



Invited Commentary | Gastroenterology and Hepatology

IPMNs of the Pancreas: More Epidemiologically Than Clinically Relevant

Stefano Crippa, MD, PhD; Gabriele Capurso, MD, PhD; Massimo Falconi, MD

The history of intraductal papillary mucinous neoplasms (IPMNs) dates to the early 1980s, when small reports from Japan described rare cystic, mucin-producing tumors of the pancreas. It was only after many years that they were identified as IPMNs, with the specific clinicopathological features that characterize these lesions, allowing them to be distinguished from other pancreatic neoplasms. IPMNs can exhibit different degrees of dysplasia, with the potential to evolve over time from low-grade dysplasia to invasive carcinoma. As a consequence, clinicians considered IPMNs as providing the unique opportunity to make an early treatment of a lethal cancer, such as pancreatic ductal adenocarcinoma. With the advance of knowledge, the situation has become even more complex. It became clear that the risk of malignant transformation was relevant for IPMNs that involved the main pancreatic duct (main-duct or mixed IPMNs) while IPMNs arising from branch ducts (BD-IPMNs) were largely benign. Consequently, while at the beginning of this story all IPMNs underwent resection, nonoperative management was then considered for an increasing number of BD-IPMNs. These observations were subsequently incorporated into guidelines that identified worrisome features (WFs) and high-risk stigmata (HRS) as different categories of risk for malignant neoplasms, recommending active surveillance for BD-IPMNs lacking WFs and HRS.¹ This approach proved to be safe, with few patients with low-risk IPMNs who developed pancreatic malignant neoplasms during surveillance.²

Meanwhile, the clinical-radiological diagnosis of IPMNs has dramatically increased in the last decades because of the widespread use of high-resolution imaging techniques and a greater awareness of IPMNs among radiologists. A systematic review and meta-analysis of 17 studies with 48 860 patients³ showed a pooled prevalence of pancreatic cysts of 8% in the population. However, precise data of the prevalence of IPMNs in the general population are lacking, as are data regarding the occurrence of pancreatic cancer (PC) in these patients. Most studies describe surgical series or selected cohorts from high-volume centers, frequently include all pancreatic cysts, and are characterized by significant heterogeneity among imaging modalities.

The study by de la Fuente et al⁴ tries to overcome this literature limitation by analyzing the Rochester Epidemiology Project (REP), a medical records linkage system that provides longitudinal, population-based medical data. First, the authors selected 2114 individuals aged 50 years or older who underwent contrast enhanced computed tomography scan (CT cohort) between 2000 and 2015 to evaluate IPMN prevalence. The age cutoff of 50 years was selected given that IPMNs occur more frequently after the sixth decade of life; therefore, the authors focused on the age range that is epidemiologically typical for the disease. Then, they identified from REP all patients with pancreatic cancer and with IPMN-associated pancreatic cancer between 2000 and 2019 (PC cohort). They found that the estimated population prevalence of IPMNs was 10.9%, with BD-IPMNs the most common IPMN type (90.9%); 81% of patients had IPMNs with no WFs or HRS. Because CT is the most common cross-sectional imaging modality in the US, the authors used it as the referral imaging technique to identify as many IPMNs as possible. Guidelines suggest that magnetic resonance imaging is more sensitive to detect small cysts and the communication between those and the main pancreatic duct.¹ It is possible that some small BD-IPMNs were missed. On the other hand, a strength of the study was the careful revision process for all CT images by experienced radiologists, with revision from more radiologists if image findings were uncertain. Therefore, it is likely that the risk of some underestimation of the number of IPMNs is possible but with limited impact on study results. Another issue is the systematic lack of certain histological or cytological diagnoses of IPMNs or of

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cystic fluid data suggestive for a mucinous lesions. IPMNs included in the study should be defined as presumed IPMNs as is done in all radiological studies. However, by a clinical point of view, these lesions are considered full-fledged IPMNs, and this diagnostic limitation, although methodologically correct, does not reduce the clinical value of the study.

A very important result is the analysis of PC development during IPMN follow-up. After a median follow-up of 12 years, only 4 of 231 individuals with IPMNs developed PC (1.7%). This is similar to a rate in invasive cancer of 1.1% detected during active surveillance in a selected cohort of 837 European patients with low-risk BD-IPMNs.⁵ The PC incidence rate per 100 person-years was 34.1 incidents for patients with IPMNs with WFs or HRS, but it was only 0.16 incidents for low-risk IPMNs, a result not significantly different compared with that of patients without IPMNs (0.11 incidents; $P = .62$).⁴ That the risk of pancreatic cancer in patients with IPMNs without WFs or HRS was similar to that expected in individuals without IPMNs is reassuring and allows us to reassess the need for lifetime active surveillance in all patients with low-risk IPMNs. This applies specifically to older patients with IPMN stability over time, and in this context, surveillance discontinuation has been proposed.⁶

Finally, de la Fuente et al⁴ found that approximately 10% of PCs developed in the background of an IPMN. Compared with non-IPMN PC, IPMN-associated PC was more frequently localized, nonmetastatic, and amenable of a higher rate of surgical resection and of improved survival. These are not new findings. Better outcomes for IPMN-associated PC are probably associated with earlier diagnosis of PC in patients with IPMNs. This may be true even in the setting of a population-based study given that some patients with IPMNs included in this cohort were likely part of surveillance programs.

Once considered a rare disease, IPMNs are now very common findings due to tremendous technological advances that have improved diagnostics. In keeping with data from surveillance studies, this population-based study found that most IPMNs lacking WFs or HRS at diagnosis did not progress to PC, suggesting that some were likely an example of overdiagnosis and excessive medicalization. Obviously, it is not possible to generalize given that some IPMNs have the potential to progress to cancer over time. Although results of this study should be validated in larger cohorts, they represent useful clinical data from an unselected population-based cohort that helps challenge current IPMN surveillance policies that recommend lifetime active surveillance for all fit individuals. In the future, a multiomics approach with clinical-radiological, metabolic, and molecular and genomic data may increase the probability of finding accurate biomarkers associated with risk stratification of IPMNs and their management in view of personalized medicine. Currently, we can use follow-up data from studies like this one to identify patients with IPMNs who are not at risk of progression based on clinical-radiological parameters. We can furthermore start selecting subgroups of patients with limited life expectancy due to age or comorbidities to be considered for surveillance discontinuation.

ARTICLE INFORMATION

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Corresponding Author: Stefano Crippa MD, PhD, Division of Pancreatic Surgery and Transplantation, Pancreas Translational and Clinical Research Center, Vita Salute San Raffaele University, Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy (crippa.stefano@hsr.it).

Author Affiliations: Division of Pancreatic Surgery and Transplantation, Pancreas Translational and Clinical Research Center, Vita Salute San Raffaele University, Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Scientific Institute, Milan, Italy (Crippa, Falconi); Division of Pancreato-Biliary Endoscopy and Endosonography, Pancreas Translational and Clinical Research Center, Vita Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Milan, Italy (Capurso).

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