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Precursors to Pancreatic Cancer⁺

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Abstract

Infiltrating ductal adenocarcinoma of the pancreas is believed to arise from morphologically distinct non-invasive precursor lesions. These precursors include the intraductal papillary mucinous neoplasm, the mucinous cystic neoplasm, and pancreatic intraepithelial neoplasia. Intraductal papillary mucinous neoplasms are grossly visible mucin-producing epithelial neoplasms that arise in the main pancreatic duct or one of its branches. The cysts of mucinous cystic neoplasms do not communicate with the major pancreatic ducts and these neoplasms are characterized by a distinct ovarian-type stroma. Pancreatic intraepithelial neoplasia is a microscopic lesion. This review focuses on the clinical significance of these three remarkable precursor lesions with emphasis on their clinical manifestations, detection, and treatment.

Introduction

Infiltrating ductal adenocarcinoma of the pancreas, also known as *pancreatic cancer*, is one of the most lethal of all cancers. In the United States it is estimated that 37,170 Americans will be diagnosed with pancreatic cancer in 2007 and that 33,370 will die from the disease(1). One of the reasons that pancreatic cancer is so overwhelmingly lethal is that it is usually not diagnosed until after the cancer has spread to other organs(2). The early detection and treatment of non-invasive precursor lesions arguably offers the greatest hope in the fight against this disease.

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Precursor lesions have been recognized in the pancreas for over a century(3), but it took many decades to define the various histologic types of precursor lesions in the pancreas, and only over the last ten years have careful molecular analyses firmly linked histologically well-defined precursor lesions in the pancreas to invasive pancreatic cancer(3-6).

The challenge now is to translate these advances in our understanding of precursor lesions in the pancreas to better patient care; to cure pancreatic neoplasms before they progress to incurable invasive cancer.

Definition of Precursor

Intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs), and pancreatic intraepithelial neoplasia (PanIN) all meet rigorous criteria for “precursor” lesions. A working definition of a cancer precursor (although employing the less desirable and more deterministic term precancer) was recently developed by a National Cancer Institute-sponsored consensus conference(7). Five criteria were established to define a precursor to invasive cancer, and all three lesions in the pancreas (IPMN, MCN and PanIN) fulfill these five criteria (Table 1)(7).

The first criterion is that a precursor to invasive cancer must be associated with an increased risk of the cancer. While this can be hard to prove in an inaccessible organ such as the pancreas, it has been well-established in mouse models of PanIN and in humans for both IPMNs and MCNs(4;8-14). For example, 7 of the 197 patients with pancreatic cystic lesions prospectively followed by Tada et al. developed a pancreatic malignancy with an observed incidence of pancreatic cancer (0.95% per year) 22.5 times greater than expected(14).

The second criterion established for a cancer precursor is that when it progresses to cancer, the resulting cancer arises from cells within the precursor(7). This has been clearly demonstrated at the molecular level for IPMN, MCN and PanIN(15-17). For example, Moskaluk et al. microdissected paired PanIN lesions and infiltrating cancers from patients with pancreatic cancer, and in one case, were able to demonstrate identical *p16/CDKN2A* gene mutations in a PanIN lesion as in the patient's paired infiltrating cancer(17).

Third, a precursor should differ from the normal tissue from which it arises(7). This is certainly true for IPMN, MCN and PanIN. The epithelium in all of these lesions differs architecturally and cytologically from normal ductal epithelium in the pancreas. For example, the normal ductal epithelium is flat and composed of cuboidal cells, while IPMNs are often composed of columnar mucin-filled cells arranged in tall papillary projections.

The fourth criterion for a cancer precursor is that it should differ from the cancer into which it develops (7). By definition, this is true for IPMNs, MCNs, and PanINs. In all three lesions, the neoplastic epithelium has not penetrated through the basement membrane and, thus, has not invaded the surrounding pancreatic parenchyma. In contrast, by definition, the neoplastic cells of invasive pancreatic cancer have breached the basement membrane.

The fifth and final criterion for a precursor to invasive cancer is that there be a method in which the precursor can be diagnosed. IPMNs, MCNs and PanINs are all diagnosable by light microscopy. Thus, IPMNs, MCNs and PanINs meet all five recently developed rigorous criteria for a cancer precursor (precancer)(7). The salient features of these three neoplasms are summarized in Table 2.

Mucinous Cystic Neoplasms

Clinical Features

Mucinous cystic neoplasms are defined as mucin-producing cyst-forming epithelial neoplasms of the pancreas with a distinctive ovarian-type stroma (Figures 1 and 2)(2). MCNs are far more common in women than men (female to male ratio of 20 to 1), and the mean age at diagnosis is between 40 and 50 years, with a range of 14-95 years(2;18-21). Patients typically present with epigastric discomfort, a sense of abdominal fullness, or an abdominal mass(20;21). Some MCNs are discovered in asymptomatic patients imaged for other indications (22). As expected from a precursor lesion, patients with non-invasive MCNs are on average 5 to 10 years younger than patients with MCN with an associated invasive carcinoma(2;19;20;23). Serum carcinoma antigen 19-9 (CA 19-9) levels are usually elevated only if there is an associated invasive carcinoma (24).

Computerized tomography (CT) often reveal a well-demarcated thick-walled multilocular mass composed of large (1-3 cm) cysts(2;19;25). The radiologic attenuation of the cysts vary. Mural nodules are more common in mucinous cystic neoplasms with an associated invasive carcinoma compared to non-invasive mucinous cystic neoplasms. Endoscopic retrograde cholangiopancreatography (ERCP) usually reveals a displaced or compressed pancreatic duct, and in the vast majority of cases, the cysts do not communicate with the pancreatic ducts, a feature that may be used to distinguish mucinous cystic neoplasms from intraductal papillary mucinous neoplasms.

Pathologic and Molecular Features

Most (90%) MCNs arise in the body or tail of the pancreas(2;26;27). The cysts usually measure from 1-3 cm in size, and, as demonstrated radiographically, do not communicate with the larger pancreatic ducts(2;19). The cysts contain mucin (Figure 1) or hemorrhagic fluid, which helps explain the different attenuations observed in individual cysts on CT scanning(2).

By light microscopy, the cysts of MCNs are lined by columnar mucin-producing epithelium which can have a broad spectrum of dysplasia (Figure 2) (2;26;28). Mild dysplasia ("MCN adenoma") is composed of uniform columnar cells with abundant supranuclear mucin. The nuclei are basally located, small and uniform in size. Neoplastic epithelium with moderate dysplasia ("MCN-borderline") has, as the name suggests, a moderate degree of architectural and cytologic atypia. The nuclei vary slightly in size and shape, and there is slight loss of nuclear polarity. MCN with marked (severe) dysplasia, a designation that is preferred over the term "MCN carcinoma *in situ*", shows significant architectural and cytologic atypia. The degree of atypia in these lesions parallels that seen in invasive cancer. However, these lesions, by definition, are non-invasive.

In addition to neoplastic epithelium, MCNs have a distinctive ovarian-type of stroma (2). The stroma typically forms a band beneath the epithelium. Immunohistochemical labeling can be used to demonstrate expression of progesterone receptors, estrogen receptors, and inhibin by the stromal cells(2;30). One-third of MCNs have an associated invasive adenocarcinoma(2; 19). Invasive carcinoma is usually of the tubular or ductal type (2). It may arise focally in a MCN, and several studies have shown that the depth of invasion is an important prognosticator (2;21).

At the molecular level, activating point mutations in the *KRAS* gene are early events in the development of MCNs, while *TP53* and *SMAD4* gene mutations represent late changes (2; 32;33). Aberrant methylation of the *p16/CDKN2A* gene occurs in a minority of MCNs (2; 34).

Natural History and Treatment

The disease-specific 5-year survival rate is close to 100% for patients with a surgically resected MCN without invasive carcinoma (21;29). The mean 5-year survival rate is 50-60% for patients with a surgically resected MCN with an associated invasive cancer (2;19;21;31). MCNs highlight the importance of early detection. MCNs are almost always unifocal (2). Therefore, non-invasive MCNs, even those with marked dysplasia, are curable neoplasms if they can be completely resected (21;29). In contrast, almost half of patients with an invasive carcinoma associated with an MCN die of disease within five years (2;19;21;31). The challenge, therefore, is to detect and remove these neoplasms before they progress to invasive carcinoma. It also follows that the term "mucinous cystic carcinoma" should be avoided because it encompasses an entirely curable lesion (the mucinous cystic neoplasm with high-grade dysplasia) with a fully malignant neoplasm (an invasive carcinoma arising in association with a mucinous cystic neoplasm)(2).

Deserving special note is the misconception that some non-invasive MCNs metastasize(32). Reports of metastasizing non-invasive MCNs almost certainly represent cases in which a resected neoplasm was incompletely sampled for histologic examination(2;29). Dysplasia, and even invasive carcinoma, can arise focally in an MCN, and if these foci are not sampled, a malignant neoplasm may be misdiagnosed as benign(2;21;29). Indeed, we were recently shown a case in which invasive carcinoma associated with an MCN wasn't identified until the 108th histologic section.

The observation that invasive carcinomas usually arise focally within an MCN has a second important implication: that, whenever possible, partial resection of MCNs should be avoided even if biopsies reveals only mild dysplasia(20;29). Biopsy or partial resection may miss a focal invasive component. The only way to be certain that an MCN harbors an invasive carcinoma is to resect it completely and examine it thoroughly by histologic evaluation (29).

Intraductal Papillary Mucinous Neoplasms

Clinical Features

IPMNs are grossly-visible non-invasive mucin-producing epithelial neoplasms that usually form long finger-like papillae (Figures 3 and 4)(2;33). Most are ≥ 1 cm in size (33). In contrast to MCNs, IPMNs, by definition, involve the main pancreatic duct or one of its branches (Figure 3)(2;34). IPMNs arise in the head of the pancreas more frequently than the tail, and IPMNs lack an ovarian-type stroma (2;33;35). IPMNs affect men slightly more often than woman (male to female ratio of 3 to 2). The mean age at diagnosis is near 65 years, with a range of 25 to 95 years(2;35-37). Common presenting signs and symptoms include abdominal pain, pancreatitis, nausea and vomiting, diabetes mellitus, weight loss, jaundice and back pain(2; 35;37;38). With the increased use of imaging, a greater proportion of IPMNs are discovered incidentally in asymptomatic patients(22). Serum oncoproteins, such as carcinoembryonic antigen and CA 19-9 levels, are usually normal unless the IPMN is associated with an invasive cancer(2).

Computerized tomography usually reveals a dilated main pancreatic duct or a collection of cysts that represent dilated branch ducts(2). The finding of mucin extruding from a patulous ampulla of Vater is a classic, almost diagnostic, feature at endoscopy(2). In contrast to MCNs, ERCP demonstrates a dilated pancreatic duct, and filling defects, caused by intraluminal mucous plugs or papillary projections of the neoplasm itself. Magnetic resonance cholangiopancreatography (MRCP) may demonstrate ductal dilatation and mural nodules.

Similar to MCNs, the mean age of patients with mild dysplasia is significantly younger than patients with an associated invasive carcinoma (63 years versus 68 years in one series)(36;

37). In addition, many patients with an IPMN report a long history of symptoms(39;40). The patients reported in one series developed pancreatitis a mean of 43 months before they were diagnosed (39). These observations help define the time frame for progression from a non-invasive to an invasive IPMN, and they highlight the window of opportunity that exists to cure these neoplasms if they can be detected while they are still non-invasive.

Pathologic and Molecular Features

Non-invasive IPMNs are grossly subdivided into two groups- main duct type and branch duct type(2;41-44). Main duct type IPMNs, as the name suggests, predominantly involve the main pancreatic duct (Figure 3). Branch duct type IPMNs involve a side branch of the main duct, and, of course, mixed examples involving both the main and branch ducts occur as well. Non-invasive IPMNs are graded histologically according to the degree of architectural and cytologic atypia, into IPMN with mild dysplasia (IPMN adenoma), IPMN with moderate dysplasia (Figure 4), and IPMN with marked (severe) dysplasia (carcinoma *in situ*). Main duct IPMNs tend to have higher degrees of dysplasia and are more often associated with an invasive carcinoma compared to the branch duct type (38;44-46). Histologically, the papillary epithelium may show gastric mucinous cells, intestinal-type cells with goblet cells, or pancreaticobiliary-type epithelium. Often, a mixture of two or even three types of epithelium are present within a single tumor.

A distinctive histologic variant of IPMN, termed intraductal oncocytic papillary neoplasm (IOPN), deserves mention. IOPNs are composed of neoplastic epithelial cells with abundant eosinophilic cytoplasm(47). The distinctive appearance of IOPNs is a manifestation of numerous mitochondria within neoplastic cells(47). The few IOPNs reported are insufficient to determine whether their clinical behavior differs from that of typical IPMNs.

One-third of IPMNs have an associated invasive adenocarcinoma(2;35;48;49). Approximately, 50% of these invasive adenocarcinomas are of the colloid type (Figure 5) and the other half are tubular/ductal adenocarcinomas(2;50). It is important to distinguish the colloid from the tubular/ductal types of invasive carcinoma because patients with the former have a better prognosis than patients with the latter (see below) (51). IPMNs may be associated with extrapancreatic malignancies(61-63). Twelve of 79 patients with an IPMN reported by Kamisawa et al. had a synchronous or a metachronous gastric cancer, and 7 had colon cancer (62). Similarly, in a series of 69 patients with an IPMN reported by Eguchi et al. 12% had a preoperative personal history of colorectal cancer and 4% a preoperative history of gastric cancer(61). The rate of colorectal cancer was 5.4 times greater than expected in the general population(61).

A variety of molecular alterations have been reported in IPMNs. Furthermore, the mutational spectrum of IPMNs differs slightly from that observed in infiltrating ductal adenocarcinoma (2). The frequency of *KRAS* gene mutations increases with increasing degrees of dysplasia (32). The reported frequency of *TP53* and *p16/CDKN2A* gene inactivation varies from series to series. However, *SMAD4* gene mutations are relatively uncommon (2;51). In contrast, *LKB*, which is a gene associated with the Peutz-Jeghers syndrome, is biallelically inactivated in 25%, and the *PIK3CA* gene is mutated in 10%, of IPMN's (52;53).

Natural History and Treatment

Similar to MCNs, the critical prognosticators for patients with IPMNs are the presence and size of an associated invasive carcinoma(37;52). The term “*intraductal papillary mucinous carcinoma*” should be avoided because it includes both a potentially curable lesion (the intraductal papillary mucinous neoplasm with high-grade dysplasia) and a malignant neoplasm (invasive carcinoma arising in association with an intraductal papillary mucinous neoplasm)

(2). The overall five-year survival rate for surgically resected patients with an invasive carcinoma arising in association with an IPMN is 45%(2;37).

However, unlike MCNs, non-invasive IPMNs may be multifocal. Thus, patients with surgically resected non-invasive IPMNs usually cannot be considered cured of their disease(36;48;50; 53-55). A small but significant fraction of patients develop a second pancreatic neoplasm, and some will die of their disease(36). For example, in a series reported by Chari et al. five of 60 patients with non-invasive IPMNs treated with partial pancreatectomy recurred a median of 40 months after diagnosis(36). Most recurrences were caused by multifocal disease, since none of the 13 patients with non-invasive IPMNs who underwent a total pancreatectomy developed a recurrence(36). Therefore, patients who have had an IPMN resected, even a non-invasive IPMN with negative margins, should be followed carefully for evidence of metachronous disease(56;57).

While it is generally agreed that IPMNs greater than 3 cm in size, those with a mural nodule, or associated with dilatation of the main pancreatic duct should be resected, the most appropriate clinical management of patients with a small IPMN is controversial. This is due to the fact that 1. small pancreatic cysts are remarkably common in otherwise healthy patients, 2. most cysts less than 3 cm in size do not show significant dysplasia, and 3. surgical resection of pancreatic neoplasms is associated with a significant risk of mortality and morbidity (58). For example, Schani et al. reported that only 3 of 86 pancreatic cysts that measured less than 3 cm in greatest dimension harbored high grade dysplasia (*in-situ* carcinoma) (58). Allen et al. have, therefore, recently suggested that the risk of surgical mortality is about equal to the risk of malignancy for patients with small (<3 cm) cysts (59). These data suggest that great care should be exercised before resecting smaller (< 3cm) pancreatic cysts. Indeed, recently proposed international guidelines advocate clinical observation with regular CT or magnetic resonance imaging (MRI) for patients with branch duct IPMNs less than 3 cm in size, unless the cysts have a mural nodule and/or are associated with significant dilatation of the main pancreatic duct(60).

The recent report described earlier from Tada et al, however, suggests that there is also risk in observing patients with cystic lesions of the pancreas(14). In that study, 7 of 197 patients with pancreatic cysts developed pancreatic cancer upon follow-up (0.95% per year), a rate 22.5-fold greater than expected(14). Remarkably, three of the seven cysts that progressed to cancer were ≤ 1 cm in size (14). Evidence-based criteria to determine when to follow, and when to operate, on cystic lesions in the pancreas are clearly needed.

Pancreatic Intraepithelial Neoplasia

Clinicopathologic Features

Pancreatic intraepithelial neoplasia (PanIN) was originally recognized by Holst over a century ago(3). However, it wasn't until this decade that the PanIN nomenclature was developed and careful molecular studies were performed to establish that PanINs are a precursor to invasive adenocarcinoma of the pancreas(4;64).

PanINs are non-invasive microscopic epithelial neoplasms, located in the smaller pancreatic ducts, characterized by cytologic and architectural atypia (Figure 6)(2;33;65). PanINs are divided into three grades based on the degree of epithelial atypia. Lesions with only minimal atypia are designated PanIN-1, those with moderate atypia PanIN-2, and those with marked atypia PanIN-3(33;65). In addition, PanIN-1 lesions are further subdivided into flat (PanIN-1A) and papillary types (PanIN-1B)(33;65).

PanINs are remarkably common lesions(66-68). Similar to invasive cancer, PanINs increase with age and are more common in the head than the tail of the pancreas (66;67). PanINs are more common in pancreas with invasive carcinoma and in those with chronic pancreatitis (66;67;69;70). Cubilla and Fitzgerald carefully studied 227 pancreata from patients with pancreatic cancer and 100 pancreata from patients without pancreatic cancer. They found that PanIN-2 lesions were three times more common in pancreata with cancer compared to pancreata without cancer. In fact, PanIN-3 lesions were only observed in pancreata with cancer (69). More recently, Andea et al. reviewed a series of 234 pancreata and identified PanIN lesions in 82% of pancreata with invasive cancer, in 60% of pancreata with chronic pancreatitis, and in 16% of otherwise normal patients (66). PanINs also occur adjacent to other periampullary neoplasms. Agoff et al. identified PanINs in 40% of pancreata surgically resected for ampullary cancer, and Stelow et al. observed PanINs in pancreata resected for acinar cell carcinoma, mucinous cystic neoplasms, serous cystic neoplasms, well-differentiated pancreatic endocrine neoplasms and solid-pseudopapillary neoplasms(71;72).

Molecular Features

Molecular analyses have demonstrated that PanIN harbors many of the same genetic alterations found in infiltrating ductal adenocarcinoma of the pancreas (2). These include activating point mutations in the *KRAS* gene, and inactivation of the *p16/CDKN2A*, *TP53* and *SMAD4* genes (70;79;80). Of interest, recently developed genetically engineered mouse models in which mutant *KRAS* is expressed in the pancreas, develop PanIN lesions histologically identical to those in humans. In fact, these mice eventually develop invasive pancreatic cancer as well (9;81)

Diagnosis and Treatment

While studies of genetically engineered mice, and careful molecular and morphologic analyses, clearly establish that PanINs are a precursor to invasive cancer, significant hurdles must be overcome before these lesions can be clinically detected and treated. First, the frequency and rate that PanINs progress to invasive cancer has not yet been determined. If all PanINs were to inextricably and rapidly progress to invasive cancer, then it would follow that all PanINs should be aggressively treated, whenever possible. If, on the other hand, PanINs only rarely and slowly progress to invasive cancer, then PanINs may not represent a valid target for therapy. Terhune et al. attempted to calculate, mathematically, the probability of a single PanIN lesion progressing to cancer(73). Estimating that 0.8% of pancreata develop cancer, that 37.5% of the general population develops PanIN, and that the average pancreas has 5 foci of PanIN, they calculated that ~1% of PanIN lesions progress to invasive cancer(73). These calculations are, however, based on a number of assumptions and estimates. The risk of disease progression cannot be accurately assessed until there is more evidence on the frequency and rate that PanINs progress to invasive cancer. Second, technologies need to be developed that can help detect PanIN lesions. A variety of molecular tests are being developed to screen for these lesions. For example, Shi et al. developed a novel technology, called LigAmp that can be used to detect rare mutant *KRAS* genes shed from neoplasms, such as PanIN lesions(74). These tests are doubtlessly years away from clinical practice, raising the question of what can be done today?

A recent study by Brune et al. suggests that morphologic changes in the pancreatic parenchyma adjacent to PanIN lesions may be detectable using currently available imaging technologies, such as endoscopic ultrasound (EUS)(75). Brune et al. demonstrated that multifocal PanINs are frequently associated with a lobulocentric form of pancreatic parenchymal atrophy, which is detectable by EUS(75). Clearly, more work has to be done, but the authors of this review are confident that in the near future some PanIN lesions, particularly when multifocal, may be detectable using a combination of molecular and imaging technologies.

Who Should Be Screened?

Even if technological challenges of screening for small microscopic lesions in an inaccessible organ, such as the pancreas, can be overcome, we would still be faced with the very real challenge of identifying the appropriate population to screen. Pancreatic cancer, although extremely deadly, is simply too uncommon to make a non-selective screening effort practical. The incidence of pancreatic cancer in the United States is 9 per 100,000 per year (76). Enormous sensitivity and specificity would be needed in order for a screening test to detect a disease with the rarity of pancreatic cancer without unnecessarily alarming large numbers of non-disease carriers. A critical first step in applying a screening test for precursor lesions in the pancreas would, therefore, be to identify populations that harbor an increased risk of developing pancreatic cancer. Individuals with a strong family history of pancreatic cancer, and individuals with a germ line genetic defect that increases their risk of pancreatic cancer, may constitute such a group.

To date, at least five genetic syndromes are known to increase the risk of pancreatic cancer (Table 3) (77-84). For example, germ line (inherited) mutations in the second breast cancer gene (*BRCA2*), are associated with a three- to 10-fold increased risk of pancreatic cancer (78;85-88). In addition, individuals with a strong family history of pancreatic cancer also have an increased risk of developing pancreatic cancer (87;89-91). The risk of pancreatic cancer is doubled in individuals with one first-degree relative with pancreatic cancer, increasing to 6.4-fold in individuals having two first-degree relatives with pancreatic cancer, and reaches a 32-fold increase in individuals having three or more first-degree relatives with pancreatic cancer (90;91). Risk-prediction models, such as the PancPRO model developed by A. Klein et al. can be used to quantify individual risk, and, therefore, could be used to determine whether an individual's risk of developing pancreatic cancer is high enough to justify screening (92).

Screening for Asymptomatic Precursors

Our discussion on screening up to this point has been largely theoretical. Nonetheless, a recent prospective controlled study by Canto et al. established that high-risk populations may be screened using existing technologies (92;94). Canto et al. screened 78 asymptomatic individuals with either a strong family history of pancreatic cancer or with the Peutz-Jeghers syndrome, and 149 controls, using CT and EUS (93;94). Eight patients with neoplastic lesions of the pancreas were identified among the cases (10% yield of screening). These included six patients with IPMNs, and one patient with PanIN, who were treated surgically, and one patient with an IPMN who chose not to be treated. This latter patient later developed an invasive cancer. This study, as well as others like it, establish that 1. individuals at high risk can be identified, 2. that they can be screened using existing technologies, and 3. if found to have a precursor can be treated before their curable pancreatic neoplasm progresses to incurable invasive cancer (93-95).

Summary and Conclusions

Three well-defined precursor lesions of adenocarcinoma of the pancreas have been identified. There is general agreement that, when possible, mucinous cystic neoplasms should be completely resected and, when resected, examined completely by histology in order to identify, or rule out, small foci of infiltrating carcinoma. There is also general agreement that large (>3cm) intraductal papillary mucinous neoplasms should be resected, particularly when they contain a mural nodule or are associated with dilatation of the main pancreatic duct. The management of smaller intraductal papillary mucinous neoplasms is less clear. The risks of surgery must be balanced with the risks of leaving a cancer precursor in the patient. Even when non-invasive intraductal papillary mucinous neoplasms are surgically resected, the patient

should be followed for possible multifocal pancreatic disease and perhaps even for extrapancreatic malignancies.

Pancreatic intraepithelial neoplasia lesions are too small to be detected using currently available imaging methods, but improvements in imaging and a better understanding of both the molecular alterations present in PanINs and the parenchymal changes associated with PanINs, may allow for their early detection in asymptomatic individuals.

Screening the general population for non-invasive precursor lesions in the pancreas may not be realistic at the present time, but we are already able to identify populations at increased risk and to quantify this risk - important steps in the clinical application of any potentially clinically useful screening test.

Reference List

1. American Cancer Society. Cancer. New York: New York, American Cancer Society; 2007. Cancer Facts & Figures 2007; p. 1-52.
2. Hruban, RH.; Pitman, MB.; Klimstra, DS. Atlas of tumor pathology. Fascicle 6. Washington, DC: American Registry of Pathology and Armed Forces Institute of Pathology; 2007. Tumors of the pancreas. Fourth
3. Hulst SPL. Zur kenntnis der Genese des Adenokarzinoms und Karzinoms des Pankreas. Virchows Arch (B) 1905;180:288–316.
4. Hruban RH, Goggins M, Parsons JL, Kern SE. Progression model for pancreatic cancer. Clin Cancer Res 2000;6:2969–2972. [PubMed: 10955772]
5. Brat DJ, Lillemoe KD, Yeo CJ, Warfield PB, Hruban RH. Progression of pancreatic intraductal neoplasias to infiltrating adenocarcinoma of the pancreas. Am J Surg Pathol 1998;22(2):163–169. [PubMed: 9500216]
6. Brockie E, Anand A, Albores-Saavedra J. Progression of atypical ductal hyperplasia/carcinoma in situ of the pancreas to invasive adenocarcinoma. Ann Diagn Pathol 1998;2(5):286–92. [PubMed: 9845751]
7. Berman JJ, Albores-Saavedra J, Bostwick D, Delellis R, Eble J, Hamilton SR, et al. Precancer: A conceptual working definition Results of a Consensus Conference. Cancer Detect Prev 2006;30(5): 387–394. [PubMed: 17079091]
8. Hruban RH, Iacobuzio-Donahue CA, Wilentz RE, Goggins M, Kern SE. Molecular pathology of pancreatic cancer. Cancer J 2001;7(4):251–258. [PubMed: 11561601]
9. Hingorani SR, Petricoin EF, Maitra A, Rajapakse V, King C, Jacobetz MA, et al. Preinvasive and invasive ductal pancreatic cancer and its early detection in the mouse. Cancer Cell 2003;4(6):437–450. [PubMed: 14706336]
10. Hyde GL, Davis JB, McMillin RD, McMillin M. Mucinous cystic neoplasm of the pancreas with latent malignancy. Am Surg 1984;50:225–229. [PubMed: 6712017]
11. Probst JG, Blumenthal HT. Progressive malignant degeneration of a cystadenoma of the pancreas. Arch Surg 1960;81:683–689. [PubMed: 13738110]
12. Campbell JA, Cruickshank AH. Cystadenoma and cystadenocarcinoma of the pancreas. J Clin Pathol 1962;15:432–437. [PubMed: 14018131]
13. Williams TM, Weiner DB, Greene MI, Maguire HC Jr. Expression of c-erbB-2 in human pancreatic adenocarcinomas. Pathobiology 1991;59:46–52. [PubMed: 1675057]
14. Tada M, Kawabe T, Arizumi M, Togawa O, Matsubara S, Yamamoto N, et al. Pancreatic Cancer in Patients With Pancreatic Cystic Lesions: A Prospective Study in 197 Patients. Clin Gastroenterol Hepatol. 2006
15. McCarthy DM, Brat DJ, Wilentz RE, Yeo CJ, Cameron JL, Kern SE, et al. Pancreatic intraepithelial neoplasia and infiltrating adenocarcinoma: analysis of progression and recurrence by *DPC4* immunohistochemical labeling. Hum Pathol 2001;32:638–642. [PubMed: 11431719]
16. Hustinx SR, Leoni LM, Yeo CJ, Brown PN, Goggins M, Kern SE, et al. Concordant loss of MTAP and p16/CDKN2A expression in pancreatic intraepithelial neoplasia: evidence of homozygous deletion in a noninvasive precursor lesion. Mod Pathol 2005;18(7):959–963. [PubMed: 15832197]

17. Moskaluk CA, Hruban RH, Kern SE. p16 and K-ras gene mutations in the intraductal precursors of human pancreatic adenocarcinoma. *Cancer Res* 1997;57:2140–2143. [PubMed: 9187111]
18. Klöppel G, Kosmahl M. Cystic lesions and neoplasms of the pancreas. The features are becoming clearer. *Pancreatology* 2001;1(6):648–655. [PubMed: 12120249]
19. Le Borgne J, de Calan L, Partensky C. Cystadenomas and cystadenocarcinomas of the pancreas: a multiinstitutional retrospective study of 398 cases. French Surgical Association. *Ann Surg* 1999;230(2):152–61. [PubMed: 10450728]
20. Sarr MG, Carpenter HA, Prabhakar LP, Orchard TF, Hughes S, van Heerden JA, et al. Clinical and pathologic correlation of 84 mucinous cystic neoplasms of the pancreas: can one reliably differentiate benign from malignant (or premalignant) neoplasms? *Ann Surg* 2000;231(2):205–212. [PubMed: 10674612]
21. Zamboni G, Scarpa A, Bogina G, Iacono C, Bassi C, Talamini G, et al. Mucinous cystic tumors of the pancreas: clinicopathological features, prognosis, and relationship to other mucinous cystic tumors. *Am J Surg Pathol* 1999;23(4):410–422. [PubMed: 10199470]
22. Fernandez-del Castillo C, Targarona J, Thayer SP, Rattner DW, Brugge WR, Warshaw AL. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. *Arch Surg* 2003;138(4):427–3. [PubMed: 12686529]
23. Warshaw AL, Compton CC, Lewandrowski KB, Cardenosa G, Mueller PR. Cystic tumors of the pancreas. New clinical, radiologic, and pathologic observations in 67 patients. *Ann Surg* 1990;212:432–445. [PubMed: 2171441]
24. Bassi C, Salvia R, Gumbs AA, Butturini G, Falconi M, Pederzoli P. The value of standard serum tumor markers in differentiating mucinous from serous cystic tumors of the pancreas: CEA, Ca 19-9, Ca 125, Ca 15-3. *Langenbecks Arch Surg* 2002;387(78):281–285. [PubMed: 12447553]
25. de Calan L, Levard H, Hennen H, Fingerhut A. Pancreatic cystadenoma and cystadenocarcinoma: diagnostic value of preoperative morphological investigations. *Eur J Surg* 1995;161(1):35–40. [PubMed: 7727604]
26. Compagno J, Oertel JE. Mucinous cystic neoplasms of the pancreas with overt and latent malignancy (cystadenocarcinoma and cystadenoma). A clinicopathologic study of 41 cases. *Am J Clin Pathol* 1978;69:573–580. [PubMed: 665578]
27. Fukushima N, Mukai K. Differential diagnosis between intraductal papillary-mucinous tumors and mucinous cystic tumors of the pancreas. *Int J Surg Pathol* 2000;8(4):271–278. [PubMed: 11494004]
28. Albores-Saavedra J, Angeles-Angeles A, Nadji M, Henson DE, Alvarez L. Mucinous cystadenocarcinoma of the pancreas. Morphologic and immunocytochemical observations. *Am J Surg Pathol* 1987;11:11–20. [PubMed: 3789255]
29. Wilentz RE, Albores-Saavedra J, Zahurak M, Talamini MA, Yeo CJ, Cameron JL, et al. Pathologic examination accurately predicts prognosis in mucinous cystic neoplasms of the pancreas. *Am J Surg Pathol* 1999;23(11):1320–1327. [PubMed: 10555000]
30. Goh BK, Tan YM, Chung YF, Chow PK, Cheow PC, Wong WK, et al. A review of mucinous cystic neoplasms of the pancreas defined by ovarian-type stroma: clinicopathological features of 344 patients. *World J Surg* 2006;30(12):2236–2245. [PubMed: 17103100]
31. Ridder GJ, Maschek H, Klempnauer J. Favourable prognosis of cystadeno- over adenocarcinoma of the pancreas after curative resection. *Eur J Surg Oncol* 1996;22(3):232–236. [PubMed: 8654602]
32. Yoshizawa K, Nagai H, Sakurai S, Hironaka M, Morinaga S, Saitoh K, et al. Clonality and K-ras mutation analyses of epithelia in intraductal papillary mucinous tumor and mucinous cystic tumor of the pancreas. *Virchows Arch* 2002;441(5):437–443. [PubMed: 12447672]
33. Iacobuzio-Donahue CA, Wilentz RE, Argani P, Yeo CJ, Cameron JL, Kern SE, et al. Dpc4 protein in mucinous cystic neoplasms of the pancreas: frequent loss of expression in invasive carcinomas suggests a role in genetic progression. *Am J Surg Pathol* 2000;24(11):1544–1548. [PubMed: 11075857]
34. Kim SG, Wu TT, Lee JH, Yun YK, Issa JP, Hamilton SR, et al. Comparison of epigenetic and genetic alterations in mucinous cystic neoplasm and serous microcystic adenoma of pancreas. *Mod Pathol* 2003;16(11):1086–1094. [PubMed: 14614047]

35. Thompson LDR, Becker RC, Przygodzki RM, Adair CF, Heffess CS. Mucinous cystic neoplasm (mucinous cystadenocarcinoma of low-grade malignant potential) of the pancreas: a clinicopathologic study of the pancreas. *Am J Surg Pathol* 1999;23(1):1–16. [PubMed: 9888699]
36. Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol* 2004;28(8):977–987. [PubMed: 15252303]
37. Fukushima N, Mukai K. Pancreatic neoplasms with abundant mucus production: emphasis on intraductal papillary-mucinous tumors and mucinous cystic tumors. *Advances in Anatomic Pathology* 1999;6(2):65–77. [PubMed: 10331069]
38. Kimura W, Makuuchi M, Kuroda A. Characteristics and treatment of mucin-producing tumor of the pancreas. *Hepatogastroenterology* 1998;45(24):2001–2008. [PubMed: 9951854]
39. Chari ST, Yadav D, Smyrk TC, DiMagno EP, Miller LJ, Raimondo M, et al. Study of recurrence after surgical resection of intraductal papillary mucinous neoplasm of the pancreas. *Gastroenterology* 2002;123(5):1500–1507. [PubMed: 12404225]
40. Sohn TA, Yeo CJ, Cameron JL, Hruban RH, Fukushima N, Campbell KA, et al. Intraductal papillary mucinous neoplasms of the pancreas: an updated experience. *Ann Surg* 2004;239(6):788–797. [PubMed: 15166958]
41. Doi R, Fujimoto K, Wada M, Imamura M. Surgical management of intraductal papillary mucinous tumor of the pancreas. *Surgery* 2002;132(1):80–85. [PubMed: 12110799]
42. Azar C, Van de Stadt J, Rickaert F, Deviere M, Baize M, Klöppel G, et al. Intraductal papillary mucinous tumours of the pancreas. Clinical and therapeutic issues in 32 patients. *Gut* 1996;39(3):457–464. [PubMed: 8949654]
43. Cellier C, Cuillierier E, Palazzo L, Rickaert F, Flejou JF, Napoleon B, et al. Intraductal papillary and mucinous tumors of the pancreas: accuracy of preoperative computed tomography, endoscopic retrograde pancreatography and endoscopic ultrasonography, and long-term outcome in a large surgical series. *Gastrointest Endosc* 1998;47(1):42–49. [PubMed: 9468422]
44. Seki M, Yanagisawa A, Ohta H, Ninomiya Y, Sakamoto Y, Yamamoto J, et al. Surgical treatment of intraductal papillary-mucinous tumor (IPMT) of the pancreas: operative indications based on surgico-pathologic study focusing on invasive carcinoma derived from IPMT. *J Hepatobiliary Pancreat Surg* 2003;10(2):147–155. [PubMed: 14505148]
45. Silas AM, Morrin MM, Raptopoulos V, Keogan MT. Intraductal papillary mucinous tumors of the pancreas. *AJR Am J Roentgenol* 2001;176(1):179–185. [PubMed: 11133563]
46. Tanaka M. Intraductal papillary mucinous neoplasm of the pancreas: diagnosis and treatment. *Pancreas* 2004;28(3):282–288. [PubMed: 15084972]
47. Terris B, Ponsot P, Paye F, Hammel PR, Sauvanet A, Molas G, et al. Intraductal papillary mucinous tumors of the pancreas confined to secondary ducts show less aggressive pathologic features as compared with those involving the main pancreatic duct. *Am J Surg Pathol* 2000;24(10):1372–1377. [PubMed: 11023098]
48. Bernard P, Scoazec JY, Joubert M, Kahn X, Le Borgne J, Berger F, et al. Intraductal papillary-mucinous tumors of the pancreas: predictive criteria of malignancy according to pathological examination of 53 cases. *Arch Surg* 2002;137(11):1274–1278. [PubMed: 12413317]
49. Ban S, Naitoh Y, Mino-Kenudson M, Sakurai T, Kuroda M, Koyama I, et al. Intraductal Papillary Mucinous Neoplasm (IPMN) of the Pancreas: Its Histopathologic Difference Between 2 Major Types. *Am J Surg Pathol* 2006;30(12):1561–1569. [PubMed: 17122512]
50. Adsay NV, Adair CF, Heffess CS, Klimstra DS. Intraductal oncocytic papillary neoplasms of the pancreas. *Am J Surg Pathol* 1996;20(8):980–994. [PubMed: 8712298]
51. Iacobuzio-Donahue CA, Klimstra DS, Adsay NV, Wilentz RE, Argani P, Sohn TA, et al. Dpc-4 protein is expressed in virtually all human intraductal papillary mucinous neoplasms of the pancreas: comparison with conventional ductal carcinomas. *Am J Pathol* 2000;157(3):755–761. [PubMed: 10980115]
52. Su GH, Hruban RH, Bova GS, Goggins M, Bansal RK, Tang DT, et al. Germline and somatic mutations of the STK11/LKB1 Peutz-Jeghers gene in pancreatic and biliary cancers. *Am J Pathol* 1999;154(6):1835–1840. [PubMed: 10362809]

53. Schonleben F, Qiu W, Ciau NT, Ho DJ, Li X, Allendorf JD, et al. PIK3CA mutations in intraductal papillary mucinous neoplasm/carcinoma of the pancreas. *Clin Cancer Res* 2006;12(12):3851–3855. [PubMed: 16778113]
54. Adsay NV, Conlon K, Brennan MF, Klimstra DS. Intraductal papillary-mucinous neoplasms of the pancreas (IPMN): an analysis of *in situ* and invasive carcinomas associated with 23 cases. *Modern Pathology* 1997;10:143A.
55. Atia GN, Brown RD, Alrashid A, Halline AG, Helton WS, Venu RP. The role of pancreatoscopy in the preoperative evaluation of intraductal papillary mucinous tumor of the pancreas. *J Clin Gastroenterol* 2002;35(2):175–179. [PubMed: 12172364]
56. D'Angelica M, Brennan MF, Suriawinata AA, Klimstra DS, Conlon KC. Intraductal papillary mucinous neoplasms of the pancreas: an analysis of clinicopathologic features and outcome. *Ann Surg* 2004;239(3):400–408. [PubMed: 15075659]
57. Adsay NV, Pierson C, Sarkar F, Abrams J, Weaver D, Conlon K, et al. Colloid (mucinous noncystic) carcinoma of the pancreas. *Am J Surg Pathol* 2001;25(1):26–42. [PubMed: 11145249]
58. Hara T, Yamaguchi T, Ishihara T, Tsuyuguchi T, Kondo F, Kato K, et al. Diagnosis and patient management of intraductal papillary-mucinous tumor of the pancreas by using peroral pancreatoscopy and intraductal ultrasonography. *Gastroenterology* 2002;122(1):34–43. [PubMed: 11781278]
59. Milchgrub S, Campuzano M, Casillas J, Albores-Saavedra J. Intraductal carcinoma of the pancreas. *Cancer* 1992;69(3):651–656. [PubMed: 1309676]
60. Navarro F, Michel J, Bauret P, Ramos J, Blanc P, Fabre JM, et al. Management of intraductal papillary mucinous tumours of the pancreas. *Eur J Surg* 1999;165(1):43–48. [PubMed: 10069633]
61. Sohn TA, Yeo CJ, Cameron JL, Iacobuzio-Donahue CA, Hruban RH, Lillemoe KD. Intraductal papillary mucinous neoplasms of the pancreas: an increasingly recognized clinicopathologic entity. *Ann Surg* 2001;234(3):313–321. [PubMed: 11524584]
62. Cuillerier E, Cellier C, Palazzo L, Deviere J, Wind P, Rickaert F, et al. Outcome after surgical resection of intraductal papillary and mucinous tumors of the pancreas. *Am J Gastroenterol* 2000;95(2):441–445. [PubMed: 10685747]
63. Inagaki M, Maguchi M, Kino S, Obara M, Ishizaki A, Onodera K, et al. Mucin-producing tumors of the pancreas: clinicopathological features, surgical treatment, and outcome. *J Hepatobiliary Pancreat Surg* 1999;6(3):281–285. [PubMed: 10526064]
64. Sahani DV, Saokar A, Hahn PF, Brugge WR, Fernandez-del Castillo C. Pancreatic cysts 3 cm or smaller: how aggressive should treatment be? *Radiology* 2006;238(3):912–919. [PubMed: 16439566]
65. Allen PJ, D'Angelica M, Gonen M, Jaques DP, Coit DG, Jarnagin WR, et al. A Selective Approach to the Resection of Cystic Lesions of the Pancreas: Results From 539 Consecutive Patients. *Ann Surg* 2006;244(4):572–582. [PubMed: 16998366]
66. Tanaka M, Chari S, Adsay NV, Fernandez-del Castillo C, Falconi M, Shimizu M, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. *Pancreatology* 2006;6(17):32.
67. Eguchi H, Ishikawa O, Ohigashi H, Tomimaru Y, Sasaki Y, Yamada T, et al. Patients with pancreatic intraductal papillary mucinous neoplasms are at high risk of colorectal cancer development. *Surgery* 2006;139(6):749–754. [PubMed: 16782429]
68. Kamisawa T, Tu Y, Egawa N, Nakajima H, Tsuruta K, Okamoto A. Malignancies associated with intraductal papillary mucinous neoplasm of the pancreas. *World J Gastroenterol* 2005;11(36):5688–5690. [PubMed: 16237766]
69. Yamaguchi K, Yokohata K, Noshiro H, Chijiwa K, Tanaka M. Mucinous cystic neoplasm of the pancreas or intraductal papillary-mucinous tumour of the pancreas. *Eur J Surg* 2000;166(2):141–148. [PubMed: 10724492]
70. Hruban RH, Wilentz RE, Kern SE. Genetic progression in the pancreatic ducts. *Am J Pathol* 2000;156(6):1821–1825. [PubMed: 10854204]
71. Hruban RH, Adsay NV, Albores-Saavedra J, Compton C, Garrett E, Goodman SN, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. *Am J Surg Pathol* 2001;25(5):579–586. [PubMed: 11342768]

72. Andea A, Sarkar F, Adsay NV. 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]
73. Kozuka S, Sassa R, Taki T, Masamoto K, Nagasawa S, Saga S, et al. Relation of pancreatic duct hyperplasia to carcinoma. *Cancer* 1979;43:1418–1428. [PubMed: 445339]
74. Mukada T, Yamada S. Dysplasia and carcinoma *in situ* of the exocrine pancreas. *Tohoku J Exp Med* 1982;137:115–124. [PubMed: 7112540]
75. Cubilla AL, Fitzgerald PJ. Morphological lesions associated with human primary invasive nonendocrine pancreas cancer. *Cancer Res* 1976;36:2690–2698. [PubMed: 1277176]
76. Volkholz H, Stolte M, Becker V. Epithelial dysplasias in chronic pancreatitis. *Virchows Arch A Pathol Anat Histopathol* 1982;396:331–349.
77. Agoff SN, Crispin DA, Bronner MP, Dail DH, Hawes SE, Haggitt RC. Neoplasms of the ampulla of Vater with concurrent pancreatic intraductal neoplasia: a histological and molecular study. *Mod Pathol* 2001;14(3):139–146. [PubMed: 11266517]
78. Stelow EB, Adams RB, Moskaluk CA. The prevalence of pancreatic Intraepithelial neoplasia in pancreata with uncommon types of primary neoplasms. *Am J Surg Pathol* 2006;30(1):36–41. [PubMed: 16330940]
79. Wilentz RE, Iacobuzio-Donahue CA, Argani P, McCarthy DM, Parsons JL, Yeo CJ, et al. Loss of expression of Dpc4 in pancreatic intraepithelial neoplasia: evidence that DPC4 inactivation occurs late in neoplastic progression. *Cancer Res* 2000;60:2002–2006. [PubMed: 10766191]
80. Wilentz RE, Geradts J, Maynard R, Offerhaus GJ, Kang M, Goggins M, et al. Inactivation of the p16 (INK4A) tumor-suppressor gene in pancreatic duct lesions: loss of intranuclear expression. *Cancer Res* 1998;58:4740–4744. [PubMed: 9788631]
81. Hruban RH, Adsay NV, Albores-Saavedra J, Anver MR, Biankin AV, Boivin GP, et al. Pathology of genetically engineered mouse models of pancreatic exocrine cancer: consensus report and recommendations. *Cancer Res* 2006;66(1):95–106. [PubMed: 16397221]
82. Terhune PG, Phifer DM, Tosteson TD, Longnecker DS. K-ras mutation in focal proliferative lesions of human pancreas. *Cancer Epidemiol Biomarkers Prev* 1998;7(6):515–521. [PubMed: 9641496]
83. Shi C, Eshleman SH, Jones D, Fukushima N, Hua L, Parker AR, et al. LigAmp for sensitive detection of single-nucleotide differences. *Nat Methods* 2004;1(2):141–147. [PubMed: 15782177]
84. Brune KA, Abe T, Canto MI, O'Malley L, Klein AP, Maitra A, et al. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. *American Journal of Surgical Pathology* 2006;30(9):1067–1076. [PubMed: 16931950]
85. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Databases: Incidence - SEER 11 Regs + AK Public-Use, Nov 2003 Sub for Expanded Races (1992-2001) and Incidence -SEER 11 Regs Public-Use, Nov 2003 Sub for Hispanics (1992-2001), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2004, based on the November 2003 submission. 2004.
86. Borg A, Sandberg T, Nilsson K, Johannsson O, Klinker M, Masback A, et al. High frequency of multiple melanomas and breast and pancreas carcinomas in CDKN2A mutation-positive melanoma families. *J Natl Cancer Inst* 2000;92(15):1260–1266. [PubMed: 10922411]
87. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. *J Natl Cancer Inst* 1999;91(15):1310–1316. [PubMed: 10433620]
88. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz-Jeghers Syndrome. *Gastroenterology* 2000;119:1447–1453. [PubMed: 11113065]
89. Goldstein AM, Fraser MC, Struewing JP, Hussussian CJ, Ranade K, Zametkin DP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. *N Engl J Med* 1995;333(15):970–974. [PubMed: 7666916]
90. Vasen HF, Gruis NA, Frants RR, van der Velden PA, Hille ET, Bergman W. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). *Int J Cancer* 2000;87(6):809–811. [PubMed: 10956390]

91. van der Heijden MS, Yeo CJ, Hruban RH, Kern SE. Fanconi anemia gene mutations in young-onset pancreatic cancer. *Cancer Res* 2003;63(10):2585–2588. [PubMed: 12750283]
92. Pogue-Geile KL, Chen R, Bronner MP, Crnogorac-Jurcevic T, Moyes KW, Downen S, et al. Palladin mutation causes familial pancreatic cancer and suggests a new cancer mechanism. *PLoS Medicine* 2006;3(12)
93. Hahn SA, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, et al. BRCA2 germline mutations in familial pancreatic carcinoma. *J Natl Cancer Inst* 2003;95(3):214–221. [PubMed: 12569143]
94. Liede A, Karlan BY, Narod SA. Cancer risks for male carriers of germline mutations in BRCA1 or BRCA2: a review of the literature. *J Clin Oncol* 2004;22(4):735–742. [PubMed: 14966099]
95. Murphy KM, Brune KA, Griffin CA, Sollenberger JE, Petersen GM, Bansal RK, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. *Cancer Res* 2002;62(13):3789–3793. [PubMed: 12097290]
96. Ozelik H, Schmocker B, DiNicola N, Shi XH, Langer B, Moore M, et al. Germline BRCA2 6174delT mutations in Ashkenazi Jewish pancreatic cancer patients. *Nat Genet* 1997;16:17–18. [PubMed: 9140390]
97. Hemminki K, Li X. Familial and second primary pancreatic cancers: a nationwide epidemiologic study from Sweden. *Int J Cancer* 2003;103(4):525–530. [PubMed: 12478670]
98. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJ, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. *Cancer Res* 2004;64(7):2634–2638. [PubMed: 15059921]
99. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, Sulem P, Kristjansson K, Arnason S, et al. Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. *PLoS Med* 2004;1(3):e65. [PubMed: 15630470]
100. Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. *J Clin Oncol* 2007;25(11):1417–1422. [PubMed: 17416862]
101. Canto MI, Goggins M, Hruban RH, Fishman EK, Axilbund JE, Griffin CA, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol* 2006;4(6):766–781. [PubMed: 16682259]
102. Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune KA, et al. Screening for pancreatic neoplasia in high-risk individuals: An EUS-based approach. *Clinical Gastroenterology and Hepatology* 2004;2(7):606–621. [PubMed: 15224285]
103. Brentnall TA, Bronner MP, Byrd DR, Haggitt RC, Kimmey MB. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. *Ann Intern Med* 1999;131(4):247–255. [PubMed: 10454945]

Figure 1.
Mucinous cystic neoplasm. Note the large size of the cysts and the presence of glistening mucin.

Figure 2.
Photomicrograph of a mucinous cystic neoplasm. The neoplastic mucin-producing columnar epithelial cells rest on a layer of cellular “ovarian-type” stroma.

Figure 3.
Intraductal papillary mucinous neoplasm involving the main pancreatic duct. The duct is dramatically distended by neoplastic papillae.

Figure 4.
Photomicrograph of an intraductal papillary mucinous neoplasm. The neoplastic mucin-producing columnar epithelial cells form long finger-like papillae. Abundant intraluminal mucin is present.

Figure 5.
Photomicrograph of a colloid carcinoma of the pancreas. The neoplastic cells are embedded in copious quantities of extra-cellular mucin.

Figure 6. Normal pancreatic duct (A), PanIN-1B (B), PanIN-2 (C), and PanIN-3 (D). PanIN lesions are significantly smaller in size compared to the IPMN illustrated in Figure 4, and the papillae are shorter in length.

Table 1
National Cancer Institute Working Group Criteria for Precursors to Invasive Cancer*

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1. The precursor to invasive cancer must be associated with an increased risk of the cancer.
 2. When a precursor to invasive cancer progresses to cancer, the resulting cancer arises from cells within the precancer.
 3. A precursor to invasive cancer should differ from the normal tissue from which it arises.
 4. A precursor to invasive cancer should differ from the cancer into which it develops.
 5. There should be a method by which the precursor to invasive cancer can be diagnosed.
-

* precursors to invasive cancer were called “precancers” in the publication that established these criteria(7)

Table 2**Common Precursor Lesions in the Pancreas**

Feature	Mucinous Cystic Neoplasm	Intraductal Papillary Mucinous Neoplasm	Pancreatic Intraepithelial Neoplasia
Predominant Age	40-50 years	In the 60's	Increases with age
Gender	Female>>male	Male>female	Male=Female
Head vs. body/tail	Body/tail	Head	Head >Body/Tail
Relation of the cysts to large ducts	Usually not connected	Always connected	N/A
Cyst Contents	Mucoid	Mucoid	N/A
Mucin oozing from ampulla	No	Yes	No
Stroma	Ovarian-type	Collagen-rich	Collagen-rich
Multifocal disease	Very rare	In 20-30%	Often

TABLE 3
Inherited Genetic Alterations Associated with an Increased Risk of Pancreatic Cancer⁺

Individual	Gene	Relative Risk (fold increase)	Risk by age 70
No History	None	1	0.5%
One FDR with pc	Unknown	2.3	1.15%
Breast Cancer	<i>BRCA1</i>	2.0	1%
	<i>BRCA2</i>	3.5-10	5%
FAMMM	<i>p16 (CDKN2A)</i>	20-34	10-17%
3 FDR with pc	Unknown	32	16%
Familial pancreatitis	<i>PRSS1</i>	50-80	25-40%
Peutz-Jeghers	<i>STK11/LKB1</i>	132	30-60%
HNPCC	<i>MLH1, MSH2, others</i>	Unknown	<5%
Familial pc	<i>PALLD</i> ⁺⁺	Unknown	Unknown
Young age onset pc	<i>FANCC</i> and <i>FANC G</i> ⁺⁺⁺	Unknown	Unknown

FDR= first-degree relatives, pc = pancreatic cancer, FAMMM= familial atypical multiple mole melanoma syndrome, HNPCC= hereditary non-polyposis colorectal cancer syndrome, pc = pancreatic cancer

⁺ Adapted from (2)

⁺⁺ A *PALLD* missense variant was linked to pancreatic cancer in one family, but was also identified in a control individual (92).

⁺⁺⁺ The proposed association with young onset has not been examined in follow-up literature (91)