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Mini Review

Prevention and early detection of pancreatic cancer

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Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a deadly disease with globally rising incidence. It is generally diagnosed late at advanced, lethal tumor stages. PDAC is predicted to become the second leading cause of cancer deaths in the United States within 10 years. Tobacco smoking, overweight, type-2-diabetes, the metabolic syndrome, physical inactivity and heavy alcohol use cause almost half of all PDAC. Thus, pursuing a healthy lifestyle is the most effective way to reduce PDAC deaths. PDAC early detection initiatives focus on high-risk individuals and on people aged 60 (50) years and over with (early) warning signs such as new-onset and deteriorating diabetes, weight loss and unexplained acute pancreatitis. The Cancer of the Pancreas Screening (CAPS) programme has provided strong evidence for improved cancer-specific survival of high-risk individuals, whose PDAC are diagnosed by surveillance. However, PDAC screening of the average-risk, asymptomatic population is not feasible and is not recommended.

Keywords: Screening, surveillance, risk stratification, hereditary pancreatitis, new-onset diabetes

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers, with a worldwide 5-year-survival of less than 10% .[1] Globally, there are more than 467 000 deaths per year. Most PDAC are incurable, as most patients present late at advanced, lethal tumor stages, when therapeutic options are limited and ineffective. In contrast, patients with early-stage PDAC who undergo tumor resection have a much better outlook. When a 1 cm-sized PDAC is diagnosed and treated as early as at an histological stage pT1 pN0 pL0 pV0 pn0, 5-year-survival may reach 80%.[2] So far, only about 3% of PDAC patients are diagnosed at such an early stage.[2]

Epidemiology

PDAC incidence increases with age and peaks in males aged 65 to 69 and females aged 75 to 79.[1] Globally, PDAC is on the rise. From 1990 to 2021 the annual average percentage change of PDAC incidence increase was 0.72% in China and 0.33% in the USA. While tobacco smoking is the main (28.3%) avoidable risk driver in Chinese men, the main preventable causes (36.4%) in the USA are metabolic risks (obesity, high fasting plasma glucose).[3] Important to note, the incidence of early onset PDAC (before the age of 50) is also rising worldwide, especially in young women.[4] 5-year survival rates from PDAC have changed little over the past decades.

Primary prevention

Primary prevention of PDAC holds great power through lifestyle changes. Pursuing a healthy lifestyle could avert almost half of all PDAC.[1–4] Following a prudent diet, avoiding excess body weight, engaging in an active exercise program, minimizing alcohol intake, avoiding chronic hepatitis C infection and completely refraining from smoking tobacco are very effective habits in PDAC prevention and are supported by ample scientific evidence. For the time being, primary prevention is the best option to significantly reduce the burden of PDAC deaths.

Tobacco smoking

The relative risk increase for developing PDAC among smokers is 1.5 to 2fold.[5] The more and longer you smoke the higher the PDAC risk. In the 2017 Global Burden of Disease Study, 21.1 percent of PDAC-related deaths were primarily attributable to smoking.[1] In the USA cessation of tobacco smoking could eliminate almost 25 percent of PDAC deaths.[5] There appears to be a (synergistic) interaction when cigarette smoking is combined with (heavy) alcohol intake. Interestingly, minimizing alcohol consumption will further reduce PDAC risk.[6]

Type 2-Diabetes, metabolic syndrome

Abnormal glucose metabolism, insulin resistance, and hyperinsulinemia

are major etiologic risk factors for PDAC. Chronic hyperinsulinemia, systemic inflammation, metabolic and hormonal dysbalances, oxidative stress, abnormalities of the insulin growth factor (IGF)-I signaling system and advanced glycation end products can create a PDAC-promoting environment. In the 2017 Global Burden of Disease Study[1] 8.9 percent of PDAC-related deaths were primarily attributable to long-standing (type 2-) diabetes. The relative risk for PDAC in patients with diabetes compared with patients without diabetes is 2.08 (95% CI 1.87-2.32).[7] Interestingly, the increased PDAC risk can be reversed by long-term remission of type-2-diabetes.[8,9] This also holds true for the metabolic syndrome. The metabolic syndrome increases PDAC risk, too.[10] Again recovering from the metabolic syndrome is associated with a decreased PDAC risk.[11] These observations underline the important role of timely lifestyle interventions or considering bariatric surgery as to lower long-term PDAC risk.

Obesity and physical inactivity

Excess body weight and lack of physical activity are associated with increased PDAC risk.[12,13] In the 2017 Global Burden of Disease Study[1] 6.2 percent of PDAC-related deaths were primarily attributable to high body mass index. Conversely, persistent weight reduction achieved in obese patients by either lifestyle intervention and/or bariatric surgery goes along with a significant reduction of PDAC risk.[8,9] Important to say, physical inactivity is associated with increased PDAC risk, too. The higher the level of physical activity, the lower the PDAC risk.[13] For the time being primary prevention is the best option to significantly reduce the burden of PDAC deaths.

Hepatitis C infection

A recent study of 6 330 856 US veterans[14] has shown that chronic hepatitis C infection increases PDAC risk about 2fold. If antiviral therapy can reverse the risk, has not been studied yet.

Screening for pancreatic cancer in high-risk groups

Hereditary PDAC

5–10% of PDAC are caused by pathogenic germline variants (PGVs) in predisposition genes associated with hereditary PDAC risk. The genes known to be associated with hereditary PDAC risk are ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2/EPCAM, MSH6, PMS2, STK11, PRSS1, and TP53. Lifetime risks for developing PDAC linked to PGVs in these predisposition genes are summarized in Table 1.[15] Members of a hereditary PDAC family who have inherited a PGV are advised to consider PDAC surveillance, see.[15] Surveillance of those family members has been shown to lead to earlier PDAC diagnosis, more early-stage PDACs and a better cancer-specific 5-year-survival.[16,17]

PDAC surveillance relies on annual contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS), with consideration of shorter intervals based on clinical judgment, for individuals found to have potentially concerning abnormalities on screening.[15] Artificial intelligence-assisted radiological imaging of the pancreas is promising but has not yet been studied prospectively in HRI.[18]

Individuals with PGV in STK11 and CDKN2A should start PDAC surveillance at age 30-35 (STK11) and age 40 (CDKN2A) or 10 years younger than the earliest PDAC diagnosis in the family, whichever is earlier. Individuals with PGV in ATM (with one or more affected first-degree blood relatives (FDBR)) and individuals with PGV in BRCA2 (with at least one affected FDBR or at least two affected relatives of any degree) should begin PDAC surveillance at age 50 or 10 years younger than the earliest PDAC diagnosis in the family, whichever is earlier. Similarly, patients suffering from PRSS1-associated chronic pancreatitis are advised to start PDAC surveillance at age 40 or 20 years after the first pancreatitis episode, whichever is earlier. In addition, several studies comprising large cohorts from India, South Korea and France argue for offering surveillance to patients suffering from SPINK1-associated chronic pancreatitis, too.[19]

Important to note, however, there are still uncertainties about the potential benefits and about cost-effectiveness of PDAC screening. A family member at risk who starts screening at age 50 years may be surveilled for as long as 30 years. If PDAC lifetime risk is 10%, PDAC will be diagnosed at a rate of about 0.33% per year of surveillance (1 per 300 person-years). With a PDAC lifetime risk of 3%, PDAC will be found at a rate of about 0.1% per year of surveillance (1 per 1000 person-years).

Table 1 Lifetime risk of PDAC among hereditary cancer syndromes[15]

Gene	Lifetime risk of PDAC[15]
ATM	~5-10%
BRCA1	≤5%
BRCA2	5-10%
CDKN2A	>15%
MLH1	<5-10%
MSH2/EPCAM	<5-10%
MSH6	<5-10%
PALB2	2-5%
STK11	>15%
TP53	~5%
PRSS1 (with pancreatitis phenotype)	~25-44%*

*lifetime PDAC risk is significantly lower in non-smokers

ATM: Ataxia Telangiectasia Mutated; BRCA: Breast Cancer Associated; CDKN2A: Cyclin-Dependent Kinase Inhibitor 2A; MLH1: MutL Homolog 1; MSH: MutS Homolog; EPCAM: Epithelial Cell Adhesion Molecule; PALB2: Partner And Localizer Of BRCA2; STK11: Serine/Threonine Kinase 11; TP53: Tumor Protein P53; PRSS1: Serine Protease 1

Familial pancreatic cancer

PDAC aggregates in some families without a known PDAC genetic predisposition syndrome. Familial PDAC (FPC) is defined as a family with two or more individuals with PDAC who are first-degree relatives without a PGV identified in a PDAC susceptibility gene. A person with two or three first-degree blood relatives (FDBR) diagnosed with PDAC have a lifetime risk that is increased by 6.4-fold and 34-fold, respectively.[20–22] PDAC surveillance starting at age 50-55 years (or 10 years younger than the youngest PDAC in the family) is recommended to any FPC family member who is FDBR of a PDAC patient.[23]

Pancreatic cystic tumors, IPMN

Mucinous pancreatic cysts, including intraductal papillary mucinous

neoplasms (IPMN) and mucinous cystic neoplasms are believed to give rise to 5–15% of PDAC. Several guidelines on how to manage patients with pancreatic cysts or cystic pancreatic tumors are available and conferences for a more uniform, generally consented guideline are being organized.[24,25] In IPMN-patients risk stratification and indications for surgery are based on high-risk stigmata, worrisome features and the individual situation of the patient, see Kyoto guidelines.[24]

Early detection of sporadic PDAC

The incidence of sporadic PDAC in the Western population ≥50 years of age is about 25-35 per 100,000 people. In light of this low incidence PDAC screening of asymptomatic people at average risk is not recommended. Even when considering an almost perfect test with 99% sensitivity and with 99% specificity PDAC screening will result in a large number of false positive findings. Thus, PDAC screening of 100,000 asymptomatic people with such an almost perfect test will produce 1000 false-positive results. If specificity is set to 95%, the false-positives rise to 5000. Despite correctly identifying most of the 25 to 35 PDAC cases (among the 100,000 being screened) the many false-positive findings argue against PDAC screening of the average-risk asymptomatic population.

New-onset diabetes

Early detection initiatives focus on high-risk individuals (HRI) with a familial, genetic and hereditary PDAC trait as well as on older (>50-60 years of age) symptomatic patients with (early) warning signs such as (glycemically-defined) new-onset and worsening diabetes,[26,27] unintended weight loss[28] or unexplained acute pancreatitis.[29–32] PDAC risk in new-onset diabetes (NOD) has recently been reported in a large prospective study of 18, 838 patients (>50 years of age) with NOD identified at its first glycemic evidence (GNOD) using health system-wide electronic medical records.[26] The age, sex and race adjusted incidence of PDAC within three years GNOD date was ~0.62 %. In white patients aged 60 or over 3-year-PDAC risk was higher than 1%, When considering a 3-year-surveillance period after GNOD, PDAC will be diagnosed at a rate of 0.2 to 0.33% per one year of surveillance. Currently, there are still uncertainties about the potential benefits and cost-effectiveness of PDAC screening in patients over 50 (60) with NOD; but the results of an ongoing prospective clinical trial will be available by next year.[33] CT screening of all patients with NOD is not feasible. However, patients over 60 years of age presenting with both NOD and unintended weight loss have a 10-25fold increased risk of harboring an underlying PDAC.[34] Therefore, the NICE institute in London has been recommending for several years that NOD patients with concurrent weight loss who are >60 years of age should undergo radiological imaging for PDAC within a fortnight.[28,35]

Unexplained acute pancreatitis

PDAC can induce acute pancreatitis (AP) by obstructing the main pancreatic duct, with an incidence of 0.9%- 12.4%.[29–32] Unexplained acute pancreatitis after the age of 60 years has been suggested as an early indicator of PDAC.[36] If the cause of AP remains unclear after a thorough work-up, 4-year-PDAC risk in an AP- patient aged 60 or over may be as high as 3–7%.[29–32]

A recent retrospective study conducted by Yamao et al.[32] has shown the efficacy of early imaging post-AP in detecting occult PDAC in patients with presumed idiopathic or alcoholic AP. Performing magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) within three months following AP significantly improved early PDAC detection and enhanced overall survival rates compared to delayed or absent monitoring.[32] Patients (median age of 72.5 years) in the early surveillance PDAC group were diagnosed earlier than those in the non-early surveillance group (median, 52 vs. 886 days; p< 0.01). Surgical resection rate was higher in the early surveillance PDAC group (91.7%vs. 40.0 %; p<0.01), and early-stage PDAC (stages 0 and I) was more frequently detected in this group (83.3%vs. 6.7 %; p<0.01). In addition, primary tumor size was smaller in the early surveillance PDAC group (median, 10 mm vs. 25 mm; p<0.01). During a median follow-up of 1027 days PDAC was diagnosed in 17 out of 263 patients (6.5%) with presumed idiopathic AP.[32] Although controlled prospective studies are still lacking, current guidelines advise to consider underlying PDAC in older (>60 years of age) patients and to repeat pancreatic imaging 3 to 6 months, after AP of unknown cause was diagnosed. Interestingly, biomarker signatures have recently been shown to assist in PDAC surveillance, too.[37,38] Future prospective studies will have to define the time intervals, the duration and the modalities of optimal PDAC surveillance in this group of patients.

Biomarkers

Earlier diagnosis of PDAC is key to improving overall survival in patients with this hard-to-treat cancer. The Cancer of the Pancreas Screening (CAPS) programme has shown that despite yearly EUS and/or MRCP imaging as many as 43% of PDAC in high-risk groups are still diagnosed at advanced stages.[17] Biomarkers are being developed to assist early PDAC detection in high-risk groups. While metabolic biomarkers are being evaluated in urine, breath samples, pancreatic/duodenal juice and blood, liquid biopsies and proteomics focus on blood. There are more than 20 ongoing controlled prospective clinical trials evaluating the efficacy of various novel biomarkers for early PDAC detection. Several of those novel biomarkers are very promising indeed.[39] Carbohydrate antigen 19-9 (CA 19-9) yet remains the only valid biomarker, which has been used in real-world clinical PDAC management so far. Recently, two biomarker signatures have been successfully evaluated for PDAC screening in high-risk groups.[37,38] First, the plasma m-Metabolic signature is a mass-spectrometry-based tool, designed to achieve a very high negative predictive value, with high specificity (93.6%) to safely exclude PDAC in patients with chronic pancreatitis or pancreatic lesions necessitating further diagnostic assessment.[37] Second, a serum biomarker signature composed of tissue inhibitor of metalloproteinase 1, intercellular adhesion molecule 1, cathepsin D, thrombospondin 1, and carbohydrate antigen 19-9 has been tested for detection of early-stage PDAC in high-risk groups. That biomarker signature distinguished early-stage PDAC (n=202) from high-risk controls (n=864) with 78.5% sensitivity (95% CI, 72.5%-83.9%) and 93.5% specificity (95% CI, 91.9%-95.2%), significantly outperforming carbohydrate antigen 19-9 alone (P< .001).[38] Envisaged controlled trials will now prospectively evaluate the diagnostic accuracy of either test in large cohorts of HRI.

Conclusions

Tobacco smoking, overweight, type 2-diabetes, the metabolic syndrome, physical inactivity and heavy alcohol use are responsible for almost half of all PDAC. Pursuing a healthy lifestyle holds a lot of promise as to reduce personal PDAC risk. PDAC surveillance is being increasingly performed in HRIs, providing hope of earlier PDAC detection and improved long-term survival. However, there remains debate about which HRI should be eligible for surveillance, about tools and time intervals of surveillance. Early detection initiatives of sporadic PDAC currently focus on older (>60 years) patients presenting with unexplained acute pancreatitis or with glycemically-defined NOD and concurrent weight loss. Both biomarkers and artificial intelligence-

assisted radiological imaging are promising new tools for early PDAC detection in high-risk groups.

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None.

Conflicts of interest

None.

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