Biomarker panel to screen for pancreatic cancer may be possible

June 19 2012

The development of a highly accurate, blood-based pancreatic adenocarcinoma screen that would be accurate enough to test the general population for this deadly disease may not be far out of reach, according to data presented at the American Association for Cancer Research's Pancreatic Cancer: Progress and Challenges conference, held here June 18-21, 2012.

Matthew Firpo, Ph.D., a research assistant professor at the Huntsman Cancer Institute at the University of Utah, came to the conclusion that screening a panel of biomarkers might be effective by embracing the idea that pancreatic adenocarcinoma has vast genetic heterogeneity, meaning no single biomarker exists that is strongly correlated with its diagnosis across the population of people who develop the disease.

Although it is widely accepted that earlier detection of pancreatic adenocarcinoma would improve survival outcomes, research efforts to date have been unsuccessful at identifying a biomarker or biomarker panel that has a high diagnostic sensitivity.

"Any tool that we deploy in the general population to screen for this disease would have to be very accurate," Firpo explained. "Because this cancer is rare, if everyone older than age 50 in the United States was screened with a test that was only 95 percent accurate, we would have more than three million people each year with a false positive identification of pancreatic adenocarcinoma."

Therefore, Firpo said that any test for pancreatic adenocarcinoma deployed to the general population must have an accuracy of greater than 99 percent. To see if such levels of accuracy were possible, the researchers measured the levels of nine biomarkers of pancreatic adenocarcinoma in the blood of 117 healthy control participants, 58 participants with chronic pancreatitis and 159 patients with pancreatic adenocarcinoma.

Using a statistical model, they determined that many of these weak biomarkers present in those patients with pancreatic adenocarcinoma had 95 percent specificity for the disease, but, on average, only a 32 percent sensitivity.

"Based on the data, and specifying 99 percent specificity, it would take a panel of 40 biomarkers with 32 percent average sensitivity each and 95 percent specificity, of which seven biomarkers were above this threshold," Firpo said.

The key to the study, according to Firpo, is accepting the fact that pancreatic adenocarcinomas are genetically heterogeneous. By developing a model that accounted for the heterogeneity they were able to get over 99 percent accuracy.

"Identifying 40 biomarkers is reasonable. We believe we can find 40 biomarkers that are weak classifiers of the disease," he said. "That means that based on the current understanding of biomarkers that we have, there is hope for developing a panel that would have greater than 99 percent accuracy."

Firpo said that the next step is to systematically identify 40 to 50 biomarkers that have these characteristics — 32 percent sensitivity and 95 percent specificity — or better.

More information:

Abstract

Prospects for developing a biomarker panel for accurate detection of pancreatic adenocarcinoma. Matthew A. Firpo, Kenneth M. Boucher, Sean J. Mulvihill. University of Utah, Salt Lake City, UT

Most patients with pancreatic adenocarcinoma (PA) present after the disease has advanced to an incurable stage. Screening for PA would likely improve outcomes through earlier detection, but could result in unacceptable levels of false-positive diagnoses using current biomarkers. Recent efforts to identify individual biomarkers or biomarker panels have been disappointing. Furthermore, it is unlikely that an individual biomarker will provide sufficient accuracy for detection of PA given the high amount of molecular heterogeneity in the disease. We propose a novel, intuitive panel design that allows for diverse biomarker selection for accurate diagnosis. Using characteristics of nine PA biomarkers measured in human sera to model the behavior of biomarker panels, we delineate the number of biomarkers required for accurate detection of PA in our panel design.

Levels of AXL, CA 19-9, haptoglobin, hyaluronic acid, MMP-7, MMP-11, osteopontin, serum amyloid A, and TIMP-1 were measured in sera from 117 healthy control subjects and 58 chronic pancreatitis patients, and 159 PA patients prior to treatment.. Threshold indicators were constructed for individual biomarkers at the 95th percentile of the control value. We modeled the behavior of a biomarker panel consisting of a sum of indicator variables, then chose a cutoff for the sum to force specificity to be high, and calculated the resulting sensitivity. To generate correlated biomarkers, we simulated correlated continuous biomarker data, made a 95th percentile cutoff for each biomarker, and then assessed performance as above.

Between 17% and 75% of the PA cases had values above the 95th percentile of control values with an average sensitivity for all biomarkers of 32%. The correlation between the indicator variables was near zero in controls and slightly positive in PA cases. None of the biomarkers were highly correlated. The model shows that a panel consisting of 40 biomarkers characterized individually by 32% sensitivity at 95% specificity would require any 7 biomarkers to be above the threshold and would result in a panel specificity and sensitivity of 99% each. The addition of correlation assumptions reduced sensitivity for the 40 biomarker panel to 94% at an average correlation of 0.05 and 84% at an average correlation of 0.15.

Our modeling shows that a highly accurate, blood-based PA diagnostic panel can be developed from a reasonable number of individual serum biomarkers that are relatively weak classifiers when used singly. The model provides a framework for maximizing biomarker sensitivities and minimizing biomarker correlation. A panel constructed as described is advantageous in that a high level of specificity can be forced and allows for heterogeneity among patients and their tumor characteristics.

Provided by American Association for Cancer Research