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Screening for Pancreatic Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: We conducted a systematic evidence review to support the U.S. Preventive Services Task Force (USPSTF) in updating its recommendation on screening for pancreatic cancer. Our review addresses the following Key Questions (KQs):

1. Does screening for pancreatic adenocarcinoma improve cancer morbidity or mortality or all-cause mortality? and
   a. Does screening effectiveness vary by clinically relevant subpopulations (e.g., by age group, family history of pancreatic cancer, personal history of new-onset diabetes, or other risk factors)?
2. What is the diagnostic accuracy of screening tests for pancreatic adenocarcinoma?
3. What are the harms of screening for pancreatic adenocarcinoma?
4. Does treatment of screen-detected or asymptomatic pancreatic adenocarcinoma improve cancer mortality, all-cause mortality, or quality of life?
5. What are the harms of treatment of screen-detected pancreatic adenocarcinoma?

Data Sources: We searched Cochrane Central Register of Controlled Trials, Medline, and PubMed, and reference lists of relevant systematic reviews. We searched for articles published from 2002 to October 3, 2017, and updated our search on April 27, 2018. We also searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform for relevant ongoing studies.

Study Selection: We reviewed 19,596 abstracts and 824 articles against specified inclusion criteria. Eligible studies included those written in English and conducted in adults age 18 years or older with or without risk factors for pancreatic cancer. For KQs on screening, we included imaging-based screening protocols. For KQs on treatment, we included studies of adults with screen-detected or asymptomatic pancreatic adenocarcinoma.

Data Analysis: We conducted dual, independent critical appraisal of all provisionally included studies and abstracted study details and results from fair- and good-quality studies. Because of the limited number of studies and the population heterogeneity, we provided a narrative synthesis of results and used summary tables to allow for comparisons across studies. After confirming that the yield of different imaging modalities was similar across studies, we calculated a pooled diagnostic yield across studies and produced forest plots to illustrate the range of effects seen across studies. For harms of screening (KQ3) and harms of treatment (KQ5), we stratified results by procedural and psychosocial harms.

Results: We included 13 unique prospective cohort screening studies (in 24 articles) reporting results for 1,317 persons. Studies were conducted in the United States, Canada, and Europe, and all screening populations except one small comparison group were exclusively in persons at elevated familial or genetic risk for pancreatic cancer. No studies reported on the effect of screening for pancreatic adenocarcinoma on cancer morbidity, mortality, or all-cause mortality (KQ1); and no studies reported on the effectiveness of treatment for screen-detected pancreatic adenocarcinoma (KQ4).

Thirteen fair quality studies reported on the diagnostic accuracy of screening tests for pancreatic adenocarcinoma (KQ2). Across these studies, 18 cases of pancreatic adenocarcinoma were detected. Twelve of 18 cases (66.7%) were detected at stage I or II or classified as "resectable." Pooled yield for all screening tests to detect pancreatic adenocarcinoma on initial screening in high-risk populations was 7.8 cases per 1,000 persons (95% confidence interval [CI], 3.6 to 14.7); and for total yield including both initial and repeat screening, it was 15.6 cases per 1,000 persons (95% CI, 9.3 to 24.5).

Harms of Screening for Pancreatic Adenocarcinoma
Procedural harms of screening were evaluated in eight screening studies (n=675); psychological harms were assessed in two studies (n=277). Details on the assessment of harms were variably reported. In two studies (n=277) in which 150 individuals received endoscopic retrograde cholangiopancreatography as a diagnostic followup test, 15 persons (10%) reported acute pancreatitis, nine of which required hospitalization. No evidence of increased worry, distress, depression, or anxiety after screening was reported, compared with before screening.

Harms of Treatment of Screen-Detected Pancreatic Adenocarcinoma
Of the 57 persons who underwent surgery across all studies, six studies (n=32 persons receiving surgery) assessed harms of treatment of screen-detected pancreatic adenocarcinoma (KQ5), with seven harms detected in two studies. Methods of assessing harms were variably reported. Harms included one person experiencing stricture to the hepaticojejunal anastomosis at 11 months after surgery, one with unspecified postoperative complications, two with postoperative fistula, and three cases of diabetes. In the two studies that systematically assessed harms in all surgical patients (n=12 persons receiving surgery), no harms were reported.

Limitations: No randomized trials of screening were identified. The body of evidence includes observational screening studies with limited sample sizes and focused on populations with known familial risk, many with a substantial proportion of persons with known genetic mutations. No studies included a clinical followup or unscreened comparison group, limiting assessment of diagnostic accuracy. Of those studies that reported harms of screening or treatment, limitations included inadequate description of the methods of assessing harms, including whether all participants were systematically assessed.

Conclusions: Imaging-based screening in groups at high familial risk can detect pancreatic adenocarcinoma with limited evidence of minimal harms. However, the clinical impact of screening is not well documented. There is insufficient evidence to assess benefits or harms of surgical intervention for screen-detected pancreatic adenocarcinoma.

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Chapter 1. Introduction

Purpose

The U.S Preventive Services Task Force (USPSTF) will use this report to update its 2004 recommendation against routine screening for pancreatic cancer.[1]

Condition Background

Condition Definition

There are two types of pancreatic tumors: exocrine tumors, which develop from exocrine cells that form glands and ducts that make pancreatic enzymes to digest foods, and endocrine tumors, which develop from endocrine cells that produce hormones such as insulin.[2]

This report focuses on pancreatic ductal adenocarcinoma. Most pancreatic tumors (95%) are exocrine tumors with malignant histologies; 90 percent of these are ductal adenocarcinoma. Typically, pancreatic cancer is synonymous with pancreatic adenocarcinoma. Less than 5 percent of pancreatic tumors are endocrine tumors, also known as neuroendocrine tumors or islet cell tumors, which are not addressed in this review. Other exocrine tumors include solid-pseudopapillary neoplasm (<1%), acinar cell carcinoma (<1%), pancreatoblastoma (<1%), and serous cystadenocarcinoma, a benign lesion (<1%).

Prevalence and Burden

Pancreatic adenocarcinoma is the third most common cause of cancer death among men and women in the United States, and the 11th most common case of incident cancer.[3] In 2018, an estimated 55,440 persons will be diagnosed with pancreatic adenocarcinoma, with 44,330 deaths.[4] Data from the Surveillance Epidemiology and End Results (SEER) registry show the incidence rates of pancreatic adenocarcinoma decreased by 19 percent among men and by 5 percent among women from 1977 to 2005, possibly because of decreased exposure to risk factors such as smoking.[5]

Between 2005 and 2014, incidence rates of pancreatic adenocarcinoma rose 0.5 percent each year, while death rates (10.9 per 100,000 persons per year) over the same time period were stable.[6, 7] As treatment and screening advances improve for other cancers, pancreatic adenocarcinoma may be the leading cause of cancer mortality by 2030.[8]

SEER data show that men are more likely to be diagnosed with pancreatic adenocarcinoma than women (14.2 new cases in men per 100,000 persons vs. 11.1 new cases in women per 100,000 persons).[6] The highest incidence rates occur in African American males (17.0 per 100,000 persons) and the lowest incidence rates occur in American Indian/Alaskan Native females (8.3 per 100,000 persons).[6, 9] Incidence increases sharply with increasing age (70.4 cases per 100,000

persons age 65 years and older) with a median age at diagnosis of 71 years.[6, 9]

According to the American Cancer Society, the overall 5-year survival rate for pancreatic adenocarcinoma is 8 percent;[10] however, survival rates vary by subtype and stage at diagnosis. More than 80 percent of incident cases are detected at advanced stage when surgical intervention is not recommended, and 5-year survival is 2 to 5 percent. Only 9 percent of cases are detected at stage I or II, when surgery is most likely to improve survival (**Table 1**). Eligibility for surgical resection improves prognosis but is typically an option only for early-stage tumors. Additional factors such as positive resection margins, poor tumor differentiation, larger tumor size, lymph node involvement, and high levels of carbohydrate antigen 19-9 (CA 19-9) adversely affect prognosis.[9]

Natural History and Prognosis

Early- and Late-Stage Pancreatic Adenocarcinoma

The prognosis of pancreatic adenocarcinoma depends largely on stage at diagnosis and whether the tumor can be surgically resected. Typically, resectable tumors include those where the tumor has not grown large enough to invade any major blood vessels. Persons with resectable cancers are recommended for primary curative surgery if they have a performance status and comorbidity profile capable of withstanding major abdominal surgery.[11]

According to the American Cancer Society, the average 5-year survival rate for patients with early-stage disease is 32 percent,[4] but this varies by whether patients underwent surgery. Data from SEER and the National Cancer Database (NCDB) have shown that the median survival among persons who underwent surgery ranged from 15 to 27 months.[12-17] Among persons who did not undergo surgery, median survival ranged from 3 to 8 months.[12-17] All of these observational database studies may be limited by selection bias, where persons who did not have surgery may have been sicker to begin with than persons who did have surgery. Therefore, survival may not be directly comparable between persons who do or do not undergo surgery for pancreatic cancer. One long-term SEER study estimated 10-year overall survival of 14,868 cases of invasive pancreatic adenocarcinoma (any stage) diagnosed between 1973 and 2009 and *not* treated with surgery at 1 percent.[18]

Survival among persons with early-stage disease also varies by patient age, tumor grade, extent of excision, and additional treatment received. A SEER study evaluated pancreatic adenocarcinoma survival stratified by American Joint Committee on Cancer (AJCC) stage and tumor grade.[19] Among 8,082 persons, all of whom had cancer-directed surgery, higher grade was an independent predictor of survival across all stages; low-grade stage I patients survived a median of 25 months compared with 17 months for high-grade stage I patients.[19] A study of 19,031 persons from the NCDB with stage I or II pancreatic adenocarcinoma, all of whom survived at least 90 days after surgical resection, showed that median survival was 17.6 months in the surgery-only group compared with 22.1 months in the group who underwent surgery plus adjuvant chemotherapy ($p<0.001$).[20]

Borderline resectable tumors may be treatable by surgery, but often are larger and close to major

arteries, raising concerns that resection may be incomplete, thus leaving the patient with positive surgical margins or undetected microscopic metastases. These tumors may be recommended for preoperative therapy, such as chemotherapy, and then restaged before surgical planning.[11] One study from the NCDB including 44,852 stage IIA to III patients diagnosed from 2004 to 2013 showed that 58 percent did not undergo surgical treatment.[21] Median survival was 10.3 months for this group compared with 13.1 months for patients who did have surgery with negative surgical margins. Less than 7 percent of the total population received neoadjuvant therapy, and median survival for this group was 23.2 months for patients who had negative surgical margins, but these results may reflect selection bias.

Persons with locally advanced disease or metastatic disease generally are not recommended for curative surgery. A small proportion may still undergo palliative surgery; however, survival for these stages is poor overall regardless of treatment received. According to the American Cancer Society, the average 5-year survival rate for patients with regional disease is 12 percent.[4] Half of all cases of pancreatic adenocarcinoma are diagnosed at a distant stage and the 5-year survival rate is 3 percent.[4] A SEER study of 28,918 persons with stage IV metastatic pancreatic adenocarcinoma showed that 1.6 percent underwent surgery, primarily persons younger than age 70 years, with smaller tumor sizes located in the head of the pancreas.[22] The median survival times were 7 months for the group who underwent surgery and 2 months for the group who did not.

Potential Precursors to Pancreatic Adenocarcinoma

Diagnosing potential precursor lesions via screening is an active area of research because it has potential to reduce pancreatic cancer incidence; however, surgical treatment of these lesions also has the potential to increase harms. Precursor lesions to invasive pancreatic adenocarcinoma include pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN); these lesions are classified as low- or high-grade (high-grade also may be called carcinoma in situ).[23] Typically, high-grade precursor lesions are considered for surgical intervention while low-grade lesions are observed.[24] IPMN and MCN may co-occur with invasive carcinoma (2% to 3% and 1% of all exocrine tumors, respectively).

PanIN is a microscopic (<5 mm) precursor lesion for pancreatic adenocarcinoma located in the pancreatic duct.[23, 25, 26] PanIN lesions can exhibit papillary or flat growth with mucinous secretion.[23] They are classified into one of four groups (PanIN-1A, PanIN-1B, PanIN-2, and PanIN-3) reflecting progression of histologic grade toward invasive cancer. A recently proposed classification system suggested reclassifying as two groups: low-grade (all except PanIN-3) and high-grade (PanIN-3 only, also referred to as carcinoma in situ).[23] Two autopsy studies have shown carcinoma in situ may be found in a quarter of cases with pancreatic cancer (whether clinically known or detected on autopsy), but not in controls.[27, 28]

PanIN lesions are difficult to detect on imaging due to their small size;[26, 29] lesions are often detected postoperatively, so preoperative screening, treatment, and surveillance strategies are unclear.[26] One study of 152 persons who had pancreatic surgery or biopsy for an indication other than pancreatic adenocarcinoma showed that 82 persons (54%) had a PanIN lesion.[30] A study of

584 persons who underwent pancreatic resection for diagnoses other than adenocarcinoma or IPMN at a U.S. cancer center showed that 153 (26%) resected lesions had PanIN histology.[31] After a median followup of 3 years in 134 of these persons, only one person (with an initial PanIN-1B diagnosis) developed pancreatic adenocarcinoma. Long-term survival of persons with PanIN lesions that do not progress to pancreatic adenocarcinoma is unknown.[31, 32]

IPMN is a larger (>10 mm) precursor lesion for pancreatic adenocarcinoma characterized by papillary growth and mucinous secretion either in the side-branch pancreatic ducts or main pancreatic duct.[23, 25, 26] A population-based study conducted in Olmsted County, Minnesota estimated the prevalence of IPMN as 26.0 cases per 100,000 persons (95% confidence interval [CI], 14.5 to 37.4).[33] Side-branch IPMNs have a lower subsequent malignancy rate (estimated between 1% and 25%) compared with main duct IPMNs (estimated between 40% and 50%).[34-38] IPMNs can be classified as having low-, intermediate-, or high-grade dysplasia (also referred to as carcinoma in situ); they may also be associated with an invasive carcinoma.[23] IPMN can be detected on imaging and may be preceded by symptoms similar to pancreatitis, including pain, diabetes, and weight loss; patients may also be asymptomatic.[39, 40]

Persons with IPMN may be recommended for surgical treatment if they have additional high-risk features such as main duct involvement, cyst size of 4 cm or greater, rapid changes in size over time, or an invasive component.[41, 42] Persons with IPMN without invasion may be recommended for regular imaging surveillance. One review suggested that 6 to 12 percent of asymptomatic, small, branch duct lesions enlarged or progressed to malignancy over an unspecified amount of time.[34] A surveillance study of 577 persons with branch duct IPMN found that 4.3 percent developed pancreatic adenocarcinoma within 5 years of IPMN diagnosis.[43] An analysis of 136 persons who underwent surgery for IPMN at a U.S. hospital between 1987 and 2003 found that 38 percent had IPMN associated with invasive carcinoma.[44] Five-year survival rates were 77 percent for noninvasive IPMNs and 43 percent for IPMNs with invasive carcinoma. Four out of nine deaths in the noninvasive group were due to adenocarcinoma, whereas all 21 deaths in the invasive group were from adenocarcinoma.

Unresected IPMN lesions may regress over time, but the evidence on regression is limited.[45] One study showed that among 664 persons with pancreatic cystic lesions (including IPMN), 15 (2.3%) decreased in size over a median followup of 33 months.[38] A systematic review and meta-analysis of studies in persons with IPMN who were not surgically treated showed malignant progression to invasive disease occurred in 11.4% of patients over followup durations ranging from 25 to 70 months.[46] The IPMN-specific mortality rate (regardless of progression) was 23 deaths per 1,000 person-years.

MCN typically presents as a large (average of 50 mm or larger) solitary pancreatic cyst characterized by mucin-producing cells and a thick ovarian-like stroma with estrogen and progesterone receptors.[35, 47-49] MCN lesions are rarer than IPMN, with one study showing that among 851 resected pancreatic cystic neoplasms from a single U.S. hospital over 33 years, 23 percent were diagnosed as MCN compared with 38 percent as IPMN.[50] Similar to IPMNs, MCNs are classified as low, intermediate-, or high-grade dysplasia (also referred to as carcinoma in situ) and up to one-third are associated with invasive carcinoma.[23, 47, 48] MCN can be detected on imaging and can present with symptoms of abdominal pain, abdominal fullness, jaundice, or

nausea; they also may be detected incidentally without symptoms.[35, 47, 51] Approximately 95 percent of MCN diagnoses occur in women.[35, 47-49]

Surgical treatment is recommended for all MCN lesions. Persons with MCN often have better prognosis than those with IPMN because of less aggressive tumor biology.[52, 53] In addition, 98 percent of MCN lesions occur in the tail of the pancreas (as opposed to the head) where distal pancreatectomy is less complex.[47-49] The 5-year survival of MCN without associated invasive carcinoma is 100 percent, and additional surveillance following successful surgery is not recommended.[35, 47] For persons with MCN with an invasive component, the 5-year survival is lower, at around 60 percent.[35, 47, 48] The proportion of MCN lesions that progress to pancreatic adenocarcinoma and timeframe for progression are unclear.[35]

Risk Factors

Based on data from 2013 to 2015, approximately 1.6% of persons in the general population will be diagnosed with pancreatic cancer during their lifetime.[7] Germline mutations, older age, family history, diabetes, and tobacco use are well-established risk factors; comorbid conditions such as chronic pancreatitis and obesity also increase risk for pancreatic adenocarcinoma.[54-57]

Genetic and Hereditary Factors

Family History

Approximately 5 to 10 percent of cases of pancreatic adenocarcinoma are familial with no known genetic mutations.[55-58] According to one meta-analysis and one pooled analysis, having a positive family history for pancreatic adenocarcinoma (defined as having at least one first-degree relative with pancreatic adenocarcinoma in most studies) is associated with a relative risk (RR) of 1.8.[59, 60]

Known Genetic Mutations

An estimated 3 to 5 percent of cases of pancreatic adenocarcinoma have inherited genetic mutations.[58] Mutations in several genes are associated with the development of pancreatic adenocarcinoma, with risk ratios ranging from 3.5 for *BRCA2* gene mutation to 132 for Peutz-Jeghers syndrome:[55, 61]

- Peutz-Jeghers Syndrome, caused by a mutation in the *STK11/LKB1* gene
- *CDKN2A/p16* mutations
- *BRCA1* or *BRCA2* mutations
- Hereditary pancreatitis caused by *PRSS1* and/or *SPINK1* mutations; *CTFR* mutations
- Lynch syndrome, caused by *MLH1*, *MSH2*, *MSH6*, or *PMS2* germline mutations
- *ATM* mutations[55, 56, 61, 62]

Ashkenazi Jewish Heritage

Ashkenazi Jewish persons have an increased risk of pancreatic adenocarcinoma, with RRs of

approximately 1.4[63] to 1.8[64] compared with non-Jewish persons. These risk estimates may be even higher for Jewish persons with one of several genetic mutations (*BRCA1, BRCA2, MSH2,* or *MSH6*).[65-67] Eldridge and colleagues noted that the increased risk for pancreatic adenocarcinoma in Jewish persons was not explained by other nongenetic risk factors such as smoking, obesity, and diabetes, and may be predominantly due to genetics.[63] Persons with *BRCA1*, *BRCA2*, or other high-risk genetic mutations may be recommended for pancreatic adenocarcinoma screening regardless of whether they are of Ashkenazi Jewish ancestry.

Hereditary Pancreatitis

Chronic pancreatitis may be hereditary if associated with one of several genetic mutations (*PRSS1*, *SPINK1*, and *CTFR*) and/or an incidence of disease within a family that is higher than one would expect by chance alone. Hereditary pancreatitis has been associated with RRs for pancreatic adenocarcinoma ranging from 50 to 80.[55] Despite the high increased risk of pancreatic adenocarcinoma associated with pancreatitis, patients with hereditary pancreatitis account for a very small fraction of all cases of pancreatic adenocarcinoma.

Other Risk Factors

Age

Most cases of pancreatic adenocarcinoma occur in persons older than age 55 years.[7]

Chronic Pancreatitis

A history of chronic pancreatitis (inflammation of the pancreas that impairs one's ability to digest food and produce hormones) has been associated with RRs for pancreatic adenocarcinoma ranging from 2.71 to 13.3.[68, 69] As opposed to acute pancreatitis, which often develops in response to pancreatic injury, chronic pancreatitis involves progressive inflammatory pancreas changes that can lead to permanent structural damage and impairment of exocrine and endocrine function.

Existing or New-Onset Diabetes

Diabetes has been studied the most and has been consistently associated with an increased risk of pancreatic adenocarcinoma across seven meta-analyses and seven pooled analyses.[56] A 2011 meta-analysis with 20,410 cases of pancreatic adenocarcinoma from 35 cohort studies found a summary RR of 1.94 (95% CI, 1.66 to 2.27) associated with diabetes mellitus.[70] Diabetes also appears to be associated with increased pancreatic adenocarcinoma mortality relative to persons with pancreatic adenocarcinoma and no diabetes diagnosis.[71, 72]

New-onset diabetes in adulthood may be an early manifestation of pancreatic adenocarcinoma.[73, 74] In a U.S.-based case-control study (510 cases, 463 controls), 15 percent of cases of pancreatic adenocarcinoma had developed new-onset diabetes less than 3 years before diagnosis compared with 3 percent of controls (adjusted odds ratio [OR], 6.40 [95% CI, 3.37 to 12.2]); a loss of more than 3 percent of body weight was also more common in cases vs. controls (71% vs. 7%;

adjusted OR, 27.0 [95% CI, 17.1 to 42.6]).[75] A larger, U.K.-based case-control study found similar results in primary care patients: new-onset diabetes less than 2 years before pancreatic adenocarcinoma diagnosis appeared in 13.6 percent of cases and 6 percent of controls (adjusted OR, 2.46 [95% CI, 2.16 to 2.80]).[76]

Tobacco Use

Smoking is the most well-established modifiable risk factor for pancreatic adenocarcinoma. A 2014 review and meta-analysis showed that the relative risk for pancreatic adenocarcinoma associated with any current cigarette use ranged from 1.5 to 2.2.[56] RR estimates varied by dose in several studies,[77-79] with one study showing an RR of 1.2 (95% CI, 1.2 to 1.3) among persons who smoked 5 cigarettes per day to 2.0 (95% CI, 1.7 to 2.2) among those who smoked 40 cigarettes per day.[78] The association with history of tobacco use or smokeless tobacco use is less certain. Former cigarette use was associated with an increased risk of pancreatic adenocarcinoma in some studies but not all. Smokeless tobacco was associated with an RR for pancreatic adenocarcinoma of 1.6 (95% CI, 1.1 to 2.2) in one study,[80] but not in others.[81, 82]

Obesity

According to several meta-analyses and pooled analyses, obesity, as measured by a body mass index (BMI) of 30 kg/m^2 or greater, has been associated with an increased RR for pancreatic adenocarcinoma ranging from 1.19 to 1.47.[83-86] Several studies have shown a dose-response relationship between BMI and pancreatic adenocarcinoma risk, with the highest risk estimates for persons in BMI categories above 35 kg/m^2.[84, 85] A large cohort study demonstrated that obese patients undergoing bariatric surgery had a reduced risk of pancreatic cancer (hazard ratio, 0.46 [95% CI, 0.22 to 0.97]) compared with BMI- and comorbidity-matched persons who did not undergo surgery.[87] Obesity may also be associated with increased risk of pancreatic adenocarcinoma mortality,[88] with a dose-response relationship associated with obesity in adulthood in one meta-analysis[89] and one pooled analysis of case-control studies.[90]

Other Modifiable Risk Factors

Diet, alcohol, additional medical conditions, and certain types of medication may be associated with pancreatic adenocarcinoma risk.[54, 56] Red meat, processed meat, and elevated sugar intake may be associated with a moderately increased risk (RR, 1.1 to 1.4) of pancreatic adenocarcinoma.[56] Drinking more than three glasses of any alcoholic beverages per day may increase pancreatic adenocarcinoma risk by 20 percent.[56] A meta-analysis of 19 prospective cohort studies including data on more than 4 million persons found that high (≥24 g per day)—but not low or moderate—alcohol consumption was associated with increased risk for pancreatic adenocarcinoma (RR, 1.15 [95% CI, 1.06 to 1.25]).[91] Several meta-analyses showed *Helicobacter pylori* infection was associated with increased risk of pancreatic cancer, with RRs ranging from 1.28 to 1.65.[56] The use of antidiabetic drugs other than metformin (e.g., insulin and sulfonylurea) may be associated with a moderate increased risk of pancreatic adenocarcinoma (RR, 1.5 to 1.9), whereas metformin has been associated with a reduced risk (RR, 0.5 to 0.9).[56] Statin use may reduce risk for pancreatic adenocarcinoma and reduce mortality.[92, 93] Aspirin use was associated with reduced risk for pancreatic adenocarcinoma in one study.[94]

Screening for Pancreatic Cancer

Currently, only a fraction of incident cases of pancreatic adenocarcinoma are detected at resectable (9%) or borderline resectable (10%) stages.[7] Screening for pancreatic adenocarcinoma could detect more cancer at a stage where resection is possible, and improve survival through surgical resection. By this same reasoning, screening also could improve quality of life and limit harms associated with chemotherapy.

Imaging-Based Screening

Several imaging tests are used to detect pancreatic adenocarcinoma, including endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), abdominal ultrasonography, and computed topography (CT). EUS and MRI are considered the most accurate of these imaging tools, which are used primarily for diagnostic testing. However, they may also have a role in screening for persons at high risk of pancreatic adenocarcinoma, such as those with known genetic mutations or a family history of pancreatic adenocarcinoma.[95, 96]

- EUS examines the upper and lower gastrointestinal tract, including the pancreas, via insertion of a small tube with an ultrasound probe through the mouth and down into the stomach. Tissue can be sampled during EUS via fine needle aspiration (FNA) to evaluate lesions for malignancies and subsequent staging.[97] ERCP, a procedure that combines endoscopy with X-rays, can be used as a diagnostic tool.[95] The International Cancer of the Pancreas Screening (CAPS) Consortium discourages the use of ERCP as a screening tool because of risk for post-ERCP acute pancreatitis.[95]
- MRI allows for imaging of the entire abdomen and pelvis. It does not involve exposure to ionizing radiation and is less invasive than EUS, but cannot sample tissue so may require a separate biopsy procedure, which is invasive and carries risks.[98] MRCP also does not involve radiation exposure and is a noninvasive alternative to ERCP for imaging pancreatic ductal anatomy for suspicious lesions.[98]
- CT for pancreatic adenocarcinoma often involves the use of a contrast dye, given by mouth or injection. CT scans are associated with potential harm from radiation exposure. They are used for diagnosis, tumor staging, and determining resectability.[9, 98]

Biomarker-Based Screening

Despite an expanding literature on biomarkers and their potential diagnostic accuracy, there are currently no validated biomarkers for early detection of pancreatic adenocarcinoma.[99-104]

CA 19-9 has long been considered the best single candidate for a screening biomarker for early detection. CA 19-9 is elevated in the serum of persons with pancreatic adenocarcinoma and may be used clinically as a prognostic tool in pancreatic cancer management for some patients.[105] However, its limited sensitivity and specificity have limited its usefulness as a screening method. A meta-analysis found the median sensitivity and specificity of CA 19-9 for the detection of pancreatic adenocarcinoma to be 75.5 and 77.6 percent, respectively, with a positive predictive value of 0.5 to 0.9 percent.[106]

Other potential single biomarker tests include carcinoembryonic antigen, which is used in the management of several gastrointestinal cancers, but lacks accuracy to support its use as a screening test.[105] Cell-surface proteins, 283 proteins according to one estimate,[96] are also overexpressed in pancreatic adenocarcinoma, but discriminatory abilities of these proteins in detecting pancreatic adenocarcinoma are largely unknown.

Micro-RNA patterns from circulating exosomes, hypermethylation of specific genes in circulating DNA (e.g., *BNC1*, *ADAMST1*, *NPTX2*, *ppENK*, *p16*, or *CDKN2a*),[107] and detection of circulating tumor cells are potential emerging biomarkers.[96, 108] Mutated DNA and biomarkers may be detected in pancreatic juice,[109-111] a liquid secreted by the pancreas which contains various enzymes.[112]

Multiple biomarker panels may have the highest potential as a noninvasive screening test for pancreatic adenocarcinoma, given the heterogeneity of tumor types and the limited accuracy of any single biomarker.[96, 113, 114] For example, a CA 19-9-based multiple biomarker panel was found to discriminate early-stage pancreatic adenocarcinoma from healthy controls with an area under the curve of 0.89 (95% CI, 0.82 to 0.95) for all early-stage cancer (p=0.03) compared with CA 19-9 alone.[115] Other studies have also found promising results, finding areas under the curve above 0.9 for multiple biomarker panels.[116, 117] Most biomarker-based screening would require serum-based testing; however, stool- or saliva-based testing also have been explored.[99, 118, 119]

Treatment Approaches

There are no known interventions to prevent pancreatic adenocarcinoma. Tobacco cessation or avoidance, healthy diet, and regular exercise may reduce modifiable risk for pancreatic adenocarcinoma along with several other cancers and chronic diseases.

Current treatment recommendations include surgery for early-stage cancers (currently about 20% of all new cases), chemotherapy, and radiation (**Table 2**).

Surgical resection is the only treatment for pancreatic adenocarcinoma that offers a potential cure, but only persons with nonmetastatic disease are eligible for surgery.[120] Pancreatic cancers eligible for surgical treatment are generally classified as “resectable” or “borderline resectable” based on the likelihood of complete surgical resection.[57] Surgical options include a pancreaticoduodenectomy (known as the Whipple procedure), which removes the head of the pancreas, gallbladder, bile duct, and parts of the stomach and small intestine; a total pancreatectomy, which removes the whole pancreas, bile duct, gallbladder, spleen, nearby lymph nodes, and parts of the stomach and small intestine; and a distal pancreatectomy, which removes the body and tail of the pancreas as well as the spleen.

Any type of surgical resection for pancreatic adenocarcinoma carries significant morbidity (complication rates 20% to 50%) and perioperative mortality risks (1% to 8%).[121] Patients typically require a 1- to 3-week postoperative hospital stay and 3 to 6 months for full recovery.[122] Complications can include fistula or leakage, delayed gastric emptying, acute pancreatitis, sepsis, and infection.[123, 124] Since complication rates are lower at high-volume centers, the National

Comprehensive Cancer Network recommends pancreatic resections be done at institutions that perform at least 15 to 20 resections annually.[120]

Despite the favorable effect of surgical intervention on survival for persons with early-stage pancreatic adenocarcinoma, many patients still do not undergo surgery. In one NCDB study (n=9,559), 38 percent of persons with resectable tumors (stage I only) diagnosed between 1995 and 2004 were never offered surgery.[16] A more recent analysis of SEER data (n=6,742) found that only 25 percent of persons with localized pancreatic adenocarcinoma (excluding anyone with blood vessel or lymph node invasion) underwent surgery between 1988 and 2010, with no change in this proportion over time.[12] Persons treated at community hospitals are much less likely to undergo surgery or chemotherapy treatment.[14, 15]

Current Clinical Practice and Recommendations of Others

No organizations currently recommend population-based screening for pancreatic adenocarcinoma. Screening for pancreatic adenocarcinoma detection in persons with known genetic mutations or strong family history is recommended by several organizations (**Table 3**). Several countries maintain screening programs for persons at high risk for pancreatic adenocarcinoma. For example, Denmark has a national screening program for residents with hereditary pancreatitis or a family history of pancreatic adenocarcinoma;[125] the Netherlands has a screening program for persons with a family history of pancreatic adenocarcinoma, carriers of known genetic mutations associated with hereditary syndromes, and persons with Peutz-Jeghers syndrome;[126] and the Canadian province of Ontario has a screening program for persons with a family history of pancreatic adenocarcinoma, carriers of known genetic mutations, persons with Peutz-Jeghers syndrome, and persons with hereditary pancreatitis.[127] Germany, Sweden, and Spain all have national familial pancreatic adenocarcinoma registries with screening recommendations for persons age 18 years and older.[128-130]

Cancer programs in the United States may also refer family members of pancreatic adenocarcinoma patients for further evaluation, typically by multidisciplinary teams. U.S. registries for individuals at high risk of pancreatic adenocarcinoma include programs based at Johns Hopkins University,[131] Memorial Sloan-Kettering Cancer Center,[132] Columbia University Medical Center/New York Presbyterian Hospital,[133] University of Washington,[134] Oregon Health and Science University,[135] the Mayo Clinic,[136] University of Nebraska Medical Center,[137] and Thomas Jefferson University Hospital/Sidney Kimmel Cancer Center.[138]

Previous USPSTF Recommendation

In 1996 and again in 2004, the USPSTF recommended against routine screening for pancreatic cancer in asymptomatic adults using abdominal palpation, ultrasonography, or serologic markers (D recommendation).[1, 139]

In its 2004 recommendation, the USPSTF concluded there was no evidence that screening for pancreatic cancer is effective in reducing mortality, and that the harms of screening exceeded any potential benefit.[1] It concluded that there is a potential for significant harm because of the

very low prevalence of pancreatic adenocarcinoma, limited accuracy of available screening tests, the invasive nature of diagnostic tests, and the poor outcomes of treatment.

The USPSTF noted in clinical considerations an interest in primary prevention of pancreatic cancer, including tobacco cessation and dietary measures, but that the evidence for diet-based prevention of pancreatic cancer is limited and conflicting.

The brief evidence review supporting the 2004 recommendation did not publish an analytic framework or inclusion and exclusion criteria. The search included systematic reviews, meta-analyses, randomized clinical trials, cost-effectiveness analyses, editorials, and commentaries, but did not include observational studies. This review noted gaps in evidence for the benefit or harm of identifying and screening high-risk groups, including the potential use of tumor markers in screening, and ongoing randomized clinical trials exploring treatment for pancreatic adenocarcinoma.[140]

Chapter 2. Methods

Scope and Purpose

The USPSTF will use this evidence review to update its 2004 D recommendation on screening for pancreatic cancer.[1] This review addresses the benefits and harms associated with screening and treatment of screen-detected pancreatic adenocarcinoma.

Key Questions and Analytic Framework

We developed an analytic framework with five key questions (KQs) based on the previous review and a scan of the research conducted since the previous review (**Figure 1**).

KQs

1. Does screening for pancreatic adenocarcinoma improve cancer morbidity or mortality or all-cause mortality?
   a. Does screening effectiveness vary by clinically relevant subpopulations (e.g., by age group, family history of pancreatic cancer, personal history of new-onset diabetes, or other risk factors)?
2. What is the diagnostic accuracy of screening tests for pancreatic adenocarcinoma?
3. What are the harms of screening for pancreatic adenocarcinoma?
4. Does treatment of screen-detected or asymptomatic pancreatic adenocarcinoma improve cancer mortality, all-cause mortality, or quality of life?
5. What are the harms of treatment of screen-detected pancreatic adenocarcinoma?

Data Sources and Searches

We worked with a research librarian to develop our literature search (**Appendix B**). All search strategies were peer reviewed by a second research librarian.

We re-evaluated all articles included in the previous USPSTF evidence report on pancreatic cancer screening.[140] Bridging from this previous review, we searched for articles published from 2002 to October 3, 2017. We searched Cochrane Central Register of Controlled Trials, MEDLINE, and PubMed, as well as publisher-supplied to locate relevant studies for all KQs (**Appendix B**). Results of the literature search were imported into EndNote. We supplemented our database searches by reviewing reference lists from recent and relevant systematic reviews.[95, 141-151] We also searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform for relevant ongoing studies (**Appendix C**). We ran the searches again on April 27, 2018, to capture new literature from the intervening months.

Study Selection

A total of 19,596 abstracts were reviewed. Initial identification of low-relevance abstracts was conducted using key words relating to exclusion criteria. This identified 2,168 citations that were reviewed by a single investigator. The remaining 17,428 abstracts were dual reviewed by two independent reviewers using Abstrackr, an online abstract reviewing platform. From the two processes, the team reviewed 824 full-text articles (**Appendix B Figure 1**) against specified inclusion criteria (**Appendix B Table 1**). We resolved discrepancies through consensus and consultation with a third investigator. We excluded articles that did not meet inclusion criteria or those we rated as poor quality.

For screening KQs (KQs 1, 2, 3), the population of interest was adults age 18 years or older with or without risk factors for pancreatic adenocarcinoma (e.g., family history of pancreatic adenocarcinoma, personal history of new-onset diabetes, or other risk factors). We excluded studies that focused solely on persons with confirmed genetic syndromes (e.g., Peutz-Jeghers syndrome, Lynch syndrome, hereditary pancreatitis, or known mutations in *CDKN2A*, *BRCA1*, *BRCA2*, *CTFR*, or *ATM* genes). Studies with persons with high-risk genetic mutations or syndromes in addition to persons with other risk factors were included. We included any imaging-based screening protocol, and excluded studies using biomarker-based initial screening protocols as no validated biomarkers currently exist.[99] For diagnostic accuracy (KQ2), we included trials or cohort studies. For harms of screening (KQ3), we included randomized, controlled trials; controlled clinical trials; cohort studies; or case-control studies. Outcomes of interest were pancreatic adenocarcinoma–specific morbidity or mortality, all-cause mortality, or quality of life (KQ1); measures of diagnostic accuracy, including sensitivity, predictive value, and diagnostic yield (KQ2); or procedural or psychosocial harms of screening (KQ3).

For KQs on treatment (KQs 4, 5) the population of interest was adults with screen-detected, asymptomatic, or incidentally detected pancreatic adenocarcinoma. We excluded studies of surgical intervention for early-stage pancreatic adenocarcinoma that was detected clinically or as a result of symptoms, as these study populations may not be an adequate proxy for screen-detected, asymptomatic, or incidentally detected populations. We excluded studies of persons with pancreatic endocrine or exocrine tumors other than adenocarcinoma. We included studies reporting on surgical resection with or without chemotherapy or radiation. We excluded studies on chemotherapy or palliative care alone. Studies eligible for KQ4 needed to have a comparison group of either no treatment or delayed treatment; thus, we excluded comparative effectiveness screening or treatment studies. Outcomes of interest were morbidity or mortality, quality of life (KQ4), or any surgical harms (KQ5).

For all KQs we limited studies to settings conducted in countries categorized as “Very High” in the Human Development Index.[152]

Quality Assessment and Data Abstraction

At least two reviewers independently critically appraised all articles that met the inclusion criteria based on the USPSTF's design-specific quality criteria for trials (**Appendix B Table 2**). We rated articles as good, fair, or poor quality. A good-quality study met all criteria. A fair-quality study did not meet, or it was unclear if it met, at least one criterion but had no known important limitations that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations; we excluded poor-quality studies from this review. Disagreements about critical appraisal were resolved by consensus and, if needed, in consultation with a third independent reviewer.

One reviewer extracted key elements of included studies into a Microsoft Access® database (Microsoft Corporation, Redmond, WA). A second reviewer checked the data for accuracy. Evidence tables were tailored for each KQ. Tables generally included details on study design and quality, setting and population (e.g., country, inclusion criteria, age, sex, and race/ethnicity), screening or treatment details, length of followup, and outcomes.

Data Synthesis and Analysis

We synthesized results by KQ. We used a standardized summary of evidence table to summarize the overall strength of evidence for each KQ. This table included the number and design of included studies, summary of results, consistency or precision of results, reporting bias, summary of study quality, limitations of the body of evidence, and applicability of the findings.

Because of the limited number of studies and the population heterogeneity, we provided a narrative synthesis of results and used summary tables to allow for comparisons across studies. For screening test performance (KQ2), we could only report on the yield of cancers as the (diagnostic) outcome, as we could not calculate sensitivity and specificity from the included studies. For harms of screening (KQ3), we stratified results by type of harm (i.e., procedural or psychosocial).

For quantitative analyses, we calculated diagnostic yield of pancreatic adenocarcinoma and 95 percent CIs assuming binomial distribution. After confirming that the yield of different imaging modalities was similar across studies, we also calculated a pooled diagnostic yield across studies and produced forest plots to illustrate the range of effects seen across studies. We calculated diagnostic yield from initial screen (baseline) and from initial screening and repeated screening combined where possible. We could not calculate the screening rate for repeat screenings alone because the number of participants undergoing repeated screenings was not clearly or consistently reported across studies.

Grading the Strength of the Body of Evidence

We graded the strength of evidence by each KQ according to guidance from the Agency for Healthcare Research and Quality for Evidence-based Practice Centers,[153] which was informed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.[154] For each KQ we grade the evidence according to consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (i.e., study limitations). These are four of the five suggested domains; we did not address the fifth required domain—directness—in the summary of evidence as directness is addressed in the design and structure of the KQs (i.e., whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Reporting bias was rated as suspected, undetected, or not applicable (e.g., when there is insufficient evidence for a particular outcome). Study quality reflects the quality ratings of the individual trials and indicates the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias. The body of evidence limitations field highlights important restrictions in answering the overall KQ (e.g., lack of replication of interventions or nonreporting of outcomes important to patients).

We provide an overall assessment of the strength of evidence for each KQ. "High" indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. "Moderate" suggests moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effects. "Low" indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effects. A grade of "insufficient" indicates that evidence is either unavailable or does not permit estimate of an effect. Applicability assesses how the overall body of evidence would apply to the U.S. population based on settings, populations, and intervention characteristics. Two independent reviewers rated each KQ according to consistency, precision, reporting bias, and overall strength of evidence grade. We resolved discrepancies through consensus.

Expert Review and Public Comment

A draft research plan that included the analytic framework, KQs, and inclusion criteria was available for public comment from April 27, 2017, through May 24, 2017. We made no substantive changes to our review methods based on the comments received.

A draft version of this report was reviewed by invited content experts and federal partners, who are listed in the acknowledgements. Comments received during this process were presented to the USPSTF during its deliberation of the evidence and, subsequently, addressed in this version of the report. A draft version of this report was posted for public comment on the USPSTF website from February 5, 2019, through March 4, 2019. All comments were reviewed and

considered in finalizing this report; no substantial changes to the content or conclusions were implemented.

USPSTF Involvement

We worked with four USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and KQs and to resolve issues regarding the scope of the final evidence review. This research was funded by the Agency for Healthcare Research and Quality under a contract to support the work of the USPSTF. Agency staff provided oversight for the project, assisted in external review of the draft report, and reviewed the draft report.

Chapter 3. Results

We included 13 unique prospective cohort screening studies, reported in 24 articles (**Table 4**), none of which were included in the previous evidence review.[140] No studies reported on the effect of screening for pancreatic adenocarcinoma on cancer morbidity, mortality, or all-cause mortality (KQ1); 13 studies (in 24 articles)[125-127, 129, 133, 155-173] reported on the diagnostic accuracy of screening tests for pancreatic adenocarcinoma (KQ2); nine studies (in 18 articles)[125-127, 129, 133, 155-162, 166-170] reported on the harms of screening for pancreatic adenocarcinoma (KQ3); no studies reported on the effectiveness of treatment for screen-detected pancreatic adenocarcinoma (KQ4); and six studies (in 12 articles)[125, 129, 133, 156, 157, 160-163, 165, 169, 173] reported on the harms of treatment of screen-detected pancreatic adenocarcinoma (KQ5).

Articles most commonly were excluded due to lack of relevance to pancreatic adenocarcinoma screening or treatment, ineligible population (populations with personal history of pancreatic adenocarcinoma, symptomatic populations, or studies focusing only on populations with known genetic mutations associated with increased risk of pancreatic adenocarcinoma), ineligible study design (comparative effectiveness studies, case reports, case series, or narrative reviews), and ineligible outcomes (not reporting morbidity, mortality, quality of life, diagnostic accuracy, screening harms, or treatment harms). The most common reasons for poor quality exclusion were insufficient information on patient recruitment or screening process (**Appendix B Table 1**). **Appendix C** provides a list of all excluded studies, with the main reason for their exclusion.

Description of Included Studies

In total, 13 included screening studies reported screening results for 1,317 persons. All studies used a prospective cohort design. These cohorts were relatively small; the study samples ranged from 38 to 239 persons. No included studies included an unscreened comparison arm, and none were designed to evaluate test accuracy. One study included a comparison group of persons undergoing EUS or ERCP for nonpancreatic indications.[160]

Seven studies (n=776) were conducted in the United States,[133, 155, 159, 160, 165, 171, 172] one in Canada,[127] and five in Northern European countries (two in the Netherlands,[126, 157] one in Sweden,[164] one in Denmark,[125] and one in Germany[129]). All studies were conducted in or in conjunction with academic medical center settings, typically specialty care settings connected to high-risk surveillance clinics.[127, 129, 159, 160, 164, 165, 171, 172] All U.S.-based studies were conducted in the context of cancer centers or large tertiary care academic centers.[133, 155, 159, 160, 165, 171, 172] Non-U.S.–based studies were conducted in the context of screening or surveillance programs in countries with national healthcare systems[125, 126, 129, 164] or at academic medical centers.[127, 157] Seven studies used existing familial pancreatic cancer registries to recruit participants.[125, 127, 133, 155, 159, 160] Other recruitment methods included clinician or genetic counselor referral. Three studies were conducted at multiple sites.[126, 129, 165]

Included Populations

All screening populations except one small comparison group were exclusively in persons at elevated risk for pancreatic adenocarcinoma, and included predominantly persons with family history of pancreatic adenocarcinoma, with or without confirmed genetic mutations or syndromes (**Table 5**). In 10 studies, more than 50 percent of the study population had a family history of cancer; in eight studies, 90 to 100 percent of the study population had a family history of cancer.[129, 133, 159, 160, 164, 165, 172] Only three studies (n=232) exclusively included relatives of persons with pancreatic adenocarcinoma.[129, 133, 155] One study included an asymptomatic control group of persons receiving imaging for other clinical indications unrelated to the pancreas (n=138).[160]

Definitions of family history varied widely across studies, but all studies had inclusion criteria aimed at identifying those at greatest risk for pancreatic adenocarcinoma. Inclusion criteria generally required at least two affected relatives and at least one affected first-degree relative for study entry. For example, two U.S.-based studies limited study entry to persons with three or more relatives with pancreatic adenocarcinoma, one or two of which were first-degree relatives.[159, 160] Another U.S.-based study required two or more relatives with pancreatic adenocarcinoma or one with pancreatic adenocarcinoma at age younger than 55 years to be considered moderate risk; 43 percent of the study population had two affected relatives, while an additional 26 percent had three or more affected relatives.[133]

Twelve studies included persons with confirmed genetic mutations or syndromes; typically these populations made up less than 25 percent of the study population with the exception of three studies whose populations exceeded 50 percent persons with confirmed genetic conditions; one was conducted in the United States,[171] and the other two were conducted in the Netherlands: the Dutch Familial Pancreatic Cancer (FPC) study (n=139)[126, 158, 167, 170] and the study by Poley and colleagues (n=44).[157] No studies reported on flow through the screening program separately for individuals with confirmed genetic mutations or syndromes.

Personal history of other types of cancer or diabetes also were reported. Diabetes status was reported in six studies, and ranged from 4 percent to 24 percent of the study population.[125, 127, 133, 159, 160, 165] Two studies specified that patients with diabetes (3.9%[133] and 4.2%[165] of study population) had type 2 diabetes; the other 4 studies did not specify type of diabetes. One study specified that patients with diabetes (5.0% of study population) were diagnosed prior to 1 year ago;[127] the other five studies did not report time since diagnosis. Personal history of non-pancreatic cancer was reported in six studies which ranged from 6 percent to 43 percent of the study populations.[126, 127, 133, 159, 160, 171]

Study populations contained a slightly higher proportion of female participants compared to male (range of female participants 53.6% to 71.6%; the population in the single study with an asymptomatic comparison group was 43% female). Mean age of participants ranged from 50 to 60 years. Race and ethnicity were inconsistently reported across studies. Eight studies reported Ashkenazi Jewish ancestry, which accounted for from less than 10 percent of the study population[129] to more than 49 percent in one study.[133] Eight studies also reported race/ethnicity, and in these eight studies the proportion of white participants was 88 percent to 100 percent.

Three of the six studies that did not report on white race/ethnicity were conducted in Northern European countries (Sweden, Denmark, and the Netherlands).[125, 126, 164] The other three studies that did not report on white race/ethnicity were based in the United States: One was based at Johns Hopkins University[159] and reported that 13.2 percent of participants were of Ashkenazi Jewish ancestry, one was at the Greater Midwest Pancreatic Screening Clinic in Wisconsin,[171] and one was at the Moffitt Cancer Center in Florida.[172]

Various behavioral risk factors were included in eleven studies. All eleven reported on smoking status, in which the proportion of current smokers ranged from 0 percent to 25 percent. Alcohol use was reported in six studies; measures of alcohol use varied across studies but ranged from 40 percent to 56 percent in studies reporting "regular" use. One study reported social or occasional alcohol use at 77 percent,[133] and one reported history of heavy alcohol use at 10 percent.[172]

Protocols for Initial and Repeated Screening

Initial Screening Protocols

A total of nine small, prospective, fair quality studies (n=885) evaluated EUS (with or without additional imaging) as the initial screening test for pancreatic abnormalities. Four studies evaluated EUS as the sole screening test: one at Johns Hopkins University in the United States (n=38);[159] one at the Moffitt Cancer Center in the United States (n=58);[172] one from the Danish National Screening Program (n=71);[125] and one from the Netherlands (n=44, a study that pre-dated the Dutch Familial Pancreatic Cancer Study).[157] Two additional studies from the United States evaluated multiple screening modalities in which the screeners were blinded to the results from either test: EUS and CT screening (n=78 high-risk persons and 138 asymptomatic controls who underwent EUS only) at Johns Hopkins Hospital,[160] and EUS, CT, and MRI screening (n=216) within the Cancer of the Pancreas Screening Study 3 (CAPS3) consortium including 5 U.S. hospitals.[165] The last three studies evaluated EUS plus MRI (or MRCP) in: the Dutch FPC Study (n=139),[126] the United States (n=31),[133] and the Familial Pancreatic Cancer (FaPaCa) study in Germany (n=72).[129]

Two small, prospective, fair quality studies (n=294) evaluated CT imaging to screen for pancreatic abnormalities.[160, 165] Both took place in the United States and were led by the same author, but do not overlap in populations. One evaluated CT and EUS screening in 78 persons (screeners were blinded to the results of either screening test),[160] and the other evaluated CT with EUS and MRI in 216 persons (again, screeners were blinded to the results of any other test).[165]

A total of eight small, prospective, fair quality studies (n=849) evaluated MRI or MRCP as the initial screening test for pancreatic abnormalities. Three studies evaluated MRI as the sole screening test, one from the Greater Midwest Pancreatic Cancer Screening Clinic in the United States (n=65),[171] one from the Toronto Screening Program in Canada (n=175),[127] and the other from Sweden (n=40);[164] one additional study from the United States evaluated MRCP alone (n=109).[155] Three studies evaluated MRI and/or MRCP as initial screening tests along with EUS: the Dutch FPC Study in the Netherlands (n=139),[126] a study based at Columbia University Medical Center (n=51),[133] and the FaPaCa study in Germany (n=72).[129] One study, the CAPS3 study from the United States, evaluated MRI plus EUS and CT (n=216).[165]

All studies had final pathology determined using samples obtained by FNA and/or surgery.

Surveillance and Clinical Followup

After initial screening, followup time ranged from 12 to 60 months. All studies included at least 12 months of followup after screening. Eleven studies conducted annual followup repeat screening for screen-negatives, while one study used a 1- to 3-year range for followup testing.[165] For persons with abnormal results, screening protocols typically had branches for immediate biopsy (typically with EUS-guided FNA) or surgery for solid lesions or those otherwise likely malignancies, or surveillance at 3–6 months for less concerning abnormalities. Detailed descriptions of all included screening programs are in **Table 6**. All studies reported final pathology of detected cases of pancreatic adenocarcinoma.

Outcome Assessment

Diagnostic Accuracy Outcomes

All included studies conducted followup diagnostic testing only on individuals with abnormal screening results and did not provide followup data on screen-negative populations. Further, test-positive rates were not consistently reported, and many cases of precursor lesions were detected and removed surgically. Therefore, only diagnostic yield of each screening test is possible, whereas sensitivity, specificity, predictive value, and other measures of diagnostic accuracy are not available. Most studies with multiple imaging tests did not report whether pancreatic adenocarcinoma or other pathology findings were detected on one or more screening exams, so we cannot evaluate yield based on individual imaging tests. No included studies reported results separately for risk-based subgroups of family history, known genetic mutations, or other risk factors.

Screening Harms (Procedural)

Eight studies (n=763) reported screening procedure harms.[125, 126, 129, 133, 155, 157, 159, 160] However, five of these studies do not report how harms were assessed or if they were assessed routinely for all participants or for which procedures.[125, 126, 129, 133, 157] Three studies (n=386) assessed procedure-related harms by calling patients within a week after the procedure.[155, 159, 160] Of these, all three studies reported harms of EUS or ERCP (one with or without FNA[159]), one reported harms of CT,[160] and one reported harms of MRI.[155]

Further, overdiagnosis as a potential harm of screening was difficult to assess, since pathology data is often not available before surgical intervention, and the detection and surgical removal of precursor lesions may represent clinical benefit.

Screening Harms (Psychosocial)

Two screening programs (n=271), the Dutch FPC[126, 158, 167, 170] and Toronto programs,[127, 166, 168] assessed potential psychosocial harms longitudinally between pre- and post-screening. The

Dutch FPC program (n=140) assessed outcomes via survey before the initial screening, shortly after initial screening, as well as four other time points during subsequent screenings (up to 2 years and 2 subsequent screenings). Outcomes assessed included perceived risk, cancer worry, and anxiety and depression, as well as a battery of individual items that assessed concern about a variety of potential issues that could arise from screening from informing children or family.[126, 158, 167, 170] The Toronto study (n=131) assessed, also via survey, perceived pancreatic cancer risk and worry, as well as a measure of general distress derived from the Brief Symptom Inventory (BSI) before initial screening and 3 months after screening in persons with familial pancreatic cancer.[127, 166, 168] Neither study's assessment of harms included a comparison group or reference population.

Clinical Followup of Detected Cases (Treatment Effectiveness)

Possibly due to sparse detection of pancreatic adenocarcinoma, studies typically reported details of detected cases in a case report format. Details were variably provided across studies and included risk factors, family history, stage at detection, whether detected on initial or repeated screening, treatment received, and possibly clinical status at followup.

Treatment Harms

Surgical harms were reported in six studies (n=32 persons receiving surgery).[125, 129, 133, 157, 160, 165] Methods of harm assessment were inconsistently reported across studies. Two studies assessed surgical procedure-related harms through clinical followup of all patients for at least 12 months;[160, 165] no other studies reported how surgical harms were assessed or if they were assessed routinely for all participants or all procedures.

Quality

All studies were fair quality. In all studies, only participants with positive screening results underwent the reference test. More than half of studies had small sample sizes (<75 participants). Five studies reported blinding during the screening process.[126, 129, 159, 160, 165] In four studies, screeners were blinded to each patient's other test results. In one study, the radiologist was blinded to patient risk factors. Less common were issues with incomplete reporting of the participant selection process, the threshold for a positive screening result, participant flow through the screening program, intervals between the screening test and the reference standard, and how harms were assessed. Followup rates were reported in six studies and ranged from 67.0 percent to 97.1 percent.

KQ1. Does Screening for Pancreatic Adenocarcinoma Improve Cancer Morbidity or Mortality or All-Cause Mortality?
KQ1a. Does Screening Effectiveness Vary by Clinically Relevant Subpopulations (e.g., by Age Group, Family History of Pancreatic Cancer, Personal History of New-Onset Diabetes, or Other Risk Factors)?

No studies met inclusion criteria for KQ1 or KQ1a.

KQ2. What Is the Diagnostic Accuracy of Screening Tests for Pancreatic Adenocarcinoma?

Summary of Results

Of 1,317 persons screened, 57 underwent surgery; 14 ended up having confirmed pancreatic cancer and 38 having precursor lesions. Four additional persons had advanced pancreatic cancer diagnosed without surgical intervention.

Across all studies (n=1,317), 18 cases of pancreatic adenocarcinoma were detected: nine on initial screening, eight on repeat screening, and one case in which the timing of detection was not reported. Six studies (n=824) found no cases of pancreatic adenocarcinoma on initial screening;[125, 127, 160, 165, 171, 172] three of these found 6 cases of pancreatic adenocarcinoma on repeat screening. The remaining seven studies (n=493) found a total of nine cases on initial screening and an additional two cases on repeat screening.[126, 133, 155, 157, 159, 164] The single study reporting screening results in an average risk comparison population (n=138) found no cases of pancreatic adenocarcinoma or precursor lesions.[160] Pooled yield for all screening tests to detect pancreatic adenocarcinoma on initial screening in high-risk populations was 7.8 per 1,000 (95% CI, 3.6 to 14.7); and for total yield including both initial and repeat screening, it was 15.6 per 1,000 (95% CI 9.3 to 24.5) (**Figure 2**)

EUS was the most commonly reported initial screening modality. Across studies using EUS or MRI screening, diagnostic yield for pancreatic adenocarcinoma ranged from 0 to 75.0 per 1,000 (7.5%), with three of the smallest studies finding the largest yields and wide confidence intervals around the estimates. For studies with larger sample sizes, yields ranged from 0 to 28.2 per 1,000 (2.8%). The yield of CT for pancreatic adenocarcinoma ranged from zero to 12.8 per 1,000 across two studies.

All screening modalities detected precursor lesions of IPMN, PanIN, or IPMN/PanIn combined. For detection of these precursor lesions, diagnostic yield ranged from 17.2 to 105.3 per 1,000 (1.72% to 10.53%) for EUS alone, to 0 to 50.0 per 1,000 for MRI/MRCP alone. For detection of

precursor lesions across studies using multiple screening modalities, yields ranged from 7.2 to 129.0 per 1,000.

Detailed Results

Of 1,317 persons screened across all studies, screen-positive results were inconsistently reported across studies, prohibiting assessment of false positive rates. Biopsy rates were also inconsistently reported. In total, 57 surgeries were reported across all studies; of these, 14 resulted in a diagnosis of pancreatic adenocarcinoma. Of the remaining 43 surgeries, 38 removed precursor lesions with IPMN or PanIN, and 5 contained either neuroendocrine tumors, liver hyperplasia, or benign serous cystadenoma. Four additional persons had advanced pancreatic adenocarcinoma diagnosed without surgical intervention (**Table 7**).

In total, 18 cases of pancreatic adenocarcinoma were detected: nine on initial screening, eight on repeated screening or during surveillance of abnormal screening results, and one at an unspecified point during the screening program (**Tables 8 and 9**). All cases of pancreatic adenocarcinoma were detected in high-risk study populations.

Detected cases were in persons with a mean age of 59.9 years at detection (range 44 to 81); 12 of 18 cases were in women (66.7%). The mean number of affected relatives was three (range 1 to 7 relatives) in 15 persons with a diagnosis of cancer. Nine of 18 cases (52.9%) were detected on initial screening, and eight were detected on repeated screening (one NR). Seven of 11 cases (63.6%) had a known genetic mutation (2 FAMMM, 4 *BRCA2*, 1 *CDKN2A*).

Twelve of 18 cases (66.6%) were detected at stage I or II or classified as "resectable." Of these, eight were detected through initial screening, three were detected on repeat screening, and one was detected during surveillance following previous abnormal findings (a person with IPMN on initial screening and stage IIA cancer detected at 24 months; Case #5 in **Table 10**). Of the six cases detected at stage III or IV, one was detected at initial screening, three were detected on repeat screening, one was detected at an unspecified point in the screening program, and one was detected during surveillance following previous abnormal findings (a person with cysts identified on initial screening, duct abnormalities detected at 12 months, and an unresectable mass at 14 months that was later confirmed as stage IV disease; Case #9 in **Table 10**).

Yield of Screening EUS to Detect Pancreatic Adenocarcinoma

The yield of EUS-based screening in nine studies (n=885) ranged from 0 to 68.2 cases per 1,000 high-risk persons. Among 11 total pancreatic adenocarcinoma cases detected with EUS across all nine studies, seven were detected on initial screening, three were detected on repeat screening, and one was detected at an unspecified point in the screening program. Of these pancreatic adenocarcinoma cases, three were detected at stage I, one was stage IIA, three were stage IIB, three were metastatic, and one was reported as resectable with no stage given.

Two small studies found diagnostic yields of 68.2 per 1,000 (6.8%)[157] and 64.5 per 1,000 (6.45 %),[133] but confidence intervals were wide in both studies. In the Dutch study by Poley and colleagues (n=44), the population was 52.3 percent persons with known genetic mutations or

syndromes;[157] in a study based at Columbia University Medical Center (n=51), 100 percent of the study population had a family history of pancreatic adenocarcinoma.[133] In the Dutch study by Poley and colleagues, all three detected pancreatic adenocarcinoma cases were persons with known mutations (2 with FAMMM and one with *BRCA2*).[157]

Yield of Screening CT to Detect Pancreatic Adenocarcinoma

In two studies reporting CT (n=294),[160, 165] the yield of CT for pancreatic adenocarcinoma ranged from zero to 12.8 per 1,000.

Yield of Screening MRI to Detect Pancreatic Adenocarcinoma

Across eight studies reporting MRI screening results (n=849), the yield of pancreatic ductal adenocarcinoma following MRI screening ranged from 0 to 75.0 cases per 1,000 persons. Among a total of 11 pancreatic adenocarcinoma cases detected across all eight studies, five were detected on initial screening, three were detected on repeat screening, one was detected at an unspecified point in the screening program, and two were detected during surveillance of IPMN or other cysts. Of these pancreatic adenocarcinoma cases, two were detected at stage IA, two were stage IIA, one was stage IIB, one was stage III, four had metastatic disease, and the remaining case was reported as resectable with no stage given.

Detection of IPMN or PanIN Precursor Lesions

In total, the screening programs identified a total of 38 individuals with IPMN (n=5), PanIN (n=13), or both IPMN and PanIN (n=20). (**Table 8**) It is unclear if the clinical significance of these findings suggests potential clinical benefit or potential harm from overdiagnosis.

KQ3. What Are the Harms of Screening for Pancreatic Adenocarcinoma?

Summary of Results

Procedural harms of screening were evaluated in eight screening studies (n=675);[125, 126, 129, 133, 155, 157, 159, 160] psychological harms were assessed in two studies (n=271).[126, 127] Details on the assessment of harms were variably reported. In two studies (n=277)[159, 160] in which 150 individuals underwent ERCP as a diagnostic followup test, 15 persons (10%) reported acute pancreatitis, nine of which required hospitalization. No evidence of increased worry, distress, depression, or anxiety after screening was reported, compared to before screening.[168, 170]

Detailed Results

Procedural Harms

Eight screening studies (n=675) reported screening procedure-related harms (**Table 11**).[125, 126,

[129, 133, 155, 157, 159, 160] Five studies (n=485) reported harms of EUS alone,[125, 126, 133, 155, 157, 160] two studies (n=150) reported harms of diagnostic followup ERCP,[159, 160] and two studies (n=45) reported harms of diagnostic followup FNA.[129, 159] Two studies (n=160) reported harms of MRI and one (n=98) reported harms of MRCP.[155] One study reported harms of CT.[160]

Six of eight studies (n=421) identified no harms related to screening procedures.[125, 126, 129, 133, 155, 157] Two studies identified harms from EUS, CT, and followup ERCP for abnormal EUS.[159, 160]

Harms of EUS Plus or Minus Followup ERCP and/or FNA

Five studies (n=340) reported no complications related to EUS.[125, 126, 133, 157] One study (n=38) reported no fever, bleeding, pain, or pancreatitis[159] for EUS with or without FNA. One study found that in 216 persons receiving EUS, mild post-EUS pain was reported in 55 (25.5%), and adverse events related to anesthesia were reported in 13 persons (6.0%).[159]

Of 150 individuals who underwent ERCP as an intermediate test across two studies,[159, 160] 15 (10%) reported acute pancreatitis, nine of which required hospitalization. One study (n=24 receiving ERCP) found two cases of acute pancreatitis, one requiring hospitalization[159] and the other (n=126 receiving ERCP) found eight cases (6.3%) of pancreatitis requiring hospitalization (mean hospital stay 8.25 days) and five cases not requiring hospitalization. Cases of acute pancreatitis were similar between high-risk and control groups.

Across two studies[129, 159] and 45 persons receiving EUS-guided FNA for diagnostic followup from initial EUS screening, no adverse events were reported.

Harms of MRI or MRCP

No complications were reported in two studies describing 240 persons receiving screening MRI or MRCP.

Harms of CT

In 78 high-risk individuals and an unreported number of asymptomatic participants receiving CT in a single study,[160] there was one case (0.005%) of mild reaction to contrast that resolved.

Psychosocial Harms

Two screening studies (n=271)[126, 127] assessed psychosocial harms (**Table 12**). In the Dutch FPC study,[126, 158, 167, 170] the majority of respondents reported normal levels of distress at all time points.[170] Cancer Worry Scale scores decreased steadily and significantly over time (14.4 at baseline, 12.1 at 3 years, $p<0.01$), indicating reduced levels of worry from pre-screening to post-screening. Though there is no hard threshold for scoring the CWS, a score of 12 or higher (on a scale of 8, lower worry to 32, higher worry) may indicate severe worry levels,[170] so this change may indicate some clinical relevance.

In the Toronto program,[127, 166, 168] scores of perceived pancreatic cancer risk, pancreatic cancer

worry, and general distress were all similar between baseline and 3 months post-screening (**Table 13**).[168] On a Likert self-rated worry scale from 1 (not at all) to 4 (a lot) points, mean scores were between 1 and 2, and were similar at baseline and 3 months followup. Levels of distress were in the normal range at both time points; perceived risk as a self-reported percentage chance was 42.07 percent at baseline and 37.68 percent at 3 months followup (change not significant).

KQ4. Does Treatment of Screen-Detected or Asymptomatic Pancreatic Adenocarcinoma Improve Cancer Mortality, All-Cause Mortality, or Quality of Life?

No studies met inclusion criteria for KQ4.

No studies met our criteria, typically because of the lack of comparison groups in the studies' designs. This lack of comparison prohibits direct comparison of treatment outcomes in screen-detected compared to clinically detected cancers. However, some studies reported treatment outcomes for select individual cases; and several studies have published longer-term followup at the cohort level. This information is provided in **Appendix D**. Briefly, five individuals—out of 10 for which data were available—were alive at 12 to 63 months followup,[125, 129, 157, 159] two with distant metastases reported at 12 and 16 months.[129, 157]

KQ5. What Are the Harms of Treatment of Screen-Detected Pancreatic Adenocarcinoma?

Of the 57 persons who underwent surgery across all studies, harms of surgery were assessed in six studies, including 32 receiving surgery (56.1%) (**Table 14**).[125, 129, 133, 157, 160, 165] Methods of assessing harms were only reported in two U.S.-based studies, and were defined as clinical followup at 1 year in one study (n=5 receiving surgery)[165] and clinical followup at 1 month and 12 months after surgery (n=7 receiving surgery).[160] In the remaining studies, methods of assessing harms, and whether they were assessed in all study patients, were not reported. No studies reported assessing or identifying psychosocial harms following surgical intervention.

Harms following surgery were reported in seven persons in two studies.[125, 129] In the Danish screening program, stricture to the hepaticojejunal anastomosis was reported in one person 11 months after surgery, and unspecified post-operative complications in the other.[125] In the FaPaCa study of 10 persons receiving surgery, two cases of post-operative fistula were reported, as well as three cases of diabetes, though it is not clear whether these were caused by surgery or existing co-morbidities.[129] In the two studies that systematically assessed harms in all surgical patients (n=12 persons receiving surgery), no harms were reported.[160, 165] The remaining two studies, neither of which reported methods of assessing harms (n=8 persons receiving surgery), reported absence of surgical harms.[133, 157]

Chapter 4. Discussion

Summary of Evidence

Thirteen fair quality prospective cohort screening studies of asymptomatic individuals at high familial risk for pancreatic adenocarcinoma (n=1,317) met inclusion criteria for this review. Other than one study that included a small average risk comparison group (n=138), no screening studies in persons without genetic syndromes or a strong family history met our inclusion criteria. All included studies represent new evidence since the previous evidence review, which did not identify any studies of screening for pancreatic adenocarcinoma.[140] While these populations are at particularly high risk and would normally be outside of the scope of the USPSTF, these represent the most clinically relevant populations for screening.

A summary of the evidence is provided in **Tables 15 and 16**. We found no studies evaluating whether screening for pancreatic adenocarcinoma impacts morbidity or mortality. We found low strength of evidence that imaging-based screening can detect pancreatic adenocarcinoma and its precursor lesions in individuals at high familial risk, and low strength of evidence that screening is associated with minimal to no psychosocial or procedural harms. We found insufficient evidence to assess measures of diagnostic accuracy, including sensitivity, specificity, predictive value, or false positives. Additionally, we found insufficient evidence to assess the benefits or harms of surgical intervention for screen-detected pancreatic adenocarcinoma.

Detection of Pancreatic Adenocarcinoma

The yield of screening to detect pancreatic adenocarcinoma was low even in populations at elevated risk (7.8 per 1,000 for initial screening; 15.6 per 1,000 for the entire screening program). It appears that imaging-based screening with EUS or MRI can detect pancreatic adenocarcinoma, but there is insufficient evidence to evaluate the impact of screening on morbidity and mortality compared to clinical detection.

Observational data clearly suggest a survival benefit associated with earlier stage at detection, and surgical resection of early stage adenocarcinoma further enhances survival (**Chapter 1**). In this review, 12 of 18 (66.7%) cases detected through either initial screening or repeat screening were detected at stage I or II, when surgical intervention has the greatest potential to improve survival. This appears to be a more favorable proportion than the 9 percent to 19 percent of individuals who present clinically at an early stage (**Table 1**),[7] though sample sizes were limited and there was insufficient evidence to directly compare screen-detected and clinically detected pancreatic adenocarcinoma within the present review. Taken together, the included studies suggest that imaging-based screening in high-risk populations may result in stage shift. However, it is unclear if this represents a different spectrum of disease, is a result of lead-time bias, or provides evidence supporting screening. Two individuals reported in the included studies presented with advanced stage cancer during surveillance of abnormal screening findings, suggesting rapid progression of disease. Further, it is unknown if persons with screen-detected adenocarcinoma will respond to treatment similarly to those with clinically detected early stage

adenocarcinoma, or if morbidity and mortality outcomes differ for screen-detected pancreatic adenocarcinoma.

Detection of Precursor Lesions

Detection of precursor lesions of IPMN or PanIN ranged from 0 to 129 per 1,000. However, studies did not systematically follow up these lesions for progression to adenocarcinoma, so this level of detection may or may not represent a clinical benefit, since it is yet unclear if detection and management of precursor lesions results in a decrease in cancer incidence, morbidity, or mortality. Although the detection and removal of precursor lesions may be a preferable endpoint to pancreatic adenocarcinoma, in the absence of clear evidence about progression and assessment of lead time bias, potential overdiagnosis and subsequent harms associated with treatment of precursor lesions remain a possibility.

Harms of Screening and Treatment

In addition to the potential for overdiagnosis of precursor lesions, screening, followup testing, and surgical treatment may result in harms. Potential harms of endoscopic screening can include perforation (which can lead to death in a minority of cases), infection, iatrogenic pancreatitis, hemorrhage, bile peritonitis, and malignant seeding.[174] Screening for pancreatic adenocarcinoma also may be associated with psychosocial harms such as anxiety, depression, or cancer worry.[167, 175] We found sparse evidence on the harms of screening, but the available evidence suggests few harms beyond a risk of acute pancreatitis following ERCP in two studies. In two studies (n=271), no evidence of psychosocial harm was detected.

Pancreatic surgery is associated with complication rates of 20% to 50% in the post-operative period (**Chapter 1**). However, evidence on the harms of surgical intervention in screen-detected pancreatic adenocarcinoma was very limited, and could indicate an underestimate of harms in this body of evidence.

Applicability to Other Risk Groups

Although the high-risk populations included here are typically outside of the purview of the USPSTF, they represent the best data available on screening for pancreatic adenocarcinoma. Included populations were at known elevated pancreatic adenocarcinoma risk based on family history, and are enriched with persons with known genetic mutations or syndromes. Only about 10 percent of pancreatic adenocarcinoma cases have a familial basis; of those, only about 20 percent are currently attributed to inherited genetic mutations.[55, 61] Genetic mutations associated with seemingly sporadic pancreatic adenocarcinoma risk may lead to an expanded role for genetic risk stratification for screening[176] but would still apply to a minority of people. The implications of these results to other at-risk populations are unknown, including those with new-onset diabetes, smoking history, or chronic pancreatitis.

Considerations for Risk Assessment in Primary Care

Given the low prevalence of pancreatic adenocarcinoma even in high-risk groups, risk assessment and identifying subgroups at the highest risk for pancreatic adenocarcinoma is critical for improving screening.[96] Increasingly, screening protocols are expanding to include multiple behavioral and genetic risk factors that may be useful for primary care clinicians, including persons with new-onset diabetes, smokers, and persons over age 50 years.[62, 66, 99, 177-179] Clinical identification of persons who may be eligible for cancer detection based on presence of a series of otherwise nonspecific symptoms has been suggested, such as abdominal pain, back pain, pain while eating, unintentional weight loss, or diarrhea.[64, 75, 76, 99, 180, 181] A U.S.-based modeling study demonstrated that incorporating demographic and behavioral risk factors, symptoms, comorbidities, and liver, pancreas, and gallbladder function could inform combined risk assessment, suggesting potential applications for electronic health record alerts.[182]

Several validated risk assessment tools that combine symptoms and genetic and behavioral risk factors may help assess risk for pancreatic adenocarcinoma, and some are available as software packages or online tools with potential relevance to primary care (**Table 17**). These include QCancer,[183-186] which was developed and validated in the United Kingdom and provides risk estimates across a range of tumor sites; PancPRO,[187-189] which uses family history to estimate the probability an individual will develop familial pancreatic adenocarcinoma; and Your Disease Risk,[190, 191] which offers risk assessments for 12 cancers and other health conditions. These tools ask users to input information, such as age, sex, height, weight, family history of pancreatic adenocarcinoma and other conditions, personal history of cancer, chronic and hereditary conditions, symptoms, smoking status, alcohol use, and diet. Validation studies have shown these tools to have relatively high concordance, with areas under the receiver operating characteristic curve of 0.71[190] to 0.92.[186]

Limitations of Included Studies

The included body of evidence is subject to small sample sizes, not unexpected considering the low prevalence of high-risk populations and pancreatic adenocarcinoma. All studies except one[160] included only high-risk populations without controls, and many studies included a substantial proportion of people with known genetic mutations. Even among the three studies that included 100 percent of their study populations based on family history,[129, 133, 155] pancreatic adenocarcinoma detection rates varied because of small samples and subsequent detection of previously unknown genetic mutations within populations during study followup.

No randomized trials of screening were included. No studies included a clinical followup or unscreened comparison group, so complete assessment of diagnostic accuracy is not possible. Some studies that evaluated multiple screening tests did not report whether imagers were blinded to results from other imaging and, therefore, able to interpret test results independently. In addition, most studies with multiple imaging tests did not report whether pancreatic adenocarcinoma or other pathology findings were detected on one or more screening exams, so we cannot evaluate yield of individual imaging tests.

No included studies reported results stratified by family history, genetic mutation status, or other risk factors. Diagnostic yields were often reported for a multiple-test protocol, so yields within subgroups or attributable to specific screening tests were rarely reported. Harms of screening or treatment were not reported in all studies; of those studies that did, limitations included inadequate description of the methods of assessing harms, including whether all participants were systematically assessed.

Limitations of Our Approach

We included populations with family history of pancreatic adenocarcinoma, but excluded those whose study populations were solely persons with known genetic mutations or syndromes. We did this to focus on evidence for primary care-relevant risk factors; however, this criterion was somewhat arbitrary since familial aggregation represents at least some level of genetic risk, in addition to aggregation of behavioral or environmental risk factors. As such, this report should not be interpreted as an estimate of the yield of screening in persons with known genetic mutations or syndromes, as studies exclusively focused on those populations were excluded.

We included only treatment studies conducted with screen-detected or asymptomatic populations. While consistent with the goals and key questions of the review, this limited our ability to comment systematically on the extensive literature showing the survival benefits of surgery for early-stage pancreatic adenocarcinoma and the significant morbidities that can occur during the post-operative period. The sparsity of harms reported in the included evidence should be interpreted not that surgical treatment is without risks, but rather that the magnitude of these potential harms is not well understood among persons with screen-detected disease.

We excluded study populations with pancreatic endocrine tumors or exocrine tumors other than adenocarcinoma because of the distinct etiologies of these tumors. We limited our literature search to imaging-based screening studies, excluding biomarker-based screening studies, based on consensus in the field that these markers are not yet of sufficient precision to warrant screening studies.

Future Research Needs

The body of evidence in pancreatic adenocarcinoma would be strengthened with the addition of controlled trials that include screening and usual care groups of people at increased risk for pancreatic adenocarcinoma and the demonstration of improved morbidity or mortality. However, randomized trials would require large sample sizes and adequate followup time, and may not be practical to conduct. In the absence of such evidence, research is needed on how to best evaluate the health outcomes of screening using rigorous observational studies and statistical methods. Further, given the low incidence and severity of pancreatic adenocarcinoma and the potential survival benefits of early intervention, approaches to identifying individuals at the highest risk who should receive screening or followup are needed, such as through multiple risk factor assessments that may include otherwise nonspecific symptoms. As less invasive screening tests emerge, such as serum testing for multiple-biomarker panels, screening studies that include these

will be warranted. More research is also needed on the progression rates of various precursor lesions to pancreatic adenocarcinoma, and health outcomes and harms in people with these detected lesions, as well as incidentally-detected cancers. Continued understanding of the harms of screening and treatment, including those associated with the detection of precursor lesions, are also needed.

Conclusions

Imaging-based screening in groups at high familial risk can detect pancreatic adenocarcinoma and its precursor lesions with limited evidence of minimal harms. However, the impact of screening on morbidity and mortality in groups at high familial risk is not well documented, nor is the impact of screening in other groups at risk for pancreatic adenocarcinoma due to other behavioral or clinical risk factors. There is insufficient evidence to assess benefits or harms of surgical intervention for screen-detected pancreatic adenocarcinoma.

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