

Editorial

Developing Sensitive and Specific Diagnostic Screening Markers for Colon Cancer

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Mortality and morbidity from colon cancer represent a major health problem involving a malignant disease that is theoretically preventable through screening. Early detection would be greatly enhanced if accurate, practical and cost effective diagnostic biomarkers for this malignancy were available. Current screening methods (*e.g.* fecal occult blood test, FOBT) lack sensitivity, are costly, with side effects and have low compliance, or may result in mortality (*e.g.* colonoscopy).

A lengthy period of ~20 years is required for colon cancer to develop; therefore, an effective adenoma screening test needs to be performed less frequently than a test for early cancer. However, because only small minorities of adenomas are destined to progress to malignancy, their detection would involve gross overtreatment of patients, which would be costly and harmful to them. An optimal colon cancer screening test would be one that accurately detects advanced adenomas with a high chance of malignant progression. Clinical management of adenomas entails removing them at the time of detection by colonoscopy. However, many eligible patients do not wish to undertake such an expensive and invasive test because of the need for bowel preparation, dietary restrictions, abdominal pain, potential perforation of the colon and even death. Given the desirability of using a noninvasive test acceptable to the target population as an initial screen, investigators have resorted to developing molecular approaches. Important considerations for developing sound tests include: nature of the specimen (invasive *versus* non-invasive), type of specimen (stool, blood, or any other body excretory/fluid), stability of specimen when handled outside the body, number of collected specimens (one sample, or multiple samples over consecutive dates), and how the specimens are stored and delivered (room temperature or frozen, posted or collected, *etc.*). Processing of samples must also be accepted by the laboratory staff. Any test that can be automated and eventually placed on a chip would be easier, more acceptable to those performing the assay, and cheaper to apply on a large scale.

In developing countries where colon cancer is on the rise due to adoption of a Western-type diet rich in energy (fats and carbohydrates) and low in essential nutrients (vitamins and minerals), the problem is more severe, as the cost of colonoscopy often exceeds a person's yearly salary, and there are not enough

trained gastroenterologists (GIs) or adequate centers to perform these tests. Our data have shown that quantitative changes in the expression of a few micro(mi)RNA genes in non-invasive stool [1], or minimally-invasive blood [2] that are associated with colon cancer permit development of more sensitive and specific molecular markers than those currently available for a type of cancer that is deadly if not diagnosed before metastasis. A miRNA approach in stool could particularly meet the criteria for test acceptability as it is noninvasive, requires at most 1 g of stool, results for stool are comparable to those for colon tissue, sampling on consecutive dates is not required, samples can be sent by mail in cold packs, the method is able to differentiate between normal tissue and colon adenomas/carcinomas, has high sensitivity and specificity of detecting advanced polyps, and can be automated, which makes it relatively inexpensive and more suited for early detection when compared to a test such as that for mutated DNA markers.

An approach using miRNAs, which are relatively nondegradable when extracted from stool or blood by commercially available kits and manipulated thereafter, would be preferable to a transcriptomic messenger (m)RNA-, mutation DNA-, epigenetic- or a proteomic-based test. If performance criteria are met, a non-invasive miRNA test in stool based on high throughput automated technologies and quantitative expression measurements commonly used in the diagnostic clinical laboratory should be advanced to the clinical setting and will make a significant impact on colon cancer prevention by improving the noninvasive detection of this preventable disease, particularly at early TNM stages (0-I).

The market availability of powerful highthroughput approaches for global miRNA characterization, such as microarrays and simpler, universally applicable quantification assays for miRNA expression such as qPCR, suggests that the validation pipeline that often encounters bottlenecks would be more efficient for a miRNA assay. Eventually, these validated tests can be placed on chips for a more convenient testing, as has been carried out in the detection of genetically modified organisms (GMOs) in food.

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