Researchers discover early indicators of pancreatic cancer

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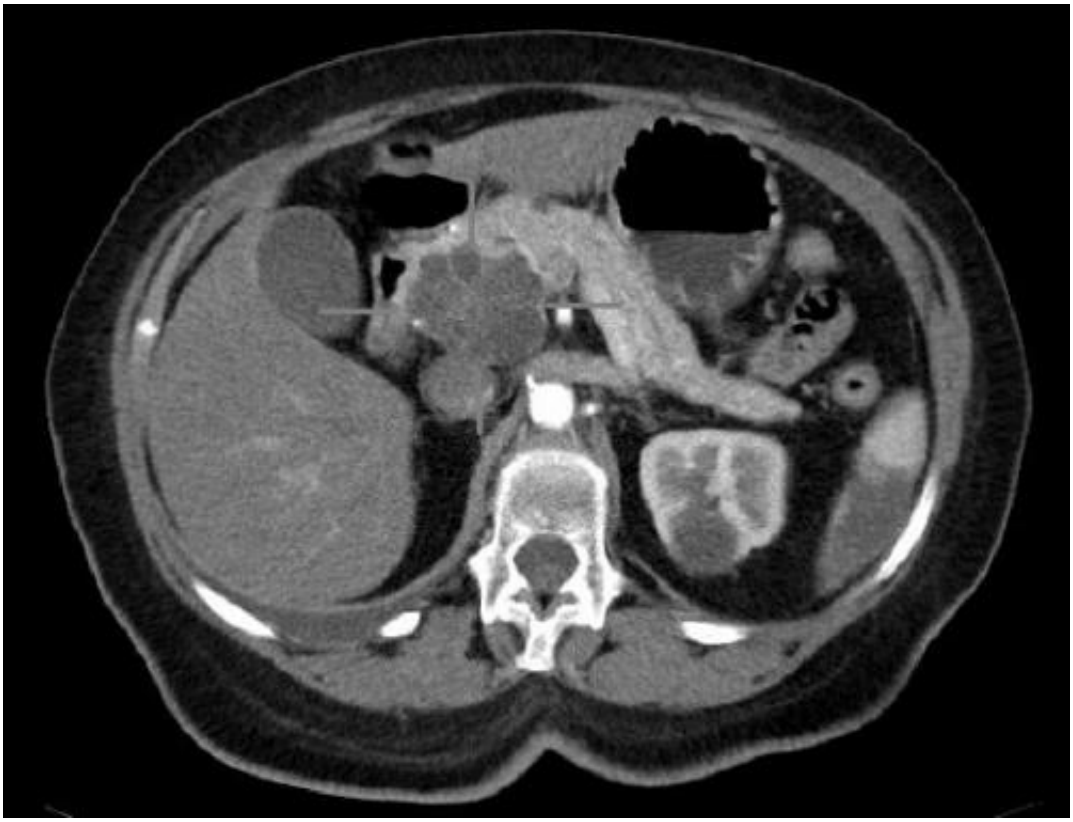

Axial CT image with i.v. contrast. Macrocystic adenocarcinoma of the pancreatic head. Credit: public domain

Pancreatic cancer, the fourth leading cause of cancer death in the United States, is often diagnosed at a late stage, when curative treatment is no longer possible. A team led by investigators at Beth Israel Deaconess

Medical Center (BIDMC) has now identified and validated an accurate 5-gene classifier for discriminating early pancreatic cancer from non-malignant tissue. Described online in the journal *Oncotarget*, the finding is a promising advance in the fight against this typically fatal disease.

"Pancreatic cancer is a devastating disease with a death rate close to the incidence rate," said co-senior author Towia Libermann, PhD, Director of the Genomics, Proteomics, Bioinformatics and Systems Biology Center at BIDMC and Associate Professor of Medicine at Harvard Medical School (HMS). "Because more than 90 percent of pancreatic cancer cases are diagnosed at the metastatic stage, when there are only limited therapeutic options, earlier diagnosis is anticipated to have a major impact on extending life expectancy for patients. There has been a lack of reliable markers, early indicators and risk factors associated with pancreatic cancer, but this new way of differentiating between healthy and malignant tissue offers hope for earlier diagnosis and treatment."

The investigators used a number of publicly available gene expression datasets for pancreatic cancer and developed a strategy to reanalyze these datasets together, applying rigorous statistical criteria to compare different datasets from different laboratories and different platforms with each other. The team then selected a subset of data for developing a panel for differentiating between pancreatic cancer and healthy pancreas tissue and thereafter applied this "Pancreatic Cancer Predictor" to the remaining datasets for independent validation to confirm the accuracy of the markers.

After demonstrating and independently validating that a 5-gene pancreatic cancer predictor discriminated between cancerous and healthy tissue, the researchers applied the predictor to datasets that also included benign lesions of the pancreas, including pancreatitis and early stage cancer. The predictor accurately differentiated pancreatic cancer, benign pancreatic lesions, early stage pancreatic cancer and healthy

tissue. The predictor achieved on average 95 percent sensitivity and 89 percent specificity in discriminating pancreatic cancer from non-tumor samples in four training sets and similar performance (94 percent sensitivity, 90 percent specificity) in five independent validation datasets.

"Using innovative data normalization and gene selection approaches, we combined the statistical power of multiple genomic studies and masked their variability and batch effects to identify robust early diagnostic biomarkers of pancreatic cancer," said first author Manoj Bhasin, PhD, Co-Director of bIDMC's Genomics, Proteomics, Bioinformatics and Systems Biology Center and Assistant Professor of Medicine at HMS.

"The identification and initial validation of a highly accurate 5-gene pancreatic cancer biomarker panel that can discriminate late and early stages of pancreatic cancer from normal pancreas and benign pancreatic lesions could facilitate early diagnosis of pancreatic cancer," said co-senior author Roya Khosravi-Far, PhD, Associate Professor of Pathology at BIDMC. "Our findings may open a window of opportunity for earlier diagnosis and, consequently, earlier intervention and more effective treatment of this deadly cancer, leading to higher survival rates."

The first diagnostic application of the panel may be for analyses of fine needle biopsies routinely used for diagnosing pancreatic cancer and for determining the malignant potential of mostly benign pancreatic cysts that can sometimes be precursors of pancreatic cancer. In addition to providing a new tool for diagnoses, the research may also lead to new insights into how pancreatic cancer arises.

"Because these five genes are 'turned on' so early in the development of pancreatic cancer, they may play roles as drivers of this disease and may be exciting targets for therapies," said Libermann. Most of the five

genes—named TMPRSS4, AHNAK2, POSTN, ECT2 and SERPINB5—have been linked to migration, invasion, adhesion, and metastasis of pancreatic or other cancers.

The scientists next plan to evaluate the precise roles of the five genes and to validate the accuracy of their diagnostic assay in a prospective clinical study. "Moving forward, we will explore the potential to convert this tissue-based diagnostic into a noninvasive blood or urine test," Libermann said.

"To further enhance the diagnostic power of this biomarker, we plan to expand it by including non-coding RNAs, proteins, metabolites and mutations associated with pancreatic cancer. This will result in development of the first of its kind biomarker that gauges pancreatic cancer alterations from multiple genomic angles for making highly accurate diagnoses," added Bhasin. Such an inexpensive and simple test could help transform the landscape of pancreatic cancer and help prevent many of the estimated 330,000 deaths that it causes worldwide each year.

Provided by Beth Israel Deaconess Medical Center