Increased Levels of Select Plasma Proteins Predict Colorectal Cancer Diagnosis

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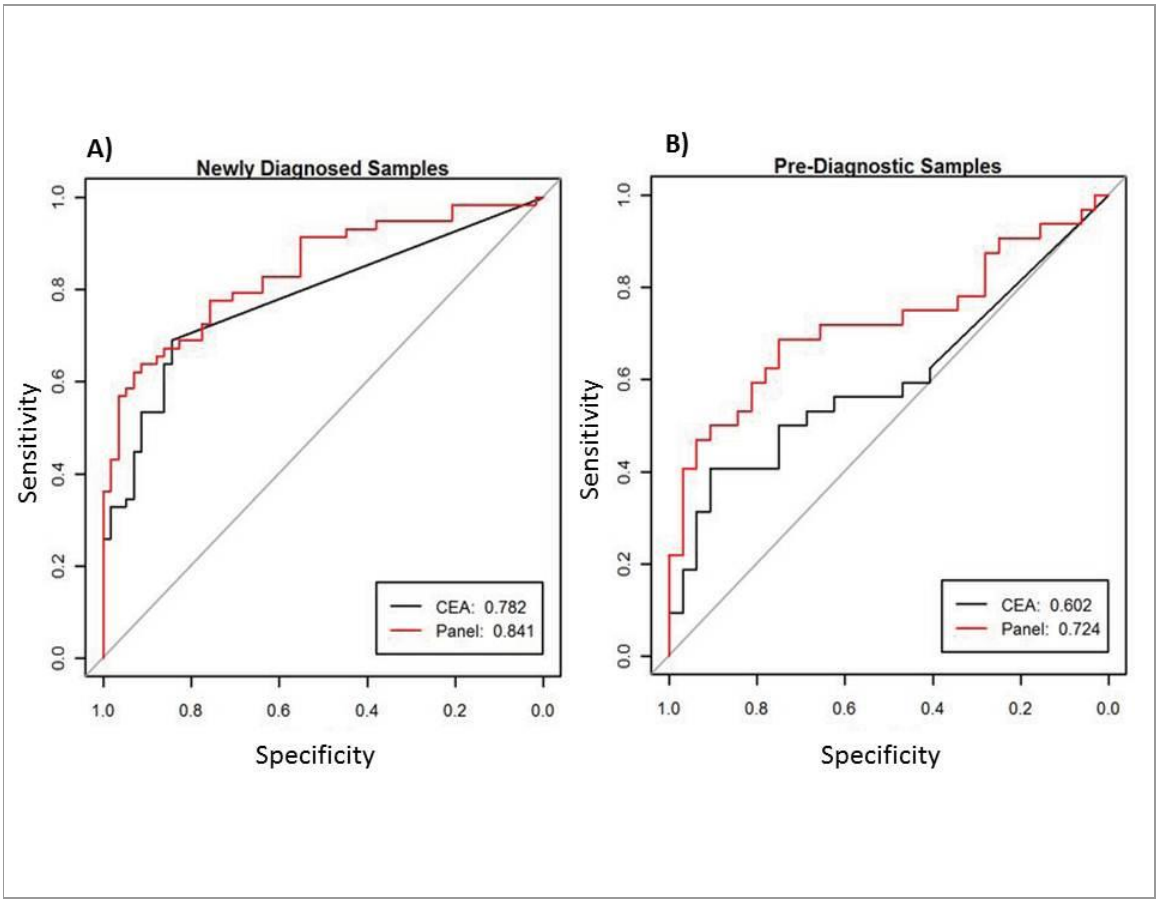
Carcinoembryonic antigen (CEA) is a tumor marker that is positively associated with poor colorectal cancer prognosis. Preoperatively, high serum CEA suggests advanced disease, while high CEA during postoperative follow-up strongly suggests recurrence. Unfortunately, CEA lacks the sensitivity and specificity necessary to be used as a diagnostic marker. Yet, the ease of sampling plasma makes it an attractive method for colorectal cancer screening and highlights the value in identifying additional serum markers that could be used to replace or augment CEA measurement.

In an effort to identify such plasma biomarkers, postdoctoral fellow Dr. Jon Ladd, Public Health Sciences Division, and several Center colleagues recently used stored samples from the Women's Health Initiative (WHI) cohort to determine quantitative differences in plasma proteins between subjects subsequently diagnosed with colorectal cancer and matched controls who remained cancer free throughout the study period. An intact protein analysis system (IPAS) was initially applied to plasma samples from 90 WHI participants diagnosed with colon cancer within 18 months following blood draw and 90 matched controls. Six proteins with significantly ($p<0.05$) elevated concentrations in cases compared to controls were identified (microtubule-associated protein RP/EB family member 1, MAPRE1; insulin-like growth factor binding protein2, IGFBP2; alpha enolase, ENO1; protein disulfide-isomerase A3, PDIA3; mesencephalic astrocyte-derived neurotrophic factor, ARMET; and leucine-rich alpha-2-glycoprotein, LRG1). Subsequent proteomic analysis in two different colorectal cancer cell lines confirmed that 5 of the 6 proteins were produced by cancer cells (MAPRE1, IGFBP2, ENO1, PDIA3 and ARMET). Enzyme linked immunosorbent assays (ELISA) were available for three identified proteins (IGFBP2, LRG1 and MAPRE1), which were assayed together with CEA in plasma samples from 58 newly diagnosed male and female patients and 58 matched controls collected at the University of Michigan. All four of the assayed proteins were significantly elevated >1.5 fold in cases compared to controls. Sensitivity and specificity analyses revealed that a panel of all four markers yielded the greatest accuracy (59% sensitivity at 95% specificity), a 23% increase over CEA alone. Finally, for validation, the panel of CEA, IGFBP2, LRG1 and MAPRE1 was evaluated using an independent set of prediagnostic WHI plasma samples, where this panel yielded 41% sensitivity at 95% specificity, compared with just 19% sensitivity for CEA alone.

Although currently available screening methods have led to a drop in colorectal cancer mortality, approximately 60% of U.S. adults 50 years and older are still not screened at recommended intervals. The predictive value of a panel of CEA, MAPRE1, IGFBP2 and LRG1 proteins in pre-diagnostic colorectal cancer plasma samples suggests that a blood-based test to aid in colorectal cancer screening could become a reality in the not too distant future.

Ladd J, Busald Buson T, Johnson M, Zhang Q, Pitteri SJ, Wang H, Brenner DE, Lampe PD, Kucherlapti RS, Feng Z, Prentice RL, Hanash SM. 2012. Increased plasma levels of the APC-interacting protein MAPRE1, LRG1 and IGFBP2 preceding a diagnosis of colorectal cancer in women. *Cancer Prevention Research* doi:10.1158/1940-6207.CAPR-11-0412.



Adapted from Ladd et al. (2012).

Figure. A) receiver operating curve (roc) analysis of a linear combination of four protein markers (IGFBP2, LRG1, MAPRE1, CEA) compared to cea in newly diagnosed samples; B) roc analysis of the same linear combination of four protein markers compared to CEA in pre-diagnostic samples.