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Hereditary pancreatic cancer: molecular bases and their application in diagnosis and clinical management. A guideline of the TTD group

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Abstract Pancreatic carcinoma (PC) represents the fourth leading cause of cancer death in Spain with a death rate of 2,400 males and 2,000 females per year. Poor outcome related to its silent nature and the lack of reliable secondary prevention measures translate into advanced-stage diagnosis, 75 % of deaths within the first year of diagnosis and 5-year survival rate of <5 %. Family history was first recognized as a risk factor for PC. Further population-based and case–control studies subsequently found that 7.8 % of patients with PC have a family history of the same tumor and individuals with a first-degree relative with PC have a 3.2-fold increased risk of developing PC. Overall, it is estimated that up to 10 % of PC have a familial component. However, known genetic syndromes account for <20 % of the observed familial aggregation of PC. We review the most important aspects in epidemiology, molecular biology and clinical management of familial PC.

Keywords Familial pancreatic cancer · Susceptibility genes · Screening

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Epidemiology and molecular diagnosis

Pancreatic carcinoma (PC) represents the fourth leading cause of cancer death in Spain with a death rate of 2,400 males and 2,000 females per year [1]. Poor outcome related to its silent nature and the lack of reliable secondary prevention measures translate into advanced-stage diagnosis, 75 % of deaths within the first year of diagnosis and 5-year survival rate of <5 % [2].

Incidence rate increases with age, particularly above 50, culminating a lifetime risk of developing PC of 1 %. Identified factors and relative risks for developing PC are family history, germ-line mutation in cancer predisposition genes, cigarette smoking and diabetes (Table 1).

Family history was first recognized as a risk factor for PC in an adenocarcinoma-prone family by Henry Lynch in 1967. Further population-based and case–control studies subsequently found that 7.8 % of patients with PC have a family history of the same tumor and individuals with a first-degree relative (FDR) with PC have a 3.2-fold increased risk of developing PC (26). Overall, it is estimated that up to 10 % of PC have a familial component [3]. However, known genetic syndromes account for <20 % of the observed familial aggregation of PC [4].

Familial PC (FPC)

This term define a group of families with two or more close relatives with confirmed PC that do not fulfill the criteria of any other cancer syndromes. International registries such as the North American National Familial Pancreatic Tumor Registry, the German National Case Collection of Familial

Table 1 Risk factors and relative risk for developing pancreatic cancer [27]

Risk factors	Relative risk
Cigarette smoking and family with PC	3.7
Diabetes >20 years	2
Family history	
One first-degree relative affected	1.5–1.75
Two first-degree relatives affected	6
Three first-degree relatives affected	14–32
Cancer susceptibility syndromes	
Hereditary breast and ovarian cancer	5.9
Familial atypical multiple mole melanoma	16
Peutz–Jeghers	36
Hereditary pancreatitis	50

PC (FaPaCa) and the European Registry of Hereditary Pancreatitis and Familial PC collect data on families in order to evaluate the characteristics and underlying gene defects. Thus far, the autosomal-dominant trait seems to be clear, as well as the possibility of anticipation and multifocal dysplasia or carcinoma within these subjects [3].

According to one prospective study conducted by Wang et al. evaluating 838 familial PC kindreds, individuals with one, two and three or more FDRs have a 4.5-, 6- and 14- to 32-fold increased risk, respectively, of developing PC [4]. The complexity in cancer assessment led to the development of a risk prediction tool based on these data that is called PancPRO [5]. Extrapancreatic malignancies, such as breast cancer (RR 1.66), ovarian (RR 2.05) and bile duct cancers (RR 2.89), are also described within these families [6].

Hereditary PC syndromes

Syndromes and genes associated with inherited PC are shown in Table 2. Pancreatic endocrine tumors are part of disorders, such as multiple endocrine neoplasia type 1 (*MEN1*), von Hippel–Lindau disease (*VHL*), von Recklinghausen disease (*NF1*) and tuberous sclerosis (*TSC*).

Multiple endocrine neoplasia 1

This syndrome is classically characterized by hyperplasia/tumors of the parathyroid, enteropancreatic endocrine tissues and anterior pituitary gland. The *MEN1* gene is localized in the chromosome region 11q13. It spanned 10 exons (9 coding) and encoded for a 610-amino-acid nuclear protein, menin, involved in transcriptional regulation, genomic stability, cell division and cell cycle control. Specifically, in the case of the pancreatic islets, recent studies demonstrated that loss of menin increases β-cell proliferation by disrupting the inhibitory effect of menin-dependent histone methylation, which maintains p27 and p18 inhibition of cyclin-dependent kinases [7].

Table 2 Inherited pancreatic cancer syndromes and causative genes

Syndromes	Genes
Multiple endocrine neoplasm type 1	*MEN1*
Von Hippel–Lindau disease	*VHL*
Neurofibromatosis type 1	*NF-1*
Tuberous sclerosis	*TSC1/TSC2*
Hereditary breast and ovarian	*BRCA2/BRCA1/PALB2*
Familial atypical multiple mole melanoma	*P16INK4a/CDKNA2*
Peutz–Jeghers	*STK11/LKB1*
Hereditary pancreatitis	*PRSS1/PRSS2/SPINK1/CFTR*

Mutations in the *MEN1* gene are detected in 78–93 % of families (1,336 mutations throughout the 9 exon-coding region) [8]. Overall, 23 % mutations are non-sense, 9 % slice-site, 41 % frameshift or insertions, 20 % missense and 1 % whole or partial gene deletions. Greater than 75 % of the mutations lead to truncated forms of menin [9].

Clinical manifestations are parathyroid hyperplasia leading to mostly symptomatic hyperparathyroidism, anterior pituitary tumors and enteropancreatic neuroendocrine tumors [10]. Other tumors, such as adrenal, thyroid, carcinoid, skin, CNS and smooth muscle tumors, have been also included. Age-specific penetrance of PC in MEN1 patients is 15, 50 and 68 at the ages of 30, 50 and 70 years, respectively [11].

Non-functional PC occur histologically in 80–100 % of MEN1 pancreas as multiple microadenomas (<0.5 cm) and 55–82 % as macroadenomas (>1 cm). The average age of diagnosis is 36 years with a mean time from MEN1 diagnosis of 5 years. Functional PCs are usually gastrinomas and insulinomas.

Von Hippel–Lindau disease

Clinically patients develop hemangioblastomas of the retina (25–60 %) and craniospinal region, endolymphatic sac tumors (10 %), renal cell carcinomas or cysts (25–60 %), pheochromocytomas (10–20 %) and epididymal cystadenomas (25–60 %). Pancreatic tumors or cysts develop in 35 to 77 % of patients. Those pancreatic tumors include cystadenomas (12 %), hemangioblastomas (<1 %) and adenocarcinomas (<1 %) [12]. VHL is an autosomal-dominant neoplastic disorder caused by germ-line mutations in the *VHL* gene on chromosome 3p25. This gene encodes a 232-amino-acid protein, which forms complexes with other protein and interact with hypoxia-inducible factors (HIF1

and HIF2). Altered pVHL lead to the failure of degrading HIF and increased expression of angiogenic growth and mitogenic factors (VEGF, PDGFb, TGFa and erythropoietin) [12].

PCs develop in 10–17 % of patients. Mostly, cases are non-functional though occasionally cause pancreatitis or pain [13]. The mean age of diagnosis ranges from 29 to 38 years and the majority of cases have a single PC. PCs present in 8–50 % of patients and liver dissemination in 9–37 % [14]. PC is an uncommon cause of death. Most patients die of metastatic renal cell cancer or from complications of cerebellar hemangioblastomas [14].

Von Recklinghausen syndrome (NF-1)

NF-1 occurs in one of 4,000–5,000 live births. The principal clinical characteristics are cafe-au-lait macules (>99 %), neurofibromas (cutaneous >99 %, deep-seated 44 %), skin-fold freckling (85 %), iris Lisch nodules (>95 %), optic pathway gliomas (15 %) and bony dysplasia (sphenoid wing and bowing of long bones). Common neurological symptoms are learning problems (30–60 %), attention deficit hyperactivity disorder (38 %) and epilepsy (6–7 %) (15). Renal artery stenosis (2 %), pheochromocytomas (2 %) and hypertension are the important features [15].

Patients diagnosed of NF-1 are rarely diagnosed of abdominal neuroendocrine tumors (10 %), mostly duodenal somatostatinomas localized in the periampullary region. Pancreatic somatostatinomas, insulinomas or non-functional PCs are even more unusual. Lately, gastrointestinal stromal tumors have been proposed as the most common gastrointestinal malignancy [16]. Mean age at death is 59 years and the most frequent cause of death is soft tissues neoplasm.

This syndrome is caused by mutations in the *NF-1* gene on chromosome 17q11.2, which encodes for a 2,485-amino-acid protein, neurofibromin. This protein is expressed specially in the nervous system and regulates cell proliferation/growth through the activation of p21 ras [15].

Tuberous sclerosis (TSC, Bourneville disease)

TSC is clinically characterized by multiple hamartomas, disabling neurologic features (epilepsy, mental retardation, autism), dermatologic features (facial angiofibromas, hypomelanotic macules, shagreen patch, ungula fibromas) and tumor-like hamartomatous lesions (cortical tubers, cardiac rhabdomyomas, subependymal nodules, renal angiomyolipomas and lymphangiomyomatosis) [14].

It is an autosomal-dominant disorder that is caused by mutations in one of two genes: the *TSC1* gene (encoding for hamartin) or the *TSC2* gene (encoding for tuberin).

PCs are very uncommon and usually occur in patients with mutations in TSC2 gene [17]. Reported functional PCs are gastrinomas and insulinomas.

Other inherited PC disorders are hereditary breast and ovarian cancer syndrome (*BRCA2*), familial atypical multiple mole melanoma syndrome (*p16*/*CDKN2A*), Peutz–Jeghers syndrome (*STK11*) and familial pancreatitis (*PRSS1*, *SPINK1*). All causative genes function as tumor suppressor genes.

Hereditary breast and ovarian cancer syndrome

BRCA2 was initially considered to be candidate pancreas tumor suppressor gene. In fact, the discovery of the homozygous deletion at 13q12.3 reported in PC supported the cloning of the *BRCA2* gene. Studies of families with germ-line mutations in the breast cancer susceptibility *BRCA2* gene show a modest and inconsistent increased risk of pancreatic cancer (3.5- to 10-fold) within these individuals. Whereas two studies evaluating *BRCA2* mutations in the familial context of two or more FDRs with PC report a mutation rate of 12–19 %, a FaPaCa recent publication of 10 years of experience reveals a mutation rate of 3 %.The median age at diagnosis of cases was 60 years (about 8–10 years younger than the median age of sporadic PC for Europeans), though 22 % of the affected patients were younger than 50 years [18]. It is less clear that *BRCA1* mutations are associated with an increased risk of PC. Whereas some large studies of *BRCA1* mutation-positive families suggested that the risk of PC is two- to threefold greater in carriers than in general population, other studies did not find BRCA1 mutation in families with PC that do not have a significant history of breast cancer.

Most recently, the *PALB2* gene has been added to familial PC genes. It codes for a protein that binds to the BRCA2 protein and helps to localize it to the nucleus. Initial data suggest the *PALB2* gene accounts for 1–3 % of familial PC [19].

Familial atypical multiple mole melanoma syndrome (FAMMM)

FAMMM is characterized by 50 or more dysplastic nevi and multiple melanomas in two or more first- and second-degree relatives. Affected subjects have a risk of PC of 13- to 22-fold greater than the average population. The metachronous occurrence of malignant melanoma and PC has been described. In addition, these individuals are also at increased risk of developing sarcomas, lung and breast cancer. It is an autosomal-dominant inherited syndrome caused by p16/*CDKN2A* gene mutations on chromosome 9p21. A recent study of 18 pancreatic carcinoma/melanoma-prone families detects a mutation rate of 11 % [20].

Individuals with a germ-line p16 mutation have a 38-fold greater risk of PC than general population.

Peutz–Jeghers syndrome (PJS)

PJS syndrome is an autosomal-dominant syndrome that occurs in 1 of 120,000 live births. It is characterized by hamartomatous gastrointestinal polyps, mucocutaneous pigmentation and an increased risk of neoplasms, such as small intestine, gastric, colon, pancreas, breast and ovarian. A clinical diagnosis of PJS can be made in individuals who have two or more of the following criteria: (1) two or more PJ polyps of the small bowel, (2) characteristic mucocutaneous pigmentation, or (3) a family history of PJS. It is caused by germ-line mutations in the *STK11/LKB1* gene on chromosome 19p13.3, which encodes a novel serine/threonine kinase that is thought to function as a tumor suppressor. Patients with known PJS have a cumulative lifetime risk of 11–36 % at age 70 of developing PC [21].

Other cancer predisposition syndromes

Studies of subjects affected either by familial adenomatous polyposis or Lynch syndrome suggest a moderated increased risk of PC within these families (RR 4 and 8, respectively) compared with the general population and their association with special histological types, such as pancreatoblastoma and young onset medullar (microsatellite instability and BRAF mutations).

Ataxia telangiectasia is an autosomal recessive inherited disease caused by germ-line mutations in the *ATM* gene. The clinical phenotype consists of cerebellar ataxia, oculocutaneous telangiectasia and cellular and humoral immune deficiencies. A low increase of the risk for PC has also been associated.

Familial pancreatitis (hereditary pancreatitis)

Familial pancreatitis is a disease clinically characterized by recurring abdominal pain attacks due to acute pancreatitis with progression to early chronic inflammation and a 40 % risk of PC at the age of 70. This rare disease is inherited in an autosomal-dominant fashion attributed in 60 % of cases to germ-line mutations of the *PRSS1* gene, which disturbs the intrapancreatic balance of proteases and their inhibitors. The risk seems to increase up to twofold in individuals with paternal inheritance and after cigarette smoking. Furthermore, such subjects face an anticipated diagnosis of 20 years. Other genes associated with chronic idiopathic and hereditary pancreatitis are *PRSS2*, *SPINK1* and *CFTR* [22].

Cystic fibrosis caused by mutations in the cystic fibrosis transmembrane regulator (*CFTR*) gene that disrupt the localization and function of the cyclic adenosine monophosphate-mediated chloride channel. Because of the low frequency of PC in cystic fibrosis families, it is difficult to estimate the actual contribution to the PC risk [22].

The early detection of exocrine pancreatic adenocarcinoma in a selection of highrisk populations

Exocrine pancreatic adenocarcinoma is usually diagnosed when the disease is widespread and surgery with curative intent is not feasible. Currently, surgery in the initial stages of development is the only curative treatment option for individuals diagnosed with PC [23]. Thus, the selection of high-risk populations to undergo screening for early detection is a promising strategy.

The overall lifetime risk of developing PC for the general population is 0.5–1 % [24]. 40 % of the cases are sporadic, 30 % are tobacco-related, 15 % are diet-related, <5 % are chronic pancreatitis-related and 10–15 % are due to an inherited predisposition. By definition, the risk of developing PC due to a FPC linkage approaches 50 %. However, it is conceivable that a large family could have two cases through probability alone [25]. Additionally, environmental factors may act as modifying factors thus increasing the risk of hereditary cancer [25, 26].

Potential inheritance scenarios include known genetic syndromes, hereditary chronic pancreatitis and familial exocrine pancreatic cancer (two or more PC cases in FDRs) [27]. Genetic syndromes are the FAMMM, Peutz–Jeghers syndrome, BRCA1 andBRCA2 germ-line mutations in breast and ovarian hereditary cancer syndromes, hereditary non-polyposis colorectal cancer, familial adenomatous polyposis and Li–Fraumeni syndrome [28, 29].

Upper gastrointestinal endoscopic ultrasound (EUS) is the standard for screening people at risk of PC. However, there is no scientifically accepted standard pattern of screening. EUS and computerized tomography (CT) in a population with a familial predisposition have visible preinvasive lesions in 15 % of the cases [30, 31]. Critically, PC is potentially curable with surgery when invasive adenocarcinomas measure <1 cm [32].

Screening would be feasible in high-risk individuals if markers or preinvasive lesions could be detected [33–35]. EUS is the most frequently used method. Its sensitivity to identify the lesions is >90 %, although false positives occur [34]. Other imaging tests such as MRI and CT are used, generally in conjunction with EUS.

This non-systematic review demonstrates that screening in high-risk populations is feasible and secure, and that preinvasive lesion detection makes this deadly disease curable.

Premalignant lesions in the pancreas

The goal of screening high-risk individuals is to identify high-grade precursors allowing intervention prior to tumor progression. Early detection will allow highly selective surgical interventions, as well as providing an opportunity to study the precursors and genetic basis of PC [36].

In certain types of cancers, lesions are considered premalignant, as they will progress to malignancy. These include pancreatic intraepithelial neoplasia (PanIN) [31], intraductal papillary mucinous neoplasm (IPMN) [30] and, more rarely, mucinous cystic neoplasm (MCN).

1. Pancreatic intraepithelial neoplasia (PanIN) refers to a small (generally <5 mm) intraductal non-invasive lesion that is a result of metaplasia and proliferation of ductal epithelium [37, 38]. PanIN can occur in the main pancreatic duct or its major branches; however, it often occurs in smaller intralobular ducts. PanIN is often associated with lobulocentric atrophy. PanIN exhibits varying degrees of dysplasia, which is graded as mild, moderate or severe (designated as PanIN-1, PanIN-2 and PanIN-3, respectively). PanIN generally occurs in the tissue surrounding the invasive cancer and shares molecular genetic alterations with the invasive carcinoma (K-ras, p16 and shortening the length of telomeres) [32]. Although PanIN is considered to represent a precursor lesion to invasive ductal adenocarcinoma, PanIN rarely progresses to invasive cancer. PanIN is more common (RR 2.75) and of a higher grade (RR 4.2) in patients with a strong family history of PC [39]. In FPC, PanIN is often multifocal, and the median of density of PanIN is 15 %. Often, different KRAS gene mutations are identified in separately microdissected precursor lesions [40].
2. An IPMN is a cystic lesion that develops from the malignant transformation of cells lining the pancreatic ducts and that is characterized by mucin production, cystic dilatation of the pancreatic ducts and intraductal papillary growth. IPMNs arise in both the main duct and branch ducts; IPMNs from the main duct are more likely to progress to malignance, although the malignant potential is determined more by the histological subtype than by location per se. An IPMN may be multifocal and may involve the entire main duct. The characteristic features of IPMNs include diffuse or segmental dilation of the pancreatic duct without structuring, intraductal expansion of mucin-producing ductal cells and dilation of either of the ampulla. There are different subtypes of IPMNs: tubular, colloid and oncocytic invasive [41]. These subtypes of IPMN have varying prognoses and arise from different epithelial subtypes. IPMNs are graded according to the degree of cellular dysplasia and the growth pattern (architecture) of the lining epithelium. They are classified as IPMN with low-, intermediate- or high-grade dysplasia, with or without invasion. IPMN can progress from low-grade dysplasia to higher-grade dysplasia. Approximately 30 % of IPMNs will progress to invasive carcinoma. 18 % of FPC versus 10 % of sporadic PC is associated with IPMN [40].

Studies have suggested that MCNs may have malignant potential. MCNs generally occur as sharply demarcated cystic lesions with a thick fibrous wall in the body or tail of the pancreas and occur more often in younger women (median age in the 40s than ductal adenocarcinoma or IPMN (median age in the 60s). MCNs are slightly less prevalent than IPMNs [42]. MCNs are considered to arise in the exocrine parenchyma rather than from the ducts [43]. The histologic hallmark for distinguishing MCNs from IPMNs is the presence of a highly cellular stromal layer immediately beneath the epithelium; it has been called "ovarian stroma" because it is composed of small spindle-shaped cells that express the estrogen and/or progesterone receptor as shown using immunohistochemistry [44]. The Armed Forces Institute of Pathology (AFIP) and World Health Organization (WHO) classifications of exocrine pancreatic tumors divide MCNs into low, intermediate and high grade on the basis of the degree of epithelial dysplasia (similar to IPMN) [45, 46]. Although it is not common, low-grade MCNs can progress to high-grade dysplasia and invasive carcinoma; <20 % progress to invasive tumors, and more often, they resemble ductal adenocarcinoma [47].

Target high-risk populations

The first step in assessing the risk of PC is the reconstruction of a complete family history, including relatives of first and second grade as well as a detailed clinical history (age at diagnosis of PC, the presence of other associated clinical conditions). At present, the risk for PC can be estimated using algorithms such as the PancPRO software, a risk assessment tool (package CancerGene http://www4.utsouthwestern.edu/breasthealth/cagene/), which provides an estimate of lifetime risk on the basis of family history, degree of relationship with family members affected and the age of onset of PC in the affected relative.

Although ~10 % of PCs are thought to have a hereditary predisposition, there is a genetic predisposition in a subset of PC kindreds. Individuals with one FDR with PC have a 1.5- to 3-fold increased risk of disease [48]. In FPC consisting of kindreds with two or more FDRs with PC, an overall ninefold increased risk of PC has been observed (95 % CI 4.5–16.1), and with three or more FDRs with PC, there is a 32-fold increased risk of disease (95 % CI

4.5–16.1) [27]. Many investigators suggest performing surveillance on people with two FDRs affected with PC or on people with three first- or second-degree relatives affected with PC.

As repored by Brand, participants of the Fourth International Symposium of Inherited Diseases of the Pancreas established the degree of risk for developing PC for a variety of factors with relevance for individual risk assessment. Using published data, the risks were classified into three categories: low (5-fold), moderate (5- to 10-fold) and high risk (≥10-fold) [33]. Individuals from kindreds with multiple family members (>3 first-degree, second-degree or third-degree relatives) diagnosed with PC represent one of the few patient populations classified as high risk.

The following individuals were also classified in the high-risk group (≥10-fold) [34]:

1. All individuals in families with FAMMM, with a case of PC in a first- or second-grade relative, are included. FAMMM is characterized by the presence of one or more relatives of a first- or second-degree relative with malignant melanoma and many moles, some of which are atypical. FAMMM transmission is autosomal dominant and is caused by germ-line mutations in the p16/INK4A (CDKN2A) gene. Carriers of germ-line mutations in the CDKN2A gene have a 38-fold higher risk of developing PC compared with the general population [49, 50].
2. Individuals with PJS, which is characterized by multiple pigmented lesions, gastrointestinal hamartomas and malignant tumors of the breast, pancreas and other locations, are included. The pattern of inheritance for PJS is autosomal dominant. It is caused by mutations in the STK11/LKB1 gene and has been estimated to yield a 132-fold increased risk of PC and a cumulative risk of 11–36 % over the life of an individual [28].
3. Individuals with hereditary pancreatitis are included. Hereditary pancreatitis is transmitted in an autosomal-dominant pattern and is primarily associated with mutations in the PRSS1 (cationic trypsinogen) gene, which is detected in ~50 % of cases [51], and variations in the PRSS2 genes, SPINK1 and CFTR. Carriers of mutations in the PRSS1 gene have a significantly higher risk for PC (SIR 87, 95 % CI 42–113) [52].
4. Potentially, carriers of BRCA1 or BRCA2 mutations with at least one case of PC in the first- or second-grade relatives should be included. The relative risk of PC in carriers of BRCA1 mutations is estimated at 2.26, and for carriers of BRCA2 mutations is between 3.5 and 10 [16, 28, 53, 54]. It is estimated that families with a case of PC have a higher risk, although this risk has not been quantified. This concept reflects the hypothesis that families with the same hereditary pancreatic cancer syndromes could share additional genetic loci predisposing them to the development of PC, and thus, may be at higher risk [33].

The Fourth International Symposium of Inherited Diseases of the Pancreas indicated that the early age of onset (before age of 50) of PC in a family in the absence of any of the above factors did not constitute a sufficiently high risk to warrant screening.

The American Gastroenterological Association (AGA) recommends PC screening to begin at age 35 for those with hereditary pancreatitis. In individuals with a positive family history, screening should begin 10 years prior to the age at which pancreatic cancer was first diagnosed [55]. Importantly, other authors have suggested that surveillance is cost-effective, if patients selected have a lifetime risk of PC that is ≥16 % [56]. Thus, identifying the proper group to screen is a critical first step in developing an effective screening test [57].

When and how often should screening begin?

There is no consensus as to the optimal age to start screening or for the frequency of screening in at-risk individuals for PC.

The age of onset for screening of individuals at high familial risk is 35 years for those with hereditary pancreatitis, and 40–50 years of age or 10 years before the age of first cancer diagnosis for individuals with FPC.

In patients with PJS, the age of diagnosis of PC is earlier; thus, it is recommended to start screening at 25–30 years of age.

The European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) proposes that other groups begin screening after age 40, even in individuals with up to a 120-fold increase in risk, although exceptions could be made because of anticipation [25].

The frequency of screening should be every 1–2 years, if there were no findings at baseline.

Screening tools for pancreatic cancer

Currently, there are no clinically proven effective screening tests available for the early detection of PC. However, several investigators have demonstrated that the detection of premalignant lesions, such as PanIN3, could improve the survival in high-risk populations [58–60].

Biomarkers

Serum cancer antigen (CA) 19.9 levels have been suggested as a possible screening tool. In a study involving more than 70,000 asymptomatic persons in Korea, subjects underwent abdominal ultrasonography and serum CA 19-9 measurement. The authors analyzed the sensitivity, specificity and predictive values of CA 19-9 for detecting PC. The number of subjects with a level of CA 19-9 above the cutoff of 37 U/mL was 1,063 (1.5 %), including 4 cases diagnosed with PC. The sensitivity was estimated at 100 % with a specificity of 98.5 %. However, the positive predictive value (PPV) of CA 19-9 for detecting PC was 0.9 % in the asymptomatic population. Thus, the authors conclude that mass screening for PC using CA 19-9 levels in asymptomatic subjects was ineffective [61].

In a prospective study, in patients selected for the presence of signs or symptoms highly suggestive for PC, the levels of CA 19-9 were evaluated. Of 110 patients included in the study, 54 had a final diagnosis of pancreatic adenocarcinoma (49 % prevalence). CA 19-9 values were higher than 40 U/mL in 45 patients with PC and in 18 of the 56 patients with other final diagnoses [sensitivity 0.83, specificity 0.68, PPV 0.71, negative predictive value (NPV) 0.81]. However, values above 120 U/mL were strongly suggestive of PC in the overall population (PPV 0.85) and were diagnostic (PPV 1.0) in the non-jaundiced population. However, this test did not shorten the diagnostic evaluation, because of the need for confirming imaging studies [62].

50 % of cancers <2 cm are associated with a rise in Ca 19-9 [63], and it is rarely elevated in the presence of dysplasia [64]. Thus, because of the lack of adequate sensitivity and specificity, CA 19-9 levels are not considered as an appropriate test for the screening of PC [65].

Other serum blood tests such as carcinoembryonic antigen (CEA), DU-PAN-2, CA 50, SLX (sialyl difucosyl Lex), ST-439 (sialyl Lex-Tn) and CA 125 are also not applicable as a single modality screening tests [25].

Hyperenzymemia, high levels of amylase or lipase, has been encountered in family members of patients with PC. The significance of this association is not clear, but it has been suggested that these individuals could be at increased risk of PC [66].

The EUROPAC study group uses a serum fasting glucose from patients on entry to the screening program and as part of the screening cycle [25]. Fasting glucose is a known marker for early cancer in sporadic cases, although this correlation has yet to be proven in FPC.

A large number of new biomarkers have been investigated to screen for PC. Many centers also collect pancreatic juice for investigational studies during an EUS or endoscopic retrograde cholangiopancreatography (ERCP) and bank blood specimens to use as a resource for current and future tumor-marker assessment [67].

European investigators extracted pancreatic juice from 146 patients with pancreatic ductal adenocarcinoma, chronic pancreatitis or biliary tract stones [68]. p53 mutations were detected in 20 of 48 (42 %) cancer cases, none of the 49 controls and 2 of the 49 (4 %) patients with pancreatitis. K-ras mutations were detected in 31 of the 57 (54 %) cancer patients, 13 of the 61 (21 %) controls and 23 of the 67 (34 %) patients with pancreatitis. Promoter methylation levels >12 % were observed in 26 of the 42 (62 %) cancer patients compared with 3 of the 24 (13 %) controls and 2 of the 26 (8 %) with pancreatitis. Mutations in p53 or high-level p16(INK4a) promoter methylation occurred in 29 of the 36 (80 %) patients with cancer, 3 of the 24 (13 %) controls and 3 of the 22 (13 %) with pancreatitis. The gallstone disease patients had a high rate of positive K-ras mutations possibly reflecting that they were not disease free. The authors concluded that combination molecular analysis increased the discrimination between patients with malignant and benign disease. This level of discrimination would allow patients in high-risk groups to be stratified from negligible risk to over 50 % probability of an early cancer.

EUROPAC has proposed a combination of different molecular tests to phase their screening program [25]. Thus, cell-free pancreatic juice samples are analyzed for the presence of K-ras and p53 mutations and the quantification of p16 promoter methylation. Following this analysis, the combination of the results from the three molecular tests was used to stratify the risk between no risk and 90 % probability of cancer. Stratification is less marked in patient groups with a background of pancreatitis ($\sim$0–50 %), but molecular analysis may conversely have the greatest impact in hereditary pancreatitis patients, where the sensitivity and specificity of conventional imaging is limited. This method of molecular analysis was used by the EUROPAC study group to determine the frequency of imaging.

Additionally, other groups have estimated that the detection and quantification of aberrantly methylated DNA in pancreatic juice is a promising approach to the diagnosis of PC [69, 70].

Imaging studies

Many centers currently use EUS as the procedure of choice based on its high sensitivity (>90 %) in detecting small pancreatic lesions and PanIN [71]. EUS often detects the combination of lobulocentric atrophy and multifocality of PanIN. Single PanIN lesions are generally too small to be grossly apparent; however, larger PanINs (2–5 mm) can be detected using EUS as anechoic, non-septated lesions, often indistinguishable from saccular dilatations of branch ducts along the main duct or small branch duct IPMNs.

Multifocal PanINs, together with their multiple foci of associated lobulocentric atrophy, produce a mosaic of fibrosis, atrophy and uninvolved parenchyma, changes very similar to chronic pancreatitis. These changes are often detectable using EUS with standard criteria for the diagnosis of chronic pancreatitis, such as heterogeneous parenchyma, multifocal lobularity and dilated main and branch pancreatic ducts [40, 72].

American investigators studied the use of EUS as a screening test in asymptomatic members of 31,105 at-risk families. In this trial, termed "Cancer of the Pancreas Screening (CAPS)," researchers screened asymptomatic patients with a strong family history of PC, as well as asymptomatic patients with PJS [64]. Nearly, 10 % of the asymptomatic individuals screened were found to have a lesion in their pancreas that resulted in surgery. Most of these lesions were IPMNs. One-fourth of the lesions discovered had significant dysplasia (carcinoma in situ), demonstrating that curable precancerous lesions could be detected and treated in asymptomatic at-risk individuals.

A study published by Poley et al. [59] evaluated EUS for screening in high-risk individuals: 13 with FAMMM families, 21 with FPC, 3 with hereditary pancreatitis, 2 with Peutz–Jeghers syndrome, 5 with BRCA 1 and 2 mutations and 1 with Li–Fraumeni syndrome. Of the individuals screened, 23 % showed anomalies using EUS (23 %). All patients underwent a pancreatectomy, with 7 % having asymptomatic cancer (2 with N1 adenocarcinomas) and 16 % having IPMN, a cancer precursor lesion.

Endoscopic retrograde cholangiopancreatography, similarly to EUS, detects non-specific lesions, such as irregular ducts, poor filling of pancreatic ducts, narrowing or dilatation of ducts and formation of cystic lesions [64].

A fine-needle aspiration (EUS-FNA) can improve the specificity of EUS. In a study at Johns Hopkins University, this strategy, occasionally with ERCP, identified nodules in 25 % of 116 at-risk individuals (109 FPC and 7 PJS). Eight were IPMN, one was a T2N1 pancreatic adenocarcinoma and another was PanIN1. In chronic pancreatitis, some authors recommend EUS plus CT to increase specificity [73, 74].

Although other imaging techniques are capable of detecting pancreatic lesions, abdominal CT (64-slice multidetector), abdominal MRI or transabdominal ultrasound are inadequate for the detection of PC at an early stage because of the small size of the lesions (<1 cm) [75, 76].

Many centers have used CT scans or ERCP as a means of screening for PC, although the latter, similar to EUS, seems unsuitable when hereditary pancreatitis is the underlying condition responsible for the cancer risk. In addition, CT scans, even with pancreatic protocols, have limited sensitivity (63–83 %) and specificity (59–93 %) in detecting the very small lesions that are potentially curable [77].

Abdominal MRI with an accompanying magnetic resonance cholangiopancreatography (MRCP) has the theoretical advantages of imaging both the pancreatic duct and gland. It has been reported that T1-weighted spin-echo MRI can be superior to spiral CT imaging for the detection of small lesions. The reported sensitivity of MRI ranges from 83 to 87 % and the specificity ranges from 81 to 100 % [78].

A study from the Dutch involved the surveillance of individuals with germ-line mutations in p16-Leiden that had a 15–20 % lifetime risk of developing PC ($n = 79$, 31 male, mean age 56 years, range 39–72 years) and offered annual surveillance by MRI and MRCP [79]. After a median follow-up period of 4 years (range 0–10 years), PC was diagnosed in seven patients (9 %). The mean age at diagnosis was 59 years (range 49–72 years). At the first examination, three of the tumors were detected, while four were detected after a negative result in the initial examination. All seven patients had a resectable lesion; five underwent surgery, three had an R0 resection and two had lymph node metastases. Possible precursor lesions (i.e., duct ectasias based on MRCP) were found in nine individuals (11 %). The authors concluded that MRI/MRCP detected small, solid pancreatic tumors and small duct ectasias.

Although there is no evidence to suggest that CT or MRI is better than EUS, some centers are suggesting the performance of a CT or MRI scan to evaluate for extrapancreatic lesions, as many of these patients are at risk for non-pancreatic neoplasms. Indeed, high-risk people are at risk for a variety of extrapancreatic abdominal malignancies, and EUS alone is not adequate for screening many of them. Wang and colleagues [4] followed families enrolled in the National Familial Pancreas Tumor Registry (NFPTR) (http://pathology.jhu.edu/pancreas/nfptr) and found that overall cancer mortality is increased both in the members of sporadic PC kindreds (defined as having at least a single PC in the kindred, but not an affected pair of FDRs; relative risk [RR] 1.55, 95 % CI 1.39–1.73) and in FPC kindreds (at least a pair of FDRs with PC; RR = 1.41; 95 %CI 1.26–1.58). Relatives of patients with FPC had an increased risk of dying from breast cancer (RR 1.66, 95 % CI = 1.15–2.34), ovarian (RR 2.05, 95 % CI = 1.10–3.49) and bile duct cancers (RR 2.89, 95 % CI 1.04–6.39).

Screening programs for PC

A consensus opinion could not be reached on a specific approach for screening these high-risk patients for PC. Most of the screening programs for PC include the use of EUS as a sole primary test or incorporate additional screening tests such as abdominal imaging with MRI or CT for asymptomatic members of at-risk families [58–60].

The Johns Hopkins group aims to identify early pancreatic masses when the lesion is either precancerous or a resectable malignancy. Canto and collaborators published a prospective study that screened for early pancreatic neoplasia and compared the pancreatic abnormalities in high-risk individuals (PJS or a strong family history of PC) with control subjects [58]. They used baseline and 12-month CT scans combined with EUS. If the EUS was abnormal, EUS-FNA and ERCP were performed. Surgery was offered to patients with potentially neoplastic lesions. Seventy-eight high-risk patients (72 from familial PC kindreds, 6 PJS) and 149 control patients were studied. Pancreatic neoplasias were confirmed in eight patients using surgery or FNA (10 % yield of screening); six patients had eight IPMNs, one had an IPMN that progressed to invasive ductal adenocarcinoma and one had PanIN. EUS and CT also diagnosed three patients with five extrapancreatic neoplasms. EUS and ERCP abnormalities suggestive of chronic pancreatitis were more common in high-risk patients than in control subjects.

In a study conducted at the Memorial Sloan-Kettering Cancer Center, 309 asymptomatic at-risk relatives were enrolled and offered screening with MRCP followed by EUS with FNA, if indicated [80]. Relatives with findings were referred for surgical evaluation. When 109 relatives had completed at least one cycle of screening, abnormal radiographic findings were present after the initial screening in 18/109 patients (16.5 %), 15 of whom underwent EUS. A significant abnormality was confirmed in 9 of the 15 patients, 6 of whom ultimately had surgery, for an overall diagnostic yield of 8.3 % (9/109). Yield was greatest in relatives >65 years old (35 %, 6/17) when compared with relatives 55–65 years (3 %, 1/31) and relatives <55 years (3 %, 2/61).

The Washington University group recommends ERCP if any suspicious image is visualized with EUS. Baseline EUS is performed 10 years prior to the earliest age of onset of PC in that family. If the EUS is normal, the patient is offered a repeat EUS in 1 year. If the EUS indicates an abnormality unrelated to pancreatitis, an ERCP is offered after a discussion of risk and benefit. Patients with an abnormal EUS and a normal ERCP undergo EUS in 1 year. Patients with an abnormal EUS and ERCP are given the option of continuing with surveillance until a mass forms or they obtain a tissue diagnosis. Histology is obtained via laparoscopic resection of the pancreatic tail, as needle biopsies would be inadequate to exclude the presence of PanINs [81]. ERCP was scheduled in 28 out of 44 high-risk persons and 13 demonstrated alterations. A pancreatectomy was performed in 12 individuals. All had high-grade dysplasia and carcinoma was not found.

There are also FPC registries in Europe, e.g., the German National Case Collection for Familial Pancreatic Cancer of the German Cancer Foundation (FaPaCa) [81] and EUROPAC [82].

Since 1999, FaPaCa has collected data from families with at least two FDRs with confirmed PC who did not fulfill the criteria of other hereditary tumor syndromes. Histopathological verification of tumor diagnoses and genetic counseling were prerequisites for the enrollment of families in FaPaCa. PC represented the sole tumor entity in 38 families (40 %). In 56 families, additional tumor types occurred, including breast cancer ($n = 28$), colon cancer ($n = 20$) and lung cancer ($n = 11$). In 70 families (74 %), the pattern of inheritance was consistent with an autosomal-dominant trait. Compared with the preceding generation, a younger age of onset was observed in the offspring of PC patients (median 57 vs. 69 years) indicating anticipation. The screening program was restricted to mutation carriers if the underlying gene defect was known in the family. The screening program started 10 years prior to the earliest age of onset in the family, and at the latest, by the age of 40 years. In prospective screenings in FPC families from July 2002 until December 2009, 72 at-risk individuals from FPC families participated in the screening program with 210 examination visits (median 2, range 1–11). Forty-six at-risk individuals (63.9 %) had a normal pancreas based on the evaluation using EUS and MRCP. Twenty-six (36.1 %) at-risk individuals showed lesions and/or abnormalities in the pancreas, of whom surgery was conducted on 10, and 16 at-risk individuals, including 5 with potential side branch IPMN, are under close observation. In one patient, surgical exploration could not confirm the small hypoechoic lesion observed using EUS; therefore, no pancreatic resection was performed. Nine at-risk individuals underwent pancreatic resection and had the following pathologies: PC ($n = 1$), serous cystadenoma ($n = 3$), PanIN3 ($n = 1$), IPMN ($n = 2$), PanIN1/2 ($n = 2$). Interestingly, one patient with IPMN also revealed multifocal PanIN2 lesions. These resulted in a diagnostic yield of malignant (PC) or potentially malignant precursor lesions of PC (IPMN, PanIN3, multifocal PanIN2) between 5.5 % (4 of 72) and 12.5 % (9 of 72), depending on the inclusion of the 5 individuals with branch duct IPMNs on imaging.

EUROPAC was created in Europe in 1997. In 2008, there were 274 families registered, with 125 of these families having a clear autosomal inheritance pattern, as well as 455 chronic pancreatitis families, with 157 of these families having an autosomal pattern. The full screening program includes a baseline analysis involving measurement of fasting glucose and CA 19-9, with imaging studies using CT scans and EUS. Where appropriate, ERCP is offered for pancreatic juice analysis rather than imaging. The baseline results lead to the participant entering either a "standard" or a "close" surveillance pathway. A deciding factor is the presence or absence of pancreatic juice DNA

abnormalities. If a patient undergoes pancreatic juice analysis and no DNA changes are detected, the standard surveillance cycle is used, where serum tests, imaging and the juice analysis are repeated on a 3-year staggered basis. Patients that do not undergo juice analysis are entered into the close surveillance group. This group undergoes annual follow-up, serum tests and imaging. In almost all FPC patients with healthy pancreatic tissue, the screening modality of choice is EUS. If the baseline imaging confirms significant fibrosis (e.g., chronic pancreatitis), CT is preferentially used.

Few studies are available concerning the cost-effectiveness of screening, although it is hypothesized that the cost of screening would outweigh the costs of a PC diagnosis and subsequent treatments [83]. Some authors calculated that the screening of hereditary pancreatitis patients was expensive ($164,285 per PC detected). In PJS-affected families, the cost per life saved was estimated at $50,000. In FPC-affected families, the costs would be $50,000 per life saved [25].

Conclusions

The effectiveness of screening depends on the selection of the population at risk. The goal of screening is to detect precursor lesions to reduce the incidence and mortality from PC. The detection and early surgical resection of curable neoplasms in at-risk individuals provides a unique opportunity for pathologists, biologists, gastroenterologists and oncologists to study the morphology of precursor lesions in individuals with a strong family history of PC. A multidisciplinary and international collaboration is essential for progress in this discipline and to achieve the maximum benefit for PC patients and their at-risk families. Furthermore, analysis of the long-term screening studies will allow the assessment of its cost-effectiveness.

Conflict of interest The authors declare that they have no conflict of interest related to the publication of this article.

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