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Will Detection of MicroRNA Biomarkers in Blood Improve the Diagnosis and Survival of Patients With Pancreatic Cancer?

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Pancreatic cancer represents the 10th most commonly diagnosed cancer, but is the 4th leading cause of cancer-related death in the United States.[1] It is estimated that approximately 45 220 new cases of pancreatic cancer will be diagnosed and that 38 460 people will die of pancreatic cancer in the United States in 2013,[1] with an estimated 227 000 deaths from pancreatic cancer occurring worldwide each year.[2] The incidence of pancreatic cancer has been slowly increasing over the last decade.[2,3] The 1- and 5-year survival rates for pancreatic cancer are about 25%and 5%, respectively, which are the lowest survival rates of all major cancers.[1,3]

Exocrine tumors are the most common type of pancreatic cancer, representing about 95% of cases. Among exocrine tumors, pancreatic ductal adenocarcinoma (PDAC) that arises from pancreatic ducts accounts for about 80% of malignant tumors of the pancreas. Other exocrine pancreatic neoplasms include acinar cell carcinoma, intraductal papillary mucinous tumor, mucinous cystic tumors, and serous cystic tumors. Endocrine pancreatic tumors represent about 5% of cases and include islet cell and neuroendocrine carcinoma.

Most patients with pancreatic cancer present with advanced stage disease because patients with early-stage pancreatic cancer often do not have symptoms. Lack of appropriate markers for early diagnosis, dissemination to distant sites in early stages, and ineffective treatments for late stages of disease result in a poor prognosis for patients with pancreatic cancer.[2] Imaging techniques have poor sensitivity and specificity for the diagnosis of pancreatic cancer. Surgical resection is the only curative modality for PDAC, but less than 20% of patients have resectable localized disease at the time of diagnosis, and the 5-year survival rate after surgery is 20.7% for patients receiving adjuvant gemcitabine for 6 months, and only 10.4% for those who do not receive any adjuvant treatment.[4] Two new combination chemotherapy regimens (folinic acid, fluorouracil, irinotecan, and oxaliplatin; and albumin-

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bound paclitaxel plus gemcitabine) were recently approved for the treatment of metastatic PDAC and provide improved overall and progression-free survival.[5,6]

The clinical and histological similarities between pancreatic cancer and pancreatitis make early diagnosis difficult. Tumor markers for diagnosis of early pancreatic cancer are not available. The detection of pancreatic cancer– associated biomarkers in blood, serum, or plasma at an early stage offers the possibility for early diagnosis and an opportunity to reduce mortality from pancreatic cancer. Conventional serum biomarkers for PDAC include the cancer antigen 19-9 (CA19-9) and carcinoembryonic antigen; however, these tests have low sensitivity and specificity for early pancreatic cancer diagnosis.[7] A wide range of genetic alterations are associated with PDAC, including specific oncogenes and tumor suppressor genes.

Recently, microRNAs have been investigated as possible biomarkers for pancreatic cancer. MicroRNAs are small, noncoding, single-stranded RNAs consisting of 18 to 24 nucleotides that regulate their target genes at the messenger RNA level, and promote oncogenesis by either inhibiting expression of tumor suppressor genes or upregulating expression of oncogenes.[8] MicroRNAs play a role in pancreatic cancer pathogenesis, progression, and metastasis, and their differential expression has been associated with patient survival.[8,9] MicroRNAs are stable molecules expressed in serum and plasma that can be readily detected by various assays. Some reports suggest a differential expression of microRNAs in PDAC cell lines, tissues, and in the circulation; some microRNAs were down-regulated, whereas others were strongly up-regulated compared with normal cells and normal pancreas tissue cells.[9] Combining the results of circulating microRNAs with CA19-9 has been investigated for the diagnosis of pancreatic cancer.[10] A few studies have investigated microRNA changes associated with precursor pancreatic intraepithelial neoplasm lesions and PDAC progression.[8,9,11]

In their study in this issue of *JAMA*, Schultz and colleagues[12] investigated the diagnostic value of detection of multiple serum micro RNAsin patients with histologically verified PDAC. Critical to the utility of this approach is the ability to distinguish between PDAC and other chronic diseases of the pancreas, in particular pancreatitis.

The authors evaluated 409 patients with pancreatic cancer and 25 patients with chronic pancreatitis included prospectively in the Danish Biomarkers in Patients with Pancreatic Cancer (BIOPAC) study from July 2008 to October 2012. Three hundred twelve healthy blood donors were included as controls (healthy participants).The blood samples were all pretreatment samples taken from patients undergoing surgery for resectable disease (n = 44) and before chemotherapy for patients with unresectable disease (n = 365). The expression of 754microRNAs was investigated in the discovery cohort (143 patients with pancreatic cancer, 18 patients with chronic pancreatitis, and 69 healthy participants).

Multivariable analysis showed that 38 microRNAs had the potential to differentiate pancreatic cancer cases from healthy participants and from patients with chronic pancreatitis. Nineteen of 36 microRNAs (2 were undetectable) selected from the discovery cohort were validated by a different method of detection in the training cohort (180 patients

with pancreatic cancer and 199 healthy participants). Based on the results in the training cohort, 2 diagnostic indices (index I, composed of 4 microRNAs; and index II, composed of 10 microRNAs) were developed. In addition, 10 of 13 microRNAs that met the .05 significance level in both the discovery and training cohorts were measured in the validation cohort (86 patients with pancreatic cancer, 7 patients with chronic pancreatitis, and 44 healthy participants) and 10 microRNAs met the significance criteria of $P < .05$ in the final validation.

Both diagnostic indices (index I area under curve [AUC] of 0.88; index IIAUCof0.92) performed better than serumCA19-9 (AUC, 0.87) in the discovery cohort. Index II (AUC, 0.93) also performed better than CA19-9 (AUC, 0.90) in the training cohort, although the CA19-9 (AUC, 0.89) performed better than the indices (index I AUC of 0.83; index II AUC of 0.81) alone in the validation cohort. Importantly, in all 3 cohorts, the combination of CA19-9 with either index I or index II was associated with increased AUC compared with serum CA19-9 (discovery: AUC of 0.88 for CA19-9 plus index I and AUC of 0.95 for CA19-9 plus index II vs AUC of 0.87 for CA19-9 alone; training: AUC of 0.93 and 0.97 vs 0.90; validation: AUC of 0.93 and 0.92 vs 0.89).

It would have been helpful if an additional method of detection of microRNAs (eg, NanoString or sequencing) had been used to confirm the validity of the findings in the discovery, training, and validation cohorts and to avoid biases due to the techniques used. Despite the modest improvements in AUC, the data reported in the study by Schultz et al[12] did not demonstrate that the microRNA signatures provided clinically significant information over serumCA19-9.Eventhoughthe study was relatively large, well-conducted, and addressed the important topic of development of noninvasive methods to detect pancreatic cancer, the authors appropriately acknowledge the exploratory nature of the investigation. Further research is necessary to understand whether the microRNA signatures have clinical implications for the early detection of pancreatic cancer and whether this information adds substantially to serumCA19-9.

An important limitation of the study is that the control participants were younger than the patients with pancreatic cancer. It is likely that microRNA expression and appearance into the blood is affected by aging.[13] Thus, the control group was not ideal, as recognized by the authors. In addition, blood cells of different lineages are present in blood in addition to the liquid component. The patterns of their microRNA expression can differ depending on the lineage and stage of differentiation and such patterns may change during aging.[13] Thus, the decision to detect microRNA dys-regulation in whole blood may complicate interpretation of the data.

This exploratory and novel study by Schultz et al[12] suggests that microRNA signatures in whole blood could provide biomarkers for the detection of pancreatic cancer. Given the dismal prognosis for patients with pancreatic cancer, it is important that new diagnostic approaches, such as the one used in this study, are sought. However, additional rigorous investigation will be necessary to support and extend these interesting findings.

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