Editorial

Pancreatic cystic neoplasms: usually incidental, rarely incident

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Pancreatic cysts

There are over 20 different types of cystic lesions of the pancreas, most of which are benign (1). The four most common pancreatic cysts with neoplastic potential are serous cystadenoma (SCA), solid pseudopapillary neoplasm (SPN), mucinous cystic neoplasm (MCN), and intraductal papillary mucinous neoplasm (IPMN). Neoplastic pancreatic cysts are further classified as mucinous (mucin-producing) or serous to determine their malignant potential. The mucin-producing lesions, IPMNs and MCNs, are considered "high-risk" since they have the potential for malignant transformation and are more often associated with pancreatic ductal adenocarcinoma (PDAC) (2). The degree of dysplasia in high-risk pancreatic cysts (along with imaging, clinical factors and symptomology) usually determines whether patients undergo surveillance, or have their cysts resected; however, even in high-volume settings and specialty clinics, the diagnosis and clinical management of pancreatic cystic neoplasms (PCN) is uncertain (2,3).

Incidental PCN prevalence

The general population prevalence of PCN was recently estimated as being between 2% and 45% (1). This rather wide range in estimated prevalence is indicative of: (I) the symptomless nature of most PCN, and lack of clinical screening programs, even for higher-risk lesions, (II) the different modalities of (incidental) PCN detection utilized—e.g., magnetic resonance imaging (MRI), computerized tomography (CT), and ultrasonography—along with their different sensitivities and specificities, as well as the increasing application of high-resolution cross-sectional imaging in medicine overall, (III) the heterogeneity and non-representativeness of many populations studied to date (e.g., clinical studies, autopsy studies), along with true variations in PCN across populations due to differences in age, lifestyle habits, and risk factors including genetic risk factors, and (IV) a paucity of data (especially population-based data) to make accurate estimates of general population prevalence.

It is sometimes stated that the detection (and perhaps prevalence or incidence) of PCN is increasing (4,5), but as mentioned in (II) above, some of the observed increase in incidence of some diseases over time can be attributed to an increase in detection due to increased utilization of an existing detection technology or screening programs, or the recent application of new diagnostic tests or detection technology. In the case of PCN, the increasing use of higher-resolution, cross-sectional abdominal imaging in medicine in recent years surely has contributed to at least part of the observed increase in detected and prevalent PCN in many studies (and this trend is likely to continue). An increasing elderly population and increasing rates of diabetes and obesity in general could also be contributing to observed increases in PCN (6). Nevertheless, the current study by Kromrey *et al.* is unique and a step forward in its ability to better estimate the general population prevalence of PCN since previous studies of PCN have been based on clinical and autopsy populations in which the *denominator* (the population base at risk of developing PCN) is for all intents and purposes unknown. The SHIP-2 cohort of northern Pomerania (Germany) utilized by Kromrey *et al.* is a prospective cohort of individuals who were sampled from the entire adult population of Pomerania using a two-stage

stratified cluster sampling procedure (7). Thus, the study by Kromrey *et al.* probably represents the first to truly be able to estimate general population prevalence of pancreatic cysts.

In their study, Kromrey *et al.* reported that the weighted prevalence of incidental pancreatic cysts detected in the SHIP-2 cohort of Northern Germany at baseline (2008–2012, mean age 55.8±12.8 years, 48.4% men) by whole body MRI and magnetic resonance cholangiopancreatography (MRCP) was 49.1%. Cyst number increased in 36% of participants during 5 years of follow-up, and almost half (49.8%) with any cyst at baseline showed an increase in maximum cyst size during the follow-up period, with a combined total of 24% of participants showing an increase in number and size of cysts over the follow-up period. So, the weighted prevalence estimate of 49.1% is pretty high and falls just outside the 2–45% range as stated above.

Risk factors and incidence

Confirming previous observations, the study by Kromrey *et al.* showed a monotonic dose-response relation between age and the prevalence, mean number, and mean size of pancreatic cysts. Body mass index (BMI) was associated with prevalence, but not number or size, of cysts. Cyst prevalence, mean number and mean size were similar in men and women. Other potential risk factors including smoking status, alcohol consumption, diabetes, HbA1c level, and lipase level (assessed within 30 days before the initial baseline assessment of PCN by MRI) were not associated with PCN in the SHIP study. However, it's worth noting that risk factors assessed 30 days before baseline may not reflect the relevant time period for a risk factor to influence PCN development, especially prevalent PCN (which presumably developed months to years before the baseline assessment of risk factors). Further, each risk factor theoretically might only be associated with risk for a specific type of PCN (e.g., MCN, main-duct IPMNs—none of which were analyzed separately in the present study), and in either a positive or inverse direction, so the conclusion that no risk factors other than age and BMI were associated with overall PCN in this study should probably be treated with caution. Since this population-based study did not utilize more invasive procedures such as endoscopic ultrasound (EUS) to clarify the nature of the cysts incidentally identified using MRI, the authors were unable to evaluate cyst type, morphology, duct involvement, or degree of dysplasia in their analysis, limiting some of the conclusions that could be made (e.g., the prevalence of main-duct IPMN, risk factors for IPMNs *vs.* MCNs, etc.).

Another recent study from Seoul, S. Korea evaluated over 21,000 participants in a screening and prevention study (not a population-based cohort like SHIP) in which abdominal CT were performed from 2003 to 2013 (8). In contrast, the overall prevalence of PCN in the Korean population was estimated as 2.2%, with the following breakdown of total PCN (n=457) by lesion type: IPMN (82%), SCN (4%), MCN (2%), and indeterminate (12%) (8). Based upon these two recent studies, and past studies, we are still faced with a rather wide range of prevalence estimates for PCN in the general population. It might be possible that a substantial proportion (but <50%) of the general population (considering all ages) carries some form of pancreatic cyst, with most of these remaining benign and symptomless for life, possibly with some even regressing, as the study by Kromrey *et al.* suggests.

Incidental, not really incident

The analysis of incident PCN (newly diagnosed, not prevalent, in those free of PCN at baseline, n=367 participants) during the 5-year follow-up period in the SHIP-2 study could theoretically yield more accurate estimates of associations for risk factors and PCN since the risk factors were measured at baseline before the appearance of incident PCN (this helps to solve the temporal bias problem of many retrospective studies where exposure is assessed after diagnosis). The yearly incidence of first PCN in this rather small group of cohort participants was 2.6% per year (or 12.9% over the 5-year follow-up period, n=48). Interestingly, neither age nor BMI measured at baseline were associated with the development of new PCN during the 5-year follow-up period. Most likely the small sample size of incident PCN and corresponding short follow-up time probably didn't allow for an accurate or useful assessment of risk factors and PCN associations is this study. This could change with additional years of follow-up. In the SHIP-2 cohort, there were only three participants who died of pancreatic cancer during the follow-up, and unfortunately, two of these did not consent to MRI at baseline, so an analysis of PDAC risk in participants with PCN at baseline could not be performed (4).

IPMNs *vs.* PanINs, and pancreatic cancer risk

The clinical management and surveillance of PCN is unclear. New biomarker assays and data are needed to

differentiate benign from high-risk malignant lesions, and well-designed surveillance studies are needed to better quantify the malignant potential of these high-risk lesions. Recent efforts to evaluate cyst fluid pre-operatively using NGS hold promise for better management of high-risk PCN (9). Despite this, it is important to remember that probably no more than 5–10% of PDAC may arise from IPMNs and MCNs, while the majority of PDAC (>90%) may arise from microscopic intraepithelial neoplasia (PanIN) lesions, which are *undetectable* by current imaging technology. Indeed, since PDAC itself is a relatively rare cancer (compared to lung, breast, prostate, and colorectal cancers) it shouldn't be surprising when a population-based study of patients with PCN followed for <10 years yields a negligible or near-zero risk of PDAC.

Since microscopic PanIN lesions, which often appear in the head of the pancreas (similar to PDAC), are clinically undetectable using current biomarker or imaging approaches, the focus of much early lesion and early detection research has been on IPMNs and MCNs which, if successful, could theoretically allow the early detection of 5–10% of PDAC. Therefore, there is an urgent need for better imaging technologies or combinations of biomarkers and imaging to non-invasively detect microscopic PanIN lesions, as well as distinguish the high-risk IPMN and MCN lesions from lower risk lesions. The characterization of pancreatic precursor lesions and subsequent PDAC risk is further complicated by the observations that microscopic PanIN lesions are often present in resected IPMN lesions (10); and that IPMN lesions are often multifocal, and recurrence at sites distant from the original resected lesion is relatively common (11-14). Further, PDAC has been found concurrently with IPMN or during follow-up of IPMN patients, and also at sites distant from the original lesion, suggesting the possibility of multifocal development of PDAC (15). The presence of independent multifocal lesions including microscopic PanINs is relatively common in patients with high-grade IPMNs (11,15). There is also molecular evidence that some IPMN lesions share some genetic alterations with PanIN lesions (16-18). Whether some IPMN represent a progression from microscopic PanIN lesions, or whether some concurrent IPMN and PanIN lesions share a common genetic background that supports their progression to PDAC is not yet entirely clear (10,15,16), but either possibility offers an update to the way we think about precursor lesions for pancreatic cancer.

Unfortunately, even if we are able to accurately identify patients with high-risk pancreatic cyst neoplasms, including somehow PanINs, and we are able to treat them relatively early, these patients will likely face a lifetime of pancreas-associated morbidity and ongoing medical surveillance. With more population-based studies such as the one by Kromrey *et al.*, and new initiatives such as the NCI-funded Pancreatic Cancer Detection Consortium (PCDC) now underway, along with the rapid pace of new molecular discoveries in precursor lesions and PDAC, there does seem to be quite a bit more hope for patients today compared to years past.

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Footnote

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