Early detection and prevention of pancreatic cancer: Is it really possible today?

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Received: December 28, 2013 Revised: January 23, 2014
Accepted: May 29, 2014
Published online: September 14, 2014

Abstract
Pancreatic cancer is the 4th leading cause of cancer-related death in Western countries. Considering the low incidence of pancreatic cancer, population-based screening is not feasible. However, the existence of a group of individuals with an increased risk to develop pancreatic cancer has been well established. In particular, individuals suffering from a somatic or genetic condition associated with an increased relative risk of more than 5- to 10-fold seem to be suitable for enrollment in a surveillance program for prevention or early detection of pancreatic cancer. The aim of such a program is to reduce pancreatic cancer mortality through early or preemptive surgery. Considering the risk associated with pancreatic surgery, the concept of preemptive surgery cannot consist of a prophylactic removal of the pancreas in high-risk healthy individuals, but must instead aim at treating precancerous lesions such as intraductal papillary mucinous neoplasms or pancreatic intraepithelial neoplasms, or early cancer. Currently, results from clinical trials do not convincingly demonstrate the efficacy of this approach in terms of identification of precancerous lesions, nor do they define the outcome of the surgical treatment of these lesions. For this reason, surveillance programs for individuals at risk of pancreatic cancer are thus far generally limited to the setting of a clinical trial. However, the acquisition of a deeper understanding of this complex area, together with the increasing request for screening and treatment by individuals at risk, will usher pancreatologists into a new era of preemptive pancreatic surgery. Along with the growing demand to treat individuals with precancerous lesions, the need for low-risk investigation, low-morbidity operation and a minimally invasive approach becomes increasingly pressing. All of these considerations are reasons for preemptive pancreatic surgery programs to be undertaken in specialized centers only.

Key words: Preemptive pancreatic surgery; Cystic tumors of the pancreas; Familial pancreatic cancer; Early detection; Pancreas cancer screening

Core tip: Pancreatic cancer is the 4th leading cause of cancer-related death in Western countries. Considering the low incidence of pancreatic cancer, population-based screening is not feasible. This review analyzes the possibility to identify a population at risk for pancreatic cancer and the strategies for clinical screening and prevention.

Del Chiaro M, Segersvärd R, Löhr M, Verbeke C. Early detection and prevention of pancreatic cancer: Is it really possible today? World J Gastroenterol 2014; 20(34): 12118-12131
Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i34/12118.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i34.12118
INTRODUCTION

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in Western countries. It ranks amongst the most lethal cancers and has a mortality rate that nearly equals the incidence rate and an overall 5-years survival of approximately 5%.[1-3]

During the last decades there has been an overall reduction in cancer-related mortality in Western countries, in particular for lung, breast, colorectal and prostate cancer.[4,5] In contrast, mortality rates increased for PC, and the prediction for the year 2013 shows the same trend.[4]

The success in reducing cancer mortality for some of the human solid tumors is not only related to the discovery of new therapeutic agents, but to a significant extent it has also been the result of the development of early detection and prevention programs. Born from this concept is a new surgical approach for patients at risk of cancer: preemptive surgery. Preemptive surgery can be defined as the prophylactic removal of an organ at high risk for malignant transformation or the resection of a precancerous lesion or an “early” malignant neoplasm in an individual with a predisposition to cancer.[5,6] Today, preemptive surgery is recognized as a useful approach for the management of various premalignant lesions or conditions and for the prevention of cancer in high-risk individuals. For patients with high-grade dysplasia in Barrett’s esophagus, esophagectomy is a therapeutic option to prevent esophageal cancer from developing.[7-10] Total gastrectomy can be performed to prevent gastric cancer in the rare case of familial gastric cancer[11,12]. Bile duct cyst resection or “early” liver transplantation in primary sclerosing cholangitis is proposed to reduce the incidence of cholangiocarcinoma.[13,14,15] Total thyroidectomy may be recommended for individuals with multiple endocrine neoplasia type 2/familial medullary carcinoma.[16] Preemptive bilateral mastectomy and possibly bilateral oophorectomy in female carriers of BRCA1 or BRCA2 mutations reduce the risk of ovarian cancer and breast cancer by more than 90%.[17,18] Patients with hereditary non-polyposis colorectal cancer or familial adenomatous polyposis can be advised to undergo prophylactic total proctocolectomy to prevent colon cancer development[19]. Furthermore, a population-wide screening program to detect premalignant lesions or early cancer is already implemented for different tumor types such as colorectal, breast and lung cancer[20,24].

Historically, PC was not considered a disease suitable for a preventive or early detection program given the aggressive biology and rapid progression of the tumor and the presumed low prevalence of high-risk individuals. Today, newly acquired knowledge regarding the biology and natural history of PC has changed this view. Even if PC is biologically aggressive at the time of diagnosis, it follows a multistep carcinogenesis process, which is very similar to that of other cancers (e.g., colon cancer) and consists essentially of a steady progression through increasing grades of dysplasia.[25] Since this process takes about a decade before the neoplastic lesion becomes an invasive cancer,[26], there is a considerable window of opportunity to potentially detect the tumor at an early (pre-)invasive stage.[27]

Today it has also been recognized that some of the neoplastic precursor lesions, such as intraductal papillary mucinous neoplasm (IPMN) or pancreatic intraepithelial neoplasia (PanIN), can be detected at an early stage using currently available imaging techniques.[28,29]

Even if population-based screening for PC is not considered cost-effective given the relatively low incidence of the disease,[28] specific screening programs for subgroups of high-risk individuals are currently evaluated by the scientific community regarding the detection of precursor lesions or early cancers and the impact on PC-related mortality.[30] In this paper we analyze the conditions that are associated with an increased risk of PC, the groups of individuals potentially suitable for screening programs, the target lesions for screening, and the potential treatment for these conditions.

GROUPS AT RISK FOR PC

A wide range of conditions are associated with an increased risk of PC. Overall, these can be divided in two distinct groups, i.e., hereditary and non-hereditary conditions.

Traditional non-hereditary conditions associated with an increased risk of PC

These non-hereditary conditions are frequently associated with potentially correctable life-style factors and habits. Although they are well-established risk factors for PC, the associated increase in risk is too low to justify screening of the affected individuals. Smoking, obesity, alcohol abuse and exposure to toxic substances (Table 1) are potentially all suitable for primary prevention. Further non-genetic conditions associated with an increased risk of PC are diabetes type 1 and 2, chronic pancreatitis and a history of peptic ulcer (Table 1).[30-36]. Only the risk associated with chronic pancreatitis seems to be sufficiently high to justify screening of affected individuals.

Novel non-hereditary lesions and conditions associated with an increased risk of PC

The majority of patients within this group suffer from a pancreatic cystic neoplasm, in particular IPMN or mucinous cystic neoplasia (MCN), which bear an established risk of malignant transformation. Furthermore, recent data indicate that patients who underwent solid organ transplantation also have an increased risk of PC.

Pancreatic cystic neoplasms

Pancreatic cystic neoplasms (PCN) are common diseases with an estimated prevalence in the general population of approximately 200,000.[37,38] A wide range of different cystic tumors has been described,[39] but IPMN and MCN seem to be the most prone to undergo malignant transformation. Furthermore, the incidence of IPMN appears to be high in individuals with a familial risk for PC[40] and,
Conversely, a positive family history for PC is a risk factor for IPMN development. The risk of cancer in IPMN patients ranges from 24% in IPMN involving the branch ducts to over 60% in lesions involving the main pancreatic duct. For this reason, follow-up or preventive surgery of these neoplasms is recommended.

### Transplanted patients

Individuals who underwent organ transplantation have recently been identified as being at risk of developing PC. Large cohort studies of transplanted patients in the United States have convincingly demonstrated that the immunosuppressive regimen used for solid organ transplantation is associated with a risk of PC, which significantly exceeds that of the general population. Furthermore, following transplantation, patients seem to be at an increased risk to develop pancreatic neoplastic precursor lesions such as IPMN.

### Hereditary conditions associated with an increased risk of PC

Three major groups of hereditary conditions can be considered associated with an increased risk of PC: a strong family history of PC, called familial pancreatic cancer (FPC), hereditary neoplastic and hereditary non-neoplastic syndromes in which PC is one of the phenotypic manifestations.

### FPC

Even if a susceptibility gene for FPC has not been identified yet, the distribution of PC in some families meets the criteria for autosomal dominant transmission with reduced penetrance. In members of such kindreds, the risk to develop PC increases with the number of affected family members. The relative risk ranges from 4.5-fold in case of a single affected first-degree relative to 32-fold if 3 or more first-degree relatives are affected. The definition of FPC is not well established yet, but an individual can be considered at risk if there are at least two first-degree relatives affected by PC, or if three or more relatives are affected regardless of the degree of relationship (Table 2). According to some prospective observational studies based on screening programs, individuals at risk are found to have an increased incidence of neoplastic precursor lesions (PanIN and IPMN).

### Table 1 Non-genetic factors associated with an increased risk to develop pancreatic cancer

| Risk factors                  | Estimated overall risk | Ref. |
|------------------------------|------------------------|------|
| Smoking                      | 1.75                   | [37,38] |
| Overweight                   | 1.12 per increased 5 kg/m² | [39-41] |
| Alcohol abuse                | 1.2                    | [42,43] |
| Type 1 diabetes              | 2.0                    | [44]  |
| New onset type 2 diabetes    | 2.0                    | [45]  |
| Chronic pancreatitis         | 14.0                   | [46]  |
| Exposure to nickel           | 1.9                    | [47]  |
| Previous gastric ulcer       | 1.8                    | [48]  |

### Table 2 Most important genetic syndromes associated with an increased risk of pancreatic cancer

| Syndrome                        | Gene                        | Relative risk | Risk at age of 70 |
|---------------------------------|-----------------------------|---------------|-------------------|
| Familial pancreatic cancer      | Unknown                     | 9             | 4%                |
| 1 or more first degree relative(s) | 1 first degree relative       | 4.5           | 2%                |
|                                 | 2 first degree relatives    | 6.4           | 3%                |
|                                 | 3 or more first degree relatives | 32          | 16%               |
| Peutz Jeghers syndrome          | LKB1/STK11                  | 132           | 30%-60%           |
| Hereditary pancreatic cancer    | PRSS1                       | 50-70         | 40%               |
| Familial atypical multiple mole melanoma | CDKN2A/p16 | 34-39         | 17%               |
| Breast and ovarian cancer       | BRCA1/BRCA2                 | 2.3-10        | 1%-5%             |
| syndrome                        | Cystic fibrosis             | 5.3           | <5%               |
| Hereditary non-polyposis colon cancer | MSH2, MLH1, MSH6, PMS, PMS2 | 4.7           | <5%               |
| Familial adenomatous polyposis  | APC                         | 4.5           | 2%                |

### Breast and ovarian cancer syndrome

This syndrome, caused by mutations of the BRCA1 or BRCA2 genes, is associated with a 2.3- to 10-fold increased risk of PC. The relative risk to develop PC appears to be higher in individuals of Ashkenazi Jewish descent. BRCA 2 mutations are also identified in about 13%–17% of the families diagnosed with FPC who do not meet the inclusion criteria of the breast and ovarian cancer syndrome.

### Familial atypical multiple mole melanoma

Familial atypical multiple mole melanoma (FAMMM) is associated with a mutation of the CDKN2A gene. The syndrome is also associated with extra-cutaneous tumors, and PC is present in 25% of individuals who carry this mutation. The relative risk to develop PC for individuals with FAMMM is 34- to 39-fold higher than in the general population. (Table 2). In a recent report from the German Familial Pancreatic Cancer surveillance program, patients with FAMMM were found more prone than patients with FPC to develop PC directly, i.e., without the development of clinically detectable precursor lesions.

### Peutz-Jeghers syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant hereditary disease that causes increased susceptibility for the development of various tumor entities. In particular, the risk of gastrointestinal tumors such as esophageal, small bowel, colorectal and pancreatic cancer is increased.
PRECURSOR LESIONS OF PANCREATIC CANCER

For several decades PanIN and IPMN have been established as precursor lesions of PC. However, it is only recently that their biology and significance are unfolding. IPMN is, as the name indicates, a neoplastic proliferation within the pancreatic duct system that is characterized by a variable degree of papillary architecture and mucin production\(^{[70]}\). The tumour cell proliferation and mucin secretion cause duct dilatation, which is the major macroscopic and radiological feature of this tumour entity (Figure 1). Based on which part of the pancreatic duct system is involved, IPMNs are divided into main-duct, branch-duct or mixed-duct type. The neoplastic epithelium can be of gastric, intestinal, pancreatobiliary or oncocytic type\(^{[71]}\). Over time, IPMNs can develop increasingly dysplastic features (graded as low, intermediate and high) and eventually transform into invasive adenocarcinoma of tubular, colloid or the rare oncocytic type. Whereas the first cancer type is morphologically and prognostically identical to conventional PC, the latter two are more indolent. Interestingly, the various features of IPMN are interrelated, as outlined in Table 3. Recent studies indi-

**Table 3** Characteristics related to epithelial subtype in intraductal papillary mucinous neoplasia

| Epithelial subtype | Gastric | Intestinal | Pancreatobiliary | Oncocytic |
|--------------------|---------|------------|-----------------|-----------|
| Location           | Branch duct > main duct | Main duct > branch duct | Branch duct > main duct | Branch duct > main duct |
| Dysplasia          | LGD/IGD 15% | IGD/HGD 30%-60% | HGD 60%-75% | HGD 25% |
| Present with invasive carcinoma | Conventional (tubular) | Colloid or conventional (tubular) | Conventional (tubular) | Oncocytic or conventional (tubular) |

LGD: Low-grade dysplasia; IGD: Intermediate-grade dysplasia; HGD: High-grade dysplasia.
cate a more complex relationship between IPMN and invasive PC. The latter may not only develop through direct malignant transformation of the IPMN proper, but seems also to occur more frequently concomitant with (but topographically separate from) an IPMN, in particular branch-duct IPMN of gastric epithelial type [72-74].

PanIN is also characterized by a neoplastic intraductal proliferation, but in contrast to IPMN, the neoplastic epithelium is flat to low-papillary, and mucin secretion is not a prominent feature [70]. The epithelial type is mainly gastric, although intestinal, oncocytic and other variants can occasionally occur [72]. Three grades of dysplasia (PanIN-1, PanIN-2, PanIN-3) are usually distinguished (Figure 2). The lower grades (PanIN-1, -2) are a common finding in otherwise healthy pancreas after the age of 40 [75,76] or in chronic pancreatitis [77-79]. In contrast, PanIN-3 is rare in the normal pancreas or chronic pancreatitis [76,80], but appears most commonly in pancreas with invasive ductal adenocarcinoma [81]. Both PanIN and IPMN are more common and more often multifocal in individuals with a strong family history of PC than in patients with sporadic disease, and the precursor lesions are of a higher grade in the former group [81,82,85].

While a certain morphological overlap exists between branch-duct IPMN of gastric type and PanIN [84,85], the main difference between PanIN and IPMN is the fact that the latter represents a macroscopically identifiable lesion [86], while PanINs are too small to be visualized by naked-eye inspection or imaging. However, it has been recently suggested that PanIN is associated by parenchymal changes [77,82,87], which may be detected by EUS [88,89]. These parenchymal changes are characterized by a combination of acinar cell loss, proliferation of small ductular structures and fibrosis, and have been coined as “lobulocentric atrophy” (LCA) (Figure 3A). The initial enthusiasm about the possibility to identify PanIN by means of detecting LCA has been dampened by recent novel developments regarding the causal relationship between both lesions. While it was first assumed that LCA is caused by the duct-obstructive effect of PanIN lesions [81,82,87], and the association between both seemed more or less obligatory, recent morphological and molecular evidence indicates that PanIN is one of the possible outcomes of LCA or the process that is often associated with LCA, so-called acinar-to-ductal metaplasia [90-92]. In the light of these recent discoveries, the use of LCA as a target for pancreatic screening of high-risk individuals requires more circumspect consideration. First, because PanIN is not the cause of LCA, the use of LCA to screen high-risk individuals requires more consideration.

Figure 2  Pancreatic intraepithelial neoplasia. Small pancreatic branch ducts are involved by a low-papillary proliferation of neoplastic columnar epithelium showing mild, moderate and severe dysplasia corresponding to pancreatic intraepithelial neoplasia (PanIN)-1, PanIN-2 and PanIN-3.

Figure 3  Lobulocentric atrophy. A: Lobules of acinar parenchyma are atrophic (asterisk) and partially replaced by tubular structures (so-called acinar to ductal metaplasia; dotted arrow) and fibrosis. Note the foci of PanIN-1 in the centre of the changes (arrows); B: Lobulocentric atrophy of neighbouring lobules (asterisk) results in a large area of fibrosis with tubular structures (dotted arrows) but without PanIN-lesion.
of LCA, the association between both lesions is not 100% [93]. LCA is in fact a common finding in the ageing pancreas or in the context of various conditions [87,90] and may be present with or without associated PanIN (Figure 3B). Conversely, PanIN may well occur in the absence of LCA, i.e. remain undetectable on EUS examination. Second, there is so far no indication that the presence of LCA correlates with the grade of PanIN. In other words, EUS detection of LCA would still not provide sufficient information for patient management, as high-grade PanIN may be an indication for preventive surgery, whereas low-grade PanIN is not. Third, the accuracy with which fine needle aspiration (FNA) would be able to assess the PanIN-lesion presumed to be associated with the focus of LCA identified on EUS has not been evaluated. While a focus of LCA may be of varying size depending on whether a single pancreatic lobule or several neighbouring lobules are affected, the associated PanIN-lesion(s) may be present only focally and could thus be missed by EUS-guided FNA. From these considerations, it appears that sampling bias may represent a limitation to the successful identification of PanIN-lesions when screening individuals with an increased risk of PC.

**SCRENNING MODALITIES FOR INDIVIDUALS AT RISK**

While various modalities are available to screen patients at risk of PC, it is currently not well defined who should be screened and how this could be done.

**Individuals with a “non-hereditary risk” of PC**

Among individuals with a “non-hereditary” risk of PC, patients suffering from chronic pancreatitis or PCN are currently enrolled for clinical screening.

 Patients with chronic pancreatitis are usually entered into a screening program to follow the evolution of the disease and detect PC at an early stage [93]. Recently, a specific algorithm based on patient history and laboratory tests has been developed to identify those chronic pancreatitis patients that have developed early PC [94]. Traditionally, screening of these patients has been based on imaging by MRI and CT scan. The use of EUS, alone or in combination with MRI, seems to offer a high accuracy in this particular patient group. The role of FNA during EUS is not conclusively defined [93], and diffusion-weighted MRI does not seem to facilitate the distinction between PC and chronic pancreatitis [96]. In the group of patients with PCN, MRI, CT scan and EUS, alone or in combination, are the most effective screening modalities. However, in view of the possible need for a prolonged screening program, CT scan is not recommended due to the risks associated with radiation exposure [88,89]. In particular for branch-duct IPMN (BD-IPMN), the surveillance strategy seems to be effective, as evidenced by the average detection rate of cancerization during follow-up, which lies between 0% and 11% [97-103] (Table 4).

**Individuals with a “hereditary risk” of PC**

Over the years, various surveillance programs have been developed for individuals with a “hereditary risk” of PC. Recently, MRI and EUS have become the most commonly used investigational modalities, whereas in the past CT scan and ERCP have also been used in this field [29]. Within this particular group, individuals affected by FAMMM deserve special mentioning. Indeed, in these individuals the development of PC follows a different pathway that is not preceded by PanIN and IPMN lesions [98]. Therefore, EUS should probably be preferred to, or used in combination with, MRI. Other methods of investigation that are potentially useful for the diagnosis of IPMN include endoscopic ultrasound and confocal laser microscopy. However, these methods are still experimental and cannot be used routinely for individuals with a hereditary risk of PC [104,105].

At present, the results of screening programs for PC are inconclusive. Most of the prospective studies performed so far report a highly variable detection rate of pancreatic findings, the yield ranging from 1% to 50% (Table 5) [106-113]. The significant divergence in detection rate is not only due to the use of different screening modalities but results also from differences in the defi-
nition of the concept “yield”. Some studies declared the identification of “early cancer” (T1N0M0) or high-grade dysplastic precursor lesions as the goal of screening, whereas others also included IPMN with low- or intermediate-grade dysplasia or PanIN of any grade of dysplasia. Some of the surveillance protocols attempted at detecting PanIN lesions by EUS, based on their association with lobulocentric atrophy. However, this histological change in the pancreas is not specific for PanIN, the ability to recognize it is very operator-dependent, and the progression and natural history of this type of lesion is not well known in individuals at risk of PC.\[29\] Consensus has not yet been reached regarding the timing and inclusion criteria for a surveillance program. National and international guidelines suggest that every individual with a 5- to 10-fold relative risk should be considered for surveillance. A further point of dissensus is the age at which an individual should be enrolled for screening. For patients at risk of FPC, age 40 or 50 has been proposed for the commencement of screening. However, an earlier age has been suggested for individuals at risk who smoke. For patients with HP (PRSS1 mutation carriers), starting surveillance at the age of 40 has been recommended, considering the younger age of onset of PC in this particular patient group. While no recommendations have been made regarding the age at which an individual could be discharged from a screening program, it seems appropriate that this should be determined by the individual's fitness for surgery. The exact timing of the screening procedures also lacks clear definition. In general, a yearly control is performed in patients without any finding on previous investigations. In case changes were detected that do not represent an indication for surgery, follow-up at 3- to 6-monthly intervals is generally recommended.\[29\]

**PRIMARY PREVENTION FOR INDIVIDUALS AT RISK OF PC**

Unfortunately, primary prevention for individuals at risk of PC is currently not available. Removal of the pancreas based exclusively on a statistical risk is not recommended. In some individuals, advice regarding a healthier lifestyle can be given, for example cessation of smoking, a diet rich in fruits and vegetables, regular exercise, and weight reduction or, if indicated, increased vitamin D intake (> 600 IU).\[117\]

**SURGERY FOR INDIVIDUALS AT RISK**

*Individuals with a “non-hereditary risk” of PC*

**Chronic pancreatitis:** In patients with sporadic chronic pancreatitis, surgery is a second line option for the treatment of local complications and symptoms, if a conservative approach has failed.\[118\] Even if a number of different surgical procedures for chronic pancreatitis have been proposed in the literature, a radical pancreatic resection should be performed whenever a suspicion of malignancy arises.\[121\] However, in selected cases, as for example of HP, some authors suggest early removal of the gland (total pancreatectomy) combined with auto-islet transplantation.\[122\] The rational of this approach, which cannot be considered the gold standard, is to treat the symptoms (mostly pain), eliminate the risk of cancer, and prevent the development of diabetes following total pancreatectomy. Today, this approach is also possible with a minimally invasive technique.\[123\]

**Pancreatic cystic neoplasms:** The indications for surgery in patients with IPMN or MCN are spelled out in European and international guidelines. For main-duct and mixed-type IPMN, surgical resection is always indicated because of the increased cancer risk. The extent of pancreatic resection should be planned based on the findings on preoperative imaging. In case of dilatation of the main pancreatic duct without signs of malignancy in the tail region, a pancreaticoduodenectomy with frozen section of the pancreatic margin is recommended. Extension of the resection is indicated if intraoperative examination shows high-grade dysplasia. Low-grade dysplasia is not considered an indication, whereas intermediate-grade dysplasia represents a grey area in which extended resection is not strongly recommended and a judicious decision depends mainly on clinical considerations specific for the individual patient. Importantly, however, extended resection for high-grade dysplasia at the margin is not strongly recommended, if invasive carcinoma is present in the pancreatic head, the reason being that the cancer will determine the patient’s outcome. Therefore, intraoperative frozen section examination may be useful if there is radiological suspicion of malignancy. Total pancreatectomy should not be considered based only of the extent of the duct dilatation, because the latter can be related to mere duct obstruction.\[19\] Regarding the indication for resection of BD-IPMN, recent guidelines recommend a surgical approach in patients with signs or symptoms of malignancy (dilatation of the main pancreatic duct up to 6 mm, mural nodules, rapid increase in size, elevated levels of CA19.9) or a lesion measuring up to 4 cm in maximum diameter.\[19\] In case of multifocal disease, only the lesions with these particular features should be resected (partial pancreatectomy). A radical resection should be performed when malignant transformation is suspected. An algorithm that combines the current European and international guidelines is proposed in Figure 4. When signs of malignancy are not present but the diagnosis is not entirely clear or the patient presents with certain clinical risk factors, parenchyma-sparing resection has been suggested by some.\[124\]

**Transplanted patients with premalignant lesions:** Even though specific guidelines regarding screening for pancreatic disease do not exist for transplanted patients, the increased risk of PC and premalignant pancreatic lesions seems to justify focused attention to this group of patients. Published in the literature is only a single
study that analyzed the clinical history of premalignant lesions in transplanted patients and found no difference in terms of progression time compared to non-transplanted patients. However, considering the short patient follow-up in this study and the natural history of the lesions under scrutiny, the data seem insufficient as a basis for the development of a strategy. A surveillance protocol for transplanted patients and the option of early parenchyma-sparing resection have been recently suggested.

Individuals with a “hereditary risk” of PC

At present, a surgical strategy for patients with FPC or other hereditary syndromes has not been well defined. In contrast to previous practice, when aggressive approaches such as total pancreatectomy and pancreas transplantation were proposed for patients with a positive family history and findings “suggestive” of dysplasia, a more conservative philosophy currently prevails. Even when national and international guidelines recognize PanIN lesions as potential targets for screening, they also underline the difficulty to obtain a correct diagnosis for these lesions and therefore the unlikely suitability of PanINs as targets for a clinical surveillance program.

The surgical results from international studies vary considerably (Table 6). The reasons for this discrepancy are differences in inclusion criteria, screening modalities and, most importantly, differences in indications for surgery. Current international guidelines recommend surgery for patients at risk with defined solid lesions, cystic tumors that meet criteria for resection even in a population that is not high-risk, and histologically proven PanIN-3 lesions. In high-risk individuals, the indication for surgery for cystic lesions can be adjusted according to the family history, the age and the patient’s perception of the problem, as suggested by the European guidelines for cystic tumors of the pancreas. The surgical treatment of patients at risk of PC should be undertaken in high-volume centers with specialization in this field.

DISCUSSION

The group of hereditary and non-hereditary conditions that are associated with an increased risk for PC has been well defined. Even though there is general agreement that individuals with a relative risk of over 5-10 times that of the general population should be considered for enrollment in a clinical surveillance program, consensus regarding the latter is currently lacking. As a result, data from clinical trials in this particular area are conflicting. In addition, a more fundamental reason lies at the root of divergent observations and results, namely the lack of knowledge about possible differences in natural history of the premalignant lesions that develop in the various hereditary and non-hereditary conditions of individuals at risk. However, in everyday clinical practice, the relentless stream of patients with premalignant lesions of the pancreas or individuals with a genetic risk of PC who seek medical advice, represents a significant clinical burden. On one hand, there is a clear need from the pancreatologist’s point of view to offer...
concrete advice, while on the other hand there is the pressing need to increase our knowledge about the natural history and biology of the lesions under scrutiny. For some of the conditions associated with an increased risk of PC, guidelines and protocols that provide the possibility to standardize treatment and give advice to patients, have already been established (e.g., for cystic tumors or chronic pancreatitis)\(^3\). New discoveries for example regarding cystic tumors of the pancreas are very promising as they may allow prediction of the future evolution of the cystic tumors and thus enable the clinician to decide for surgical or non-surgical treatment\(^3\). For patients with a hereditary syndrome, the situation is more complex. In several countries, a surveillance program can be rolled out only in the context of a clinical trial, because the cost-effectiveness of surveillance programs for this particular group of high-risk individuals has not been demonstrated yet. Furthermore, only very limited data are available regarding the screening of other groups of patients at risk, such as transplanted patients\(^2\). Despite the apparently long road that still lies ahead, the recent progress that has been achieved regarding the understanding and management of premalignant lesions of the pancreas, and the role that pre-emptive surgery has acquired in cancer syndromes other than those affecting the pancreas, render a similar development for pancreatic tumors more than likely. Along with the steadily increasing number of patients that will be treated for premalignant lesions, a growing demand for technical perfection and minimally invasive approaches appears unavoidable\(^1\). At the same time, due to increasing patients’ expectations, the need for a more evidence-based approach, and stricter cost-effectiveness regimes, the pancreatic team will be under increasing pressure to minimize diagnostic error and surgical risk and to optimize the use of limited resources in the health care system. For this reason, surveillance and treatment of individuals at increased risk of PC should be limited to high-volume and specialized centers with a specific clinical and research interest in preemptive pancreatic surgery.

### Table 6 Surgical procedure performed in patients at “hereditary risk” for pancreatic cancer (n)

| Ref. | Year | Resected | PanIN1 | PanIN2 | PanIN3 | Pancreas cancer | Other benign lesions | Other malignant lesions | Benign IPMN | Malignant or high-grade dysplasia IPMN | Malignant lesions or high-grade dysplasia |
|------|------|----------|--------|--------|--------|-----------------|---------------------|---------------------|----------|--------------------------------------|--------------------------------------|
| Brentnall et al\(^{110}\) | 2006 | 7        | 2      | 2      |        | -               | -                   | -                   | 2        | 1                                    | 42.8%                                 |
| Poley et al\(^{[96]}\) | 2009 | 3        | -      | -      | -      | 3               | -                   | -                   | -        | -                                    | 100%                                  |
| Verna et al\(^{[96]}\) | 2010 | 5        | -      | -      | -      | 1               | -                   | -                   | 4        | -                                    | 20%                                   |
| Ludwig et al\(^{[119]}\) | 2011 | 6        | 1      | 1      | 1      | 1               | -                   | -                   | -        | -                                    | 16.7%                                 |
| Vason et al\(^{[111]}\) | 2011 | 7        | -      | -      | -      | 7               | -                   | -                   | -        | -                                    | 100%                                  |
| Al-Sukhni et al\(^{[112]}\) | 2011 | 4        | -      | -      | -      | 1               | -                   | 1                   | 2        | -                                    | 50%                                   |
| Schneider et al\(^{[113]}\) | 2011 | 9        | 1      | 1      | 1      | 3               | -                   | -                   | 2        | -                                    | 22.2%                                 |
| Canto et al\(^{[114]}\) | 2012 | 5        | -      | -      | -      | -               | -                   | -                   | 3        | 1                                    | 40%                                   |
| Total | 46   | 2        | 4      | 5      | 14     | 3               | 1                   | 15                  | 2        | 47.8%                                |                                       |

\(^1\)The percentage refers to all resected patients, not to all patients included in the study. IPMN: Intraductal papillary mucinous neoplasm; PanIN: Pancreatic intraepithelial neoplasia.

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