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Predisposing factors for pancreatic adenocarcinoma: What is the role of imaging?

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Abstract  Early detection of pancreatic adenocarcinoma is the goal of imaging, enabling curative surgery. The identification of high-grade dysplastic precursor lesions is even more beneficial. Two forms are now better known: pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN). To detect these lesions with imaging, we need to know the patterns associated with them. A screening program could then be used to pinpoint them. This program could not be applied to the entire population. Identifying patients with an increased risk of pancreas adenocarcinoma is the first step of such screening.

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In cases of pancreatic adenocarcinoma, patients often present with unresectable disease, and even in early-stage cancer recurrence is relatively high. However, genomic sequencing has shown that a fifteen-year interval is observed from initiation to the metastatic stage, suggesting a sufficient window for early detection [1]. Yet screening cannot be offered to the entire population due to its cost.

Screening is primarily offered to patients when there is evidence of increased risk, rather than evidence of the screening’s effectiveness.

A better understanding of the natural history of this cancer could lead to better tailored screening. The aim of this article is to describe the different patterns of precancerous pancreatic diseases.
Description of precancerous lesions at pathology

There are two main precancerous pancreatic lesions: pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) [2]. Their pathologies are different, as described below (Fig. 1).

Pancreatic intraepithelial neoplasia (PanIN)

Amongst all the risk factors for pancreatic cancer, the latest to be described is PanIN. PanIN as a precursor of pancreatic cancer is a concept proposed by the 2000 WHO classification [3,4]. This new lesion may be associated with many pancreatic diseases, including diffuse conditions such as chronic pancreatitis, but also any type of tumor [5]. PanIN is a microscopic papillary or flat noninvasive epithelial neoplasm occurring in the pancreatic ductal epithelium with no or less than 5 mm of ductal dilatation [6,7]. It is characterized by columnar to cuboidal cells with varying amounts of mucin and different degrees of cytological and architectural atypia. Based on the degree of cellular and nuclear atypia, the lesions progress from PanIN-1 (low-grade dysplasia), which is probably indolent in nature and characterized by hyperplastic columnar ductal atypia, through PanIN-2 (moderate dysplasia) to PanIN-3 (carcinoma in situ), which shows high-grade dysplasia [6]. This grade is frequently associated with genetic abnormalities [6]. PanIN is rare in normal pancreatic tissue and are of low-grade dysplasia [7].

Intraductal papillary mucinous neoplasm (IPMN)

IPMN of the pancreas originates from a mucinous epithelium of the pancreatic duct (main duct or branch ducts) characterized by papillary growth and variable amounts of mucinous secretion causing ductal dilatation [8]. Depending on the degree of dysplasia, IPMNs may be benign or malignant. Malignancy can occur in 30% to 88% of patients, as in situ or invasive carcinomas according to the WHO classification [8]. In situ carcinoma (or high-grade ductal dysplasia) is characterized by a ductal epithelium with irregular projections lacking fibrovascular stalks. Invasive carcinoma is defined as the presence of single infiltrating cells or malignant infiltrative glands with an accompanying desmoplastic stromal reaction.

In situ carcinoma is confined to the ductal structure and appears as an intraductal nodule or lesion surrounded by a sharp margin created by the ductal wall. Invasive carcinoma infiltrates the pancreatic parenchyma and appears as a poorly circumscribed infiltrated parenchymal lesion [9].

Mucinous cystadenoma

The lesion may have a malignant form, i.e. mucinous cystadenocarcinoma. This malignancy appears in a mucinous cystadenoma, the lesions being nodular inside the unicellular cyst or focally invasive. The risk of malignancy is related to the size of the previous mucinous cystadenoma (the cutoff is over 4 cm), with focal nodules developing inside the wall of the cyst or thick septa [10,11]. A malignant lesion could progress to invasive adenocarcinoma if it is not resected.

No relationship between pancreatic parenchymal dysplasia and mucinous cystadenoma has been reported. Mucinous cystadenoma is often not mentioned in screening strategies addressing the predisposing factors for pancreatic carcinoma.

Risk factors

General extrinsic factors

Established risk factors for PC include smoking, diabetes, family history of PC, and obesity. They also apply to early-onset PC, i.e. before the age of 60 [12].

Tobacco

Cigarette smoking has been associated with over 30% of pancreatic adenocarcinoma-related deaths. Studies show a 100% to 200% increase in the risk of developing the disease correlated with the number of smoked cigarettes and smoking years. Nicotine, but not cigarette smoke, increases pancreatic carcinogenesis in mice [13].

Fatty pancreas

Fat replacement (also known as lipomatosis, adipose atrophy or fat infiltration) of the pancreas is pathologically
characterized by the replacement of pancreatic parenchymal cells with normal adipose tissue. The islets of Langerhans are usually relatively preserved. Most cases have normal exocrine pancreatic function. However, extreme degrees of fat replacement may be associated with significant depression of exocrine function.

Obesity (especially android obesity) and pancreatic fatty infiltration are risk factors for precancerous pancreatic lesions. Adipose tissue, particularly visceral fat, is known to play a key role in the metabolic dysfunctions triggered by obesity. In obesity, decreased adiponectin plasma levels are correlated with tumor development and progression [14].

There is a positive association (RR < 1.20) between increased BMI and pancreatic cancer, particularly in women. Associations have generally been similar in studies from North America, Europe, Australia, and the Asia-Pacific region [15]. Another study supports an association between pancreatic cancer mortality and central obesity, independent of BMI, and also suggests that being overweight or obese during early adulthood may be important in influencing the pancreatic cancer mortality risk later in life [16].

One study demonstrates the relationship between the presence and severity of PanIN lesions according to obesity and fatty pancreatic infiltration in a large series of patients. The data has been supported by morphological and pathological analyzes. These PanIN lesions were frequent and severe, and may account for the increasing incidence of pancreatic cancer in obese patients [17].

Diabetes mellitus

The prevalence of diabetes mellitus (DM) and associated diseases such as cancer is increasing significantly worldwide. Approximately 80% of patients with pancreatic cancer have glucose metabolism alterations. This suggests an association between type 2 diabetes mellitus and pancreatic cancer risk and progression. There are hypotheses that show metabolic links between insulin resistance, hyperglycemia, hyperinsulinemia, low-grade chronic inflammation, and alteration in the insulin/insulin-like growth factor axis. Recent-onset diabetes is associated with an increased risk of pancreatic cancer due to hyperinsulinemia and hyperglycemia [18].

**Genetic factors**

Inherited pancreatic cancers represent up to 10% of all pancreatic cancers (Table 1). History of pancreatic cancer in a family is a significant risk factor for any first-degree relative [2].

In familial pancreatic cancer, screening is currently focused on individuals at the highest risk of developing PC based on family history. A high-risk individual is defined as having two or more first-degree relatives with PC, or one first- or second-degree relative with PC with a confirmed mutation in a gene associated with PC. The BRCA2 gene is one of the most commonly linked to pancreatic-only cancer families. However, other hereditary cancer syndromes have also been associated with an increased risk of PC, including Peutz–Jeghers syndrome, familial atypical multiple mole melanoma syndrome, hereditary pancreatic cancer PRSS1, Lynch syndrome when there is one relative with pancreatic cancer, and BRCA1 [19].

**How to detect precancerous lesions: imaging**

PanINs are defined as lesions found only in the epithelium, and so obtaining direct evidence of a mass by CT or US is difficult. PanINs are often detected when evaluating cystic lesions in the pancreas. Of 22 PanIN reported in Japan, 6 were identified when a cystic lesion was examined more closely at pathology. After exploring the mechanism of PanIN cyst formation, Ito et al. reported that atrophy and fibrosis of acinar tissue due to PanIN causes inflammation around the pancreatic ducts, resulting in stenosis and dilatation of the main pancreatic duct and multiple cystic lesions [20]. Endoscopic ultrasound has identified some patterns associated with PanIN, including fibrous foci and microcysts [21]. This was also reported in one resected case [20].

**IPMN**

The main pattern encountered with IPMN is enlarged ducts, either the branch duct or main pancreatic duct (Fig. 2).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Main genetic diseases associated with a higher risk of pancreatic cancer.</th>
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<tr>
<td>Syndromes associated with PC</td>
<td>Gene</td>
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<tr>
<td>Peutz–Jeghers syndrome</td>
<td>LKB1, STK11</td>
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<tr>
<td>Familial atypical multiple mole melanoma syndrome</td>
<td>CDKN2a</td>
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<tr>
<td>Hereditary pancreatitis</td>
<td>PRSS1</td>
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<td>Familial PC</td>
<td>Over representation of BRCA2, PALPE</td>
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<td>Over representation of BRCA2, PALPE</td>
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PC: pancreatic cancer.
These patterns are often detected by chance. They can be asymptomatic small cysts detected during exploration of an extrapancreatic disease. They can also be discovered during the study of a newly discovered pancreas adenocarcinoma. IPMN imaging has benefited from abundant literature. Main duct IPMN is considered possible if its diameter is > 5 mm [6,8].

Computed tomography (CT) helps differentiate in situ and invasive carcinoma IPMNs. Malignant IPMNs often appear as intraductal nodules or pancreatic masses on CT images. It is interesting to note that mural nodules are mainly observed in situ IPMN (93%) whereas a pancreatic mass is mainly found in invasive carcinoma (89.5%). The presence of mural nodules has been reported in 18.5% to 50% of IPMNs. The tumor’s appearance on CT seems to be correlated to its histopathology since most pancreatic masses are associated with invasive carcinomas and most intraductal nodules correspond to in situ carcinomas [9] (Fig. 2).

**Fatty pancreas**

Small amounts of fat in the pancreas are commonly seen in the obese and elderly (Fig. 3). However, extreme pancreatic fat replacement is uncommon and more frequently involves the pancreatic body and tail than the head. The pancreas may appear normal in size or be massively enlarged, resulting in a condition known as lipomatous pseudohypertrophy [17].

The presence of pancreatic fat is not related to prediabetes or diabetes, which suggests that it has little clinical relevance for an individual’s glycemic status [22].

Fatty pancreas may be detected with CT [23] or MRI [24]. Many papers have studied different way to detect and quantify fat with CT or MRI. In/out techniques or T2 fat sat could be used. Ratios are calculated by comparing the signal or density of the spleen as this organ never contains fat.

There is no data making it possible to evaluate the risk of cancer related to the presence of fat. The association between android obesity and fatty pancreatic infiltration should therefore be considered a major risk factor for pancreatic cancer. Amongst those individuals at high risk of pancreatic cancer, more cautious screening should perhaps be performed in obese patients with a fatty pancreas [17]. There is no data available today, to the best of our knowledge, specifying the fat threshold or frequency of screening.

**Diabetes**

Dynamic contrast-enhanced at the arterial phase MR imaging has demonstrated increased endothelial permeability and decreased plasma volume in the pancreas in coronary artery disease patients with type 2 diabetes; patients with a history of diabetes for more than ten years showed a further increase in endothelial permeability [25].

**Chronic pancreatitis**

**Hereditary**

Patterns are similar to other forms of chronic pancreatitis except the calcifications: they are more frequently rounded, and target like.

**Alcohol consumption**

A meta-analysis including 19 prospective studies (21 cohorts) reported data from 4,211,129 individuals. Low-to-moderate alcohol intake had little or no effect on the risk of pancreatic cancer. High alcohol intake was associated with an increased risk of pancreatic cancer (risk ratio [RR], 1.15; 95% CI: 1.06–1.25). Pooled analysis also showed that high liquor intake was associated with an increased risk of pancreatic cancer (RR, 1.43; 95% CI: 1.17–1.74). Subgroup analyzes suggested that high alcohol intake was associated with an increased risk of pancreatic cancer in North America when the duration of follow-up was greater than ten years in studies scored as high quality, and in studies with adjustments for smoking status, body mass index, diabetes mellitus, and energy intake [26].
Predisposing factors for pancreatic adenocarcinoma: What is the role of imaging?

Who should be screened?

The ‘‘International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer’’ provided guidance on screening [27]. It stated that there is widespread agreement that, to succeed, a screening program should detect and treat T1N0M0 margin-negative PC and high-grade dysplastic precursor lesions (pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm).

‘‘It was agreed that the following were candidates for screening: first-degree relatives (FDRs) of patients with PC from a familial PC kindred with at least two affected FDRs; patients with Peutz–Jeghers syndrome; and p16, BRCA2 and hereditary non-polyposis colorectal cancer (HNPCC) mutation carriers with ≥ 1 affected FDR.’’

Consensus was not reached for the age to initiate screening or stop surveillance (Box 1).

Box 1: Who should be screened according to a consensus conference [2]

- Individuals with three or more affected blood relatives, with at least one affected FDR, should be considered for screening.
- Individuals with at least two affected FDRs with PC, with at least one affected FDR, should be considered for screening once they reach a certain age.
- Individuals with two or more affected blood relatives with PC, with at least one affected FDR, should be considered for screening.
- All patients with Peutz–Jeghers syndrome should be screened, regardless of family history of PC.
- p16 carriers with one affected FDR should be considered for screening.
- BRCA2 mutation carriers with one affected FDR should be considered for screening.
- BRCA2 mutation carriers with two affected family members (no FDR) with PC should be considered for screening.
- PALB2 mutation carriers with one affected FDR should be considered for screening.
- Mismatch repair gene mutation carriers (Lynch syndrome) with one affected FDR should be considered for screening.
- FDR: first-degree relative, PC: pancreatic cancer.
How to screen and monitor patients: CT, MRI or endoscopic ultrasound?

Results of the International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer

"It was agreed that initial screening should include endoscopic ultrasonography (EUS) and/or MRI/magnetic resonance cholangiopancreatography not CT or endoscopic retrograde cholangiopancreatography" [2] (Box 2).

Note that CT was not included in initial screening. There is agreement that radiation exposure and the suboptimal detection rate of cystic lesions preclude CT from routine pancreatic-screening tests.

Perhaps we could argue that calcifications can be depicted only with such imaging. This could lead to some cases of chronic pancreatitis being missed. No data on the sensitivity of calcifications with MDCT and ductal abnormalities with MRCP has been published. Therefore, we do not know if missing small calcifications could lead to chronic calcified pancreatitis being overlooked, and if so how frequently.

Avoiding frequent CT-related X-ray exposure seems preferable during follow-up. In the consensus paper, however, multidetector pancreatic-protocol CT was recommended secondly for the evaluation of solid lesions identified by EUS or MRI.

Yet the detection of solid mass (any size) in another of Canto’s papers shows that MDCT achieves a 3/216 (1.4%) rate compared to MRI 1/216 (0.4%) and endoscopic ultrasound 3/216 (1.4%). These results show clearly that two in three solid masses were missed by MRI but not by CT [27].

Results of screening

Comparison of endoscopic ultrasound, and MRI

One study involving 139 asymptomatic patients including high-risk individuals (> tenfold increased risk) found two solid lesions with one adenocarcinoma and one PanIN [2]. They were detected only by endoscopic ultrasound. This study reports that EUS and/or MRI detected clinically relevant pancreatic lesions in 6% of high-risk individuals. Both imaging techniques were complementary rather than interchangeable: unlike EUS, MRI was found to be highly sensitive for the detection of cystic lesions of any size; MRI, however, may have some important limitations with regard to the timely detection of solid lesions [28].

A meta-analysis of a familial high-risk population found 34% of pancreatic cancer versus 12% in the control group [29]. Endoscopic ultrasonography, which was the main means of detection, diagnosed 64.3% of pancreatic cancers. In comparison, endoscopic retrograde cannulation of the pancreas, magnetic resonance imaging, and computed tomography diagnosed 28.6%, 42.9%, and 21.4%, respectively. In patients with intraductal papillary mucinous neoplasms, however, the authors did not find a significant difference in outcome between surgery and follow-up without treatment [29,30].

MRI

One prospective, eight-year study of 262 cases of known genetic mutations and/or family history of cancer (mutation or familial pancreatic cancer) found 32% of pancreatic abnormalities via MRI (3 cancers: 1%, 1 NET: 0.3%, 15 IPMN, 2 resected: 6%, 0.7%, 65 simple pancreatic cysts: 25% [31]).

One paper studying ‘Pancreatic abnormalities in the High-Risk Group and the control group on T MRI with MRCP’ involved a small group with no pathological evidence. Their results highlight a ‘mass type lesion’ subgroup including nodules (small lesions, two non-operated, on an accessory spleen nodule), and four BD-IPMN (one BD-IPMN in the control group [32]).

How to treat detected patients

When should surgery be performed?

The consensus conference reported by M. Canto, with tables in open access, makes it possible to devise decision-making guidelines.

Box 2: How should high-risk individuals be screened [2]?

Initial screening should include EUS 83.7%, MRI/MRCP 73.5%, CT 26.5%, abdominal ultrasound 14.3%, ERCP 2.0%.

When previous screening did not detect an abnormality that met the criteria for shortening the interval or surgical resection, follow-up screening should include: EUS 79.6% MRI/MRCP 69.4%, CT 22.4%, abdominal ultrasound 4.1%, ERCP 2.0%.

Standardized nomenclature should be used to define chronic pancreatitis-like abnormalities.

Whenever a cystic lesion is detected, an additional ERCP should not be performed.

Patients with a cystic lesion without worrisome features for malignancy should have an imaging test after 6–12 months (Tanaka, 8).

When a solid lesion is detected, CT should also be performed, ERC should not be performed.

When a solid lesion is detected at baseline with an indeterminate diagnosis and the patient is not referred for immediate surgery, imaging should be repeated after three months.

When a new solid lesion is detected at follow-up with an indeterminate diagnosis and the patient is not referred for immediate surgery, imaging should be repeated after three months.

If an indeterminate main pancreatic duct stricture without a mass is detected, repeat imaging should be performed within three months.

MRCP: magnetic resonance cholangiopancreatography, ERC: endoscopic retrograde cholangiopancreatography.
Screening should only be offered to individuals who are candidates for surgery. Pancreatic resections should be performed at specialty centers (taking into account volume, morbidity and mortality rates, and the expertise available). Intraoperatively, further pancreatectomy (up to a possible total) should be performed in patients with otherwise reasonable life expectancy to achieve R0 resection of the cancer but should not be performed in a patient with otherwise reasonable life expectancy and no cancer but with unifocal PanIN-2 in the resected specimen but not at the margin, or in a patient without cancer in the resected specimen but with PanIN-2 at margin. Postoperatively, further pancreatectomy (up to a possible total) should not be performed in patients with otherwise reasonable life expectancy, or in a patient who did not have cancer but had unifocal PanIN-2 in the resected specimens but not at the margin, or in a patient without cancer but who has multifocal PanIN-2 in the resected specimens but not at the margin [2].

What outcome(s) of screening would be considered a ‘success’?

Some answers are also given in the consensus conference reported [2]. They include resectable carcinoma with PanINs and IPMNs potential targets for early detection and treatment. Detection and treatment of multifocal PanIN-3 and IPMNs with high-grade dysplasia should be considered a successful outcome of a screening/surveillance program.

Detection and treatment of invasive cancer T1N0M0 detected at baseline, or >T1N0M0 resectable with margins negative at baseline, and treatment of invasive cancer T1N0M0 detected at follow-up should also be considered successful outcomes of a screening program [2].

Pancreatic cancer screening in familial high-risk individuals: results

This screening is associated with a higher detection rate and longer survival, although screening may influence psychological function and increase the economic burden. Sixteen studies on pancreatic cancer screening were included. Five studies involved control groups, nine were observational studies without control groups, and the other two studies investigated the anxiety associated with pancreatic cancer risk. The authors found that pancreatic cancer screening resulted in a high curative resection rate (60% vs. 25%, \( P = 0.011 \)), longer median survival (14.5 months vs. 4 months, \( P < 0.001 \)), and a higher three-year survival rate (20% vs. 15.5%, \( P = 0.624 \)). They also found that familial HRIs had a higher diagnostic rate of pancreatic tumors than controls (34% vs. 7.2%, \( P < 0.001 \)). In patients who underwent regular physical examinations, more stage I pancreatic cancers were observed (19% vs. 2.6%, \( P = 0.001 \)). Moreover, pancreatic cancer screening in familial HRIs had a greater perceived risk of pancreatic cancer (\( P < 0.0001 \)), higher levels of anxiety regarding pancreatic cancer (\( P < 0.0001 \)), and an increased economic burden [29].

Conclusion

Imaging plays an increasingly important role in the screening of patients at risk of pancreatic cancer. However, data is scarce and research at an early stage. Yet the results are promising, as some dysplastic small lesions can be detected.

Disclosure of interest

The authors have not supplied their declaration of competing interest.

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