How can I be sure I’m using the most comprehensive noninvasive screening for colon cancer risk?

**Calprotectin**

A guaiac-based fecal occult blood test (FOBT) is commonly used as a noninvasive screening tool for colon cancer. However, the sensitivity of this test may be as low as 26%. This means that as many as 74% of patients with malignant lesions could remain undetected if only this screening method is used. Moreover, because FOBT depends on the detection of blood in the stool, it may not be effective for detecting precancerous adenomas that do not bleed. In addition, the test requires that patients collect at least 3 (or as many as 6) specimens and follow numerous dietary restrictions in order to obtain reproducible results.

Calprotectin, a neutrophil-derived protein that can be measured in stool, dramatically increases a clinician’s ability to noninvasively detect colorectal cancer (CRC). Calprotectin enters the bowel lumen as part of an inflammatory process rather than through bleeding. Calprotectin levels are believed to increase in CRC in response to white blood cell infiltration of the tumor with subsequent shedding into the lumen. This may explain the marker’s heightened sensitivity in detecting CRC.

Tibble et al. have shown that the sensitivity of calprotectin to detect CRC is 90%, compared to 58% for FOBT. This study also found that the sensitivity of calprotectin to identify adenomas was 55%, compared to only 10% for FOBT. For detecting all significant colorectal diseases, specificities of calprotectin and FOBT were 84% and 97%, and sensitivities were 77% and 39%, respectively. When only malignancy and polyps were considered, researchers calculated a sensitivity of 79% for calprotectin and a sensitivity of 43% for FOBT.

Another trial reported that calprotectin exhibits a sensitivity of 87%-98% for symptomatic CRC and 64%-82% for asymptomatic CRC, when a cut-off value of 50 mg/g is used. The same group of investigators demonstrated significantly elevated calprotectin levels in patients with multiple adenomas or adenomas with high-grade dysplasia.

Tracking patients with clinically verified CRC before and after resection, another study found that calprotectin concentrations did not differ significantly according to tumor stage, size, or localization, although levels did tend to be lower in Duke’s stage A compared to stages B, C, or D. The authors did discover a significant difference in calprotectin levels measured before and after resection, however, indicating that the presence of CRC was the main reason for increased levels. Although their data were not sufficient to support general recommendations for widespread periodic surveillance of CRC using fecal calprotectin, this may be a potentially important clinical application for this sensitive noninvasive marker.

In summary:

- Calprotectin is a more sensitive marker of CRC than FOBT
- Calprotectin is stable in stools and subject to less variation
- Calprotectin is elevated in patients with colorectal adenomas
- Calprotectin may be a useful screening tool especially in a high-risk population
Beta-glucuronidase
Several studies have correlated excessive beta-glucuronidase activity with increased risk of colon cancer. Both the incidence of colon cancer and levels of beta-glucuronidase tend to be higher in individuals consuming a western diet compared with individuals on high-fiber, low-saturated fat diet. Beta-glucuronidase appears to reflect microbial activity that can stimulate the biological activity of many exogenous and endogenous toxic or carcinogenic compounds, thus increasing colon cancer risk.

Other studies have established a more definitive link between colon cancer and enzyme activity. Kim et al. observed that the fecal beta-glucuronidase levels in colon cancer patients were 12.1 times higher than that of healthy controls, and concluded that excessive beta-glucuronidase activity is a primary factor in the etiology of colon cancer. Furthermore, beta-glucuronidase expression has been found to correlate with the degree of invasiveness of colorectal carcinoma cells, in vitro.

Monohaem®
MonoHaem® uses monoclonal antibody technology to detect fecal occult blood. Unlike other prominent FOBTs, MonoHaem® is specific for human hemoglobin, and does not require that patients follow dietary restrictions prior to testing.

Using monoclonal antibody technology, FOBT is an effective, noninvasive screening method for CRC. A study of 611 subjects found that MonoHaem® identified 91.4% of colon cancer cases, with a false-positive rate of only 8.1%. In the same study, Hemoccult® identified 66% of colon cancer cases, with a 16% false positive rate.

Furthermore, a meta-analysis of four randomized controlled trials concluded that FOBT reduced mortality from CRC by up to 23%. Many cancers develop from adenomatous polyps, so detection and removal of polyps should reduce mortality. However, polyps commonly do not bleed, making FOBT an unsuitable screen for this pathology. In these cases, other noninvasive tests such as calprotectin may be more appropriate.

n-Butyrate
Butyrate is the most important short chain fatty acid (SCFA) for the colon, acting as a preferred substrate for colonocytes and assisting in the maintenance of colonic integrity. Butyrate helps prevent colon cancer by stimulating cellular differentiation and apoptosis, inhibiting the growth of transformed cells, stabilizing DNA, and repairing damage. By decreasing the pH in the colonic lumen, butyrate also indirectly inhibits the conversion of primary bile acids to secondary bile acids. Increased fecal excretion of secondary bile acids is strongly associated with elevated colon cancer risk. Finally, butyrate reduces the exposure of the colonic mucosa to ammonia by redirecting ammonia into bacterial protein synthesis and reducing colonic pH. Ammonia has been implicated in the pathogenesis of colon cancer.

Stool pH
A large body of literature has reported an association between high colonic (or stool) pH and increased risk of colon cancer. There are a number of potential mechanisms noted, including the need for SCFAs to be uniformly distributed throughout the entire colon (low pH) to optimize cellular turnover and differentiation. Bile acids are also degraded more or less efficiently depending on stool pH; the lower the pH the greater the inhibition of secondary bile acid formation, which is a key factor in development of colon cancer. Extremes of transit time (constipation or diarrhea) are also likely to influence stool pH, with faster transit times tending to result in a lower pH.
How do I order this test?

For CDSA 2.0 test kits, Interpretive Guidelines or information, please call a GSDL Accounts Receivable representative at 888-201-8333 or use our secure web contact center at www.gsdl.com/billing.

References