



New light on the pancreatic cyst conundrum

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Pancreatic cysts present a clinically challenging conundrum of great concern. First, as a result of the common availability of high resolution imaging technology, computed tomography (CT), magnetic resonance imaging (MRI), cysts are being increasingly identified as unsuspected-incidental findings during abdominal evaluations for other unrelated reasons, such as auto accidents, abdominal pain, liver, spleen, gall bladder, kidney and pelvic disorders. Importantly, once identified, they are the cause of considerable consternation, for patients and physicians alike, since they may be early precursors of developing pancreatic cancer and these cysts may represent early premalignant disease, at a stage, where appropriate intervention may avert the devastating consequences of advanced pancreatic cancer with its dismal 5-year survival of less than 8% (1).

An important dilemma in dealing with pancreatic cysts is that the remedy, pancreatic surgery itself, when warranted, may be costly and result in considerable morbidity, even in the hands of an experienced surgeon. Thus, guidelines have been developed and revised for evaluation, follow-up and management of pancreatic cysts, especially those that are asymptomatic and incidentally detected and many institutions have developed special clinics to focus on management of pancreatic cysts. However, the resultant management algorithms are actually consensus generated rather than evidence-based (2-5).

Two recent studies now provide objective evidence for the natural history of pancreatic cysts and their evaluation that both support and extend the earlier guidelines for timing of evaluation and clinical intervention (6,7). The first, a retrospective follow-up study from the Mayo Clinic

of patients identified with pancreatic cysts over a 12-year period from 2000–2012 (6). And the other, a prospective, 5-year follow-up study of participants identified with pancreatic cysts as part of the population-based Study of Health in Pomerania (SHIP) (7).

After screening 2,000 patient records for pancreatic cysts, and excluding more than 40%, including those with probable inflammatory etiologies, parenchymal calcifications, suspected non-intraductal papillary mucinous neoplasm (IPMN) cysts, mucinous cystic neoplasms, serous cystic neoplasms, neuroendocrine tumors, pancreatic adenocarcinoma with cystic degeneration and cysts associated with polycystic kidney disease or Von Hippel-Lindau disease, as well as pancreatic cancer and those who underwent surgery within 6 months of pancreatic cyst detection, the Mayo Clinic in a retrospective series evaluated follow-up of 1,160 patients for median 4.2 years (range, 1.8 to 7.1 years). Initial imaging studies were retrospectively identified as Fukuoka positive (FP) (358 patients) and Fukuoka negative (FN) (802 patients) (6). FP patients were further identified as high risk (HR), determined by obstructive jaundice, cystic lesions in pancreas head, solid components within cysts, thickened or enhancing cyst wall, or main duct dilatation >10 mm. FP worrisome features (FPWF) included pancreatitis without other causes, cysts >3 cm, thickened walls, main duct dilatation 5–9 mm, mural nodules, lymphadenopathy, abrupt change in duct dilatation with distal pancreatic atrophy. FN cysts were identified as absence of all above parameters. The 5-year risk for developing pancreatic cancer among FPHR group was 49.7% while FPWF was 5.1% and FN 0.61%. Conversion

from FN to FP was 7.3%.

Five-year survival of patients with FPHR rapidly plummeted to ~60% within first year after cyst identification, and then plateaued at a stable level for 5 years (8). These studies did not report how many of the FPHR post-surgical survivors had early stage pancreatic malignancy identified by histopathology, thereby, suggesting that early surgery might have contributed to curable disease. Compared to the bleak 8%, 5-year survival for patients with advanced symptomatic pancreatic cancer, this result is an important indication of the potential benefit of prompt intervention in patients with pancreatic cysts which are FPHR. Survival was worst for patients with obstructive jaundice, while imaging demonstration of solid components or ductal dilatation also had negative prognostic value. In contrast to the development of pancreatic cancer in patients with FPHR characteristics, those with FN cysts showed very low levels of pancreatic cancer development with no statistical significance dependent on cyst size. These studies provide important validation for careful observation of patients with FPWF and FN features. Nonetheless, the observation that 5.1% of patients classified as FPWF developed pancreatic cancer indicates the important need for development of additional diagnostic tests.

Overall, this Mayo Clinic study provides an evidence base in support of the Fukuoka stratification guidelines and the value of FPHR criteria in predicting the occurrence of pancreatic cancer (3). The study also supports the importance of imaging follow-up within 6 months of cyst detection.

In contrast to the retrospective Mayo Clinic study, the SHIP prospective study was designed to identify and follow a cohort of subjects from a larger population-based study (7). Thus, from a population of 212,157 in Pomerania, North East Germany, 4,310 individuals were initially entered between 1997 and 2001. From the original group, 2,333 agreed to participate, of which 1,275 agreed to elective MRI and magnetic resonance cholangio-pancreatography (MRCP) between 2008 to 2013. From this group, 1,077 (521 men and 556 women, mean age 55.8 ± 12.8 years) could be analyzed, of which, 676 individuals were available for 5-year (range, 2.7–7.5 years) follow-up during 2014–2016.

At initial imaging study, subjects were identified with pancreatic cysts at a prevalence of 49.1% with no statistical difference between men or women. In 367 patients who were initially cyst free, 48 developed new cysts, for incidence 12.9% per 5 years or 2.6% per year. Overall, 1.6% cysts disappeared, 30.8% showed no change, and

24.1% increased in number and diameter. Among cyst positive patients, there were an average of 3.9 per patient, average size 2 to 29 mm, of which 63.6% were 2–5 mm and 30.6% were 5.01–10 mm. Because of imaging techniques employed, fine detail was not determined. Cyst prevalence was noted to be greater with age (75.7% in subjects over 80 whereas there were 17.1% in 30–39 year old). Cysts were more likely to occur in patients with diabetes than without, 10.7 *vs.* 5.3%, and patients with cysts compared to those who were cyst free were more likely to have elevated BMI (28.14 ± 4.32 *vs.* 27.2 ± 4.32 kg/m²). There was no correlation with smoking, lipase, HbA1c or alcohol use during the 30 days preceding imaging. Importantly, no subjects harboring pancreatic cysts developed pancreatic cancer and, using death certificate follow-up, no deaths were attributed to pancreatic diseases. However, three subjects from the original 2,333 cohort died of pancreatic cancer, two of whom had not participated in the imaging study and the other had no imaging signs of tumor or cystic lesions.

While both the Mayo Clinic (6) and the SHIP studies (7) follow the development of pancreatic cysts, many of the patients in the retrospective Mayo Clinic series apparently had advanced disease at the time of cyst detection as indicated by the fact that they were described as already having obstructive jaundice. In contrast, in the SHIP prospective population-based study, cysts were detected unexpectedly in population-based volunteer participants. However, the study did not exclude subjects with known pancreatic disease, previous pancreatic surgery or predisposition to pancreatic cysts.

As suggested by guidelines (8,9), and supported by the Mayo Clinic study (6), it is important to evaluate patients at time of cyst identification for signs and/or symptoms of pancreatic disease and to further evaluate cysts to ensure absence of any FPHR features. If any of these are present, then appropriate action including endoscopic ultrasound and fine needle aspiration and/or pancreatic surgery following the Fukuoka guidelines seem appropriate (3).

For those with incidentally detected asymptomatic pancreatic cysts, the SHIP study now provides important, although still preliminary evidence for a 5-year follow-up period (7). However, it should be noted that the SHIP study was conducted in a geographically defined population base, probably with relatively common environmental exposures. Accordingly, the study needs to be validated in groups with other exposures, risk factors and ethnic distributions.

Because of the devastating consequences associated with pancreatic cancer, telling patients that they harbor

pancreatic cysts and suggesting that they be evaluated by a pancreatic surgeon and/or be followed at a pancreatic cyst clinic is likely to cause considerable apprehension and concern. When follow-up studies are recommended, many patients are hopeful that the abnormal finding will disappear. However, based on the SHIP study (7), it is important to inform patients that disappearance is unlikely, since less than 1.6%, did so over the 5-year period. In contrast, it is also important to inform patients that, over time, the cyst(s) may increase both in size and numbers and that these changes are not necessarily associated with an adverse or even actionable outcome, again at least over the 5-year period covered by the study. Moreover, no patients in this series developed pancreatic cancer or died of pancreatic disease. Based on the high prevalence of pancreatic cysts, their increasing prevalence with age and the low midterm risk, the SHIP authors appropriately recommend that high resolution imaging studies not be used as a screening tool for pancreatic cysts.

Because of the high prevalence and the lack of progression in terms of tumor development in asymptomatic patients, the authors suggest that the frequency of repeat imaging studies be relaxed from every year to every 2 years (7). This relaxed screening frequency clearly pertains to the first 5 years where evidence exists, however, whether subsequent screening needs to be increased or decreased on further follow-up depends on the natural history of cysts over a longer time period.

It is important to note that subjects with cysts, compared to those without, had higher BMI (28.14 ± 4.32 vs. 27.12 ± 4.32 kg/m²); mean BMI for the entire group (27.59 ± 4.35 kg/m²) was in the overweight range. Nonetheless, since pancreatic cysts were associated with increased BMI and since pancreatic cancer increases with obesity (10,11). It becomes important to follow the natural history of cyst progression and disease occurrence in obese patients. This is especially of concern, since we have recently suggested that obesity, in addition to increasing risk and worsening progression for multiple malignancies, may also serve to accelerate cancer development (12). Accordingly, studies similar to SHIP are warranted in obese patients to more definitively establish likelihood of progression to pancreatic disease and cancer. Moreover, since the potential progression timeline of pancreatic cyst to pancreatic cancer, following the adenoma to carcinoma paradigm (13,14), has not been clearly defined and may well be longer than the 5-year follow-up reported in this study, it will be important to follow the SHIP and similar patient cohorts for longer intervals.

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