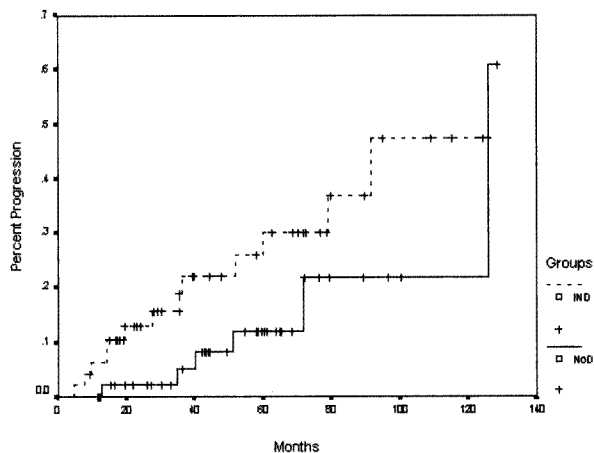


comparing progression to any grade of neoplasia and advanced neoplasia (HGD or CRC). Results: We identified 48 pts with IND and found 48 matched NoD controls. 13 of 48 IND pts (27%) progressed to neoplasia: 9 LGD, 3 HGD and 1 CRC. Mean follow-up (f/u) was 54 months; only 1 pt progressed within 12 months of initial IND finding. In the NoD cohort 6 of 48 (13%) pts progressed: 1 HGD, 0 CRC; mean f/u was 53 months. On an actuarial basis, 5-yr progression to neoplasia was 30% for IND and 12% for NoD; this difference was significant ($p=.04$) by life table analysis. (Figure) The difference in 5-yr progression to advanced neoplasia (12% and 0%) was not significant. Conclusions: Compared to patients who are free of dysplasia, a finding of IND was associated with a higher rate of progression to neoplasia. The optimal interval for surveillance examinations is not known, but our data support the practice of following patients with IND more closely.

Figure 1: Progression to Dysplasia



W1333

Fiberoptic In-Situ Detection of Dysplastic Polyps in *Apc^{min/+}* Mice Using Autofluorescence

Bhaskar Banerjee, Nicholas O. Davidson, Jeffrey O. Henderson

There is intense interest in the potential applications of non-invasive cytological and spectroscopic methods to detect early changes in the growth and malignant potential of luminal gastrointestinal tract tumors. One such method employs tissue autofluorescence. However, a significant limitation to the use of conventional tissue autofluorescence is its imprecision at longer wavelengths (450-650 nm) and reliance upon complex calculations. We have optimized a simpler method that uses autofluorescence of shorter wavelengths, in the range of 320-340 nm, to study cellular autofluorescence in dysplastic intestinal polyps in *Apc^{min/+}* mice, a robust model of adenomatous polyposis, using a small, portable fiberoptic device containing a Xenon lamp. *Apc^{min/+}* mice were sacrificed at 115 days, the intestines washed and placed mucosal side up on a matte black surface. A two-way fiberoptic probe recorded autofluorescence and the intensities were normalized to the fluorescence intensity from normal mucosa to derive an autofluorescence intensity ratio (AIR). Three readings were recorded at each site. Serial recordings of autofluorescence were made at ~1 cm intervals along one intestinal segment that contained 3 polyps. All intestinal samples were microscopically confirmed adenomas. A total of 69 polyps were studied in 11 mice; 63 were in the small intestine and 6 in the colon. The mean autofluorescence intensity ratios \pm SD for small intestinal polyps was: 1.22 ± 0.14 ($p < 0.0001$). For colonic polyps, the AIR \pm SD was 1.28 ± 0.11 ($p = 0.0016$). The sensitivity was 96%. Measurements of AIR along the length of an intestinal segment correctly identified 3 polyps from the surrounding normal mucosa. The findings demonstrate that the mean AIR was significantly higher in polyps of the small intestine and colon compared to normal mucosa. Unlike other methods, the intensity of this autofluorescence band, which is produced by alterations in cellular tryptophan abundance, increases with neoplasia and requires simple measurements without complex spectral analysis. In conclusion, fiberoptic measurement of autofluorescence accurately detects in-situ intestinal dysplasia and may be adapted to real time detection and analysis of precursor lesion development.

W1334

SELDI-TOF-MS Profiling of Serum for Early Detection of Colorectal Cancer

Richard R. Drake, Ender Manne, Bao-Ling Adam, Christina Ahn, Lisa Cazares, O. J. Semmes, William L. Bigbee, William E. Grizzle, David A. Johnson

PURPOSE: The etiology of colorectal cancer (CRC) favors an early detection strategy, thus the objective of our study is to identify a panel of multiple protein biomarkers in patient serum for early detection of CRC using SELDI-TOF-MS proteomic technologies. METHODS: The SELDI-TOF-MS (Surface Enhanced Laser Desorption/Ionization Time of Flight Mass Spectrometry) ProteinChip from Ciphergen Biosystems Inc. allows differential capture and protein profiling of biological mixtures. Serum samples from patients with sporadic colon cancer (pre-treatment, $n = 20$), healthy individuals and patients with benign colon diseases ($n = 14$), and patients with adenomatous polyps ($n = 6$) were processed for SELDI-TOF-MS analysis. Specimens were applied in duplicate to a Bioprocessor containing IMAC3-copper ProteinChip arrays. All loading and processing steps were automated using the Biomek 2000 robot. Clustering and classification analyses were performed using the Ciphergen Biomarker Wizard and Biomarker Patterns software packages, respectively. RESULTS: In the cross-validation analysis, colon cancer was predicted with sensitivities of 91-95% and

specificities of 80%-95% relative to healthy control sera or sera from patients with benign colon disease. Classification trees were generated utilizing multiple protein peaks in the mass range of 2-8 kDa. Sera from patients with adenomatous polyps were classified into both control and cancer groups. CONCLUSIONS: These initial results support the potential of this approach as an adjunct diagnostic tool for early detection of colon cancer. We are currently validating this system by processing a larger number of samples and also evaluating additional artificial intelligence/learning algorithms for the analysis of the profiling data. Supported by the National Cancer Institute Early Detection Research Network.

W1335

Analysis of mRNA Expression Profiles in Colorectal Adenomas Using K-Nearest Neighbor Cluster Analysis

Lawrence C. Lapointe, Graeme P. Young, Howard M. Chandler

BACKGROUND: Several studies have explored gene expression profiles in cancer tissues using commercially available DNA microarrays. Studies have also shown that cluster analysis techniques can be used to analyze gene expression profiles that are discriminating between normal tissues and colon cancer tissues. To be clinically useful as screening tools, these techniques must be directed toward discovering the earliest, treatable stages of clinical disease and not the late stage invasive cancers. AIM: To determine if cluster analysis can be used to identify mRNA markers that are predictive for colorectal adenomas from quantitative expression profile data. METHOD: Candidate mRNA markers for adenomas were identified by differential display and quantified using quantitative RT-PCR relative to normal tissues. The expression levels of these markers were measured in 71 tissue samples (21 normal, 20 tubular adenoma, 26 tubulovillous adenoma, and 4 villous adenoma). Expression levels were analyzed using cluster analysis based on the k-nearest neighbor (KNN) technique. This method classifies a given tissue (X) according to the class membership of the k tissues nearest to (X) in n-dimensional space described by the mRNA expression levels for a given set of markers. Tissues were considered unclassified if analysis of the k-nearest neighbors tissues failed to achieve a unanimous result, where $k = 3$ for this study. The strength of each set of markers for predicting disease state was measured by comparing the cluster analysis solution to pathology results. RESULTS: Cluster analysis showed that no combination of the markers achieved perfect classification of all 71 Normal and Adenoma tissues. However, near perfect discrimination (98.6%, 70/71) can be achieved for one set of three markers and six unique sets of four markers. In nearly all strong marker sets (6/7) the same normal tissue was incorrectly classified as adenomatous. CONCLUSIONS: Cluster analysis using the k-nearest neighbor technique is useful for identifying expression profiles that can correctly discriminate between adenomatous and normal tissues. Further, expression profiling using this technique may identify tissues that are judged 'normal' by histopathology but exhibit mRNA expression profiles that are predictive for precancerous genomic changes.

W1336

Efficacy and feasibility of Colonoscopy Screening in increased risk subjects for Colorectal Cancer: our experience after 22 months of activity

Vincenzo Matarese II, Alessandro Pezzoli, Lucio Trevisani, Giuseppina Marangoni, Viviana Cifala, Caterina Rizzo, Sergio Boccia, Sergio Gullini

Aim: The district of Ferrara has one of the highest incidence of colorectal cancer (CRC) in Italy. Since January 2000 we have started a colonoscopy (C) screening program focused on first degree relatives of CRC patients. We now report the result after 22 months of this screening. Patients and Methods: Subjects included in the screening program aged between 45-75 yr with at least one first-degree relative with CRC. When C was refused, barium enema or fecal occult blood test were suggested. Demographic features are: 205 males and 254 females. Age range 57.3 years. 351 participants had one parent, 104 one brother and 4 one son affected by CRC. Of these participants 65 (14.1%) had two first degree relatives affected by CRC. Results: From January 2000 to October 2002, 459 subjects were interviewed. In the screening we enrolled 451 subjects (98.2%); 8 (1.7%) people refused the option screening, 16 (3.5%) subjects chose to perform the barium enema and 10 (2.2%) fecal occult blood test: all had negative findings. 425 agreed to undergo endoscopic examination (92.6%); 373 C have been already performed (52 are scheduled). Adenomas and carcinoma (Dukes A) were found in 88 (24%) subjects and 3 (0.8%) subjects respectively. Histological examination of the 123 lesions found (32.9%), showed: 32 hyperplastic polyps (26%), 60 tubular adenomas (48.8%), 21 (17.1%) tubulovillous (two of them surgically treated), 7 (5.7%) with severe dysplasia and 3 adenocarcinoma (2.4%). Multiple adenomas were found in 26 (28.5%), and in 36 (39.5%) the diameter was > 1 cm. Cecum was reached in 85% of the endoscopic examinations. Sedation was used in only 21 colonoscopies (5.6%). One perforation related to polypectomy (0.3%) was observed. Conclusions: A C-based screening in selected high risk populations is well accepted (92.6% of attendance rate to C) even without sedation and relatively safe. Our results confirm a high prevalence of advanced neoplasm and early colon cancer in first degree relatives of CRC patients.

W1337

Detection of COX-2 Messenger RNA in Feces Is Beneficial for Colorectal Cancer Screening

Shigeru Kanaoka, Ken-Ichi Yoshida, Mutsuhiro Ikuma, Naoyuki Miura, Haruhiko Sugimura, Masayoshi Kajimura

Background: Fecal occult blood test (FOBT) has become an accepted technique of noninvasive screening for colorectal tumors, but lack of both sensitivity and specificity remains a problem. Early clinical studies with multi-target DNA-based stool assay suggest high sensitivity for colorectal cancer (CRC) while maintaining high specificity; however, clinical study with RNA-based stool assay for colorectal cancer has not been reported. We aimed to develop RNA-based stool assay for CRC detection with high sensitivity and specificity. We picked COX-2 because it is overexpressed in most CRC, it theoretically provide an optimal molecular marker for detecting CRC. Methods: Standard histological techniques were used to stage