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CCR Translations

Commentary on Brand et al., p. 805

Markers of Pancreatic Cancer: Working Toward Early Detection

Michael Goggins

Because early detection of pancreatic cancer is the best way to cure this disease, investigators continue to try to identify accurate markers of early pancreatic cancer. Because early-stage pancreatic cancer is generally asymptomatic, the only reliable way to detect it is by targeting individuals at increased risk for pancreatic screening. *Clin Cancer Res*; 17(4); 635–7. ©2011 AACR.

In this issue of *Clinical Cancer Research*, Brand and colleagues report on their evaluation of the diagnostic performance of measuring 83 circulating proteins in sera of patients with pancreatic ductal adenocarcinoma ($N = 333$), compared with those with benign pancreatic conditions ($N = 144$, benign pancreatic cysts, pancreatitis), and healthy controls ($N = 227$; ref. 1). The selected markers required using commercially available antibodies and were detected in multiplex fashion with the Luminex platform. The markers included those previously reported to have potential diagnostic utility for pancreatic cancer [CA19–9, CEA, osteopontin, MIC-1, TIMP-1, HIP (REG3), osteoprotegerin, ICAM-1, SAA]. The remaining markers were mostly cytokines, chemokines, hormones, and apolipoproteins. Samples were split randomly into training and blinded validation sets prior to analysis. The best 3-marker panel identified for discriminating patients with pancreatic cancer from healthy controls (CA19–9, ICAM-1, osteoprotegerin) yielded a sensitivity-specificity (SN-SP) of 78 to 94% in the validation set. The best 3-marker panel identified for discriminating patients with pancreatic cancer from disease controls (CA19–9, CEA, TIMP-1) yielded a SN-SP of 71 to 90%, superior to the performance of CA19–9 alone (SN-SP, 51 to 90%). Several other marker combinations had similar diagnostic utility.

The strengths of this multicenter study include the large number of cases, disease controls, and healthy controls enrolled; the use of antibody-based assays; and standardized sample processing and rigorous data analysis. The study provided insight into the performance of many markers and identified marker combinations with improved performance over serum CA19–9 measurements alone. One important limitation was the inclusion of

patients with all stages of pancreatic cancer, approximately half of whom had stage IV disease. As pancreatic cancer progresses and spreads beyond the pancreas, abnormalities that are not specific to pancreatic cancer accumulate. As a result, marker behavior is likely to be significantly different among patients with early- versus late-stage pancreatic cancer (see Fig. 1). Although the use of disease controls can help identify nonspecific alterations, advanced pancreatic cancer is associated with many secondary changes including pancreatic injury, inflammation and fibrosis, obstructive jaundice, diabetes, weight loss, cachexia, tumor invasion into the duodenal wall and other surrounding organs, and metastases to the liver, peritoneum, and elsewhere, and it is difficult to account for all of the nonspecific abnormalities associated with advanced pancreatic cancer using disease controls. Even CA19–9, a relatively specific marker of pancreatic ductal adenocarcinomas, reaches higher levels and achieves greater diagnostic accuracy when measured in patients with advanced compared with early-stage pancreatic cancer.

Many of the elevated markers evaluated by Brand and colleagues in pancreatic cancer patients were acute phase reactants (SAA, ICAM-1, CRP, osteoprotegerin) whose expression is regulated by inflammatory cytokines and whose primary source is probably not pancreatic cancer cells. These markers are elevated in many inflammatory conditions and have limited diagnostic utility. For example, elevations of ICAM-1 and/or osteoprotegerin are observed not only in chronic inflammatory conditions but are also in patients with conditions common to a pancreatic cancer population, including diabetes, hypercholesterolemia, atherosclerotic disease, obesity, and hypertension. This observation likely explains why markers that did best in the Brand study were proteins thought to arise predominantly from pancreatic cancer cells (CA19–9, CEA, and TIMP-1). Although some of the acute-phase reactant markers tested did show some ability to discriminate between pancreatic cancers and the benign pancreatic conditions, their diagnostic performance may not be as useful in real world settings where many patients with suspected pancreatic cancer have comorbidities such as diabetes, atherosclerosis, etc. For these reasons, investigating marker behavior in patients with advanced pancreatic

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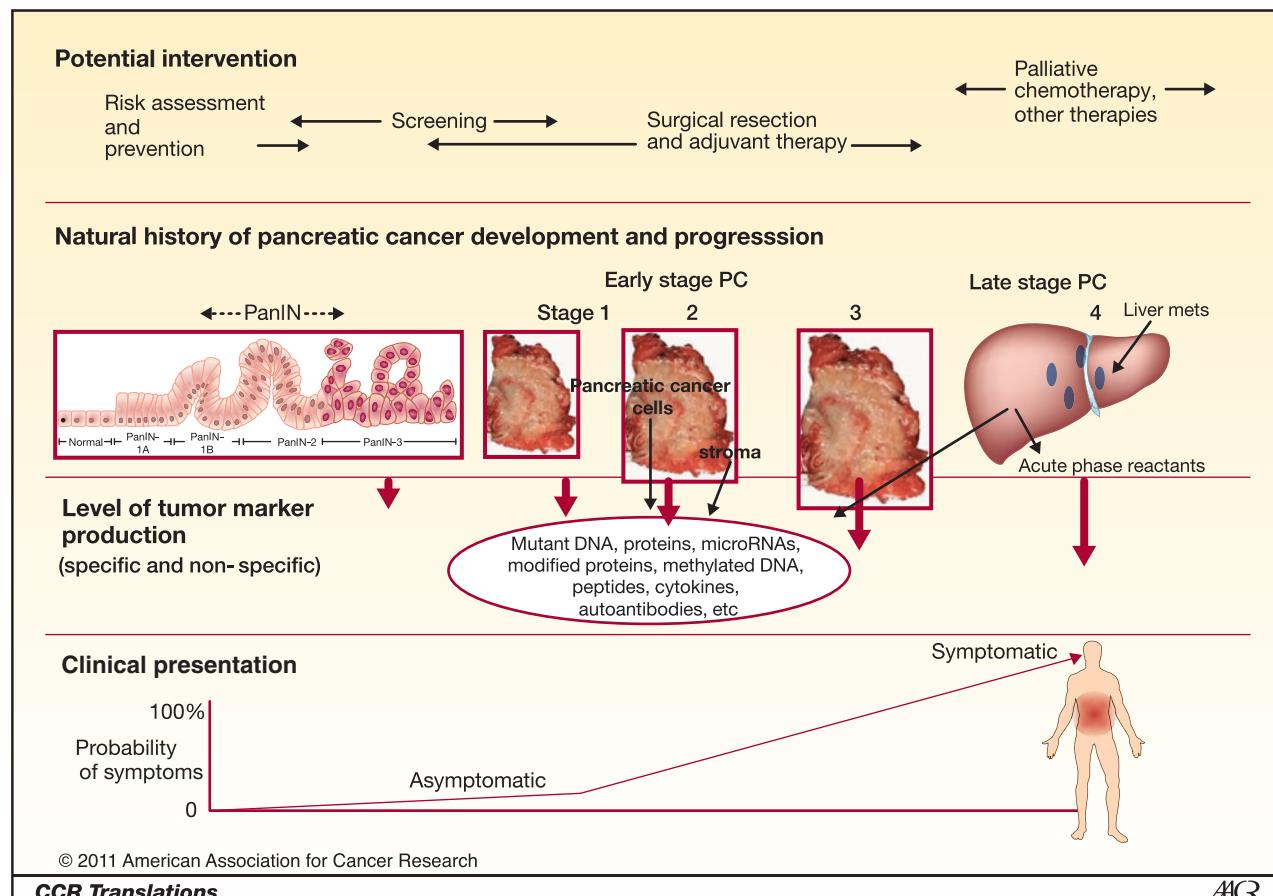


Figure 1. The production of tumor markers at different stages in the natural history of pancreatic cancer development. Markers that become readily detectable only in advanced stages of pancreatic ductal adenocarcinoma after the onset of clinical symptoms will not provide opportunities for early detection and cure. Detecting pancreatic ductal adenocarcinoma and its precursors at a curable stage requires screening asymptomatic individuals with markers that can reliably detect early-stage disease such as PanIN-3 or stage I pancreatic cancer.

cancer may not be the best strategy for identifying specific markers of early pancreatic cancer.

In current clinical practice, markers have a limited role in diagnosing pancreatic cancer. The best initial diagnostic test for suspected pancreatic cancer is a pancreatic-protocol computerized tomography (CT) scan. Endoscopic ultrasound is also highly accurate for detecting pancreatic neoplasms. Only highly accurate marker(s) will supplant pancreatic imaging tests as initial tests for pancreatic cancer. For this reason, research efforts are continuing to try to identify highly accurate markers with better performance than the panel identified by Brand and colleagues. Circulating mutant DNA levels reflect tumor burden in patients with colorectal cancer (2) and could prove to be useful for diagnosing pancreatic cancers. Currently, assays measuring circulating mutant DNA are research tools but could become part of clinical practice in the near future. Efforts are underway to develop newer antibody-based tests for proteins overexpressed in pancreatic cancer (3). In addition to ongoing proteomics research for protein markers, other markers are under investigation for their diagnostic utility, including aberrantly methylated DNA

(4), autoantibodies, aberrantly glycosylated molecules (5), and microRNAs (6).

When evaluating an early detection marker, it is important to determine the goal of early detection. Although recent estimates of cancer evolution suggest that pancreatic cancers can reside in the pancreas for several years before metastasis (7), anecdotal evidence from pancreatic screening studies suggests that some patients can progress from apparently noninvasive pancreatic disease to metastatic pancreatic cancer between short screening intervals. And because cure of invasive pancreatic cancer is rarely achieved even for patients with early-stage pancreatic cancer, the primary goal of pancreatic screening programs for high-risk individuals has been to prevent pancreatic cancer developing by detecting and resecting pancreatic precursor lesions. These precursor lesions include pancreatic intraepithelial neoplasias (PanIN) and intraductal papillary mucinous neoplasms (IPMN; ref. 8). Although low-grade PanINs are common, high-grade PanINs (PanIN-3, carcinoma *in situ*) are usually found in pancreata with an invasive pancreatic cancer and in high-risk individuals

screened for pancreatic neoplasia. PanINs are too small to be detected by pancreatic imaging, but thanks to better pancreatic imaging, IPMNs are increasingly diagnosed and treated. Removing IPMNs or widespread PanIN by pancreatic resection in patients with a strong family history of pancreatic cancer seems to prevent the development of pancreatic cancer (9, 10). The prevalence of detectable neoplasia identified by pancreatic screening depends on the risk of those being screened. Most screening programs target individuals aged ≥ 50 with multiple first-degree relatives with pancreatic cancer or *BRCA2/p16* and other germline mutation carriers with a family history of pancreatic cancer. Using endoscopic ultrasound as a screening tool, ~10% of individuals screened have prevalent IPMNs ($>1\text{cm}$ in diameter), and many also have suspected PanIN (10). Risk estimates and recent experience of screening indicate that individuals with less extensive family histories of pancreatic cancer probably have a sufficiently increased risk of pancreatic cancer to justify screening (Kurtz RC, Frucht H, et al., unpublished data; ref. 11).

What is the best early detection strategy? Initial results of the CAPS3 multicenter screening trial (NCT00438906)⁴ indicate that pancreatic cystic lesions are detected more often using endoscopic ultrasound and MRI than with CT (12). If the goal of early detection is the accurate detection

of preinvasive disease, then marker research should focus on markers of preinvasive disease. Research is attempting to identify markers in pancreatic fluid that could reliably identify high-grade PanIN (4). Because screening brings with it the risk of overtreatment, more controlled trials are needed to better determine the risks, benefits, and optimal approaches to pancreatic screening.

The available evidence indicates that the best way to prevent the development of pancreatic cancer and to identify early pancreatic cancer is to follow high-risk individuals with screening protocols. Investigating marker behavior in these high-risk groups is likely to be the best way to identify accurate markers of early pancreatic cancer that can improve the accuracy of pancreatic screening.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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⁴<http://clinicaltrials.gov/ct2/results?term=NCT00438906>