

Pancreatic Cancer in Hereditary Pancreatitis: Consensus Guidelines for Prevention, Screening and Treatment

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Background

Pancreatic cancer is the fourth largest cancer killer among adults in the USA [1] and one of the top ten cancer killers in Europe and industrialized countries [2, 3]. Eighty-five to 90% of patients present with disease that is not resectable at the time of diagnosis [4]. Of those who undergo 'curative' resection, 5-year survival ranges from 10 to 24%, depending on the study quoted [4]. Against this dismal background, three strategies have emerged in the fight against this deadly disease: (1) prevention through risk factor reduction and vaccine development; (2) screening of high-risk groups in an attempt to identify tumors at a curable stage, and (3) improved neoadjuvant, surgical, adjuvant and palliative therapy.

Hereditary pancreatitis (HP) is an autosomal dominant disorder with an estimated 80% phenotypic penetrance typically consisting of recurrent episodes of acute pancreatitis, frequent progression to chronic pancreatitis and an approximately 50- to 70-fold increased risk of pancreatic cancer [5, 6]. Well over 200 kindreds have been identified worldwide. The criteria for diagnosis of HP are thoroughly discussed within another consensus document in this issue [7]. Mutations in the cationic trypsinogen gene (R122H, N29I) cause the disease in 60–70% of kin-

dreds [8–12]. In vitro biochemical studies suggest that these mutations enhance trypsin activity within vesicular compartments of pancreatic acinar cells [13–16]. Additional mutations in the same gene have been identified (A16V, D22G, K23R) [17–21]. Unfortunately, inadequate clinical data and small numbers have so far precluded establishment of a cause-and-effect relationship for these mutations [22, 23].

The autosomal dominant inheritance pattern and high phenotypic penetrance of HP, our ability to confirm the diagnosis through genetic testing in up to 70% of kindreds and the high tumor risk make it an ideal model for prevention and screening protocols. The growing awareness of HP and the responsible gene defects mandates that we as pancreatologists provide guidelines with regard to cancer prevention, screening and therapy in these patients. It was with this intent that pancreatologists, scientists, surgeons, pathologists and geneticists convened at the Third International Symposium on Inherited Diseases of the Pancreas in Milan, Italy from April 5 to 7, 2001 (see www.inherited-diseases-pancreas.com). The following sections of this paper summarize the consensus recommendations, supported by the Council of the International Association of Pancreatology and others. These recommendations apply only to patients with HP and should not be applied to patients with other risk factors for pancreatic cancer or sporadic tumors [24, 25].

An alphabetical list of the authors appears in the Appendix.

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Epidemiology of Pancreatic Cancer in HP

Two large independent epidemiologic studies utilizing databases created by the International Hereditary Pancreatitis Study Group and the European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC) have calculated an approximately 50- to 70-fold increased risk of pancreatic cancer in patients with HP [26, 27]. The age-accumulated risk in both studies began to rise between 40 and 50 years of age, with a 40% cumulative risk by the age of 70 years. The report by Lowenfels et al. [26] noted a 70% cumulative risk by the age of 70 years in HP of paternal inheritance. This raised the specter of genetic imprinting. Other groups have subsequently reported pancreatic tumors in HP patients with paternal and maternal inheritance [27–29]. Pancreatic cancer has been reported in kindreds with R122H mutations, N29I mutations or no identifiable gene mutations in the setting of an obvious HP phenotype [26, 27]. However, the number of tumors varies somewhat from kindred to kindred.

Pathogenesis, Histology and Pathophysiology of Pancreatic Cancer in HP

The occurrence of tumors in families with R122H trypsinogen gene mutations, N29I mutations or no detectable mutation supports the theory that pancreatic cancer develops within the regenerative milieu of acute/chronic pancreatitis [30]. The interkindred variance of tumor prevalence supports a role for environmental and genetic modifiers of pancreatic cancer risk in HP [31]. The vast majority of these tumors exhibit ductal morphology [26, 27, 32]. There are no data comparing the molecular profiles of ductal pancreatic tumors harvested from patients with HP, nonhereditary chronic pancreatitis or otherwise normal pancreata. As of yet, there are no data suggesting that the pathways driving tumor growth and spread in the setting of HP vary from those characterized in sporadic tumors [33–35].

Prevention of Pancreatic Cancer in HP

There is no proven chemoprevention or vaccine for pancreatic cancer. In this setting, we advocate risk factor reduction as the best preventive strategy. Data presented by Lowenfels et al. [36] suggest that smoking significantly increases the risk of pancreatic cancer in the setting of HP. Members of HP kindreds should be counseled at a young

age to avoid smoking should they exhibit the HP phenotype and/or genotype. Physicians should also strongly encourage cessation of smoking in those who already do. The impact that this will have on cancer risk is not yet clear.

Another possible preventive measure is the reduction of risk factors for recurrent acute and chronic pancreatitis [37–39]. A reduction in the frequency of episodes of acute pancreatitis might delay progression to chronic pancreatitis [38, 39]. Elimination of factors known to cause chronic pancreatitis independently of HP may also help to slow disease progression [39]. If successful, such measures may positively influence the regenerative milieu within the pancreas.

Based upon this theory, we recommend that those exhibiting the HP phenotype and/or genotype refrain from alcohol use. Medications known to cause pancreatitis should be avoided when possible. Metabolic derangements including hypertriglyceridemia and hypercalcemia should be corrected. Patients exhibiting the HP phenotype should undergo radiologic and endoscopic evaluation in an attempt to identify and treat structural problems (e.g. choledocholithiasis, dominant pancreatic duct stricture) which may contribute to recurrent attacks of acute pancreatitis and/or progression to/of chronic pancreatitis [38, 39].

The prevalence of sphincter of Oddi dysfunction (SOD) and pancreas divisum has yet to be established in HP [38]. With the exception of type I SOD, specific testing for these conditions in the setting of HP cannot be advocated at this time. A subset of patients with ampullary stenosis in certain HP kindreds has been reported [10]. The current literature, though less than optimal, supports a benefit of endoscopic therapy in patients with type I SOD and recurrent acute pancreatitis [40]. We acknowledge that controversy surrounds the role of SOD in acute pancreatitis and therefore realize that investigations for and treatment of this phenomenon will vary from physician to physician and institution to institution.

Screening for Pancreatic Cancer in HP

There is no screening protocol that has proven effective in any cohort at risk for pancreatic adenocarcinoma. This is almost certainly due to: (1) low tumor yield in all but the highest-risk cohorts (i.e. HP and hereditary pancreatic cancer) [41]; (2) the lack of tumor markers (serum, pancreatic juice or stool) alone or in combination with sufficient sensitivity, specificity, positive predictive value

and negative predictive value to alter management independent of radiologic imaging [42, 43], and (3) the assumed inefficiency of radiologic imaging techniques [e.g. multiphasic helical computed tomography (CT), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP)] in detecting tumors at a resectable stage [44–50].

No prospective study has actually addressed the clinical utility or cost effectiveness of multiphasic helical CT, EUS, ERCP and/or MRI/MRCP in the screening of patients with HP or those belonging to a hereditary pancreatic cancer kindred [43]. The assumed inefficiency of these modalities in the screening of HP patients has been based on the highly metastatic nature of even small tumors, the detection limits in the setting of chronic pancreatitis and cost [42–50].

One theoretical analysis discussed at the Symposium estimated that yearly screening of 250 patients with known HP between 40 and 50 years of age for 5 years with multiphasic helical CT/ERCP/EUS plus serum and pancreatic juice markers would cost USD 362,857 per tumor detected [43]. Actual cost, not the amount billed, for each test was based on levels at the University of Cincinnati, Ohio, USA. Screening of the same cohort at yearly intervals with EUS plus collection and storage (but not testing) of blood/serum and pancreatic juice would cost USD 69,643 per tumor detected. The appeal of the latter strategy is the ability to image the pancreas, biopsy suspicious lesions and collect pancreatic juice from the duodenum following secretin stimulation, all at the same time. Even assuming that 30% of tumors are detected at a stage resectable for cure, the results pale in comparison to the cost of screening mammography and breast cancer, i.e. approximately USD 1,000 per year-life saved. Alternative strategies are being investigated in an attempt to reduce the cost of screening [51].

Despite these less than optimistic numbers, it was the unanimous opinion of the consensus conference that screening should be offered to HP patients ≥ 40 years of age. Optimally, screening should be done at medical centers expert in the care of patients with HP with state-of-the-art imaging technology. Ideally, screening should be performed yearly and within the context of multicenter protocols assessing the efficacy of EUS or multiphasic helical CT or MRI/MRCP in conjunction with standardized collection and storage of blood/serum and pancreatic juice for future analysis. Despite the logical appeal of EUS, the consensus conference agreed that all of these

imaging modalities exhibit limitations in the setting of chronic pancreatitis [42–50]. Therefore, definitive statements cannot be made at this time favoring one over the other.

The use of ERCP in screening protocols is particularly controversial. Certain investigators argue that ERCP facilitates the detection and sampling of ductal pancreatic dysplasia/malignancy while allowing optimal collection of pancreatic juice [51, 52]. Other investigators feel that the same objectives can be accomplished with lower morbidity and mortality through EUS with needle biopsy of suspicious lesions and aspiration of duodenal contents following secretin stimulation [42, 43, 50, 53]. Similar arguments can be made in favor of multiphasic CT or MRI/MRCP when performed in conjunction with duodenal tube placement and aspiration of intestinal contents following secretin stimulation. No consensus could be reached either in opposition to or in favor of ERCP in screening protocols. However, there was general agreement that patients should be fully counseled regarding the potential risk/benefit ratio of available screening modalities before enrollment in any protocol.

The acquisition and storage of blood/serum and pancreatic juice in a standardized fashion is critical. Recent advances in molecular technology will result in the identification of a myriad of markers with the potential to predict the presence of preneoplastic and neoplastic ductal lesions. The availability of sequentially collected blood/serum and pancreatic juice samples from a cohort at high risk for pancreatic cancer will facilitate a ‘snapshot’ assessment of the clinical utility of each marker, alone or in various combinations. This strategy likely holds the key to cost-effective screening of patients with HP.

We acknowledge that some HP patients eligible for screening will, for whatever reason, not be able to undergo evaluation at a pancreatic disease center with state-of-the-art technology and involved in a multicenter screening protocol. Physicians caring for a patient with HP in these circumstances should contact a pancreatologist expert in the care of HP for advice concerning the best imaging modality based on local equipment and expertise. This will also facilitate attempts to collect blood/serum and/or pancreatic juice within the context of Institutional Review Board-approved protocols. The list of pancreatologists contributing to this document should prove helpful in this regard (Appendix).

Management of the Patient with HP and Pancreatic Cancer

Staging of the patient with HP and pancreatic adenocarcinoma is no different than that in patients with sporadic tumors [54, 55]. The consensus conference agreed that those patients with HP undergoing attempted curative resection should have their entire pancreas removed. While there are no prospective data supporting this view, logic dictates that a tumor within a pancreas afflicted with hereditary pancreatitis reflects the presence of a regenerative milieu sufficient to sprout malignancy, thus the recommendation for total pancreatectomy. A recently published study from the Mayo clinic reported comparable morbidity and mortality rates for total pancreatectomy (47 and 5%, respectively) and pancreatoduodenectomy (32 and 3%, respectively) [56]. As discussed previously, there are no data suggesting that the pathophysiology of ductal pancreatic tumors in HP varies from those arising sporadically. Therefore, neoadjuvant, adjuvant and palliative therapy should not differ between the two [42, 57–60].

Conclusions

Patients with HP are at a substantially increased risk of developing ductal pancreatic adenocarcinoma. The increased risk apparently begins at about the age of 40 years. All patients exhibiting the HP phenotype and or genotype should refrain from smoking and alcohol ingestion. Every attempt should be made to identify and eliminate concomitant risk factors for recurrent acute and chronic pancreatitis. Patients with the HP phenotype should be offered screening beginning at the age of 40 years. Minimally invasive imaging options include EUS, multiphase helical CT or MRI/MRCP. The use of ERCP, a more invasive option associated with a higher frequency of complications, is controversial in this setting. The imaging modality of choice will vary depending on the capabilities and preferences of the institution or hospital. In all cases, patients should be fully counseled regarding the potential risk/benefit ratio of available screening modalities before enrollment in any protocol. While many investigators advocate yearly screening, the frequency of screening may vary within particular prospective studies. Optimally, screening should be performed within multicenter Institutional Review Board-approved protocols that also include standardized collection and storage of blood/serum and pancreatic juice. Those patients un-

dergoing attempted curative resection should have their entire pancreas removed. There are no data suggesting that the pathophysiology of ductal pancreatic tumors in HP varies from those arising sporadically. Therefore, neoadjuvant, adjuvant and palliative therapy should not differ between the two.

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Appendix

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