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Screening for Pancreatic Cancer
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Pancreatic adenocarcinoma is the third most common cause of cancer death among men and women in the United States.

OBJECTIVE To systematically review benefits and harms of screening for pancreatic adenocarcinoma to inform the US Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed, and the Cochrane Collaboration Registry of Controlled Trials, from January 2002 through April 27, 2018; surveillance through March 22, 2019.

STUDY SELECTION Studies of adults with or without risk factors for pancreatic adenocarcinoma (eg, family history of pancreatic cancer, personal history of new-onset diabetes) undergoing imaging-based screening; studies of treatment for adults with screen-detected or asymptomatic pancreatic adenocarcinoma. Included study designs were randomized clinical trials, nonrandomized controlled intervention studies, diagnostic accuracy studies with a reference standard, cohort studies, and case-control studies (for evaluation of harms only). Studies consisting entirely of populations with known genetic syndromes associated with pancreatic cancer were excluded.

DATA EXTRACTION AND SYNTHESIS Two investigators independently reviewed abstracts and full-text articles and rated included studies for quality; data were quantitatively analyzed to calculate a pooled diagnostic yield and narratively synthesized.

MAIN OUTCOMES AND MEASURES Mortality, morbidity, or quality of life; diagnostic accuracy of screening tests; any harm of screening or treatment.

RESULTS Thirteen fair-quality prospective cohort screening studies (N = 1317) conducted predominantly in populations at high familial risk for pancreatic adenocarcinoma were included. No studies reported on the effect of screening on morbidity or mortality or on the effectiveness of treatment for screen-detected pancreatic adenocarcinoma. Although no studies evaluated the diagnostic accuracy of screening tests, all 13 studies reported the diagnostic yield. Yields ranged from 0 to 75 cases per 1000 persons in studies using endoscopic ultrasound, magnetic resonance imaging, and/or computed tomography–based screening. In total, 18 cases of pancreatic adenocarcinoma were detected in 1156 adults at increased familial risk and 0 cases were detected in 161 average-risk adults. In 8 studies (n = 675) assessing procedural harms of screening, no serious harms from initial screening were reported. Two studies (n = 271) found no evidence of psychosocial harms related to screening. Evidence of surgical harms was limited.

CONCLUSIONS AND RELEVANCE Imaging-based screening in groups at high familial risk can detect pancreatic adenocarcinoma with limited evidence of minimal harms. However, the effect of screening on morbidity and mortality in groups at high familial risk has not been studied, and no data are available in average-risk populations. There is limited evidence to assess benefits or harms of surgical intervention for screen-detected pancreatic adenocarcinoma.

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Pancreatic adenocarcinoma is the third most common cause of cancer death in the United States.[1] The mean 5-year survival rate for patients with early-stage disease was 32% in 2014[2]; however, more than 80% of incident cases diagnosed between 2005 and 2011 were detected at advanced stages, for which 5-year survival is less than 5%.[3] Screening to detect pancreatic cancers and their potential precursor lesions could improve survival if it facilitated surgical resection for early-stage disease. However, since incident pancreatic cancer is rare, with 12.6 new cases per 100 000 people in the United States in 2011-2015,[4] identifying populations at the highest risk for pancreatic cancer is critical to developing meaningful screening or early detection programs.

In 2004, the US Preventive Services Task Force (USPSTF) recommended against routine pancreatic screening in asymptomatic adults (D recommendation).[5] This systematic review addresses the benefits and harms associated with screening and treatment of pancreatic adenocarcinoma. It was conducted to support an updated USPSTF recommendation for screening in asymptomatic adults.

Methods

Scope of Review

This review addressed 5 key questions (KQs) (**Figure 1**). Methodological details (including study selection, a list of excluded studies, and description of data analyses), as well as detailed results for each study (including descriptions of all screening programs), are available in the full evidence report[7] at https://www.uspreventiveservicestaskforce.org/Page/Document/UpdateSummaryFinal/pancreatic-cancer-screening1.

Data Sources and Searches

All articles included in the previous USPSTF evidence report on screening for pancreatic cancer[8] were evaluated for inclusion. MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials were searched from January 1, 2002 to April 27, 2018 (eMethods in the Supplement). The database searches were supplemented by scanning reference lists of existing reviews and primary studies. Ongoing surveillance was conducted through article alerts and targeted searches of high–impact-factor journals identified by the USPSTF[6] to identify major studies published in the interim. The last surveillance was conducted on March 22, 2019, and identified no new studies.

Study Selection

A single investigator reviewed the titles or abstracts of citations initially identified as of low relevance using key words relating to exclusion criteria. The remaining abstracts were dual-reviewed by 2 independent investigators. From the 2 processes, the remaining full-text articles were reviewed for consistency with prespecified inclusion criteria (eTable 1 in the Supplement). Discrepancies were resolved through consultation with a third investigator.

For key questions on screening (KQ1, KQ2, KQ3), the population of interest was adults 18 years or older with or without risk factors for pancreatic adenocarcinoma (eg, family history of pancreatic adenocarcinoma, personal history of new-onset diabetes, or other risk factors). Studies consisting entirely of persons with confirmed genetic syndromes (eg, Peutz-Jeghers syndrome, Lynch syndrome, hereditary pancreatitis, known mutations in *CDKN2A*, *BRCA1*, *BRCA2*, *CTFR*, or *ATM* genes) were excluded. Any imaging-based screening protocol—including endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), or computed tomography (CT)—was included. Studies using biomarker-based initial screening protocols were excluded, since no biomarkers have been validated as screening tests at the time of the review.[9]

For key questions on treatment (KQ4, KQ5), the population of interest was adults with screen-detected, asymptomatic, or incidentally detected pancreatic adenocarcinoma treated with surgical resection with or without chemotherapy or radiation. Study populations with pancreatic adenocarcinoma detected clinically or symptomatically were excluded to focus the review on treatment for screen-detected cancers. Studies eligible for KQ4 needed to have a comparison group of either no treatment or delayed treatment; thus, comparative effectiveness treatment studies were excluded.

Included study designs were randomized or nonrandomized controlled intervention studies (KQ1, KQ3, KQ4, KQ5), diagnostic accuracy studies with a reference standard (KQ2), prospective cohort studies (KQ3, KQ4, KQ5), and case-control studies (KQ3, KQ5).

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); procedural or psychosocial harms of screening (KQ3); morbidity, mortality, or quality of life (KQ4); or any surgical harms (KQ5). For KQ2, additional outcomes of interest were pancreatic adenocarcinoma or its associated precursor lesions, including pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm, and mucinous cystic neoplasm.

Data Extraction and Quality Assessment

Two investigators critically appraised all articles that met inclusion criteria based on the USPSTF design-specific quality criteria (eTable 2 in the Supplement). Each study was rated as good, fair, or poor quality. A good-quality study met all quality criteria. A fair-quality study failed to meet at least 1 criterion but had no known issue that would invalidate its results. Poor-quality studies were those with a major risk of bias and were excluded from this review. The most common reasons for poor-quality exclusion were insufficient information on patient recruitment or the screening process. Disagreements about quality rating were resolved by consensus.

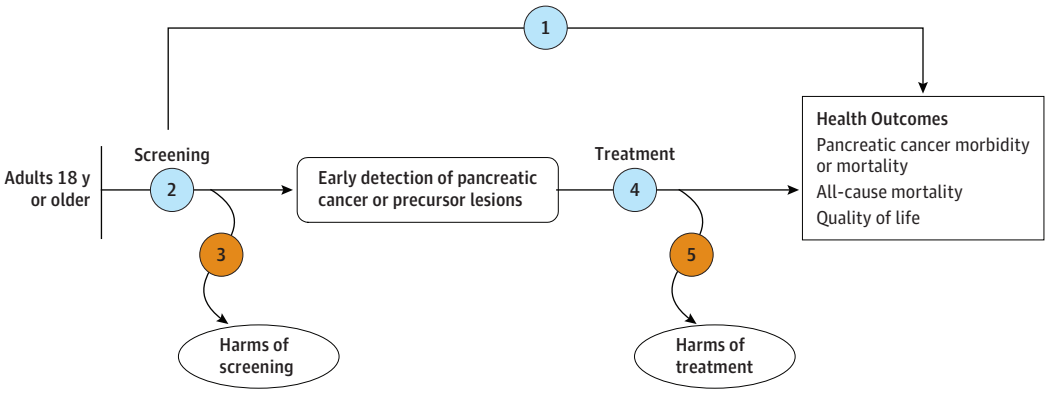
One investigator completed primary data abstraction; a second investigator checked all data for accuracy and completeness.

Data Synthesis and Analysis

For each KQ, data were summarized narratively using tables that included details on study design and quality, setting, population, screening program details, length of follow-up, outcomes, and reported harms.

For KQ2, data on diagnostic yield were quantitatively synthesized, as it was not possible to calculate sensitivity and specificity from the included studies. The diagnostic yield of pancreatic adenocarcinoma and 2-sided 95% confidence intervals were calculated assuming binomial distribution; for studies that detected 0 relevant findings, 1-sided 97.5% confidence intervals were calculated. After confirming that the yield of different imaging modalities was similar across studies and none visually appeared to be outliers, a pooled diagnostic yield was calculated and illustrated in forest plots to show

Figure 1. Analytic Framework: Screening for Pancreatic Cancer



Key questions

1 Does screening for pancreatic adenocarcinoma improve cancer morbidity or mortality or all-cause mortality?

a. Does screening effectiveness vary by clinically relevant subpopulations (eg, 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?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions (KQs) that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. Further details are available in the USPSTF procedure manual.[6]

the range of effects across studies. Diagnostic yield was calculated for initial screening and, when possible, from initial and repeated screening combined. Diagnostic yield could not be calculated for repeat screenings alone because the number of participants undergoing repeat screenings was not consistently reported across studies. All analyses were conducted in Stata version 15 (StataCorp).

Results

A total of 19 596 abstracts were reviewed (**Figure 2**), including 2168 citations initially identified as of low relevance. The remaining 17 428 citations were reviewed by 2 independent investigators. From the 2 processes, the team reviewed 824 full-text articles.

Thirteen unique prospective cohort screening studies reported in 24 articles[11-34] and with results for 1317 people (**Table 1**) were included. All screening populations except 1 small comparison group in 1 study were exclusively persons at elevated familial risk for pancreatic adenocarcinoma, with or without confirmed genetic mutations or syndromes. No studies reported the effect of screening for pancreatic adenocarcinoma on cancer morbidity, mortality, or all-cause mortality (KQ1). All 13 studies reported diagnostic yield of screening tests for pancreatic adenocarcinoma (N = 1317, KQ2); 9 of these studies (18 articles)[11-20,24-31] reported on the procedural harms (n = 675) or psychological harms (n = 271) of screening (KQ3). No studies on the effectiveness of treatment for screen-detected pancreatic adenocarcinoma (KQ4) met inclusion criteria. Six studies (12 articles)[12-14,16,18-21,23,27,29,34] reported on the harms of treatment of screen-detected pancreatic adenocarcinoma (n = 32, KQ5). The studies were conducted in the United States, Canada, and Europe; all included studies were of fair quality.

Effectiveness of Screening

Key Question 1. Does screening for pancreatic adenocarcinoma improve cancer morbidity or mortality or all-cause mortality?

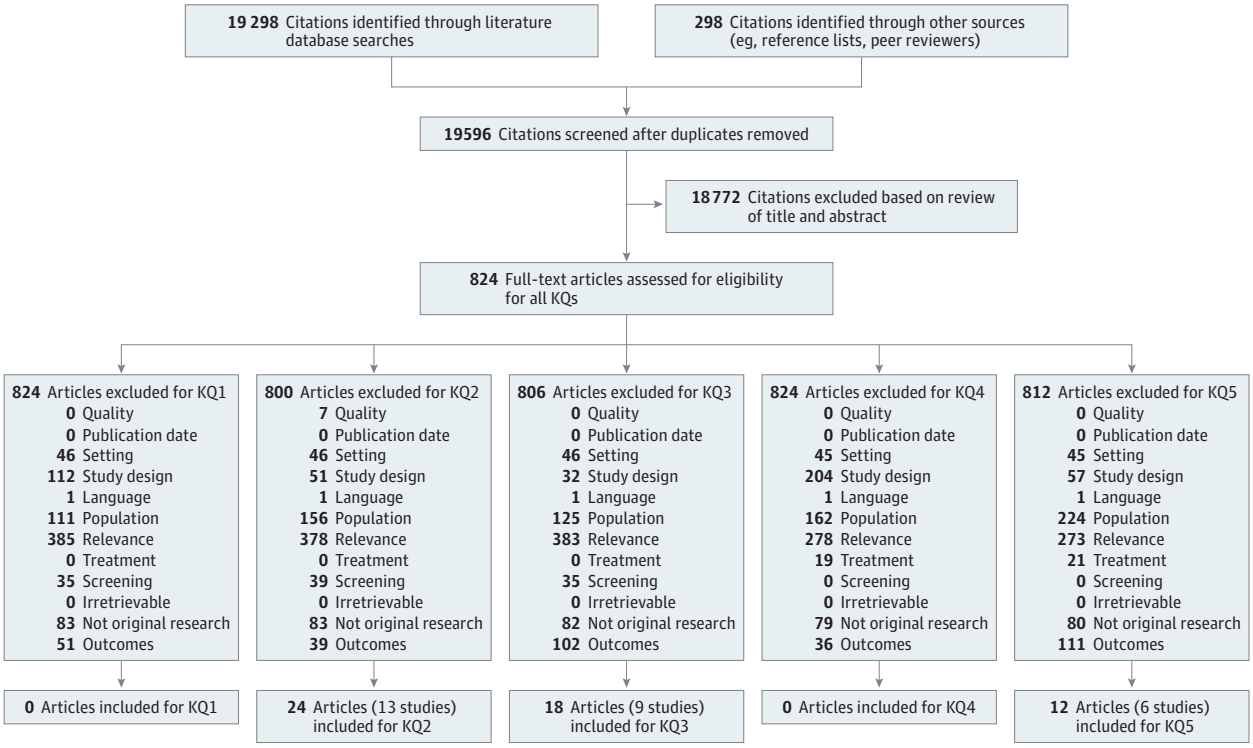
Key Question 1a. Does screening effectiveness vary by clinically relevant subpopulations (eg, by age group, family history of pancreatic cancer, personal history of new-onset diabetes, or other risk factors)?

No studies met inclusion criteria for KQ1.

Key Question 2. What is the diagnostic accuracy of screening tests for pancreatic adenocarcinoma?

Thirteen studies reported in 24 articles (n = 1317) met inclusion criteria for KQ2 (Table 1).[11-34] Screening programs used EUS, CT, and/or MRI screening alone or in combination with another screening modality. Studies evaluating more than 1 type of screening

Figure 2. Literature Search Flow Diagram: Screening for Pancreatic Cancer



All eligible full-text articles could be reviewed for more than 1 key question (KQ). Reasons for exclusion: Quality: Study was poor quality. Publication date: Primary results published before included date range. Setting: Study was not conducted in a country relevant to US practice (those categorized as "Very High" on the United Nations Human Development Index).[10] Study design: Study did not use an included design. Language: Publication was not in English. Population: Study was not conducted in an included population. Relevance: Study was not relevant to screening or treatment for pancreatic cancer. Treatment: Study used an ineligible treatment modality. Screening: Study used an ineligible screening modality. Irretrievable: Publication was not available or accessible. Not original research: Study was not original research. Outcomes: Study did not have relevant outcomes or had incomplete outcomes.

reported abnormal results and yield of pancreatic adenocarcinoma by type of test. Follow-up time after initial screening ranged from 12 to 60 months. All studies reported final pathology determined using fine-needle aspiration biopsy, surgery, or both.

Nine studies (n = 885) evaluated EUS-based screening, with yields of pancreatic adenocarcinoma ranging from 0 (97.5% CI, 0.0-16.9) to 68.2 (95% CI, 14.3-186.6) cases per 1000 persons.[13,14,16-18,23,27,31,33] In 2 studies reporting CT findings (n = 294),[18,23] the yield of CT for pancreatic adenocarcinoma ranged from 0 (97.5% CI, 0.0-16.9) to 12.8 (95% CI, 0.3-69.4) per 1000. Eight studies reported MRI screening results (n = 849), with yields of pancreatic ductal adenocarcinoma ranging from 0 (97.5% CI, 0.0-16.9) to 75.0 (95% CI, 15.7-203.9) cases per 1000 persons.[16,22-24,27,31,32]

In total, 18 cases of pancreatic adenocarcinoma were detected among 1156 screened persons at increased familial risk: 9 on initial screening (yield, 7.8 per 1000 persons [95% CI, 3.6-14.7]), 8 on repeated screening or during surveillance of abnormal screening results (yield, 15.6 per 1000 persons [95% CI, 9.3-24.5]), and 1 at an unspecified time point (**Figure 3**). Twelve of 18 cases (66.6%) were detected at stage I or II or classified as resectable, whereas 6 (33.3%) were detected at stage III or IV. One study with 161 screened average-risk adults found no cases of pancreatic adenocarcinoma.[18] Screen-positive results, biopsy rates, and follow-up of screen-negative results were inconsistently reported, prohibiting calculation of diagnostic accuracy.

Eleven of the 13 studies reported the number of precursor lesions, including pancreatic intraepithelial neoplasia, intraductal papillary mucinous neoplasm, and other nonmalignant pancreatic lesions in addition to pancreatic adenocarcinoma. In total, the screening programs identified a total of 38 individuals with intraductal papillary mucinous neoplasm (n = 5), pancreatic intraepithelial neoplasia (n = 13), or both intraductal papillary mucinous neoplasm and pancreatic intraepithelial neoplasia (n = 20). These findings are not considered false-positives because they often serve as indications for surgical resection, the individuals are enrolled in surveillance programs to monitor lesion progression, or both.

Harms of Screening

Key Question 3. What are the harms of screening for pancreatic adenocarcinoma?

Nine studies met the inclusion criteria for KQ3 (Table 1). Eight of these studies reported on procedural harms from screening (n = 675).[11,13,14,16-18,27,31] No serious harms from initial screening were reported. One study (n = 216) reported prevalence of 25.5% for mild pain after EUS. Adverse events related to anesthesia were reported in 13 people (6.0%).[17] No harms were reported in 2 studies

Table 1. Included Prospective Cohort Screening Studies and Population Characteristics[a]

Source	Recruitment Period	Country and Setting	No. of Participants	Age, Mean (SD) [Range], y	Family History of PDAC, No. (%)	Known Genetic Mutation or Syndrome, No. (%)	Initial Screening Protocol	Follow-up, mo	Included for KQ(s)
Barnes et al,[32] 2018	2012-2017	United States; pancreatic cancer screening clinic, academic medical center	75 enrolled; 65 screened	56 (14) [NR][b,c]	33 (44.0)[b,d]	42 (56.0)[b]	MRI	NR	2
Gangi et al,[33] 2018	2007-2017	United States; comprehensive cancer center, academic medical center	58	60 (NR) [NR]	57 (98.3)	10 (17.2)	EUS	Planned, 60.0	2
Dutch Familial Pancreatic Cancer Study Konings et al,[15] 2017 Harinck et al,[31] 2016 Konings et al,[30] 2016 Harinck et al,[26] 2011	2006-2013	The Netherlands; academic medical center; multisite	139 (from 81 families)	51.1 (9.7) [20-73]	68 (48.9)[e]	71 (51.1)	EUS and MRI	Planned, 12.0	2, 3
Danish National Screening Program Joergensen et al,[13] 2016	2006-2014	Denmark; hereditary pancreatitis registry, academic medical center	71 (from 30 families)	51.1 (NR) [26-72]	40 (56.3)[f]	NR[f]	EUS[g]	Mean (range), 60.0 (2.0-92.0)	2, 3, 5
Del Chiaro et al,[22] 2015	2010-2013	Sweden; academic medical center	40	49.9 (NR) [23-76]	38 (95.0)	8 (20.0)[h]	MRI	Mean (range), 12.9 (0-36.0)	2
Toronto Screening Program Al-Sukhni et al,[24] 2012 Hart et al,[25] 2012 Maheu et al,[28] 2010	2003-2011	Canada; academic medical center	262 (from 158 families)	54 (NR) [22-89]	159 (60.7)	93 (35.5)	MRI	Mean (range), 50.4 (0-98.4)	2, 3
CAPS3 Shin et al,[21] 2015 Canto et al,[23] 2012	2006-2009	United States; academic medical center; multisite	216	56.1 (NR) [28-79]	195 (90.3)	21 (9.9)	EUS and CT and MRI/MRCP	Mean (range), 28.8 (14.0-47.2)	2, 5
Ludwig et al,[11] 2011	2002-2009	United States; familial pancreatic cancer registry, academic cancer center	109	54 (11.4) [33-86]	109 (100)	7 (6.4)	MRCP or CT for those unwilling to undergo MRCP	Planned, 24.0	2, 3
FaPaCa Bartsch et al,[12] 2016 Vasen et al,[20] 2016 Potjer et al,[19] 2013 Schneider et al,[16] 2011 Langer et al,[29] 2009	2002-2009[i]	Germany; familial pancreatic cancer registry, academic medical center; multisite	72	60 (NR) [35-85]	76 (100)	2 (2.7)	EUS and MRI/MRCP	Median, 44.0	2, 3, 5
Verna et al,[27] 2010	2005-2008	United States; familial pancreatic cancer registry, academic medical center	51 (from 43 families)	52 (12.3) [29-77]	51 (100)	7 (13.7)[j]	EUS or MRI	NR	2, 3, 5
Poley et al,[14] 2009	2005-2007	The Netherlands; academic medical center	44	NR (NR) [32-75]	21 (47.7)	23 (52.3)	EUS	NR	2, 3, 5
Canto et al,[18] 2006	2001-2004	United States; academic medical center	High-risk: 78 Controls: 161	High-risk: 52 (NR) [32-77] Controls: 54 (NR) [30-80]	High-risk: 72 (92.3); Controls: 0	High-risk: 8 (10.3); Controls: NR	High-risk: EUS and CT; Controls: EUS and/or ERCP	Planned, 12.0	2, 3, 5
Canto et al,[17] 2004	1998-2001	United States; familial pancreatic cancer registry, academic medical center	38	56.5 (NR) [NR]	37 (97.4)	1 (2.6)	EUS	Mean (range), 22.4 (11.3-50.5)	2, 3

Abbreviations: CAPS3, Cancer of the Pancreas Screening Study 3; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FaPaCa, Familial Pancreatic Cancer; KQ, key question; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NR, not reported; PDAC, pancreatic ductal adenocarcinoma.

[a] All studies were of fair quality (assessed using US Preventive Services Task Force criteria[6]).

[b] Population characteristics provided for the 75 individuals enrolled in the study. Population characteristics not reported separately for the 65 individuals who underwent screening.

[c] Study reported age as median (interquartile range) rather than mean (SD).

[d] Thirty-three participants were classified as having "familial pancreatic cancer" ([A] ≥3 relatives with PDAC, including ≥1 first-degree relative; or [B] 2 first-degree relatives with PDAC; or [C] 1 first-degree relative and 1 second-degree relative with PDAC and PancPRO risk ≥5%). The remaining 42 were classified as having a known genetic mutation; however, the inclusion criteria specify that those with *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CDKN2A*, or Lynch syndrome also had to have 1 or more first-degree relatives or second-degree relatives with PDAC. Only patients with Peutz-Jeghers syndrome (n = 1) could be enrolled in the study regardless of family history of PDAC.

[e] Sixty-eight participants were classified as having "familial pancreatic cancer" (member of a family with [A] ≥2 affected first-degree relatives; or [B] ≥3 relatives in which the affected cases are first-degree or second-degree relatives of each other; or [C] ≥2 second-degree relatives, of whom at least 1 was aged <50 years at time of diagnosis). The remaining 71 (classified as having a known genetic mutation) have a range of 0 to 7 relatives with PDAC; the authors do not report the total number of study participants who have relatives with PDAC.

[f] Population classified as having familial pancreatic cancer (n = 40 [56.3%]) and hereditary pancreatitis (n = 31 [43.7%]). Some patients in the latter group also had a family history of PDAC. Of the 30 enrolled families, 76.6% had a family history of PDAC, but the number of individuals with family history not reported. Of the 30 enrolled families, 26.7% had a *PRSS-1* variant, but the number of individuals with this variant not reported.

[g] Two patients underwent ultrasound because of severe claustrophobia.

[h] Genetic testing during the study identified 4 patients (10.0%) with a p16 variant, 3 (7.5%) with *BRCA2* variant, and 1 (2.5%) with *BRCA1* variant. The authors do not report whether any patients had multiple variants.

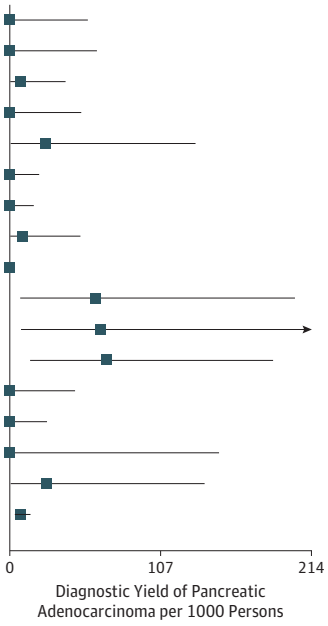
[i] FaPaCa registry started recruitment in July 1999 but screening program started in 2002.

[j] Nineteen patients were tested for *BRCA1* and *BRCA2*, and 7 of the 19 (36.8%) tested positive for *BRCA1* or *BRCA2*.

Figure 3. Diagnostic Yield of Pancreatic Adenocarcinoma per 1000 Persons in Prospective Cohort Screening Studies of High-Risk Populations

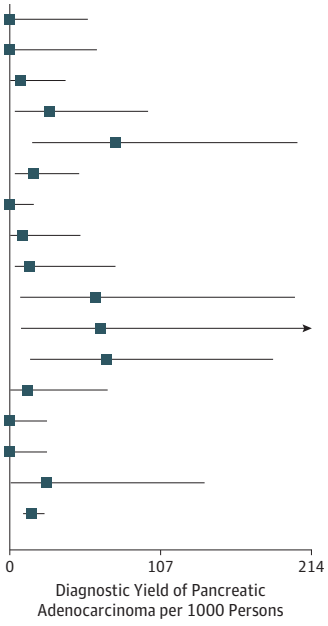
A Diagnostic yield (PDAC) from initial screening only

Study	Screening Protocol	No. of Patients	Diagnostic Yield per 1000 Persons (95% CI)
Barnes et al,[32] 2018	MRI	65	0.00 (0.00-55.20)
Gangi et al,[33] 2018	EUS	58	0.00 (0.00-61.60)
Dutch Familial Pancreatic Cancer Study,[15,26,30,31] 2016	EUS, MRI	139	7.20 (0.20-39.40)
Joergensen et al,[13] 2016	EUS	71	0.00 (0.00-50.60)
Del Chiaro et al,[22] 2015	MRI	40	25.00 (0.60-131.60)
Toronto Screening Program,[24,25,28] 2012	MRI	175	0.00 (0.00-20.90)
Canto et al,[23] 2012	EUS, CT, MRI	216	0.00 (0.00-16.90)
Ludwig et al,[11] 2011	MRCP	109	9.20 (0.20-50.10)
FaPaCa,[12,16,19,20,29] 2011	EUS, MRI, MRCP	72	0.00 (0.00-0.00)
Verna et al,[27] 2010	MRI	51	60.60 (7.40-202.30)
	EUS	51	64.50 (7.90-214.20)
Poley et al,[14] 2009	EUS	44	68.20 (14.30-186.60)
Canto et al,[18] 2006	EUS, CT	239	0.00 (0.00-46.20)
Canto et al,[18] 2006 (controls)	EUS[a]	138	0.00 (0.00-26.40)
	ERCP[a]	23	0.00 (0.00-148.20)
Canto et al,[17] 2004	EUS	38	26.30 (0.70-138.10)
Total		1156	7.80 (3.60-14.70)



B Total diagnostic yield

Study	Screening Protocol	No. of Patients	Diagnostic Yield per 1000 Persons (95% CI)
Barnes et al,[32] 2018	MRI	65	0.00 (0.00-55.20)
Gangi et al,[33] 2018	EUS	58	0.00 (0.00-61.60)
Dutch Familial Pancreatic Cancer Study,[15,26,30,31] 2016	EUS, MRI	139	7.20 (0.20-39.40)
Joergensen et al,[13] 2016	EUS	71	28.20 (3.40-98.10)
Del Chiaro et al,[22] 2015	MRI	40	75.00 (15.70-203.90)
Toronto Screening Program,[24,25,28] 2012	MRI	175	17.10 (3.50-49.30)
Canto et al,[23] 2012	EUS, CT, MRI	216	0.00 (0.00-16.90)
Ludwig et al,[11] 2011	MRCP	109	9.20 (0.20-50.10)
FaPaCa,[12,16,19,20,29] 2011	EUS, MRI, MRCP	72	13.90 (3.50-75.00)
Verna et al,[27] 2010	MRI	51	60.60 (7.40-202.30)
	EUS	51	64.50 (7.90-214.20)
Poley et al,[14] 2009	EUS	44	68.20 (14.30-186.60)
Canto et al,[18] 2006	EUS, CT	239	12.80 (0.30-69.40)
Canto et al,[18] 2006 (controls)	EUS[a]	138	0.00 (0.00-26.40)
	ERCP[a]	23	0.00 (0.00-26.40)
Canto et al,[17] 2004	EUS	38	26.30 (0.70-138.10)
Total		1156	15.60 (9.30-24.50)



CT indicates computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FaPaCa, Familial Pancreatic Cancer; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PDAC, pancreatic ductal adenocarcinoma.

[a] The control group for Canto 2006 (n = 161) was not included in the total N or total diagnostic yield.

Table 2. Summary of Evidence by Key Question

No. of Studies (No. of Observations), Study Designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ1: Effect of Screening on Health Outcomes					
No studies	NA	NA	NA	Insufficient for benefit	NA
KQ2: Diagnostic Accuracy of Screening					
13 Prospective cohort studies (1317) EUS: 9 (885) MRI/MRCP: 8 (849) CT: 2 (294)	Across all studies (N = 1317), 18 cases of PDAC were detected; 9 on initial screening No evidence available for diagnostic accuracy Pooled yield for all screening tests to detect PDAC on initial screening was 7.8 per 1000 (95% CI, 3.6-14.7) and for total yield, including both initial screening and repeated screening, was 15.6 per 1000 (95% CI, 9.3-24.5) Diagnostic yield similar for EUS/ERCP and MRI/MRCP Initial screening with CT (n = 294) yielded 1 PDAC case (yield, 12.8 per 1000)	Inconsistent, imprecise	Small sample sizes; no unscreened comparison groups; little to no subgroup analyses of screening yield in different risk groups Reporting bias not detected All studies were of fair quality	Low for accuracy	Most applicable to populations who are white or with Northern European ancestry with established increased family history or genetic risk for pancreatic cancer seen in tertiary care centers
KQ3: Harms of Screening					
9 Prospective cohort studies (938) Procedural harms: 8 (675) EUS/ERCP: 7 (574) MRI/MRCP: 2 (240) CT: 1 (78) FNA: 2 (45) Psychosocial harms: 2 (271)	Procedural harms: EUS: 55/216 (25%) mild post-EUS pain; 13/216 (6%) adverse events related to anesthesia ERCP: 15/150 (10%) acute pancreatitis, 9 requiring hospitalization MRI/MRCP: None reported CT: 1/78 mild reaction to contrast (1 study) FNA: None reported Psychosocial harms: Cancer worry: 1 study reported (benefit); decrease in worry between prescreening and postscreening Cancer distress, depression, or anxiety: no evidence of harm	Inconsistent, imprecise	Not all studies reported methods of assessment of harms; few studies assessed psychosocial harms Reporting bias not detected All studies were of fair quality	Low for harms	Most applicable to populations who are white or with Northern European ancestry with established increased family history or genetic risk for pancreatic cancer seen in tertiary care centers
KQ4: Effect of Treatment on Health Outcomes					
No studies	NA	NA	NA	Insufficient for benefit	NA
KQ5: Harms of Treatment					
6 Prospective cohort studies (32 people receiving surgery)	Seven instances of surgical harms were reported in 32 cases of surgery; 1 (stricture to hepaticojejunal anastomosis) occurred 11 mo postoperatively, and the others (diabetes, fistula) in the immediate postoperative period No information was reported about assessment or instances of psychosocial harms	Inconsistent, imprecise	Harms inconsistently reported, as were the methods of assessing harms For studies reporting harms, whether they were assessed consistently in all study participants was not well reported Reporting bias not detected All studies were of fair quality	Insufficient for harms	NA

Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; KQ, key question; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; NA, not applicable; PDAC, pancreatic ductal adenocarcinoma.

of 240 people screened with MRI or magnetic resonance cholangiopancreatography (MRCP),[11,27] while 1 person reported a mild reaction to contrast in 1 study of CT screening (n = 78).[18] Of 150 individuals who underwent follow-up testing with endoscopic retrograde cholangiopancreatography (ERCP) across 2 studies,[17,18] 15 people (10%) reported acute pancreatitis, 9 of which required hospitalization. One of these studies (n = 24 receiving ERCP) found 2 cases of acute pancreatitis, 1 requiring hospitalization[17]; the other study (n = 126 receiving ERCP)[18] found 8 cases (6.3%) of pancreatitis requiring hospitalization (mean hospital stay, 8.25 days) and 5 cases not requiring hospitalization.

Psychosocial harms were assessed in 2 studies, which assessed distress and cancer worry before and after screening. Distress levels remained in normal ranges at all time points in both studies (n = 271).[28,30] In the 1 study assessing cancer worry,[30] worry declined steadily over time (Cancer Worry Scale score, 14.4 at baseline and 12.1 at 3 years; difference, 2.3 points [$P < .01$]; with scores above 12 indicating severe worry levels), indicating a possible benefit to screening. In the other study,[28] perceived cancer risk remained stable between prescreening and 3 months' follow-up.

Effectiveness of Treatment

Key Question 4. 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.

Table 3. Summary of Existing and New Evidence, by Screening and Treatment

Rationale and Foundational Evidence for Previous D Recommendation (2004)[5,8]	New Evidence Findings	Limitations of New Evidence	Consistency of New Evidence With Foundational Evidence and Current Understanding
Benefits			
Screening: The 2004 evidence update found no direct evidence on the benefits of screening for pancreatic cancer and no high-quality evidence on the accuracy of screening tests Treatment: There was no established evidence of the effectiveness of surgery, adjuvant chemotherapy, or radiation therapy for pancreatic cancer	Screening: Based on 13 prospective screening studies, imaging-based screening in groups at high familial risk can detect pancreatic adenocarcinoma and its precursor lesions Across all studies (N = 1317), 18 cases of pancreatic adenocarcinoma were detected, 12 at early-stage disease There was no direct evidence of the effect of screening on morbidity or mortality Treatment: No included studies	Screening: Inconsistent reporting of test positives and no follow-up of screen-negative people prohibit assessment of sensitivity or specificity screening tests Current evidence applies primarily to populations at high risk because of family history Treatment: No included studies	Screening: Included studies provide new evidence on the diagnostic yield of screening high-risk populations at increased familial risk Treatment: A survival advantage associated with surgical intervention for early stage cancer is established, but there continues to be very limited evidence on the outcomes of treatment in screen-detected pancreatic adenocarcinoma
Harms			
Screening: The USPSTF concluded that there is potential for significant harm because of the low prevalence of pancreatic cancer, limited accuracy of screening tests, and the invasive nature of diagnostic tests Treatment: The USPSTF concluded that there are poor outcomes from treatment for pancreatic cancer	Screening: EUS was associated with mild post-EUS pain and adverse events related to anesthesia (7 studies) ERCP was associated with acute pancreatitis Harms of MRI (2 studies) or CT (1 study) were minimal There was no evidence of psychosocial harm from screening (2 studies) Treatment: In 32 cases of surgery, 7 instances of surgical harms were reported, including stricture to hepaticojejunal anastomosis, diabetes, fistula, or unspecified complications There was no included evidence on the psychosocial harms of surgical intervention	Screening: Harms were inconsistently reported, as were methods of assessment Treatment: Harms were inconsistently reported, as were methods of assessment	Screening: All studies on screening harms represent new evidence Treatment: All studies on treatment harms represent new evidence While the morbidities of surgical intervention are established, there is little evidence to estimate these events following treatment of screen-detected pancreatic adenocarcinoma

Abbreviations: CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; USPSTF, US Preventive Services Task Force.

Harms of Treatment

Key Question 5. What are the harms of treatment of screen-detected pancreatic adenocarcinoma?

Harms of surgical treatment were limited, assessed in 6 studies (n = 32).[13,14,16,18,23,27] Among the 32 people, a total of 7 (25%) experienced a harm from surgery, including diabetes (n = 3), pancreatic fistula (n = 2), stricture of hepaticojejunal anastomosis with cholangitis (n = 1), and other postoperative complications not further specified (n = 1). However, only 3 of the 6 studies assessed harms in all participants, limiting conclusions for this question.

Discussion

The findings of this evidence review are summarized in **Table 2**. All included studies represent new evidence since the previous evidence review, which did not identify any studies of screening for pancreatic adenocarcinoma.[8] A broader summary of the previous and new evidence is provided in **Table 3**. No studies evaluating mortality and morbidity as an effect of screening met inclusion criteria. There was limited evidence that imaging-based screening can detect pancreatic adenocarcinoma and its precursor lesions in individuals at high familial risk, and limited evidence that screening is associated with minimal to no psychological or procedural harms.

Collectively, the included studies suggest that imaging-based screening in populations at increased familial risk can identify pancreatic adenocarcinoma and may result in stage shift toward earlier stage at detection. A robust body of observational data clearly suggests a survival benefit associated with earlier stage at detection, and surgical resection of early-stage adenocarcinoma further enhances survival.[7,34] However, in the absence of longer-term follow-up data, it is unclear if the available evidence represents a true clinical benefit, different spectrum of disease, or lead-time bias. There was also little evidence to inform sensitivity, specificity, predictive value, or false-positives of screening tests. Similarly, pancreatic surgery is associated with postoperative complication rates of 20% to 50%,[7] but evidence on the harms of surgery for screen-detected pancreatic adenocarcinoma was very limited in this review.

Detection of pancreatic adenocarcinoma precursor lesions (intraductal papillary mucinous neoplasms or pancreatic intraepithelial neoplasia) was also observed. The detection and removal of precursor lesions may prevent pancreatic adenocarcinoma and could represent a promising way forward for screening. However, in the absence of clear evidence about progression of precursor lesions and assessment of lead time bias, overdiagnosis and harms associated with treatment of precursor lesions remain possibilities. As such, it is unclear if detection and management of precursor lesions results in a decrease in pancreatic adenocarcinoma incidence, morbidity, or mortality.

The applicability of this body of evidence is limited to populations at known elevated risk for pancreatic adenocarcinoma based on family history, noting that the study populations

in the included body of evidence were enriched with people with known genetic mutations or syndromes. The implications of these results to other at-risk populations are unknown, including people with new-onset diabetes, smoking history, or chronic pancreatitis.

Identification and risk assessment for people at the highest risk is critical for improving screening programs.[35] Only about 10% of pancreatic adenocarcinoma cases have a familial basis; of those, only about 20% are currently attributed to inherited genetic mutations.[36,37] 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. 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. Given the low incidence and high severity of pancreatic adenocarcinoma coupled with the potential survival benefits of early intervention, approaches to identifying individuals at the highest risk and using less invasive screening tests are warranted. More research is also needed on the progression rates of precursor lesions to pancreatic adenocarcinoma, and health outcomes and harms in people with these 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, is also needed.

Limitations

This review had several limitations. First, it excluded studies with populations solely comprising people with known genetic mutations or syndromes. As such, it should not be interpreted as an estimate of the yield of screening in people with known genetic mutations or syndromes. Second, the review intentionally included only those treatment studies conducted with screen-detected or asymptomatic populations. Third, it did not systematically assess the extensive literature showing survival benefits of surgery for early-stage pancreatic adenocarcinoma and the significant morbidities that can occur during the postoperative period. Fourth, the limited data about harms reported in the included evidence should not be interpreted to suggest that surgical treatment is without risks but rather that the magnitude of these potential harms is not well studied among people with screen-detected disease.

Conclusions

Imaging-based screening in groups at high familial risk can detect pancreatic adenocarcinoma with limited evidence of minimal harms. However, the effect of screening on morbidity and mortality in groups at high familial risk has not been studied, and no data are available in average-risk populations. There is limited evidence to assess benefits or harms of surgical intervention for screen-detected pancreatic adenocarcinoma.

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Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Henrikson, Aiello Bowles, Blasi, Morrison, Nguyen, Pillarisetty.
Drafting of the manuscript: Henrikson, Aiello Bowles, Blasi, Morrison, Nguyen.
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Statistical analysis: Henrikson, Aiello Bowles.
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