ADVANCES IN COUNSELLING AND SURVEILLANCE OF PATIENTS AT RISK FOR PANCREATIC CANCER

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INTRODUCTION

Pancreatic cancer has the poorest survival rate of any common malignancy. The American Cancer Society estimates 33 730 diagnoses of pancreatic cancer and 32 300 deaths from this cancer in 2006 in the USA.[1] Similarly, world-wide estimates for the year 2000 by the World Health Organization showed an incidence of 201 506 cases and 200 865 deaths, demonstrating the near-universal lethality of this disease.[2] Survival rates are stage-dependent, with a 5-year survival rate in the USA of 17% for local disease.[1] However, only a minority of patients present with local disease. This is a consequence of our inability to diagnose pancreatic cancer early based on symptoms alone, and the current lack of a blood test or other screening techniques that can accurately detect pancreatic cancer in the general population before the onset of symptoms. Although presently available techniques for detecting early pancreatic cancer in the general population are unfeasible, impractical or not cost-effective, they may have a use for surveillance in certain well-defined, high-risk groups of patients.

Based on the success of creating consensus guidelines for genetic testing for hereditary pancreatitis[3] and the prevention, screening and treatment for pancreatic cancer in hereditary pancreatitis[4] as part of the Third International Symposium of Inherited Diseases of the Pancreas, it was decided by the organisers of the Fourth International Symposium (7–9 November, 2003 in Chicago, Illinois, USA) to develop consensus practice recommendations for counselling people at risk for the development of pancreatic adenocarcinoma and to summarise these in the present review.

A similar approach to that employed by the previous consensus meeting was used, with a group of pancreatologists, geneticists, surgeons, basic scientists and pathologists assembling at the symposium to highlight recent advances in the clinical practice of counselling and screening people at increased risk for developing pancreatic cancer, and to formulate practice recommendations for counselling these people about individual risks, and possible preventive and surveillance measures. It is acknowledged that recommendations were essentially based on expert opinion, owing to the lack of evidence from randomised trials and population-based studies. A preliminary draft document was written[i] and then circulated to other recognised experts in the field who could not attend the conference.

BACKGROUND

Pathophysiology

Adenocarcinomas are responsible for >90% of the neoplastic processes of the pancreas. It is now recognised that there are several different scenarios that lead to the development of an adenocarcinoma. Most adenocarcinomas mimic the phenotype of pancreatic duct cells, arising either from duct cells or resident stem cells. The genetic alterations of these pancreatic ductal adenocarcinomas are well characterised.[5] K-*ras* is the most commonly activated oncogene, occurring in ~90% of pancreatic cancers. Tumour-suppressor genes that are most frequently targeted in pancreatic adenocarcinoma are *p16* (27–98%), *p53* (40%–75%) and *MADH4* (55%). Analogous to colon cancer, a model has been proposed to describe the progression from precursor lesions (termed pancreatic intraepithelial neoplasias; PanIN) to an invasive adenocarcinoma.[6] As the degree of histological atypia in the duct lesion increases, there is also an increasing frequency of genetic alterations identified in the lesions.

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Precursor lesions for pancreatic adenocarcinoma

- Pancreatic intraepithelial neoplasias
- Intraductal papillary mucinous neoplasms
- Mucinous cystic neoplasms

Although only responsible for a minority of pancreatic adenocarcinomas, both intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms can develop into adenocarcinoma, although these lesions are often identified and successfully treated at a premalignant (precursor) stage. It is beyond the scope of this paper to review the histology and genetics of these lesions. They are, however, clearly recognised, along with PanIN lesions, as well-defined precursors to invasive pancreatic adenocarcinoma.[7] Furthermore, as will be discussed later, recent studies from Johns Hopkins suggest that IPMNs may be a common precursor lesion in asymptomatic patients from kindreds prone to pancreatic cancer.[8 9]

Risk factors for pancreatic cancer

Risk factors can be classified as demographic, host-related or environmental.[10] The most important demographic factor is advancing age, with 80% of pancreatic cancers occurring between the ages of 60 and 80.[11] Other demographic factors that are associated with a modest (<2-fold) increased risk include male gender, Jewish descent and black ethnicity.[11] Cigarette smoking is the most significant and reproducible environmental aetiological risk factor, with most case–control studies reporting a twofold increase (range 1.5–5-fold).[10] No other environmental factor is sufficiently common or produces a sufficiently marked increase in risk to be of clinical importance. In particular, epidemiological studies have not confirmed that alcohol[12 13] or caffeine[12 14] increase the risk for developing pancreatic cancer.

The greatest risk factor for the development of a pancreatic cancer is genetic predisposition. It is estimated that approximately 10% of patients with pancreatic cancer will have ⩾1 first-degree or second-degree relatives with pancreatic cancer.[15 16] However, inherited factors were felt to be causative for 36% of pancreatic cancers in a study of cohorts of twins from Sweden, Denmark and Finland, suggesting a lack of knowledge regarding low-penetrance or recessive genes in pancreatic carcinogenesis.[17] Studies of extended multiple-case families prone to pancreatic cancer have repeatedly identified a pattern indicative of an autosomal dominant transmission of inheritance.[18–20] In most of these families, the responsible germline mutation is unknown. Note also that recessively inherited genetic predisposition or low-penetrance genetic changes may present as seemingly sporadic cases of cancer. Some pancreatic cancers arise in patients with a recognised inherited cancer syndrome.[16] These hereditary syndromes include hereditary pancreatitis,[21 22] hereditary breast cancer (*BRCA1* and *BRCA2*),[23 24] a subset of kindreds with familial atypical multiple mole melanoma (FAMMM) syndrome affected with a *p16* germline mutation,[25] and Peutz–Jeghers polyposis.[26]

Diabetes or impaired glucose tolerance has been observed in up to 80% of pancreatic cancer patients at the time of diagnosis.[27] However, the association between diabetes and pancreatic cancer has remained a matter of controversy, with some studies supporting and others refuting this association.[11 28–30] A recent population-based study suggests that an adenocarcinoma of the pancreas will be detected in about 1% of diabetics >50 years who had their diabetes diagnosed within 3 years of cancer diagnosis.[31] Most (56%) of these patients had been diagnosed with diabetes within 6 months of cancer detection. Only 3 of the 18 pancreatic cancers in this cohort were resectable, challenging the question of whether screening diabetics would detect "early" stage disease. Chronic pancreatitis appears to predispose to pancreatic cancer, as shown in a cohort study of more than 2000 patients from six countries, which found a 14-fold increased risk in patients after a minimum follow-up period of 5 years.[32] The magnitude of this increased risk has been questioned by several other studies, which found an approximately fourfold increased pancreatic cancer risk.[33 34] However, a more recent study from France appears to support the former estimates, with findings of a standardised incidence ratio of 19-fold.[35] Other factors associated with an apparent modest increase risk include an approximately twofold risk for *Helicobacter pylori* infection[36] and cystic fibrosis.[37]

DEFINING THE DEGREE OF RISK FOR DEVELOPING PANCREATIC CANCER

We attempted to establish the degree of risk for developing pancreatic cancer for a variety of factors with relevance for individual risk assessment, and used published data from the recent literature to this end. As shown in table 1, we classified them into three categories: low (<5-fold), moderate (5–10-fold) and high risk (>10-fold).

People from kindreds in which multiple family members have been diagnosed with pancreatic cancer represent one of the few patient populations classified as high risk. A recent prospective study from the National Familial Pancreas Tumour

Table 1 Categories associated with specific pancreatic cancer risk factors

Low (<5-fold)
Male
Black
Ashkenazi Jewish descent
Obesity
Smoking
Diabetes mellitus
Helicobacter pylori infection
History of any cancer in a first-degree relative
Hereditary non-polyposis colorectal cancer
Familial adenomatous polyposis
History of PC in one first-degree relative
BRCA1 mutation carrier
Moderate (5–10-fold)
History of PC in two first-degree relatives
Cystic fibrosis
Chronic pancreatitis
BRCA2 mutation carrier
High (>10-fold)
FAMMM kindreds with *p16* germline mutation and at least one case of PC in first-degree or second-degree relative
Peutz–Jeghers syndrome
Hereditary pancreatitis
⩾3 first-degree, second-degree or third-degree relatives with PC
Possibly: *BRCA2* or *BRCA1* mutation carrier with at least one case of PC in first-degree or second-degree relative

PC, pancreatic cancer.

Registry at Johns Hopkins studied familial pancreatic cancer kindreds (defined as families having at least two first-degree relatives with pancreatic cancer), and detected a ninefold risk among first-degree relatives for developing pancreatic cancer.[38] Of note, those people with ⩾3 first-degree relatives had a 32-fold increase risk for developing pancreatic cancer, and a 6.4-fold risk was reported for people with two first-degree relatives. A recent large study from the Icelandic Cancer Registry estimates a 2.3-fold increased risk for people with a single first-degree relative with pancreatic cancer.[39] Several studies evaluating the risk for pancreatic cancer in FAMMM families with a known *p16/CDKN2A* mutation have reported risks ranging from 13-fold to 39-fold.[25 40 41] Peutz–Jeghers syndrome (PJS) was put in the high-risk category based on a recently published meta-analysis of six studies, which reported an increased relative risk of 132-fold for pancreatic cancer.[42] A study of hereditary pancreatitis and the risk of pancreatic cancer from the International Hereditary Pancreatitis Study Group found around a 50-fold increased risk.[21]

An even greater risk for pancreatic cancer was reported from the European Registry of Hereditary Pancreatitis, with a standardised incidence ratio of 67-fold and a cumulative risk of 44% for developing pancreatic cancer at 70 years from symptom onset.[22]

Cystic fibrosis and chronic pancreatitis were placed in the moderate category, based on strikingly different results from several studies. The more recent report of cancer risk in cystic fibrosis patients from 115 centres in the USA that make up the Cystic Fibrosis Foundation registry reported a 2.6-fold risk (95% CI 0.1 to 14.4) for developing pancreatic cancer.[37] Conversely, an earlier study reporting on data obtained from European cystic fibrosis organisations found an almost 32-fold risk for pancreatic cancer.[43] However; the 95% CI in that study was quite large, ranging from 4.8 to 205. Similarly, there are conflicting results regarding the magnitude of risk from studies on chronic pancreatitis. A multimember historical cohort study from the International Pancreatitis Study Group[21] and single-centre studies from Italy[44] and France[35] found a 16.5-fold, 18.5-fold and 19-fold increased risk for developing pancreatic cancer, respectively. In contrast to these data, a case–control study from the Department of Veterans Affairs found only around a 2-fold increased risk for pancreatic cancer.[33] Additionally, a study from the Swedish Inpatient Register found a decline of pancreatic cancer risk with time. Later than 10 years after the diagnosis of chronic pancreatitis, there was a 3.8-fold risk; however, this excess risk was only seen in those patients who misused alcohol.[34] A case–control study from Northern Italy of histologically confirmed pancreatic cancer patients and hospital-based controls found a relative risk of 5.7 for a history of pancreatitis.[45] One confounding issue may be that some of the increased risk of pancreatic cancer observed in patients with chronic pancreatitis may actually represent early pancreatic cancer presenting as chronic pancreatitis. Owing to the wide variability in these cystic fibrosis and chronic pancreatitis studies, it was elected to classify these diseases as carrying a moderate risk.

BRCA2 mutation carriers pose an interesting dilemma. *BRCA2* carriers have a high risk for breast and ovarian cancer, and a 3–9-fold increased risk for developing pancreatic cancer.[24 46 47] Germline mutations of *BRCA2* were found in 3 (12%) of 26 European families in which at least two first-degree relatives had histologically diagnosed pancreatic adenocarcinoma, and 2 other families had unclassified variants, bringing the *BRCA2*-related fraction to possibly as high as 19%.[48] Although many or most unclassified variants are probably benign, certain variants may confer risk. For example, a specific polymorphic stop codon in the coding region of *BRCA2* (K3326X) has an increased prevalence in familial pancreatic cancer and is associated with an odds ratio of 4.[49] Another report from the National Familial Pancreatic Tumour Registry at Johns Hopkins determined that 5 (17%) of 29 families with ⩾3 relatives with pancreatic cancer had a *BRCA2* germline mutation.[50] A recent multicentre study screening 151 families prone to pancreatic cancer found 5 mutations (3%): 3 in the 118 (3%) higher-risk families with ⩾2 first-degree and second-degree relatives, and 2 in the 33 (6%) more moderate-risk families with ⩾2 affected second-degree relatives.[51] The lower numbers in the larger study may be partly related to these families having a lower risk than the two aforementioned smaller studies. Importantly, in all of these studies, a family history of breast and ovarian cancer may be absent in families with pancreatic cancer and germline *BRCA2* mutations. Nonetheless, it is likely that mutation carriers face high breast and ovarian cancer risks.

The recent discovery that *BRCA2* mutations are responsible for a subset of patients with Fanconi anaemia, has led to several studies examining the role of genes of the Fanconi complementation group (FANC) in pancreatic cancer development.[52 53] It appears that germline mutations in these FANC genes are present in young-onset pancreatic cancer patients. However, these genes were not found to be mutated in people from high-risk pancreatic cancer-prone families. Thus, further studies are needed to define their importance in predisposing to pancreatic cancer.

Although the association between *BRCA2* mutations and pancreatic cancer is now well-established, there is less knowledge about the association with *BRCA1*. A study of BRCA1 families ascertained for hereditary breast cancer suggested that *BRCA1* also conveys a certain risk for pancreatic cancer.[54] Results from a larger study of 700 families from the Breast Cancer Linkage Consortium suggest a modest two-fold increase risk for pancreatic cancer in *BRCA1* mutation carriers.[55]

A mutation in *palladin* has just been described in a unique pancreatic cancer-prone family followed by the University of Washington.[56] This single family demonstrates an autosomal dominant inheritance of adenocarcinoma of the pancreas in concert with insulin-dependent diabetes mellitus and exocrine insufficiency. The importance of this gene in pancreatic cancer carcinogenesis is suggested by the overexpression of Palladin RNA in tissues from both familial and sporadic pancreatic adenocarcinomas and in precancerous dysplasia. Additional studies are needed to define the role/frequency of this mutation in hereditary and sporadic cases.

Genetic–environmental interactions

Smoking

Adding to the complexity of defining high-risk groups is the need to recognise the interactions between many of the aforementioned factors and how they affect pancreatic cancer risk. For example, cigarette smoking enhances pancreatic cancer risk in patients with hereditary pancreatitis from

54-fold to 154-fold compared with the general population of non-smokers.[57] Moreover, in these patients, cancer developed on average 20 years earlier in smokers than in non-smokers. A similar difference in age of diagnosis was seen in hereditary pancreatitis patients in Europe, with a median age of 57 years for smokers and 71 years for non-smokers.[22] Another study evaluated whether a family history of pancreatic cancer increased the risk for this disease among first-degree relatives of the affected proband, and whether cigarette smoking and/or younger age (of affected patient) at cancer onset further increased risk.[58] Their findings showed that a positive family history of pancreatic cancer (ie, being related to a patient) or ever smoking cigarettes approximately doubled the risk of pancreatic cancer. The relative risk increased to 8.23 (95% CI 2.18 to 31.07) for those people who had ever smoked and were related to a patient who was diagnosed at <60 years with pancreatic cancer. A nested case-control study of families prone to pancreatic cancer, each with ≥2 members with pancreatic cancer, found the greatest risk in smokers either <50 years of age (odds ratio of 7.6) or who were male(odds ratio 5.2).[59]

Obesity

A notable result from this study was the finding that the number of affected first-degree relatives also increased risk. Interactions between obesity and physical activity have been shown to affect pancreatic cancer risk, based on findings from a study using two large US cohort studies: the Nurses' Health Study and the Health Professionals Follow-up Study.[60] The highest risk for developing pancreatic cancer was seen in people with a higher body mass index (BMI) (≥25 kg/m^2) and low total physical activity, whereas greater physical activity appears to decrease the risk of pancreatic cancer in these overweight patients. Another noteworthy finding is the lack of effect of total physical activity on people with a BMI <25 kg/m^2. Further support for the relationship between significant obesity and pancreatic cancer comes from a large cohort study of 145 000 adults in Austria. This study found that a BMI >30 kg/m^2 had a significant hazard ratio (HR) of 2.34 (95% CI 1.17 to 4.66) for the development of pancreatic cancer in men and a trend towards an association in women, with HR = 1.42 (95% CI 0.76 to 2.68).[61]

EARLY DIAGNOSIS OF PANCREATIC CANCER

The ultimate goal for the early detection of pancreatic cancer is the identification of an advanced precursor lesion, thereby allowing treatment of a patient before the development of invasive cancer. Examples of advanced precursor lesions include PanIN 3 lesions, mucinous cystadenomas and IPMNs before they progress to invasive carcinoma. Although there is no evidence to support that diagnosing an invasive pancreatic cancer at an earlier stage will improve survival, there is a substantial body of data to suggest that very early disease is associated with better prognosis. As will be subsequently discussed, owing to our current inability to reliably detect PanIN 3 lesions, an appropriate target at the present time for early diagnosis is felt to be a resectable tumour of <1.0 cm in size with negative lymph nodes, as it appears that this rare subset of patients have an excellent long-term survival rate.

Few patients with pancreatic neoplasms undergo curative surgical resection, primarily because <20% present sufficiently early, with potentially curable disease.[62] Despite excellent rates of operative mortality and morbidity, survival for patients with resectable disease still remains dismal, with a 5-year survival rate typically reported of about 20% in the most fortunate subset of patients.[1 62] An important factor in determining prolonged survival following resection is lymph-node status. A study from Johns Hopkins University reported significantly better median survival (28 vs. 13 months) and 5-year survival (36% vs. 14%) in patients with no lymph-node metastases compared with those having lymph-node metastases.[63]

Tumour size is another factor that predicts better long-term survival. Ariyama *et al*[64] found, in a study of 77 resected carcinoma patients, a postoperative 5-year cumulative survival rate of 100% for the small subset (10%) of patients with tumours <1 cm. However, irrespective of tumour size, once a carcinoma was >1.1 cm, there was no statistical difference in the survival rate. A study from the Japanese National Pancreatic Cancer Registry of patients with small pancreatic cancers that were resected at <2 cm in size illustrates the challenges of diagnosing early-stage carcinomas.[65] Of 822 patients with a tumour size <2 cm, 799 underwent pancreatic resection and about half were UICC staged as Ia (n = 197) or IIa (n = 138). Corresponding 5-year survival rates of 49.4% and 41.4%, respectively, were seen. These 5-year survival rates were substantially better than for the other patients with more advanced UICC stages: IIb (17.1%), III (15.8%) and IV (9.4%).

Strong support for the importance of lymph-node status and tumour size comes from the ESPAC-1 (European Study Group for Pancreatic Cancer) trial.[66] This large prospective European randomised trial of chemoradiotherapy versus chemotherapy after resection of pancreatic cancer found that the use of adjuvant chemotherapy is a favourable survival factor, whereas the finding of lymph-node involvement, increasingly undifferentiated tumours, and a maximum tumour size >2 cm (vs <2 cm) were adverse influences on survival. Results from these above reports suggest that a reasonable goal for screening is the detection of a tumour <1 cm with no spread to the lymph nodes.

Presenting symptoms

Unfortunately, it is not possible to diagnose early pancreatic cancer reliably in a patient based on symptoms alone. The more common presenting symptoms are epigastric pain, weight loss and obstructive jaundice.[67 68] Although these symptoms usually prompt evaluation of the pancreas and biliary tree, their occurrence late in tumour development means that the malignancy is usually more advanced and makes it unlikely that the patient can undergo curative resection.[69 70]

Biomarkers

To date, the clinical role of tumour markers has been limited. No tumour marker, including CA 19-9, has been shown to be useful in the screening of an asymptomatic population.[71] A recent study evaluated the usefulness of CA 19-9 in screening an asymptomatic population for pancreatic cancer. This study found a positive predictive value of only 0.9% for pancreatic cancer when a level >37 U/ml was used.[71] A study of CA 19-9 levels in 110 patients presenting with signs and symptoms of pancreatic cancer (49% prevalence of cancer) found a higher positive predictive value of 0.71 and a negative predictive value

of 0.81 using a cut-off value >40 U/ml.[72] However, this did not shorten the diagnostic evaluation, owing to the need for imaging studies.

Imaging studies

Current imaging studies such as abdominal CT, abdominal MRI or transabdominal ultrasound are inadequate for the detection of pancreatic cancer at an early stage, because these imaging techniques do not reliably detect tumours of <1–2 cm in size.[73] A limitation in evaluating the role of imaging studies in detecting pancreatic cancer is that almost all studies are performed in symptomatic patients. It is also recognised that there have been improvements in imaging technology such as the development of 64-slice multi-detector CT scans and 3 T MRI scanners; however, none of these imaging studies has to date been shown to detect a small tumour of<1 cm in size in an asymptomatic patient population.

CURRENT STATUS OF PANCREATIC CANCER SURVEILLANCE IN HIGH-RISK PEOPLE

A few published studies have evaluated surveillance in asymptomatic but high-risk groups of patients from families prone to pancreatic cancer.[8 9 74–76] Pancreatic cancer surveillance in families who inherit pancreatic cancer was first described by the University of Washington.[74] This initial study included three large kindreds who had autosomal dominant inheritance of pancreatic cancer without chronic pancreatitis. The study used both endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP). The goal of surveillance was to detect pancreatic precursor lesions (PanINs), with an emphasis on detecting carcinoma in situ (PanIN 3). The described changes seen on EUS in this study can be non-specific, with similar abnormalities also detected in patients who have pancreatitis and heavy alcohol use.[77] Abnormal findings at ERCP can include irregular ducts, poor filling of pancreatic ducts, and narrowing or dilatation of ducts. In this study, every patient with an abnormal ERCP had an abnormal EUS, and every patient with an abnormal EUS and ERCP who opted for a tissue diagnosis had precancerous changes in the pancreas (PanIN 2 and 3). A follow-up study expanding the initial University of Washington cohort to 43 patients from 24 familial pancreatic cancer kindreds who underwent surveillance has been reported.[76] EUS was the initial test of choice. ERCP was reserved for symptomatic patients or to investigate abnormal findings on EUS. Twelve of the 43 patients were noted to have abnormal findings on EUS and ERCP. After counselling, all 12 patients with abnormal imaging studies had assessment of pancreatic tissue intraoperatively and were found to have PanIN 2 and/or 3 lesions. Subsequently, after further counselling, all 12 patients and underwent total pancreatectomy. The resection specimens had no evidence of pancreatic cancer, but all specimens revealed widespread pre-cancerous (PanIN) lesions. The remaining 31 high-risk patients, who had a normal EUS, or an abnormal EUS but a normal ERCP, returned annually for repeat EUS. Follow-up of the cohort of 43 high-risk patients extended from 3 to 48 months; none of the 43 patients under surveillance developed pancreatic cancer.

A similar EUS-based surveillance programme has been described at Johns Hopkins.[8] Initially the authors reported on findings from a total of 38 asymptomatic high-risk patients, the majority of whom (31) were from kindreds with ⩾3 affected pancreatic cancer relatives, who underwent screening with EUS, and if abnormal, also underwent EUS-guided fine-needle aspiration, ERCP and spiral CT. Surgery was offered only to patients with a mass. Two of six pancreatic masses were found to be clinically significant neoplasms: one invasive pancreatic adenocarcinoma (T2N1) and one borderline IPMN. The other four masses were benign lesions.

Recently, a prospective controlled study of screening EUS and CT followed by ERCP in 78 at-risk relatives from familial pancreatic cancer kindreds and 149 control subjects demonstrated a high prevalence of chronic pancreatitis-like changes (72% by EUS and 68% by ERCP) that was unrelated to alcohol intake.[9] Moreover, 10% of high-risk patients treated by subtotal pancreatectomy had precursor lesions for adenocarcinoma consisting of IPMNs (one with carcinoma in situ).

The diagnostic value of EUS and ERCP is drastically reduced in patients in whom any variety of chronic pancreatitis conveys the risk of developing pancreatic cancer. This is because the intraductal and tissue changes associated with chronic inflammation and fibrosis prevent the early detection of premalignant lesions or small malignant tumours.[78 79]

GENETIC COUNSELLING AND TESTING

Genetic counselling fills several crucial needs for the successful implementation of these recommendations, including communication of risk of pancreatic cancer to patients and relatives, and clarification of the risks and benefits of clinical research protocols.[80] Knowledge of diverse pancreatic cancer syndromes and their management is crucial to assessing genetic risk and performing a clinical service with a high professional standard. A complete family history should be obtained to allow patients to be counselled about known mutations that predispose to pancreatic cancer: *BRCA1, BRCA2, STK11/LKB1, PRSS1* and *p16/CDKN2A*. It is premature to suggest testing for *palladin* until additional studies better define its frequency in a hereditary/sporadic setting.

Genetic testing recommendations

Genetic testing for hereditary cancer syndromes mandates full informed consent as recommended by the American Society of Clinical Oncology (ASCO) in the 2003 policy statement update on genetic testing for cancer susceptibility (Appendix 2).[81] The elements of informed consent for genetic testing have been outlined[82] and are summarised in Appendix 3. Appendix 4 summarises recommendations on when one should consider referring a patient for genetic testing for ⩾1 of the above-mentioned genes: *BRCA1, BRCA2, STK11/LKB1, PRSS1* and *p16/CDKN2A*. These recommendations are based on our present state of knowledge regarding the genetics of pancreatic cancer, and will obviously evolve as new genes are discovered to be associated with pancreatic cancer development in high-risk families. Given the considerable genetic heterogeneity and lack of a complete list of pancreatic cancer genes, a negative genetic test result in an unaffected individual is of little value unless a specific genetic mutation has been found in another relative. Thus, whenever possible, testing should be performed on affected patients rather than on unaffected relatives. It should be emphasised that these recommendations are not intended to replace formal genetic counselling, which has been shown in a small study to be valued by patients for familial pancreatic

cancer, even though the causative gene(s) in the majority of cases has not been identified at the present time.[80]

RECOMMENDATIONS FOR PREVENTION OF PANCREATIC CANCER

Similar to recommendations made from the previously mentioned consensus guidelines for pancreatic cancer in hereditary pancreatitis, risk-factor reduction is seen as the best preventive strategy,[4] because the lack of a proven agent to prevent pancreatic cancer. Smoking cessation is critical, as several studies have shown that cigarette smoking enhances pancreatic cancer risk in people from families prone to pancreatic cancer.[57 59] Although the increase in risk appears to be modest (2–3-fold), it must be recognised that a doubling of the risk in a cohort with an already high baseline risk of developing pancreatic cancer is clinically significant and is even more important than in the general population, in which the incidence of pancreatic cancer is relatively low (~1 per 10 000 per annum). Other practical but unproven approaches for decreasing risk include weight reduction, a healthy diet high in fruits and vegetables, and regular exercise. This latter recommendation is based on results from several studies.[60 84 85]

One study investigating the dietary habits and pancreatic cancer risk among Seventh-day Adventists, a religious group who have a diet high in fruits and vegetables, reported a risk reduction of 33–66% on this type of diet.[84] A recent report from the Multiethnic Cohort Study investigating meat and fat intake as risk factors for pancreatic cancer found that the intake of total and saturated fat from red and processed meat, but not dairy products, increased the risk for pancreatic cancer.[85] Higher intakes of vitamin D (>600 IU) have been shown in a recent report to be associated with a lower risk of pancreatic cancer.[86] As mentioned previously, the highest risks for developing pancreatic cancer were seen in people with a high BMI ($\geq$25 kg/m^2) and low total physical activity, whereas greater physical activity appears to decrease the risk of pancreatic cancer in these overweight patients, supporting the recommendation of regular exercise and weight control.[60]

SCREENING FOR PANCREATIC CANCER

There is no rationale to investigate early detection strategies in the general population at present, owing to the relatively low incidence of pancreatic cancer, the inaccessible location of the pancreas in the retroperitoneum, the lack of diagnostic tumour markers and the unavailability of any studies demonstrating survival benefits for such screening. After much discussion, it was felt to be appropriate to perform pancreatic cancer screening under research protocol conditions for those patients who are deemed high risk for developing pancreatic cancer (see below). It is strongly recommended that all screening (surveillance) studies be performed as part of peer-reviewed protocols with scientific evaluation and human subjects protections.

Prevention of pancreatic cancer

- Avoid smoking
- Healthy diet high in fruits and vegetables.
- Regular exercise
- Weight reduction if necessary
- Increased intake of vitamin D (>600 IU)

Who should be screened for pancreatic cancer

A person's degree of risk should be used to determine whether they should be screened for pancreatic cancer. After much consideration, it was decided to recommend a threshold: patients should be subjected to surveillance if they carry a >10-fold increased risk for developing pancreatic cancer. This degree of risk corresponds to people from the high-risk category in table 1 and includes family members with $\geq$3 first-degree relatives with pancreatic cancer and people with FAMMM (*p16* mutations), PJS and hereditary pancreatitis. Additionally, it is recommended that a subset of patients should be considered to be at high risk, based on expert opinion. These patients include people who have $\geq$3 pancreatic cancer cases among first-degree, second-degree and third-degree relatives, with at least one of these being a first-degree relative. Known mutation carriers with syndromes associated with pancreatic cancer in which the level of risk is below the 10-fold risk threshold, such as *BRCA2* mutations, but who have at least one case of pancreatic cancer within second-degree relatives, were also felt to be candidates for screening. This reflects the theoretical consideration that families with hereditary cancer syndromes in which cases of pancreatic cancer have already occurred could share additional genetic loci predisposing to the development of pancreatic cancer, and may thus be at higher risk. Many centres would also perform surveillance on people with two first-degree relatives affected with pancreatic cancer, as these people are clearly at an increased risk, albeit <10-fold. An early age of onset (before age of 50) of pancreatic cancer in a family in the absence of any of the above factors was not felt to constitute a sufficiently high risk to warrant screening.

How to screen for pancreatic cancer

No consensus opinion could be reached on a specific approach for screening these high-risk people for pancreatic cancer. Many centres presently use endoscopic ultrasound as their procedure of choice, based on the previously mentioned studies and on its ability to detect pancreatic masses (ie, islet cell tumours) <1 cm in size in the absence of chronic inflammation of the pancreas. It is suggested that patients abstain from alcohol for at least 1 month prior to EUS, because of the non-specific changes seen with alcohol use. Other centres have used CT scans or ERCP as a means for screening for pancreatic cancer, although the latter, like EUS, seems unsuitable when hereditary pancreatitis is the underlying condition responsible for the cancer risk. In addition, CT scans, even with pancreatic protocols, have had limited sensitivity thus far in detecting the

Candidates for pancreatic cancer surveillance

- $\geq$3 first-degree, second-degree, or third-degree relatives with PC in the same lineage.
- Known mutation carrier for *BRCA1*, *BRCA2* or *p16*, with at least one first-degree or second-degree relative with pancreatic cancer.
- A member, ideally a verified germline carrier, of a PJS kindred.
- Two relatives in the same lineage (directly connected) affected with pancreatic cancer, at least one a first-degree relative of the candidate.
- An affected individual with hereditary pancreatitis.

very small lesions that are potentially curable. Abdominal MRI with an accompanying MRCP has the theoretical advantages of imaging both the pancreatic duct and gland. However, to date, no studies have demonstrated improvement over EUS, particularly in a high-risk setting. Many centres also collect pancreatic juice for investigational studies during the EUS or ERCP, and bank blood specimens to use as a resource for current and future tumour-marker assessment.[87] As previously stated, there was firm agreement that screening should be performed only within the context of peer-reviewed protocols. This will serve the need to evaluate which diagnostic modalities are (or are not) useful for diagnosing pancreatic cancer at a potentially curable stage and enhance the prospective collection of biospecimen samples from high-risk families.

It must be mentioned that some centres are suggesting the performance of a CT or MRI scan to evaluate for extrapancreatic lesions, as many of these patients are also at risk for non-pancreatic neoplasms. This review does not specifically address this issue as it is focused solely on the pancreas, but it is acknowledged that some high-risk people are at risk for a variety of extrapancreatic abdominal malignancies, and that EUS alone is not adequate for screening for many of them.

When to begin screening

No clear consensus was achieved on when to begin screening. Most participants favoured a recommendation similar to that for colon cancer: commencing at 50, or starting 10 years younger than the earliest age of onset of pancreatic cancer in the family (whichever is at the earliest age). As several studies[43 45] have demonstrated an effect of smoking on age of disease onset, with one study of pancreatic cancer-prone families suggesting that smokers develop cancer a decade earlier than non-smokers (59.6 vs. 69.1 years),[45] it is reasonable to factor in the smoking history when deciding when to start screening.

Since the conference, an important study on anticipation in familial pancreatic cancer has been published.[88] This study found anticipation in their investigation of 80 affected child-parent pairs over three generations. The findings of anticipation were independent of smoking and follow-up time bias. Taking into account this new study, it is felt that screening should begin even earlier, at the age of 45, or 15 years earlier than the earliest occurrence of pancreatic cancer in the family, whichever is the earlier age. It may be reasonable to begin screening in people who have ever smoked even earlier than the above recommendations. Before the age of 40 years, screening is probably not cost-effective in any risk setting.

How frequently should screening be performed?

There was no agreement on how frequently an individual should undergo screening. This reflects the lack of knowledge on the natural history of pancreatic cancer and its rate of progression. Opinions varied from 1-year to 3-year intervals. Until there are data available to assist in decision-making, it appears reasonable to tailor recommendations on frequency by taking into account additional factors such as the patient's level of concern, clinical history and study protocols.

CONCLUSION

It is strongly suggested that those people who meet the criteria for genetic testing should undergo genetic counselling followed by genetic testing using an accredited laboratory. In many cases, the main reasons for proceeding with genetic testing may be to intervene for preventable cancers (eg, breast, ovarian, colorectal) or to clarify cancer risks for other family members. Surveillance candidates should be encouraged to participate in peer-reviewed screening protocols. An honest discussion regarding the limitations of screening, including its unproven survival benefits is essential. All patients should be counselled on preventive measures including the imperative to stop smoking and to avoid starting smoking, and the lifestyle modifications previously mentioned. In addition, it is essential to individualise these recommendations by taking into account the person's emotional status, level of concern, family history and lifestyle risk factors.

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APPENDIX 1

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APPENDIX 2

AMERICAN SOCIETY OF CLINICAL ONCOLOGY POLICY STATEMENT UPDATE: GENETIC TESTING FOR CANCER SUSCEPTIBILITY[81]

Indications for genetic testing:

- the individual has personal or family history features suggestive of a genetic cancer susceptibility condition,
- the test can be adequately interpreted, and
- the results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

ASCO recommends that genetic testing only be carried out with both pre-test and post-test counselling, which should include discussion of possible risks and benefits of cancer early detection and prevention modalities.

APPENDIX 3

BASIC ELEMENTS OF INFORMED CONSENT[82] FOR GERMLINE DNA TESTING

- Information on the specific test being performed.
- Implications of a positive and negative result.
- Possibility that the test result will not be informative.
- Options for risk estimation without genetic testing.
- Risk for passing a mutation to children.
- Technical accuracy of the test.
- Fees involved in testing and counselling.
- Risk for psychological distress.
- Risk for insurance or employer discrimination.
- Confidentiality.
- Options and limitations of medical surveillance and screening after testing.

APPENDIX 4

RECOMMENDATIONS ON WHO SHOULD BE CONSIDERED FOR GENETIC TESTING

BRCA1 and *BRCA2* (hereditary breast and ovarian cancer syndrome)

Patients diagnosed with hereditary breast and ovarian cancer syndrome (HBOC) have a hereditary predisposition to early-onset breast and ovarian cancer. Other cancers associated with this syndrome are cancers of the pancreas, colon and prostate. Women diagnosed with HBOC have around an 80% lifetime risk of developing breast cancer and 40% lifetime risk of developing ovarian cancer.

People should be referred for genetic counselling to consider testing for *BRCA1* and/or *BRCA2* mutations when at least one of the following conditions is met:

- ⩾2 family members (1st-degree relatives of each other) with pancreatic cancer with or without breast or ovarian cancer
- one pancreatic cancer case with at least two relatives with early onset (<50 years) of breast cancer, or with ovarian cancer at any age,
- one pancreatic cancer case with at least 3 cases of breast cancer, or 1 case of ovarian cancer and ⩾1 cases of breast cancer,
- Ashkenazi Jewish ancestry with 1 case of pancreatic cancer case and ⩾1 case of breast or ovarian cancer at any age in a first-degree or second-degree relative (testing for the three Ashkenazi Jewish founder mutations may be sufficient for families with limited affected cases).

STK11/LKB1 (Peutz–Jeghers syndrome)

People affected with PJS have multiple gastrointestinal hamartomatous polyps and mucocutaneous pigmentation, and are at increased risk for developing cancer of the pancreas, colon, breast, endometrial, ovarian, lung, or testes. A patient can be clinically diagnosed with PJS and should be referred for genetic counselling when at least one of the following conditions is met:

- ⩾2 histologically verified PJS polyps, small bowel polyposis, and mucocutaneous hyperpigmentation, or
- presence of small bowel polyposis, mucocutaneous hyperpigmentation, and a family history of PJS.

PRSS1 (hereditary pancreatitis)

Hereditary pancreatitis (HP) is an inherited condition characterized by recurrent episodes of acute pancreatitis attacks. In about half of these cases, the problem progresses to chronic pancreatitis. The first attack typically occurs within the first two decades of life, but can begin at any age. Symptomatic patients should be referred for genetic counselling to consider testing for a *PRSS1* mutation when at least one of the following conditions is met:

- ⩾2 attacks of acute pancreatitis of unknown aetiology,
- idiopathic chronic pancreatitis, particularly if disease onset occurs <25 years of age,[83]
- one first-degree or second-degree relative with pancreatitis,
- unexplained documented episode of childhood pancreatitis that required hospitalization and where there is concern that HP should be excluded.

Asymptomatic people should be referred for genetic counselling to consider testing for a *PRSS1* mutation when the patient has one first-degree relative with a defined HP gene mutation.

p16/CDKN2A (familial atypical multiple mole melanoma)

People with FAMMM have a familial predisposition to developing atypical moles that can develop into melanoma. Melanoma can also develop de novo. The average age of initial melanoma diagnosis is 34. Those diagnosed with FAMMM may have an increased risk of developing pancreatic cancer and astrocytomas. People should be referred for genetic counselling to consider testing for a *p16/CDKN2A* mutation when at least one of the following conditions is met:

- a personal history of melanoma and first-degree relative with melanoma,
- ⩾2 confirmed primary melanomas,
- ⩾3 (first-degree or second-degree) relatives with melanoma,
- personal or family history of pancreatic cancer and melanoma,
- personal history of melanoma and personal and/or family history of atypical moles.