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Screening for pancreatic cancer: a review for general clinicians

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Pancreatic cancer (PC) is an exceptionally lethal malignancy with increasing incidence and mortality worldwide. One of the principal challenges in the treatment of PC is that the diagnosis is usually made at a late stage when potentially curative surgical resection is no longer an option. General clinicians including internists and family physicians are well positioned to identify high-risk individuals and refer them to centers with expertise in PC screening and treatment where screening modalities can be employed. Here, we provide an up-to-date review of PC precursor lesions, epidemiology, and risk factors to empower the general clinician to recognize high-risk patients and employ risk reduction strategies. We also review current screening guidelines and modalities and preview progress that is being made to improve screening tests and biomarkers.

It is our hope that this review article will empower the general clinician to understand which patients need to be screened for PC, strategies that may be used to reduce PC risk, and which screening modalities are available in order to diminish the lethality of PC.

Key words: pancreatic cancer, cancer screening, risk factors, risk reduction, biomarkers.

INTRODUCTION

Pancreatic cancer (PC) represents a particularly challenging clinical entity with a 5-year survival rate of only 9.3% [1]. PC carries a high mortality rate due to multiple factors, including the often asymptomatic presentation of early stage PC, the anatomical proximity of PC to multiple crucial structures whose involvement can preclude surgical resection, the unique biology of PC including resistance to current immunotherapies, and the lack of both cost-effective population-wide screening protocols and PC-specific biomarkers that enable detection at early stages when potentially curative surgical resection can be offered [2, 3].

Despite challenges in screening for PC, much is known about the epidemiology of PC and both high-quality data and society guidelines provide a valuable framework to decide which individuals should be screened for PC and which screening tests should be utilized. Appropriate screening for PC can yield a significant survival benefit as localized, early-stage PC can often be surgically resected, leading to a 5-year survival rate for localized PC of 37.4% compared to less than a third of that for PC that has spread to lymph nodes or beyond [1].

In this review, we provide up-to-date information on PC precursor lesions, epidemiology and risk factors for PC, and screening tests and guidelines that exist to guide clinical decision-making. Knowledge of the risk factors for developing PC can guide risk-reduction strategies and inform the clinician as to which patients should be screened. The referral of the correct patient population to specialty centers that perform PC screening and treatment can make a life-saving impact. We also discuss screening modalities and biomarkers and overview active research being performed to improve the efficacy of PC screening.

PANCREATIC CANCER PRECURSOR LESIONS

At least 90% of primary pancreatic neoplasms are pancreatic ductal adenocarcinomas (PDACs), with the remainder divided between pancreatic neuroendocrine tumors and other more rare malignancies [4, 5]. As such, PC and PDAC are often used interchangeably, a convention this review also utilizes, though it is important to note that the other pancreatic neoplasms have different biologies, prognoses, and treatments. PDACs usually arise in a stepwise manner from pancreatic intraepithelial neoplasias (PanINs). PanINs are pathologically graded as low (PanIN-1), intermediate (PanIN-2), or high (PanIN-3) grade based on their degree of cellular and nuclear atypia [5]. DNA sequencing studies have demonstrated an escalation in genetic alterations as PanINs increase in grade and progress towards

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PDAC, with early mutations in *KRAS* followed by alterations in *P16, P53,* and *DPC4/SMAD4* among others [6]. Typically, PanINs are microscopic and difficult to find on screening, though in cases where PanINs are resected before developing invasive features the 5-year survival rate improves up to 85% [7].

A smaller number of PDACs arise from intraductal papillary mucinous neoplasms (IPMNs), which are cystic lesions with mucinous lumens and papillary growths that can readily be detected on imaging. IPMNs can be subclassified based on histology and whether they involve the main pancreatic duct (main-duct type) or side branch (branch-duct type) [8]. Approximately 20–30% of IPMNs are found to contain invasive cancer on resection, with main-duct types having the highest risk [9]. Not all IPMNs require resection, and guidelines exist to determine follow up upon their detection based on size and features [10]. IPMNs may be associated with the phenomenon of field cancerization (also called a "field defect") whereby the growth of one IPMN indicates that cancerous lesions may arise in other areas of the pancreas [11]. Further research in elucidating the biology of IPMNs, and IPMN pathology and screening guidelines are an active area of research [12].

Rarely, mucinous cystic neoplasms (MCNs), which are slow growing cystic tumors that are usually found in women, may develop into PDACs, though the malignant potential of MCNs is not clear [13]. Unlike IPMNs, MCNs are not associated with field cancerization and their resection leads to a 5-year survival rate of nearly 100% [14]. Despite a growing understanding of PC precursor lesions, only 15–20% of PC is surgically resectable at time of diagnosis due to a current lack of effective, population-wide screening tests that can identify early-stage disease [15].

EPIDEMIOLOGY AND RISK FACTORS

The incidence and mortality of PC are both increasing. According to the National Institutes of Health Surveillance, Epidemiology, and End Results (SEER) Program database, in 2019 there were an estimated 56,770 new cases and 45,750 deaths from PC in the United States, representing 3.2% of new cancer cases and 7.5% of all cancer deaths in the United States [1]. According to the most recent GLOBOCAN estimates, there were 458,918 new cases and 432,242 deaths from PC worldwide in 2018, representing 2.5% of new cancer cases and 4.5% of all cancer deaths worldwide [16]. Given current trends, worldwide PC incidence and mortality are both expected to increase by approximately 80% by the year 2040 [17].

There are many identified modifiable and non-modifiable risk factors for PC [18]. Modifiable risk factors for developing PC include acute and chronic pancreatitis, diabetes mellitus, tobacco smoking, unfavorable dietary factors (including consumption of animal products, high starch diets, and Western type diets), obesity, and physical inactivity (Table 1). A number of other modifiable risk factors, including Hepatitis B, Hepatitis C, and *H. pylori* infection, are under active investigation [18].

Table 1

Modifiable Risk Factors for the Development of Pancreatic Cancer

Risk Factor	Risk	References
Chronic pancreatitis	RR of 13.3	[19]
Cigarette smoking	RR of 1.7–2.4	[20,21]
Unfavorable diet patterns*	RR of 1.69–2.4	[22]
Diabetes mellitus	RR of 1.63–2.1	[23,24]
Acute pancreatitis	HR 2.02	[25]
Obesity (BMI ≥30 kg/m^2)	RR of 1.19–1.36	[26,27]
High physical activity (protective)**	RR of 0.78–0.93	[28]

RR = relative risk. HR = hazard ratio. * = Defined as diet patterns high in animal products, starches, or with Western features [22]. ** = compared to low physical activity [28].

The risk incurred by modifiable risk factors can be reduced by lessening or eliminating the underlying risk factor. For example, in obese individuals, each change in BMI by 5 kg/m^2 has been correlated with a proportionate change in the RR of developing PC by 1.16 in men and 1.10 in women [29]. Smoking abstinence reduces the risk of PC over time to approximately baseline risk by 20 years [30]. The presence of multiple modifiable risk factors appears to incur additional risk, though the magnitude of increased risk for each additional risk factor and the interaction between them is

unclear. The European Prospective Investigation into Cancer (EPIC) and Nutrition cohort, which investigated multiple lifestyle factors and PC risk in 400,577 participants, calculated that 19% of PC risk can be attributed to lifestyle, with 14% of PC risk still attributable to lifestyle after smoking was removed [31]. Unfortunately, many of the modifiable risk factors for PC, including diabetes mellitus, obesity, and physical inactivity are highly prevalent in the United States and worldwide, highlighting the intersection between these public health crises and PC risk.

There are a number of non-modifiable risk factors for developing PC that have been studied (Table 2). These risk factors vary from genetic cancer predisposition syndromes to other diverse risk factors that include non-O blood type, non-European descent, and family history of PC (Table 2). A key risk factor for the general clinician to know is familial pancreatic cancer (FPC), which is defined as an individual who has at least two first-degree relatives (FDRs) affected by PC without a recognized cancer-predisposing mutation. Approximately 5–10% of individuals who develop PC have FPC and identifying this subpopulation of patients is one of the most important contributions a general clinician can make to reducing PC mortality [32]. Two other key risk factors for the general clinician to recognize are Peutz-Jeghers syndrome and hereditary pancreatitis (Table 2), which endow the highest risk for developing PC and merit earlier screening as discussed below.

Table 2

Non-Modifiable Risk Factors for the Development of Pancreatic Cancer

Risk Factor	Risk	References
Genetic Syndromes		
STK11/LKB1 – Peutz-Jeghers syndrome	SIR of 132	[33]
PRSS1 – Hereditary pancreatitis	SIR of 53	[33]
CDKN2A – Familial atypical mole and melanoma syndrome	SIR of 13–38	[33, 34]
MMR* Gene Mutations – Hereditary nonpolyposis colon cancer/Lynch syndrome	HR of 8.6	[35]
TP53 – Li-Fraumeni syndrome	RR of 7.3	[36]
APC – Familial adenomatous polyposis	RR of 4.46	[37]
BRCA2 – Hereditary breast and ovarian cancer syndrome	OR of 3.5	[33]
ATM heterozygous – Ataxia telangiectasia (carrier status) *PALB2* – Hereditary breast cancer syndrome	RR of 2.41 Unclear- under active investigation	[38] [39]
Family History of Pancreatic Cancer		
3 First-degree relatives affected (FPC)	SIR of 17.02	[40]
2 First-degree relatives affected (FPC)	SIR of 3.97	[40]
1 First-degree relative affected	OR of 1.14–2.53	[41]
1 Second-degree relative affected	RR of 1.59	[42]
Blood Type		
Non-O blood group	HR of 1.32–1.72	[43]
Ethnicity		
Native Hawaiian	RR' of 1.6	[44]
Japanese American	RR' of 1.33	[44]
African American	RR' of 1.2	[44]
Latino American	RR' of 0.9	[44]

SIR = standardized incidence ratio. OR = odds ratio. HR = hazard ratio. RR = relative risk. MMR = mismatch repair. RR' = relative risk compared to patients of European descent (Huang et al 2019). * = *MLH1*, *MSH2*, and *MSH6* genes [35]. FPC = familial pancreatic cancer (at least two first-degree relatives affected).

Of note, research is underway to further characterize the effect of single-nucleotide polymorphisms (SNPs) on PC risk. SNPs are single-base changes in the sequence of a person's DNA and are typically identified by DNA sequencing or DNA microarray from samples such as DNA isolated from peripheral venous blood [33]. Many SNPs have been identified that can either increase or decrease the risk of developing PC, though the mechanism of how these SNPs affect PC risk is not clear and is an area of active research [33] As further research elucidates the impact and interrelationship of modifiable and non-modifiable risk factors for PC development, this should empower the development of better clinical decision aids to assist clinicians in identifying high-risk patients so that they can be referred for screening with the appropriate tests as described below.

SCREENING GUIDELINES

The International Cancer of the Pancreas Screening (CAPS) Consortium convened in 2011 and 2018 to produce and update extensive PC screening guidelines based on the consensus of a large, multinational group of experts in PC biology, epidemiology, and treatment. The 2019 CAPS guidelines were recently released and provide updated PC screening guidelines [45].

General agreement was reached among CAPS consortium members that high-risk individuals should be screened for PC, with risk either being genetic, familial, or both (see Table 3).

Consensus for the starting age to initiate screening in high-risk individuals was 50–55 years for patients who meet familial risk criteria, 40 for patients with Peutz-Jeghers syndrome or familial atypical mole and melanoma syndrome, and 45–50 for patients with other mutations. For all high-risk individuals, agreement was reached that screening should begin 10 years before the youngest age at which a blood relative developed PC, if this age is lower than the general age guidelines above [45]. No consensus was reached when to end screening.

The American Society of Clinical Oncology (ASCO) published a provisional clinical opinion in 2018 stating that individuals with FPC should be evaluated for PC susceptibility with a thorough family history and potentially genetic testing [46]. They recommended that individuals who develop PC should undergo hereditary and potentially germline genetic analysis, after discussion of risks and benefits, to determine familial predisposition and identify the need for PC surveillance. They also provided guidelines on which individuals should be screened based on genetic and familial risk (see Table 3). In agreement with the CAPS and the National Comprehensive Cancer Network (NCCN), ASCO recommends that PC screening should be performed at centers with appropriate expertise in managing individuals with PC risk [45–47].

Table 3

Society Guidelines on Selecting Individuals who Merit Screening for Pancreatic Cancer

Risk Category	**CAPS 2019 Guidelines** [45]	**ASCO 2018 Provisional Clinical Opinion** [46]
Genetic	All individuals with Peutz-Jeghers or FAMM syndrome. All individuals with hereditary pancreatitis after their first attack.	
Genetic + Familial	Individuals with pathologic mutations of *BRCA2, PALB2, CDKN2A, ATM,* or MMR genes* + 1 FDR with PC.	Individuals with FH of PC and pathologic mutation of *APC*, *ATM, BRCA2, BRCA1, CDKN2A,* MMR genes*, *PALB2, STK11,* or *TP53.*
Familial	Individuals with FPC or two or more BRs + 1 FDR with PC.	Individuals with at least one FDR with FPC.

CAPS = The International Cancer of the Pancreas Screening (CAPS) Consortium. ASCO = American Society of Clinical Oncology. FAMM = familial mole and melanoma syndrome. * = *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM.* PC= pancreatic cancer. FDR = first-degree relative. BR = blood relative. FH = family history. FPC = familial pancreatic cancer (PC affecting two FDRs).

The United States Preventive Service Task Force (USPSTF) published and recently reaffirmed its decision to provide a Grade "D" recommendation for PC screening in asymptomatic, average-risk individuals. This designation means that the potential benefits of PC screening in asymptomatic, average-risk adults do not outweigh the potential harms [48]. This is consistent with CAPS and NCCN guidelines [45, 47]. It is important to note that even though societies currently do not recommend screening average-risk adults, it has been demonstrated that screening high-risk populations for PC is cost-effective. For example, the Danish national screening program identified that screening patients with either FPC or hereditary pancreatitis yielded a cost per quality-adjusted life-year (QALY) of US $42,128, which is below the US $50,000 per QALY that is typically used to identify a cost-effective intervention [49]. As imaging modalities improve and more specific biomarkers are found, as discussed below, we anticipate that screening guidelines will continue to evolve and the cost effectiveness of screening will continue to improve.

SCREENING TESTS

A variety of PC screening modalities have been studied (see Table 4). When screening is indicated, the first line tests are generally magnetic resonance imaging/magnetic retrograde cholangiopancreatography (MRI/MRCP) or endoscopic ultrasound (EUS). These modalities are preferred over computed tomography (CT) because they confer higher detection rates of small pancreatic lesions and do not expose patients to ionizing radiation. In one study, MRI and EUS

detected more pancreatic lesions (33.3% and 42.5%, respectively) versus CT (11%) [50]. The concordance between MRI and EUS was better than that between EUS and CT when compared to lesion size, number, and location, and MRI detected more cases of cyst communication with the main pancreatic duct, a feature diagnostic for IPMN and concerning for malignant potential [50].

Table 4

Modalities for Pancreatic Cancer Detection

Modality	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	References
MRI	88–100	63.4–94	71.4–96.2	68.5–100	[68–70]
MRCP	97.1–100	81.8–88	94.4–97	90–100	[71,72]
EUS	79–97.5	53–90.3	82.2	71.3	[56,68,73]
EUS-FNA	85–92	96–98	90–98	72–80	[56,74,75]
CT*	66.7–100	60–100	61.5	56.7	[73,76–80]
PET/CT*	71–92	64–92	79.4–96	25–88.9	[73,76]
Transabdominal Ultrasound	75–98	90–99	86–95.9	12.2–98	[81–83]
CA 19–9	70–90	68–91	41–95	65–98	[84]
CEA	40–92	59–90	25–91	53–98	[84]

MRI = magnetic resonance imaging. MRCP = magnetic resonance cholangiopancreatography. EUS = endoscopic ultrasound. FNA = fine-needle aspiration. CT = computed tomography. PET = positron emission tomography. * = Sensitivity and specificity for CT vary drastically depending on detector and protocol [73].

EUS has been found to have higher sensitivity than MRI for detecting pancreatic lesions [51]. EUS can be coupled with fine-needle aspiration/biopsy (FNA/FNB) to sample cyst fluid and suspicious solid tissue lesions, allowing gene and protein analysis that may facilitate diagnosis of pre-malignant or malignant lesions and determine subsequent management [52]. EUS also allows pancreatic fluid collection for PC biomarker analysis, which is an active area of research [53]. Linear array EUS imaging (providing ultrasound images parallel to the long-axis of the endoscope) identifies more lesions on initial examination and has a lower lesion miss rate than radial array [54]. EUS-FNA/FNB is generally indicated for solid lesions equal to or larger than 5 mm, cystic lesions with concerning features, and suspicious main pancreatic duct strictures [45]. However, EUS-FNA/FNB does have limitations that include a low sensitivity of cytology from cystic lesions, low fluid volume yield from small cysts, and variability depending on procedure and technique employed [55]. Modified EUS protocols, including EUS elastography and contrast-enhanced ultrasound, are actively being investigated to further improve the sensitivity of EUS for PC screening [56].

CT has not traditionally been considered a first-line screening modality due to multiple limitations including a 3–5 mm size threshold for lesion detection, lack of sensitivity for detecting early lesions, and exposure of the patient to ionizing radiation [57]. CT can be employed for PC screening in individuals who cannot undergo MRI or EUS or to further evaluate solid lesions detected and inconclusively characterized by MRI and EUS. Many of the limitations of CT have been overcome by contrast-enhanced, multidetector, high-resolution pancreatic-protocol CT, which greatly increases the sensitivity for PC [58]. A typical pancreatic protocol consists of triphasic (arterial, later arterial, and venous phases) imaging. This allows for rapid anatomic coverage coupled with excellent resolution of tumor growth [71]. For intraductal papillary mucinous neoplasms (IPMNs), multidetector CT has been found to perform similarly to MRI in identifying the malignant potential of the lesions [59], revealing the utility of CT as a follow up imaging.

Transabdominal ultrasound can also be used to detect pancreatic lesions, but is not traditionally considered a first-line test due to variable diagnostic sensitivities [60]. Transabdominal ultrasonography of the pancreas is often obscured by bowel gas and can be technically challenging with the obese patient; however, sensitivity and specificity of transabdominal ultrasonography for PC can improve up to 89% and 99%, respectively, with optimizations to operator technique and increased operator expertise [61], making this modality a potentially cost-effective, noninvasive approach to PC screening when performed in the correct setting. ERCP is not recommended as an initial screening test or for follow-up testing when lesions are discovered because it does not improve diagnostic yield and incurs a risk of postprocedural pancreatitis that can be as high as 15.1% [62,63].

When pancreatic lesions are found on imaging, guidelines from the CAPS consortium [45], American

College of Gastroenterology [64], and American College of Radiology [65] provide evidence-based strategies for further management. Generally, small cysts without worrisome features or nonspecific parenchymal changes associated with chronic pancreatitis may be followed by annual screening imaging. However, cysts with complex or worrisome features, solid lesions, and pancreatic duct strictures or dilations are concerning abnormalities that will require evaluation for increased screening frequency, follow-up imaging, FNA/FNB, or surgical resection [45].

If PC is suspected based on the results of imaging, or if PC is identified on biopsy, then guidelines recommend obtaining a serum carbohydrate antigen (CA) 19–9 level [45, 47]. Given the sensitivity and specificity of CA 19–9 for PC of 78.2% and 82.8%, respectively, CA 19–9 measurements are not appropriate for population-wide PC screening, though they do have utility for prognosis and monitoring of treatment response [66]. Carcinoembryonic antigen (CEA) has limited utility for screening and diagnosis of PC given a sensitivity and specificity of 44.2% and 84.8%[66], though combining CA 19–9 and CEA measurements may increase the diagnostic accuracy for PC [67]. High-risk patients should also be screened for new-onset diabetes mellitus with a fasting glucose or hemoglobin A1c [45]. New-onset diabetes mellitus may precede PC by several years, but is an insensitive marker, projecting a three-year cancer incidence of only 1% [24]. Active research is being conducted to improve the utility of PC screening tests and identify novel biomarkers that will empower improved screening and earlier diagnosis, as described below.

FUTURE DIRECTIONS

The major limitation to PC screening is the lack of cost-effective screening modalities that can detect localized, early-stage PC that is potentially curable by surgical resection on a population-wide scale [63]. To this end, active research is seeking to both improve the efficacy of current screening modalities and to develop new biomarkers that have sufficient sensitivity for population-wide screening.

One innovative approach is the incorporation of artificial intelligence (AI) with imaging and screening, particularly deep learning, a methodology whereby a computer can take unstructured data and organize it using human modeled neural networks [85, 86]. Early studies have shown that augmentation of imaging such as EUS with AI can aid in diagnosing malignant lesions [87, 88]. Furthermore, a recent study utilizing an artificial neural network approach to analyzing personal health data found an ability to predict PC with a sensitivity and specificity as high as 87.3% and 80.8% based on health biometrics alone [89]. Although still early in development, the incorporation of AI represents a cutting-edge frontier in PC screening and risk stratification.

Another promising avenue is advancements in PC biomarkers. Currently, CA 19–9 is the only FDA approved PC biomarker but many others including Glypican 1 (GPC1), PAM4, microRNAs (miRNAs), circulating tumor DNA (ctDNA), exosomes, and others are being actively studied [90]. GPC1 expression is much higher in PC tissue cells compared to those of normal tissues and GPC1 levels are correlated to perineural invasion and poor survival [91]. An early trial of utilizing GPC1 as a biomarker found a near-perfect sensitivity and specificity for detecting PC, though further research and validation is needed [92]. PAM4/ clivatuzumab is a monoclonal antibody with specificity for early stage PC that may have utility as a theranostic agent that can both diagnose and treat PC when conjugated to radionuclides such as ^{90}Y [93]. miRNAs detected in urine and feces have been shown to have promise for PC screening, with a combination of miRNAs in urine found to have a sensitivity and specificity of 83.3% and 96.2% in one trial [94]. ctDNAs have been shown to predict recurrence and survival, and analyzing for ctDNA from venous blood samples may represent a way to screen for multiple cancers at once [95]. Pancreatic cancer cells also release exosomes that may have utility in both the diagnosis of PC and in anticancer therapy, as depletion of PC-derived exosomes has been demonstrated to sensitize PC cells to chemotherapy agents in cell culture [96]. We predict that the combination of advancements in AI and biomarkers will revolutionize detection of PC in the years to come.

CONCLUSIONS

PC is a highly lethal malignancy that is projected to nearly double in incidence and mortality over the next 20 years. An understanding of the epidemiology of PC, risk factors for developing PC, and PC screening guidelines and modalities is crucial for the general clinician. This knowledge will enable risk reduction strategies and timely referral of the appropriate patient population to centers where lifesaving, state-of-the-art PC screening modalities

can be employed (see Figure 1). As progress in PC screening continues, this should allow the development of cost-effective, population-wide PC screening programs that, combined with innovations in treatment, will improve outcomes for individuals affected by this challenging clinical entity.

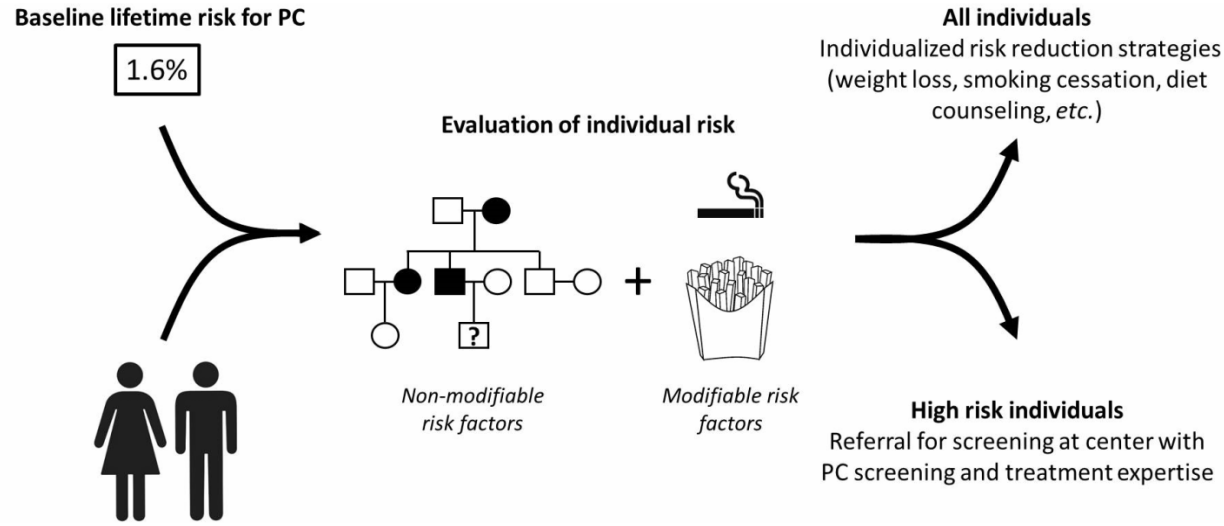

Figure 1. Pancreatic Cancer Screening for the General Clinician. The baseline lifetime risk of developing cancer for men and women for pancreatic cancer (PC) is estimated to be 1.6% [1]. Evaluation of individual risk must consider both modifiable (see Table 1) and non-modifiable (see Table 2) risk factors. All individuals should be counseled to reduce their risk as appropriate. Individuals who meet society guidelines for PC screening (see Table 3) should be referred to a center with expertise in PC screening and treatment, where PC screening modalities (see Table 4) can be appropriately employed and acted upon.

Cancerul pancreatic (PC) reprezintă o malignitate letală cu o creştere a mortalităţii şi a incidenţei la nivel mondial. Una din provocările în tratarea PC este diagnosticarea acestei patologii, întrucât diagnosticarea se realizează tardiv. Medicii internişti precum şi cei de familie pot identifica pacienţii cu risc înalt şi îi pot trimite către centre cu expertiză şi screening în PC. În acest articol sunt trecute în revistă leziunile precursoare PC, epidemiologia acestuia, precum şi principalii factori de risc care pot orienta clinicianul în a recunoaşte PC. Sunt trecute în revistă şi ghidurile pentru screening precum şi modalităţile prin care se poate îmbunătăţi diagnosticul precoce a PC. Speranţa autorilor este că acest articol tip review va ajuta clinicienii să identifice mai uşor pacienţii care trebuie să fie investigaţi pentru PC, precum şi să sublinieze strategiile prin care să fie scăzut riscul de apariţie a PC şi care sunt modalităţile de screening pentru a diminua mortalitatea cauzată de PC.

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