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Screening for Pancreatic Cancer: Why, How, and Who?

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Abstract

Pancreatic cancer is the fourth most common cause of cancer mortality in the United States, with 5 year survival rates for patients with resectable tumors ranging from 15 - 20%. However, most patients present with distant metastases, are not resectable, and have a 5-year survival of close to 0%. This demonstrates a need for improved screening to identify pancreatic cancer while the tumor is localized and amenable to surgical resection. Studies of patients with pancreatic tumors incidentally diagnosed demonstrate longer median survival as compared with tumors discovered only when the patient is symptomatic, suggesting that early detection may improve outcome. Recent evidence from genomic sequencing indicates a 15 year interval for genetic progression of pancreatic cancer from initiation to the metastatic stage, suggesting a sufficient window for early detection. Still, many challenges remain in implementing effective screening. Early diagnosis of pancreatic cancer relies on developing screening methodologies with highly sensitive and specific biomarkers and imaging modalities. It also depends on a better understanding of the risk factors and natural history of the disease in order to accurately identify high risk groups that would be best served by screening. This review summarizes our current understanding of the biology of pancreatic cancer relevant to methods available for screening. At this time, given the lack of proven benefit in this disease, screening efforts should probably be undertaken in the context of prospective trials.

Pancreatic adenocarcinoma comprises only 3% of estimated new cancer cases each year but is the fourth most common cause of cancer mortality with 44,030 new cases and 37,660 deaths expected in 2011.¹ The best chance for survival is early detection when the tumor can be treated with surgical resection. However, pancreatic cancer typically develops with few symptoms and only 10–20% of patients are diagnosed at a stage amenable to resection and possible cure. When symptoms do develop, a characteristic pattern of painless jaundice is often recognized, but commonly atypical patterns of symptoms including weight loss, abdominal pain, and malaise lead to delays in diagnosis. These factors contribute to a poor overall five year survival rate of 5% combining all stages, with a survival rate of about 20%

for patients with localized disease and 2% for those with distant metastases.² In a series of 558 patients with pancreatic adenocarcinoma treated in recent years at the Huntsman Cancer Institute of the University of Utah, markedly better survival was observed in the small subset of stage I patients compared to those of all other stages (Figure 1). Thus, one strategy for improving outcome in patients with pancreatic cancer is to develop effective screening protocols to identify more patients at an earlier stage of their disease. Recent efforts have focused on the identification of highly specific biomarkers for the disease. Similarly, groups of individuals at higher than average risk for pancreatic cancer have been identified. The challenge is to validate early diagnosis strategies and show that they reduce pancreatic cancer-specific mortality rates. Because this issue has been so highly controversial in other cancers, such as breast and prostate, a critical appraisal of data related to pancreatic cancer screening seems appropriate at this time.

The Case for Screening in Pancreatic Cancer

Despite marked improvements in medical care generally and cancer care specifically over recent decades, these advances have only had small beneficial impact for pancreatic cancer patients. The combined incidence of all cancers has decreased by 1.1% for both sexes in recent years, but pancreatic cancer incidence has increased 0.7% per year in men and 0.1% in females during 2002–2006.³ The one-year survival rate for all stages has increased from 15.1% in males and 15.2% in females from 1975–1979 to 25.4% for males and 22.6% for females in 2003.⁴ Five-year survival has increased from 2.5% for all races from 1975–1979 to only 5.6% from 1999–2005.⁴ These survival improvements have been attributed mainly to increased use of axial imaging leading to identification of incidental tumors and decreased surgical morbidity and mortality. For example, during the 1960s and 1970s, pancreaticoduodenectomy was associated with a high complication rate and a hospital mortality of 25–30%; this led some surgeons to believe that the operation should be abandoned due to its risks.⁵ Currently, the operative mortality rate of the procedure is much lower. In the National Surgical Quality Improvement Program (NSQIP), for example, participating hospitals reported an operative mortality rate of 2.5% for pancreaticoduodenectomy in over 7000 cases from 2005–2008.⁶ A volume-outcome relationship related to mortality in Whipple resection has been identified in state-wide datasets, private-sector, and Veterans Affairs hospitals, and national Medicare datasets.^{7–9} Over time, Whipple resection mortality has decreased, especially when the procedure is performed at a high volume center or by a surgeon highly familiar with the procedure.

Some improvement in survival in pancreatic cancer probably relates to identification of some tumors incidentally because of the marked increase in the use of axial imaging such as computed tomography (CT) scanning for unrelated problems. It is clear that many patients today are diagnosed in the absence of symptoms because of scans done for unrelated indications, such as trauma or hematuria. Patients with pancreatic adenocarcinoma discovered by chance through imaging (pancreatic incidentalomas) appear to have increased survival. In one study, in patients with pancreatic adenocarcinoma discovered incidentally had median survival of 30 months compared with 21 months in those with carcinoma found due to symptoms ($P = 0.01$),¹⁰ supporting the premise that earlier diagnosis can lead to improved outcome. No highly controlled data, however, are currently available.

Despite these improvements in care for resectable patients, they represent only a minority of the population of afflicted individuals. Most patients present with metastatic disease, and corresponding improvements in treatment outcomes for this group have been disappointing. Patients with advanced stage tumors are typically treated with the chemotherapy agent gemcitabine, which increases median survival to 6 months from an untreated median survival of about 3 months.^{11, 12} Numerous randomized controlled trials examining outcomes with novel chemotherapy agents and combinations with good biologic rationale have been recently published, but median survival has not increased substantially beyond 6 months (Table 1).^{11, 13-27} A very recent trial demonstrated increased survival to 11.1 months in patients treated with FOLFIRINOX, these patients also had a higher incidence of adverse side effects such as neutropenia, diarrhea, thrombocytopenia, alopecia, and sensory neuropathy.¹⁵ It is remarkable that with substantial effort and commitment to clinical trials in metastatic pancreatic cancer little has been gained in overall survival. These observations support the notion that screening to identify patients at an earlier stage might be an important strategy in improving overall pancreatic cancer outcomes.

A recent study suggests that there may be a large window of opportunity for detection of pancreatic cancer while the disease is in its earliest and treatable stages. In this study, genomic sequencing was performed on cancer cells acquired at autopsy in seven pancreatic cancer patients.²⁸ Based on the differential accumulation of mutations in primary and metastatic lesions, the authors estimated an average of 11.7 years elapsed from tumor initiation to overt cancer development and an average of 6.8 years elapsed between the development of overt cancer and the development of metastatic disease. In most pancreatic cancer cases the disease has metastasized prior to presentation and many subjects initially thought to have localized and resectable cancer succumb to recurrent or metastatic disease. The finding that pancreatic tumors are present for a significant period of time before clinical manifestation emphasizes the potential for screening and early detection. Thus, the opportunity exists for improving outcomes through identification of the disease when treatments are likely to have a benefit, assuming suitable biomarkers can be found that correspond to the pre-cancerous or pre-metastatic time periods.

Assessment of Screening Benefit in Common Cancers

The benefit of screening and early diagnosis has been controversial for many cancers.^{29, 30} Supportive evidence does exist. For example, the death rate of prostate, breast, and colorectal cancers have all decreased in the U.S. over the past decade.¹ Some of this decline in mortality has been attributed to improved and widespread screening in all three cancers, as early detection identifies localized tumors amenable to treatment. Colorectal cancer remains an example of proven improvement in overall survival due to screening. Fecal occult blood testing (FOBT), sigmoidoscopy, and colonoscopy as screening methods have all contributed to a reduction in mortality in colorectal cancer, demonstrated by several randomized controlled screening trials for FOBT.³¹⁻³⁴ Colonoscopy is becoming the gold standard for colorectal cancer screening in many countries and consensus guidelines have incorporated colonoscopy in their recommendations.³⁵ An important benefit of colonoscopic screening is the potential therapeutic benefit of resection of premalignant polyps. Current guidelines recommend mammography for breast cancer screening.³⁵ However, the

magnitude of the benefit of screening in breast cancer is debatable, as screening mammography, has been linked to reduced death rate in breast cancer in some studies^{36, 37} but not others.^{29, 38} Similar controversy exists for use of serum prostate-specific antigen (PSA) testing in men as a screening tool for prostate cancer. Expanded PSA screening has markedly increased the identification of early stage lesions but with conflicting results on any reduction in death rate, leading to conflicting screening recommendations from various professional groups.³⁹ The value of PSA screening for prostate cancer is still a subject for thoughtful debate.^{40, 41}

Screening programs all carry potential biases that could overestimate the benefits of the screening intervention, including, among others, lead-time and length bias (Figures 2 and 3).^{29, 42} Lead-time bias occurs when the population of screened patients appears to have longer survival than an unscreened population; however, the screening has had no actual impact on the natural history of the disease process. Instead, the apparent improvement in survival is related to identification of the tumor at an earlier time in its natural history (reduction in the preclinical stage of the tumor) without any change in the ultimate time of death. Length bias occurs because of the tendency of screening programs to identify tumors with a longer natural history. The identification of these relatively indolent tumors has been part of the controversy in breast and prostate cancer screening, as it is unclear whether identification and treatment of these cancers actually alters the overall outcome of this group of patients. Strategies to minimize the consequences of lead-time and length biases will need to be considered in screening validation studies for pancreatic cancer. One strategy would take advantage of recently developed genetically engineered mouse models of pancreatic cancer that recapitulate the most common clinical traits.^{43, 44} Since pancreatic cancer in these models develops with predictable time of progression from pre-neoplastic lesions to overt carcinoma and subsequent metastasis, the problems of lead-time and length bias are minimal. Given the late presentation of pancreatic cancer, clinical samples representing pre-neoplastic and early stage disease are nonexistent or scarce and mouse models provide a unique opportunity for identification of novel early detection biomarkers. Comparison studies between samples from the mouse models and human cohorts have already proven useful for both biomarker identification and validation.^{45, 46}

Problems related to screening test accuracy

To have the opportunity to detect all new pancreatic cancer cases arising in a population, a screening test would ideally be applied to the general public. There are practical barriers to this strategy, however, particularly revolving around the specificity of the chosen test and the incidence of the disease. The U.S. population is estimated to be approximately 307,000,000 individuals in 2009 according to the U.S. Census Bureau. Of these, about 21%, or 64,500,000, are 55 years old or greater and they account for at least 90% of the expected new pancreatic cancer cases.⁴ If a screening test for pancreatic cancer with sensitivity and specificity of 90% was applied to this general population of individuals 55 years of age, only 3,610 patients with pancreatic cancer would be missed annually (plus the 6,370 younger patients developing pancreatic cancer but not eligible for screening under this scenario) (Table 2). In a cancer where few are currently identified at an early stage, detection of 32,490 patients potentially at a resectable stage would be a remarkable

achievement. However, out of those without the disease, nearly 6.5 million individuals would be falsely identified as having pancreatic cancer and presumably be subjected to expensive and possibly invasive confirmatory tests. The low incidence of this cancer in the general population leads to a positive predictive value in this screening test scenario of only 0.5%; there would be a very low certainty that a person with a positive test result was correctly diagnosed as having pancreatic cancer.

In order to improve the accuracy of screening for pancreatic cancer, there are at least two possible solutions. First, a higher-performing screening test could be demanded, with sensitivity and specificity increased to as close to 100% as possible. Given current levels of knowledge about pancreatic cancer and current technology limitations, such a test is unlikely to emerge in the near term. And even if a test with a sensitivity and specificity of 99% each were developed, screening of this hypothetical population of unselected individuals 55 years of age would still be limited by the large numbers of false positive tests (Table 3). In this scenario, detection of early cancer in 35,739 individuals is attractive; however, cost and morbidity of further invasive testing in approximately 644,000 individuals with falsely positive screening tests would still be limiting. An alternate, more attractive, but not mutually exclusive strategy would be to screen only in patients with identifiable risk factors for pancreatic cancer, thereby increasing the pretest probability. The chance that a healthy adult in the general population has pancreatic cancer is approximately 1 in 10,000 individuals or 0.01%, leading to a pretest probability of 0.0001 and a posttest probability of 0.00089 or 0.0089% chance of pancreatic cancer for a biomarker with 90% sensitivity and specificity. Higher pretest probabilities in our screening scenario can improve performance to acceptable levels from a practical and economic standpoint (Table 4). Increasing this pretest probability is feasible through the greater understanding of risk factors for pancreatic cancer.

Who to Screen? Identifying Individuals Based on Risk Factors

We have an incomplete understanding of the risk factors for pancreatic cancer, although certain groups have been identified as being at a higher risk based on clinical and genetic features (Table 5). Clinical risk factors are relatively broad and non-specific, and include age, obesity, smoking, diabetes, and chronic pancreatitis. The risk for development of pancreatic cancer increases with age; it is rare in those under 18 years of age, with over 97% of cases occurring in individuals over the age of 45.⁴ Body habitus has been linked to the development of pancreatic cancer with overweight or obese individuals having an increased risk (OR of 1.8 in males, 1.22 in females) as well as earlier onset of disease.⁴⁷ Current cigarette smokers and former smokers who had quit for less than 5 years had a higher risk of pancreatic cancer than non-smokers (OR 1.71 for current smokers and 1.78 for recent past smokers), although having quit for more than five years seemed to reduce the risk to the same levels as nonsmokers.⁴⁸ Smokeless tobacco (i.e. chewing tobacco) is an area of concern as well with some authors suggesting that, while not as potentially carcinogenic as smoked tobacco, this form of tobacco use is also associated with an increased risk of pancreatic cancer.⁴⁹ Patients with diabetes are also at higher risk for pancreatic cancer (OR 1.76)⁵⁰, and new-onset of diabetes may be an early indicator of pancreatic cancer.⁵¹ Several

studies have indicated that patients with chronic pancreatitis had a higher incidence of pancreatic cancer over the general population (OR 2.23).⁵²⁻⁵⁴

A number of genetic syndromes have been described in which there is an increased risk of pancreatic cancer. Meta-analysis of seven case-control and two cohort studies involving almost 7,000 pancreatic cancer cases found an overall risk of 1.8 for the development of pancreatic cancer in individuals with an affected relative.⁵⁵ In a unique analysis of the Utah Population Database, Cannon-Albright and co-workers found a significantly increased risk of pancreatic cancer in both first (RR=1.84) and second (RR=1.59) degree relatives of pancreatic cancer patients.⁵⁶ BRCA2 mutations are associated with a 3.5–10 fold increased risk of pancreatic cancer⁵⁷ while a possible link with BRCA1 mutations has also been noted.^{58, 59} Other genetic risk factors include Peutz-Jeghers syndrome (STK11/LKB1 mutations) with a 132 fold risk, familial atypical multiple mole melanoma syndrome (CDKN2A mutations) with a 13–22 fold risk, familial adenomatous polyposis (FAP) with a four-fold increased risk, Lynch syndrome with a 8.6-fold increased risk, and hereditary pancreatitis (PRSS1 mutations) with a 53 fold risk for pancreatic cancer.^{57, 60} Applying screening strategies to patients with one or more of these risk factors could help to increase the performance of a putative screening test.

Challenges in Creating an Effective Screening Test

Current Serum Biomarkers

Current attempts to discover screening tests for early diagnosis have focused mainly on serum biomarkers. The “best” and only biomarker in widespread clinical use is CA 19-9, a carbohydrate tumor-associated antigen which is often released in the serum of patients with pancreatic cancer. However, use of CA19-9 as a screening tool for pancreatic cancer in the general population is unacceptable due to its low sensitivity and specificity. A recent review found that the median sensitivity for CA19-9 in reported series was 79% (range 70–90%) while median specificity was 82% (range 68–91%).⁶¹ CA19-9 is elevated in patients with other upper gastrointestinal tumors, biliary obstruction, inflammatory diseases and other benign conditions such as primary sclerosing cholangitis.⁶² In addition, 5–10% of the population who are Lewis antigen negative are genetically unable to produce this antigen, and their serum CA19-9 levels are normal in the face of pancreatic cancer.⁶³ The main accepted use for CA19-9 today is as a monitoring tool assessing response in patients under treatment.^{64, 65}

Recently, several promising candidate serum biomarkers have been identified that successfully discriminated between pancreatic adenocarcinoma and controls in small studies.⁶⁶⁻⁷⁴ CEACAM1, heat shock protein 27, macrophage inhibitory cytokine 1, and osteopontin showed improved diagnostic accuracy over CA 19-9 alone, but their ability to discriminate pancreatic adenocarcinoma from chronic pancreatitis was either not measured or not significant. This feature is an important limitation, as the discrimination of chronic pancreatitis from pancreatic cancer is difficult using clinical and radiographic criteria. Other serum/plasma markers, including matrix metalloproteinase 7 (MMP-7) and adenosine deaminase, successfully distinguished pancreatic adenocarcinoma from chronic pancreatitis, but showed no improvement in accuracy over CA 19-9 alone.^{68, 71} The only assay to satisfy

both criteria was based on a new monoclonal antibody to mucin 1 (MUC1)⁶⁶, a membrane associated glycoprotein that is over expressed in multiple cancers including pancreatic adenocarcinoma and from which the CA 19-9 antigen is derived. However, with a sensitivity of 77% and specificity of 95% in the study, this MUC1 immunoassay remains below desirable accuracy levels.

Combinations of markers in a panel screen might have increased power to accurately diagnose pancreatic adenocarcinoma over any single marker alone. This idea is supported by the fact that several markers, including CEACAM1, osteopontin, and MMP-7, when combined with CA 19-9, showed increased accuracy in distinguishing cancer from normal over the individual markers alone.^{69, 71, 74} Two studies in which a panel screen of three markers, one examining CA 19-9, CEA, and TIMP metalloproteinase inhibitor 1 (TIMP-1) and the other examining CA 19-9, haptoglobin and serum amyloid A, did show improved diagnostic accuracy compared to the individual markers suggesting that larger panels, with appropriate marker combinations, might improve pancreatic adenocarcinoma diagnosis.^{75, 76} These studies demonstrate promise that a biomarker panel may be realized that improves sensitivity and specificity. However, given the high genetic heterogeneity of pancreatic adenocarcinoma⁷⁷, such a panel may require a large number of analytes.

Prospects for Novel Biomarkers

Examination of the known potential biomarkers has not been exhaustive and systematic analysis of the 168 secreted proteins commonly over expressed in pancreatic cancer⁷⁸ will likely provide new candidates for a panel screening tool. The potential for tapping other resources for circulating biomarkers has been demonstrated in other cancers and are worthy of examination in pancreatic cancer. Micro RNA patterns from circulating exosomes have shown promise as diagnostic markers in brain, breast, lung, and ovarian cancers.⁷⁹⁻⁸² Similarly, hypermethylation of specific genes in circulating DNA also show potential as cancer biomarkers.⁸³⁻⁸⁶ Although a recent sequencing analysis of 24 pancreatic cancers identified an average of 63 genetic mutations per tumor,⁷⁷ a relatively small set of genes are commonly mutated in all pancreatic cancers.⁸⁷ A screening test that takes advantage of these known mutations would require access to cancer cells, preferably without invasive and potentially morbid biopsy. A possible method to identify these mutations is to examine circulating tumor cells (CTCs). The challenge today is finding sufficient CTCs in an inexpensive screening test. Early efforts at identification of CTCs or shed cancer cells in stool offer some promise.^{88, 89} Another source of shed cancer cells might be found in pancreatic juice.

Early studies have shown promising diagnostic results through examinations of cancer cell mutations as well as protein biomarkers.⁹⁰⁻⁹² The main disadvantage of this screening method is the technical difficulty and risk associated with obtaining pancreatic juice. In comparison to serum biomarkers, a more costly and invasive procedure is necessary, usually involving endoscopic retrograde cholangiopancreatography (ERCP) or endoscopic ultrasonographic-guided fine-needle aspiration (EUS-FNA). One of the most serious complications that can occur after ERCP is pancreatitis, with an incidence ranging from 1.6% to 15.1% in trials in recent years, although in clinical practice the range is thought to

be closer to 4 – 7%.^{93, 94} Some biomarkers have also been identified using ductal brushing and cytology of the cells obtained. However, these results have not yielded a high enough sensitivity to be used over serum biomarkers to diagnose pancreatic cancer.⁹⁵ Therefore, unless highly specific and sensitive biomarkers are discovered in pancreatic juice, it is currently less useful than serum biomarkers to diagnose pancreatic neoplasms.

Use of Imaging in Screening

Various methods of imaging are utilized to identify neoplasms in patients who are symptomatic or have a high suspicion of pancreatic malignancy. The main modalities of imaging for the detection of pancreatic cancer are abdominal ultrasound (US), endoscopic ultrasound (EUS), endoscopic retrograde cholangiopancreatography (ERCP), CT, magnetic resonance imaging (MRI), and positron emission tomography (PET). Of these, ultrasound is often the best initial screening modality because it is minimally invasive, easily available, and does not expose the patient to ionizing radiation. However, due to the location of the pancreas in the retroperitoneum, abdominal ultrasound is often not accurate in identifying the pancreas, with sensitivity usually below 70%.⁹⁶ Instead, endoscopic ultrasound is often utilized due to its ability to biopsy pancreatic tissue at the same time, and due to a sensitivity that has been noted to be as high as 98%.⁹⁷

Contrast enhanced CT scans may be the best modality to assess resectability of a tumor given its high sensitivity and specificity, with less inter-observer variability than ultrasound.⁹⁶ Due to recent advances in CT technology, sensitivity can be as high as 90% and specificity as high as 99%.⁹⁶ However, CT exposes patients to ionizing radiation and, due to the requirement for intravenous contrast, it is not ideal for use in all patients, especially those with renal failure. MRI has been used more recently for pancreatic imaging, often in those patients with a high suspicion of a pancreatic lesion that cannot be assessed by CT or ultrasound.⁹⁸ MRI has been noted by some to have a similar sensitivity and specificity to CT.⁹⁹ Still, it is often more cumbersome to use, given patients must remain motionless in order to obtain an accurate image as well as the high cost and decreased availability of instrumentation, and therefore is generally utilized only after ultrasound or CT.⁹⁸

A major disadvantage of imaging in screening programs is the cost and high rate of false positive examinations. In a recent review of whole body imaging for screening, for example, only 6 additional days of life were expected at an average cost of more than \$2500 per subject in a screening CT protocol. Over 90% of subjects were found to have an abnormality on CT screening, yet in only 2% was the finding clinically important.¹⁰⁰

Identification of High Risk Premalignant Lesions: PanINs and IPMNs

One of the challenges in identification of an accurate screening test for pancreatic cancer is the lack of consensus regarding its cell of origin and the role of premalignant lesions such as pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN). PanINs are likely precursors to pancreatic cancer in some patients.¹⁰¹ Examination of 1,174 autopsy patients found that ductal hyperplasia of the pancreas increased in frequency with age, reaching a maximum prevalence of 54.5% of examined cadavers over the age of 80, with lesions found twice as frequently in the head of the pancreas compared to

the body and tail.¹⁰² Ductal hyperplasia was approximately 10 times more common than pancreatic cancer in each age group, and was also more frequently discovered in patients with pancreatic cancer compared to those without.¹⁰² A similar comparison of the pancreata from 227 patients with pancreatic cancer and 100 non-pancreatic cancer age and gender matched controls also found ductal hyperplasia three times more prevalent in those with pancreatic cancer.¹⁰³ In 234 patients where the pancreas was resected for various reasons, 82% of patients with ductal adenocarcinomas of the pancreas had PanIN, compared to 63% of chronic pancreatitis and 28% of normal patients.¹⁰⁴ PanIN lesions have been found in higher rates in patients with familial pancreatic cancer as opposed to sporadic pancreatic cancer patients.¹⁰⁵ These associations of PanIN and pancreatic cancer support a possible pathogenic link. Recent genetic studies have shown stepwise acquisition of mutations and deletions in PanINs consistent with the known genotypic characteristics of pancreatic cancer.^{77, 101, 106} These factors make it likely that PanIN lesions develop, under environmental stress and genetic alterations, and lead progressively to pancreatic cancer. At this point, however, the rate of progression and the relative risk of cancer developing in individuals with PanIN lesions are unclear. A major current limitation is the inability to identify and follow PanIN lesions without invasive pancreatic biopsy. Today, PanIN lesions, if identified, place individuals in a high risk category for the development of pancreatic cancer, but by themselves are not useful as part of a screening strategy.

IPMNs have the potential to develop into invasive carcinoma, although the majority of patients with IPMNs do not appear to develop cancer in the short-term. The location of the IPMN predicts the risk of malignancy, with the prevalence of cancer ranging from 57 to 92% in main duct IPMN as compared with only 6 to 46% in branch duct IPMN as reported in a recent consensus.¹⁰⁷ IPMNs have also been found at higher rates in patients with familial pancreatic cancer as opposed to sporadic pancreatic cancer patients, suggesting that they may play a greater role in pancreatic cancer development when family history is present.¹⁰⁵ Strategies focused on the identification of biomarkers that are specific to IPMN and PanIN may have future roles in screening for pancreatic cancer. Reasonably accepted criteria have been developed for balancing risk of pancreatectomy versus risk of cancer development in untreated IPMN.¹⁰⁷ These guidelines could be adapted into screening guidelines when IPMN is identified. However, there is also a risk of over-treating an indolent condition in those patients where PanIN and IPMN do not lead to pancreatic cancer.

Initial Clinical Studies of Screening in Pancreatic Cancer

Attempts to screen for pancreatic cancer have been limited to studies of high-risk populations.¹⁰⁸⁻¹¹⁶ These studies have largely utilized surveillance by EUS, ERCP, and cross sectional imaging (CT and/or MRI with MRCP), usually in a defined clinical protocol in high risk individuals. These studies are summarized in Table 6. Of the 410 high-risk patients reported to date, 43 patients underwent surgical resection because of suspicion for malignancy. Eight cases of invasive pancreatic ductal adenocarcinoma were detected resulting in diagnostic yield for malignancy of 1.95% (8/410). EUS appeared to have the highest sensitivity in detecting pancreatic lesions. Benign lesions with malignant potential, including IPMN and PanINs were found in 36 patients. In addition, unrelated lesions without risk of progression to cancer, such as serous cystadenoma and pancreatitis were

identified in numerous patients. It is clear from these studies that a limiting feature of imaging-based screening programs is the relatively high rate of identification of innocent lesions that subsequently require additional invasive evaluation.

While these studies focused on screening high-risk populations, pancreatic cancer is only diagnosed in about 10% of patients with syndromic risk factors or a family history of pancreatic cancer, subjects who would currently be considered candidates for screening. Thus, further assessment of potential risk factors, including possibly serum biomarkers predictive of risk would appear to be a research priority. It is likely that in a population of more average risk, relatively more patients with innocent lesions will be identified. To date, there have been no clinical trials specifically designed to capture sporadic cases of pancreatic cancer in the general population. No randomized or population-based evaluations of the benefit of screening for pancreatic cancer have yet been published.

Will Early Detection Increase Survival?

The key question to address with regards to early detection is if whether or not survival of afflicted patients is actually increased and if the population death rate from pancreatic cancer is decreased because of the screening program. As with the controversies in breast and prostate cancer screening, there is the possibility that, despite earlier diagnosis, the natural history of the cancer in affected patients would not be altered. These issues of lead-time and length bias will have to be addressed in carefully designed and conducted trials once a screening strategy with high accuracy is identified.

The Future of Screening for Pancreatic Cancer

The likely practical future of screening for pancreatic cancer will involve a panel of serum biomarkers, readily available via a multiplex assay. It is possible that a biomarker panel could have applicability in not only in screening, but also in other aspects of patient management. Today, the identified applications of a biomarker panel include: 1) identification of apparently normal individuals at elevated risk of developing pancreatic cancer in the future, 2) early diagnosis of pancreatic cancer in asymptomatic individuals, 3) prediction of response to therapy in pancreatic cancer patients allowing improved treatment selection, and 4) in ascertaining prognosis in ways complementary to traditional TNM-type staging systems, which currently are suboptimal. Patients identified as high risk for developing pancreatic cancer on the basis of a serum biomarker screening test would likely enter an imaging-based confirmatory screening program involving axial imaging with CT or MRI and EUS evaluation with biopsy of suspicious lesions. While the goals of screening are admirable, many barriers remain in the development of validated biomarkers and overcoming the practical difficulty of false positive examinations.

Opportunities for Prevention

The most difficult but most rewarding goal with any disease is prevention. Certain behavioral changes should be encouraged in all individuals, such as reducing alcohol consumption, tobacco cessation, and encouraging a healthy lifestyle to reduce excess body weight. These lifestyle modifications can help reduce the risk of not just pancreatic cancer

but multiple other disorders, including heart disease, diabetes, hypertension, as well as other forms of cancer. Our current knowledge of the genetic underpinnings of pancreatic cancer offers a glimpse at a future of opportunities to intervene at the genetic or functional protein level to abort the carcinogenic process. Biomarkers will be key assets in identification of a population to target these preventive approaches and in assessing the efficacy of the preventive interventions.

Conclusion

Prostate, breast, and colorectal cancers are three of the most commonly occurring malignancies in the U.S. and early detection has probably helped to reduce their mortality. As the American population ages and death due to these common cancers and heart disease decreases, we will likely observe an increase in death from other age-related diseases, including pancreatic cancer. The incidence and population death rate from pancreatic cancer are high enough to consider screening. These screening efforts are currently being focused on high risk groups with syndromic or familial risk of pancreatic cancer, however they represent the minority of affected individuals. In the larger group of patients with sporadic pancreatic cancer, no biomarkers with high enough accuracy are currently available for use in screening. An urgent need exists to identify biomarkers and imaging strategies in this disease. Today, given the paucity of data demonstrating benefit from screening for pancreatic cancer, these efforts should probably be conducted in the context of prospective trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *CA Cancer J Clin.* 2011; 61(4): 212–36. [PubMed: 21685461]
2. Compton CC, Mulvihill SJ. Prognostic factors in pancreatic carcinoma. *Surg Oncol Clin N Am.* 1997; 6(3):533–54. [PubMed: 9210355]
3. Edwards BK, Ward E, Kohler BA, et al. Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer.* 2010; 116(3):544–73. [PubMed: 19998273]
4. Howlader, N.; Noone, AM.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975–2008 Vol. National Cancer Institute; Bethesda, MD: 2011. http://seer.cancer.gov/csr/1975_2008/
5. Crile G Jr. The advantages of bypass operations over radical pancreatoduodenectomy in the treatment of pancreatic carcinoma. *Surg Gynecol Obstet.* 1970; 130(6):1049–53. [PubMed: 4192028]
6. Parikh P, Shiloach M, Cohen ME, et al. Pancreatectomy risk calculator: an ACS-NSQIP resource. *HPB (Oxford).* 12(7):488–97. [PubMed: 20815858]

7. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med.* 2002; 346(15):1128–37. [PubMed: 11948273]
8. Glasgow RE, Jackson HH, Neumayer L, et al. Pancreatic resection in Veterans Affairs and selected university medical centers: results of the patient safety in surgery study. *J Am Coll Surg.* 2007; 204(6):1252–60. [PubMed: 17544083]
9. Nathan H, Cameron JL, Choti MA, et al. The volume-outcomes effect in hepato-pancreato-biliary surgery: hospital versus surgeon contributions and specificity of the relationship. *J Am Coll Surg.* 2009; 208(4):528–38. [PubMed: 19476786]
10. Winter JM, Cameron JL, Lillemoe KD, et al. Periapillary and pancreatic incidentaloma: a single institution's experience with an increasingly common diagnosis. *Ann Surg.* 2006; 243(5):673–80. discussion 680-3. [PubMed: 16633003]
11. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol.* 1997; 15(6):2403–13. [PubMed: 9196156]
12. Park JK, Yoon YB, Kim YT, et al. Survival and prognostic factors of unresectable pancreatic cancer. *J Clin Gastroenterol.* 2008; 42(1):86–91. [PubMed: 18097296]
13. Abou-Alfa GK, Letourneau R, Harker G, et al. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol.* 2006; 24(27):4441–7. [PubMed: 16983112]
14. Colucci G, Labianca R, Di Costanzo F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol.* 2010; 28(10):1645–51. [PubMed: 20194854]
15. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011; 364(19):1817–25. [PubMed: 21561347]
16. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol.* 2009; 27(33):5513–8. [PubMed: 19858379]
17. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol.* 2006; 24(24):3946–52. [PubMed: 16921047]
18. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol.* 2007; 25(16):2212–7. [PubMed: 17538165]
19. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol.* 2010; 28(22):3617–22. [PubMed: 20606091]
20. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol.* 2005; 23(15):3509–16. [PubMed: 15908661]
21. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007; 25(15):1960–6. [PubMed: 17452677]
22. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol.* 2010; 28(22):3605–10. [PubMed: 20606093]
23. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol.* 2009; 27(23):3778–85. [PubMed: 19581537]
24. Riess HHA, Niedergethmann I. A randomised, prospective, multicenter, phase III trial of gemcitabine, 5-fluorouracil (5-FU), folinic acid vs gemcitabine alone in patients with advanced pancreatic cancer. *J Clin Oncol.* 2005; 23(suppl 16)(1092) Abstract 4009.

25. Spano JP, Chodkiewicz C, Maurel J, et al. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. *Lancet*. 2008; 371(9630):2101–8. [PubMed: 18514303]
26. Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer*. 2006; 95(5):587–92. [PubMed: 16909140]
27. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol*. 2009; 27(13):2231–7. [PubMed: 19307500]
28. Yachida S, Jones S, Bozic I, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature*. 2010; 467(7319):1114–7. [PubMed: 20981102]
29. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. *JAMA*. 2009; 302(15):1685–92. [PubMed: 19843904]
30. O'Shaughnessy M, Konety B, Warlick C. Prostate cancer screening: issues and controversies. *Minn Med*. 2010; 93(8):39–44. [PubMed: 20862878]
31. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet*. 1996; 348(9040):1472–7. [PubMed: 8942775]
32. Kronborg O, Fenger C, Olsen J, et al. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet*. 1996; 348(9040):1467–71. [PubMed: 8942774]
33. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med*. 1993; 328(19):1365–71. [PubMed: 8474513]
34. Walsh JM, Terdiman JP. Colorectal cancer screening: scientific review. *JAMA*. 2003; 289(10):1288–96. [PubMed: 12633191]
35. Smith RA, Cokkinides V, Brooks D, et al. Cancer screening in the United States, 2011: A review of current American Cancer Society guidelines and issues in cancer screening. *CA Cancer J Clin*. 2011; 61(1):8–30. [PubMed: 21205832]
36. Berry DA, Cronin KA, Plevritis SK, et al. Effect of screening and adjuvant therapy on mortality from breast cancer. *N Engl J Med*. 2005; 353(17):1784–92. [PubMed: 16251534]
37. Shen Y, Yang Y, Inoue LY, et al. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. *J Natl Cancer Inst*. 2005; 97(16):1195–203. [PubMed: 16106024]
38. Gotzsche PC, Nielsen M. Screening for breast cancer with mammography. *Cochrane Database Syst Rev*. 2009; (4):CD001877. [PubMed: 19821284]
39. Hankey BF, Feuer EJ, Clegg LX, et al. Cancer surveillance series: interpreting trends in prostate cancer--part I: Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. *J Natl Cancer Inst*. 1999; 91(12):1017–24. [PubMed: 10379964]
40. Carroll PR, Whitson JM, Cooperberg MR. Serum prostate-specific antigen for the early detection of prostate cancer: always, never, or only sometimes? *J Clin Oncol*. 2011; 29(4):345–7. [PubMed: 21189396]
41. Loeb S, Vonesh EF, Metter EJ, et al. What is the true number needed to screen and treat to save a life with prostate-specific antigen testing? *J Clin Oncol*. 2011; 29(4):464–7. [PubMed: 21189374]
42. Croswell JM, Ransohoff DF, Kramer BS. Principles of cancer screening: lessons from history and study design issues. *Semin Oncol*. 2010; 37(3):202–15. [PubMed: 20709205]
43. Hingorani SR, Petricoin EF, Maitra A, et al. Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. *Cancer Cell*. 2003; 4(6):437–50. [PubMed: 14706336]
44. Hingorani SR, Wang L, Multani AS, et al. Trp53R172H and KrasG12D cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice. *Cancer Cell*. 2005; 7(5):469–83. [PubMed: 15894267]
45. Fukuda A, Wang SC, Morris JPt, et al. Stat3 and MMP7 contribute to pancreatic ductal adenocarcinoma initiation and progression. *Cancer Cell*. 2011; 19(4):441–55. [PubMed: 21481787]

46. LaConti JJ, Shivapurkar N, Preet A, et al. Tissue and serum microRNAs in the Kras(G12D) transgenic animal model and in patients with pancreatic cancer. *PLoS One*. 2011; 6(6):e20687. [PubMed: 21738581]
47. Li D, Morris JS, Liu J, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA*. 2009; 301(24):2553–62. [PubMed: 19549972]
48. Vrieling A, Bueno-de-Mesquita HB, Boshuizen HC, et al. Cigarette smoking, environmental tobacco smoke exposure and pancreatic cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer*. 2009
49. Boffetta P, Hecht S, Gray N, et al. Smokeless tobacco and cancer. *Lancet Oncol*. 2008; 9(7):667–75. [PubMed: 18598931]
50. Ansary-Moghaddam A, Huxley R, Barzi F, et al. The effect of modifiable risk factors on pancreatic cancer mortality in populations of the Asia-Pacific region. *Cancer Epidemiol Biomarkers Prev*. 2006; 15(12):2435–40. [PubMed: 17164367]
51. Chari ST, Leibson CL, Rabe KG, et al. Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology*. 2005; 129(2):504–11. [PubMed: 16083707]
52. Bansal P, Sonnenberg A. Pancreatitis is a risk factor for pancreatic cancer. *Gastroenterology*. 1995; 109(1):247–51. [PubMed: 7797022]
53. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. *N Engl J Med*. 1993; 328(20):1433–7. [PubMed: 8479461]
54. Malka D, Hammel P, Maire F, et al. Risk of pancreatic adenocarcinoma in chronic pancreatitis. *Gut*. 2002; 51(6):849–52. [PubMed: 12427788]
55. Permuth-Wey J, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. *Fam Cancer*. 2009; 8(2):109–17. [PubMed: 18763055]
56. Shirts BH, Burt RW, Mulvihill SJ, Cannon-Albright LA. A population-based description of familial clustering of pancreatic cancer. *Clin Gastroenterol Hepatol*. 2010; 8(9):812–6. [PubMed: 20570637]
57. Shi C, Hruban RH, Klein AP. Familial pancreatic cancer. *Arch Pathol Lab Med*. 2009; 133(3):365–74. [PubMed: 19260742]
58. Al-Sukhni W, Rothenmund H, Borgida AE, et al. Germline BRCA1 mutations predispose to pancreatic adenocarcinoma. *Hum Genet*. 2008; 124(3):271–8. [PubMed: 18762988]
59. Lynch HT, Deters CA, Snyder CL, et al. BRCA1 and pancreatic cancer: pedigree findings and their causal relationships. *Cancer Genet Cytogenet*. 2005; 158(2):119–25. [PubMed: 15796958]
60. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA*. 2009; 302(16):1790–5. [PubMed: 19861671]
61. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol*. 2007; 33(3):266–70. [PubMed: 17097848]
62. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. *J Clin Oncol*. 2006; 24(33):5313–27. [PubMed: 17060676]
63. Tempero MA, Uchida E, Takasaki H, et al. Relationship of carbohydrate antigen 19-9 and Lewis antigens in pancreatic cancer. *Cancer Res*. 1987; 47(20):5501–3. [PubMed: 3308077]
64. Barton JG, Bois JP, Sarr MG, et al. Predictive and prognostic value of CA 19-9 in resected pancreatic adenocarcinoma. *J Gastrointest Surg*. 2009; 13(11):2050–8. [PubMed: 19756875]
65. Reni M, Cereda S, Balzano G, et al. Carbohydrate antigen 19-9 change during chemotherapy for advanced pancreatic adenocarcinoma. *Cancer*. 2009; 115(12):2630–9. [PubMed: 19353729]
66. Gold DV, Modrak DE, Ying Z, et al. New MUC1 serum immunoassay differentiates pancreatic cancer from pancreatitis. *J Clin Oncol*. 2006; 24(2):252–8. [PubMed: 16344318]
67. Grote T, Logsdon CD. Progress on molecular markers of pancreatic cancer. *Curr Opin Gastroenterol*. 2007; 23(5):508–14. [PubMed: 17762556]
68. Ibis M, Koklu S, Yilmaz FM, et al. Serum adenosine deaminase levels in pancreatic diseases. *Pancreatol*. 2007; 7(5-6):526–30. [PubMed: 17901713]

69. Koopmann J, Fedarko NS, Jain A, et al. Evaluation of osteopontin as biomarker for pancreatic adenocarcinoma. *Cancer Epidemiol Biomarkers Prev.* 2004; 13(3):487–91. [PubMed: 15006928]
70. Koopmann J, Rosenzweig CN, Zhang Z, et al. Serum markers in patients with resectable pancreatic adenocarcinoma: macrophage inhibitory cytokine 1 versus CA19-9. *Clin Cancer Res.* 2006; 12(2): 442–6. [PubMed: 16428484]
71. Kuhlmann KF, van Till JW, Boermeester MA, et al. Evaluation of matrix metalloproteinase 7 in plasma and pancreatic juice as a biomarker for pancreatic cancer. *Cancer Epidemiol Biomarkers Prev.* 2007; 16(5):886–91. [PubMed: 17507610]
72. Melle C, Ernst G, Escher N, et al. Protein profiling of microdissected pancreas carcinoma and identification of HSP27 as a potential serum marker. *Clin Chem.* 2007; 53(4):629–35. [PubMed: 17303689]
73. Rosty C, Christa L, Kuzdzal S, et al. Identification of hepatocarcinoma-intestine-pancreas/pancreatitis-associated protein I as a biomarker for pancreatic ductal adenocarcinoma by protein biochip technology. *Cancer Res.* 2002; 62(6):1868–75. [PubMed: 11912167]
74. Simeone DM, Ji B, Banerjee M, et al. CEACAM1, a novel serum biomarker for pancreatic cancer. *Pancreas.* 2007; 34(4):436–43. [PubMed: 17446843]
75. Firpo MA, Gay DZ, Granger SR, et al. Improved diagnosis of pancreatic adenocarcinoma using haptoglobin and serum amyloid A in a panel screen. *World J Surg.* 2009; 33(4):716–22. [PubMed: 19082654]
76. Zhou W, Sokoll LJ, Bruzek DJ, et al. Identifying markers for pancreatic cancer by gene expression analysis. *Cancer Epidemiol Biomarkers Prev.* 1998; 7(2):109–12. [PubMed: 9488584]
77. Jones S, Zhang X, Parsons DW, et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science.* 2008; 321(5897):1801–6. [PubMed: 18772397]
78. Harsha HC, Kandasamy K, Ranganathan P, et al. A compendium of potential biomarkers of pancreatic cancer. *PLoS Med.* 2009; 6(4):e1000046. [PubMed: 19360088]
79. Friel AM, Corcoran C, Crown J, O'Driscoll L. Relevance of circulating tumor cells, extracellular nucleic acids, and exosomes in breast cancer. *Breast Cancer Res Treat.* 2010; 123(3):613–25. [PubMed: 20549336]
80. Rabinowits G, Gercel-Taylor C, Day JM, et al. Exosomal microRNA: a diagnostic marker for lung cancer. *Clin Lung Cancer.* 2009; 10(1):42–6. [PubMed: 19289371]
81. Skog J, Wurdinger T, van Rijn S, et al. Glioblastoma microvesicles transport RNA and proteins that promote tumour growth and provide diagnostic biomarkers. *Nat Cell Biol.* 2008; 10(12): 1470–6. [PubMed: 19011622]
82. Taylor DD, Gercel-Taylor C. MicroRNA signatures of tumor-derived exosomes as diagnostic biomarkers of ovarian cancer. *Gynecol Oncol.* 2008; 110(1):13–21. [PubMed: 18589210]
83. Bryzgunova OE, Morozkin ES, Yarmoschuk SV, et al. Methylation-specific sequencing of GSTP1 gene promoter in circulating/extracellular DNA from blood and urine of healthy donors and prostate cancer patients. *Ann N Y Acad Sci.* 2008; 1137:222–5. [PubMed: 18837951]
84. Chan KC, Lai PB, Mok TS, et al. Quantitative analysis of circulating methylated DNA as a biomarker for hepatocellular carcinoma. *Clin Chem.* 2008; 54(9):1528–36. [PubMed: 18653827]
85. Ellinger J, Albers P, Perabo FG, et al. CpG island hypermethylation of cell-free circulating serum DNA in patients with testicular cancer. *J Urol.* 2009; 182(1):324–9. [PubMed: 19447423]
86. Radpour R, Barekati Z, Kohler C, et al. Hypermethylation of tumor suppressor genes involved in critical regulatory pathways for developing a blood-based test in breast cancer. *PLoS One.* 2011; 6(1):e16080. [PubMed: 21283676]
87. Deer EL, Gonzalez-Hernandez J, Coursen JD, et al. Phenotype and genotype of pancreatic cancer cell lines. *Pancreas.* 2010; 39(4):425–35. [PubMed: 20418756]
88. Kurihara T, Itoi T, Sofuni A, et al. Detection of circulating tumor cells in patients with pancreatic cancer: a preliminary result. *J Hepatobiliary Pancreat Surg.* 2008; 15(2):189–95. [PubMed: 18392713]
89. Stott SL, Hsu CH, Tsukrov DI, et al. Isolation of circulating tumor cells using a microvortex-generating herringbone-chip. *Proc Natl Acad Sci U S A.* 2010; 107(43):18392–7. [PubMed: 20930119]

90. Shi C, Fukushima N, Abe T, et al. Sensitive and quantitative detection of KRAS2 gene mutations in pancreatic duct juice differentiates patients with pancreatic cancer from chronic pancreatitis, potential for early detection. *Cancer Biol Ther.* 2008; 7(3):353–360. [PubMed: 18075308]
91. Suehara N, Mizumoto K, Tanaka M, et al. Telomerase activity in pancreatic juice differentiates ductal carcinoma from adenoma and pancreatitis. *Clin Cancer Res.* 1997; 3(12 Pt 1):2479–83. [PubMed: 9815650]
92. Uehara H, Nakaizumi A, Tatsuta M, et al. Diagnosis of pancreatic cancer by detecting telomerase activity in pancreatic juice: comparison with K-ras mutations. *Am J Gastroenterol.* 1999; 94(9): 2513–8. [PubMed: 10484017]
93. Cheng CL, Sherman S, Watkins JL, et al. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. *Am J Gastroenterol.* 2006; 101(1):139–47. [PubMed: 16405547]
94. Williams EJ, Taylor S, Fairclough P, et al. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. *Endoscopy.* 2007; 39(9):793–801. [PubMed: 17703388]
95. Volmar KE, Vollmer RT, Routbort MJ, Creager AJ. Pancreatic and bile duct brushing cytology in 1000 cases: review of findings and comparison of preparation methods. *Cancer.* 2006; 108(4):231–8. [PubMed: 16541448]
96. Long EE, Van Dam J, Weinstein S, et al. Computed tomography, endoscopic, laparoscopic, and intra-operative sonography for assessing resectability of pancreatic cancer. *Surg Oncol.* 2005; 14(2):105–13. [PubMed: 16125619]
97. DeWitt J, Devereaux B, Chriswell M, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. *Ann Intern Med.* 2004; 141(10):753–63. [PubMed: 15545675]
98. Sahani DV, Shah ZK, Catalano OA, et al. Radiology of pancreatic adenocarcinoma: current status of imaging. *J Gastroenterol Hepatol.* 2008; 23(1):23–33. [PubMed: 18171340]
99. Bluemke DA, Fishman EK. CT and MR evaluation of pancreatic cancer. *Surg Oncol Clin N Am.* 1998; 7(1):103–24. [PubMed: 9443989]
100. Beinfeld MT, Wittenberg E, Gazelle GS. Cost-effectiveness of whole-body CT screening. *Radiology.* 2005; 234(2):415–22. [PubMed: 15670999]
101. Hruban RH, Goggins M, Parsons J, Kern SE. Progression model for pancreatic cancer. *Clin Cancer Res.* 2000; 6(8):2969–72. [PubMed: 10955772]
102. Kozuka S, Sassa R, Taki T, et al. Relation of pancreatic duct hyperplasia to carcinoma. *Cancer.* 1979; 43(4):1418–28. [PubMed: 445339]
103. Cubilla AL, Fitzgerald PJ. Morphological lesions associated with human primary invasive nonendocrine pancreas cancer. *Cancer Res.* 1976; 36(7 PT 2):2690–8. [PubMed: 1277176]
104. Andea A, Sarkar F, Adsay VN. Clinicopathological correlates of pancreatic intraepithelial neoplasia: a comparative analysis of 82 cases with and 152 cases without pancreatic ductal adenocarcinoma. *Mod Pathol.* 2003; 16(10):996–1006. [PubMed: 14559982]
105. Shi C, Klein AP, Goggins M, et al. Increased Prevalence of Precursor Lesions in Familial Pancreatic Cancer Patients. *Clin Cancer Res.* 2009; 15(24):7737–7743. [PubMed: 19996207]
106. Hruban RH, Maitra A, Goggins M. Update on pancreatic intraepithelial neoplasia. *Int J Clin Exp Pathol.* 2008; 1(4):306–16. [PubMed: 18787611]
107. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatol.* 2006; 6(1-2):17–32. [PubMed: 16327281]
108. Brentnall TA, Bronner MP, Byrd DR, et al. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. *Ann Intern Med.* 1999; 131(4):247–55. [PubMed: 10454945]
109. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol.* 2006; 4(6):766–81. quiz 665. [PubMed: 16682259]
110. Canto MI, Goggins M, Yeo CJ, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clin Gastroenterol Hepatol.* 2004; 2(7):606–21. [PubMed: 15224285]

111. Chu D, Kohlmann W, Adler DG. Identification and screening of individuals at increased risk for pancreatic cancer with emphasis on known environmental and genetic factors and hereditary syndromes. *JOP*. 2010; 11(3):203–12. [PubMed: 20442513]
112. Klapman J, Malafa MP. Early detection of pancreatic cancer: why, who, and how to screen. *Cancer Control*. 2008; 15(4):280–7. [PubMed: 18813195]
113. Langer P, Kann PH, Fendrich V, et al. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut*. 2009; 58(10):1410–8. [PubMed: 19470496]
114. Ludwig E, Olson SH, Bayuga S, et al. Feasibility and yield of screening in relatives from familial pancreatic cancer families. *Am J Gastroenterol*. 2011; 106(5):946–54. [PubMed: 21468009]
115. Poley JW, Kluijt I, Gouma DJ, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. *Am J Gastroenterol*. 2009; 104(9):2175–81. [PubMed: 19491823]
116. Verna EC, Hwang C, Stevens PD, et al. Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. *Clin Cancer Res*. 2010; 16(20):5028–37. [PubMed: 20876795]

Figure 1. Stage-dependent survival in 502 patients with pancreatic adenocarcinoma treated at the Huntsman Cancer Institute of the University of Utah. Numbers of patients and median survival in months by stage are given. Stage I patients represent a minority of individuals with this cancer, but their survival is favorable compared to other stages.

Figure 2. Screening programs have potential biases that make demonstration of benefit difficult. In lead-time bias, earlier detection of tumors via screening (scenario A) may appear to result in longer survival than control subjects identified by clinical symptoms (scenario B), however, the natural history of the tumor may not have been altered.

Figure 3.

In this schematic, a screening tool has been applied to a hypothetical population of patients at intervals. Each patient is represented by a bar. The length of the bar represents the cancer-related survival of the patient. Length bias refers to the tendency of screening programs to identify patients with tumors with more favorable biology (i.e. slower growth rates or less risk of metastasis) whereas patients with tumors with aggressive biology (rapidly growing tumors or those with a high risk of metastasis) may not be identified because of a short natural history until death. The finding of longer survival in patients identified through screening may not be related to the screening intervention – the benefit could lie in the natural history of those tumors.

Table 1
Recent randomized controlled trials of novel chemotherapy regimens for metastatic pancreatic cancer

Trial	Group	N	Median OS	Reference
Burris (1997)	5-FU	63	4.4 mo	11
	Gem	63	5.7 mo (n.s.)	
Riess (2005)	Gem	233	6.2 mo	24
	Gem-5FU	233	5.8 mo (n.s.)	
Louvet (2005)	Gem	156	7.1 mo	20
	Gem-Ox	157	9.0 mo (n.s.)	
Heinemann (2005)	Gem	98	6.0 mo	17
	Gem-Plat	97	7.5 mo (n.s.)	
Abou-Alfa (2006)	Gem	174	6.2 mo	13
	Gem-Exatecan	175	6.7 mo (n.s.)	
Stathopoulos (2006)	Gem	74	6.5 mo	26
	Gem-Irinotecan	71	6.4 mo (n.s.)	
Herrmann (2007)	Gem	159	7.2 mo	18
	Gem-Cap	160	8.4 mo (n.s.)	
Moore (2007)	Gem	284	5.9 mo	21
	Gem-Erlotinib	285	6.4 mo ($P = 0.038$)	
Spano (2008)	Gem	34	5.6 mo	25
	Gem-Axitinib	69	6.9 mo (n.s.)	
Van Cutsem (2009)	Gem-Erlotinib	301	6.0 mo	27
	Gem-Erl-Bev	306	7.1 mo (n.s.)	
Poplin (2009)	Gem	275	4.9 mo	23
	Gem Fixed Dose Rate	277	6.2 mo	
	Gem-Ox	272	5.7 mo (n.s.)	
Cunningham (2009)	Gem	266	6.2 mo	16
	Gem-Cap	267	7.1 mo (n.s.)	
Philip (2010)	Gem	371	6.3 mo	22

Trial	Group	N	Median OS	Reference
	Gem-Cetuximab	372	5.9 mo (n.s.)	
Kindler (2010)	Gem	302	5.9 mo	19
	Gem-Bevacizumab	300	5.8 mo (n.s.)	
Colucci (2010)	Gem	199	8.3 mo	14
	Gem-Cisplatin	201	7.2 mo (n.s.)	
Conroy (2011)	Gem	171	6.8 mo	15
	FOLFIRINOX	171	11.1 mo ($P < 0.001$)	

Table 2
True and false positive results from screening a hypothetical U.S. population of 64,500,000 individuals 55 years for pancreatic cancer with a test characterized by a sensitivity of 90% and specificity of 90%

	Patients with Pancreatic Cancer	Patients without Pancreatic Cancer
Positive Test	32,490 (90%)	6,446,390 (10%)
Negative Test	3,610 (10%)	58,017,510 (90%)
All Patients	36,100	64,463,900

Table 3
True and false positive results from screening a hypothetical U.S. population of 64,500,000 individuals 55 years for pancreatic cancer with a test characterized by a sensitivity of 99% and specificity of 99%

	Patients with Pancreatic Cancer	Patients without Pancreatic Cancer
Positive Test	35,739 (99%)	644,639 (1%)
Negative Test	361 (1%)	63,819,261 (99%)
All Patients	36,100	64,463,900

Table 4
Influence of pretest probability on the posttest probability of disease, using a screening test with 90% sensitivity and specificity

Incidence in Screened Population	Pretest Probability	Posttest Probability
1:10,000 ^{*a}	0.0001	0.00089
1:100	0.01	0.0833
1:10	0.10	0.50
1:2 ^{*b}	0.50	0.90

^{*a} In the United States, the incidence of pancreatic cancer in the general population is about 1 in 10,000.

^{*b} In the highest risk group known, Peutz-Jeghers syndrome, the lifetime risk of pancreatic cancer is estimated at 50%, or 1 in 2.

Table 5
Clinical and Genetic Risk Factors for Pancreatic Cancer

High-Risk Groups for Pancreatic Cancer:	
Clinical Risk Factors:	Genetic Risk Factors:
<ul style="list-style-type: none"> • Age • Smoking • Chronic pancreatitis • Diabetes • Obesity • IPMN and PanIN • Family history of pancreatic cancer 	<ul style="list-style-type: none"> • p16/FAMM • BRCA2 and BRCA1/HBOC • STK11/Peutz-Jeghers • MSH2, MLH1/HNPCC • APC/FAP mutations • PALB2 mutation • PRSS1/SPINK1 mutations • p53/Li-Fraumeni

IPMN—intraductal papillary mucinous neoplasm; PanIN—pancreatic intraepithelial neoplasia; FAMM—familial atypical mole melanoma; HBOC—hereditary breast and ovarian cancer; HNPCC—hereditary nonpolyposis colorectal cancer; FAP—familial adenomatous polyposis

Table 6

Summary of Current Screening Efforts for Pancreatic Cancer

Author	Institution	Year	High-Risk Subjects Screened	Premalignant Lesions Identified	Malignant Lesions Identified	Reference
Brennall et al.	University of Washington, Seattle	1999	14	7	0	108
Canto et al.	Johns Hopkins University, Baltimore	2004	38	5	1	110
Canto et al.*	Johns Hopkins University, Baltimore	2006	78	6	1	109
Poley et al.	Erasmus University, Rotterdam	2009	44	7	3	115
Langer et al.	Phillips University, Marburg	2009	76	4	0	113
Verna et al.	Columbia University, New York	2010	51	4	2	116
Ludwig et al.	Memorial Sloan-Kettering, New York	2011	109	7	1	114
TOTALS			410	36	8	

* Also identified 1 IPMN out of 138 normal controls evaluated