancreatitis and pancreatic cancer risk: a nationwide matched-cohort study in Denmark. *Gastroenterology*. 2018;154:1729–1736.
4. Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin Gastroenterol Hepatol*. 2016;14:738–746.
5. Sadr-Azodi O, Oskarsson V, Discacciati A, et al. Pancreatic cancer following acute pancreatitis: a population-based matched cohort study. *Am J Gastroenterol*. 2018;113:1711–1719.
6. Vipperla K, Papachristou GI, Slivka A, et al. Risk of new-onset diabetes is determined by severity of acute pancreatitis. *Pancreas*. 2016;45:e14–e15.
7. Rijkers AP, Bakker OJ, Ahmed Ali U, et al. Risk of pancreatic cancer after a primary episode of acute pancreatitis. *Pancreas*. 2017;46:1018–1022.

Reply:

We thank Drs Li and Liu[1] for their comments on our recent article published on the prior history of remote acute pancreatitis (AP) accelerating the development of pancreatic adenocarcinoma (PC).[2] We appreciate the opportunity to respond on behalf of our coauthors.

We agree that the use of parenchymal calcifications alone as the definition of chronic pancreatitis (CP) may underestimate the prevalence of CP. However, additional morphologic characteristics of CP on cross-sectional imaging, such as parenchymal atrophy, ductal dilatation, or ductal irregularity, are commonly seen in patients with PC and limit the ability to confidently differentiate these 2 entities in a cross-sectional analysis. We therefore used parenchymal calcifications as a reliable indicator of preexisting CP for this study.

Acute pancreatitis is the presenting symptom of PC in up to 10.7% of patients.[3] In many of these patients, the diagnosis of PC is only established in the ensuing weeks or months. Therefore, in epidemiologic studies, a diagnosis of AP up to 2 years prior to PC diagnosis is routinely considered as a manifestation of PC. Because the focus of our analysis was to assess the relationship between remote AP and PC, we excluded patients who received a diagnosis of AP 2 years or less prior to PC from our primary analysis.

We agree that recurrent attacks of AP and transition to CP will be important factors in increasing the risk of subsequent PC. As stated earlier, our focus was to evaluate the association of remote AP with PC. Therefore, we excluded patients with obvious CP from the analysis. We did not have detailed information available on severity and number or timing of recurrent AP attacks in all patients. However, we did control for other potential confounders, such as sex, smoking, alcohol, diabetes, and obesity in multivariable analyses. In light of prior animal studies showing persistent inflammation contributing to an oncogenic milieu,[4] we believe that subclinical inflammation after AP in humans is a potential mechanism for accelerating oncogenesis in this population. Our findings are similar to a recent large study that showed that the median age at PC diagnosis was 5 years lower in patients with prior AP as compared with patients without a history of AP.[5] Observations in these analyses should be considered hypothesis generating and confirmed in future well-designed epidemiologic and experimental studies.

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REFERENCES

1. Li J, Liu F. The relationship of acute pancreatitis and pancreatic cancer. *Pancreas*. 2019;48:e57.
2. Phillips AE, Shah N, Borhani AA, et al. Prior history of pancreatitis accelerates the development of pancreatic adenocarcinoma. *Pancreas*. 2018;47: 1262–1266.
3. Munigala S, Kanwal F, Xian H, et al. Increased risk of pancreatic adenocarcinoma after acute pancreatitis. *Clin Gastroenterol Hepatol*. 2014; 12:1143–1150.e1.
4. Rhim AD, Mirek ET, Aiello NM, et al. EMT and dissemination precede pancreatic tumor formation. *Cell*. 2012;148: 349–361.
5. Kirkegård J, Cronin-Fenton D, Heide-Jørgensen U, et al. Acute pancreatitis and pancreatic cancer risk: a nationwide matched-cohort study in Denmark. *Gastroenterology*. 2018;154:1729–1736.

Mathematical Model and Study Design Could Be Optimized in Spatial Distribution Analysis of Pancreatic Stones

To the Editor:

We read with great interest the article by Zeng et al[1] on the spatial distribution of pancreatic stones in chronic pancreatitis (CP). They establish a standard to describe the spatial distribution of pancreatic stones in CP and found that compared with idiopathic CP, patients with alcoholic CP were prone to more pancreatic stones that distribute more uniformly. However, it would be more informative if the authors could optimize the mathematical model and details of the study.

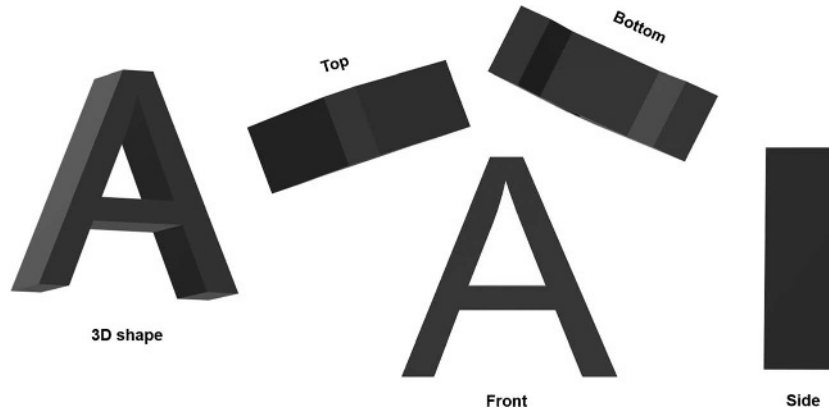

FIGURE 1. A lot of information would be lost during the conversion of 3D images into 2D images (figure cited from ux.brookdalecc.edu).

First, the mathematical model used for the spatial distribution analysis was based on the hypothesis that the pancreas has a standard spherical shape.[2] In reality, the pancreas is long, narrow, and not symmetrical. The unreasonable model may have resulted in great errors in spatial distribution analysis. If the stones were uniformly distributed, σ should be 0 theoretically. However, based on the standard spherical model, σ would not be 0. We recommend depicting the outline of the pancreas as the basis of the model to minimize the error.

Second, in Figure 1, the authors have acquired and presented the three-dimensional (3D) reconstruction of a pancreatic computed tomography image. They applied 2D coronal projection and preprocessing of the 3D image. Stone edge recognition and spatial distribution analysis were processed based on the 2D image. However, a lot of information would be lost during the conversion of the 3D images into 2D images (Fig. 1).[3] For example, stones sharing the same x and y axes values but different z axis value were overlapping in the 2D images. Therefore, it would be more accurate and informative to use 3D images to do spatial distribution analysis.

Third, this study could have answered an important question in the field of pancreatic extracorporeal shock wave lithotripsy, namely, whether stones in the branch ducts need to be fragmented.[4–6] We could not tell whether the stones were in the main pancreatic duct (MPD) or in the branch ducts. It would be instructive for clinical practice if authors could depict the MPD in the 3D images and figure out the rates of stone clearance in the MPD and branch ducts, respectively. With the follow-up data, we would know whether it is worth it to treat the branch stones.

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REFERENCES

1. Zeng XP, Zhu XY, Li BR, et al. Spatial distribution of pancreatic stones in chronic pancreatitis. *Pancreas*. 2018;47:864–870.
2. Eck S, Wörz S, Müller-Ott K, et al. A spherical harmonics intensity model for 3D segmentation and 3D shape analysis of heterochromatin foci. *Med Image Anal*. 2016;32:18–31.
3. Cazasnoves A, Sevestre S, Buyens F, et al. Statistical content-adapted sampling (SCAS) for 3D computed tomography. *Comput Biol Med*. 2018;92:9–21.
4. Hu LH, Ye B, Yang YG, et al. Extracorporeal shock wave lithotripsy for Chinese patients with pancreatic stones: a prospective study of 214 cases. *Pancreas*. 2016;45:298–305.
5. Li BR, Liao Z, Du TT, et al. Risk factors for complications of pancreatic extracorporeal shock wave lithotripsy. *Endoscopy*. 2014;46: 1092–1100.
6. Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy*. 2012;44: 784–800.