

Hold out your finger

By SYLVIA WROBEL • Illustration by SARA CUMINGS

Biomarker—any biologic measurement that correlates with the risk of getting a disease (for example, elevated cholesterol for heart disease), with disease progression (such as rising levels of prostate specific antigen for prostate cancer), with exposure to something that may affect the risk of getting a disease (blood cotinine levels to assess amounts of exposure to second-hand cigarette smoke).



Robin Bostick wants to do for colon and rectal cancer what earlier scientists did for heart disease. He is working to develop a simple blood test to detect biomarkers of risk that can be treated before disease occurs. The epidemiologist already has identified biomarkers that predict colon cancer in apparently healthy people. And he has evidence that some of these can be modified in as little as six months with supplemental calcium.

But does altering the biomarkers of risk alter the risk itself? Bostick believes it does. He is studying more than 1,300 people to see if calcium and vitamin D will alter the biomarkers and prevent the recurrence of colon polyps, a precursor to colon cancer. His findings could change dramatically the screening for and prevention of colon and other cancers.

The parallel with heart disease

After decades of research, biologic measurements of risk for developing cardiovascular disease have become a standard part of medical exams. Cholesterol, blood pressure, blood sugar, and body size/shape are simple and relatively inexpensive to measure and monitor. Drug treatments and lifestyle changes such as diet, exercise, and stress reduction have immediate, quantifiable effects on biomarker “scores,” helping reinforce healthy behaviors. As a result, death rates from heart disease have been falling, sometimes dramatically, for close to three decades.

By contrast, the statistics for colon cancer are less encour-

aging. It is second only to lung cancer as the leading cause of cancer death in the United States for both men and women. Deaths from colon cancer have experienced only a modest decline, much of that due to earlier diagnosis and diligent removal of precancerous polyps. No clear biomarkers of risk for colon cancer have been found.

Not, that is, until Bostick discovered a panel of biologic changes and differences in the mucosal tissue of people who later developed colon cancer, which differed significantly from those who remained cancer-free.

A calcium escort

When Bostick became interested in the impact of calcium on disease, a link between calcium and colon cancer was still a far-flung concept. However, epidemiology studies tracking people who emigrated from countries with low colon cancer rates indicated high correlations with the disease and Western diet and lifestyle.

Bostick also noticed the complex molecular pathways from normal to cancerous cells contained multiple points where diet, calcium, and vitamin D can have an effect, both singly and in tandem with other interactions. For example, the body produces bile acids when it digests fat. While these acids can cause damage to the colon, dietary calcium can intervene and bind to the bile molecules, escorting them out of the system before they cause harm. Vitamin D not only enhances the absorption of calcium but also stimulates the production of



an enzyme that degrades bile acids. It also directly affects the cell cycle and immune system.

Bostick became so interested in this research that he made a life-changing decision to close his medical practice in Beaufort, South Carolina,

and pursue a research career. That eventually led him to Emory, where he is a Georgia Cancer Coalition scholar and a professor in the Rollins School of Public Health.

He has continued to hone in on identification of new biomarkers for colon cancer. Among these discoveries are early alterations in the genes involved in the normal structure and function of the colon; subtle aberrations in the normal growth, repair, and death cycle of the cells themselves; the appearance of inflammation; and the rise of potent growth factors, hormones that stimulate proliferation and differentiation of cells.

Growing evidence

Bostick's hunch about the chemopreventive effects of calcium is no longer a far-fetched hypothesis. In an initial groundbreaking study of 200 participants, he analyzed mucosal tissue to demonstrate that cell proliferation is a powerful biomarker of risk for developing colon cancer. He recently completed a study of the effects of calcium and vitamin D, separately and combined, on a panel of biomarkers in 88 Emory Clinic patients with precancerous colon polyps. The biomarkers are of protein expression such as p21 (colon cancer differentiation, or maturation) and COX-2 (colon cell inflammation). Initial data analysis indicates that treating patients with both calcium and vitamin D has a synergistic effect on the biomarkers.

Although the approach works for biomarkers, will it work in clinical outcomes? Bostick and colleague Jack Mandel are trying to find out as principal investigators of the South Carolina and Georgia components of a multicenter study involving 2,457 people who have regular colonoscopies.

Headed by Dartmouth's John Baron, the study investigates whether adding vitamin D to calcium supplementation will reduce polyp recurrence.

Bostick also won additional funding from the National Cancer Institute to piggyback biomarker research with this study. The additional research will confirm whether treating biomarkers actually leads to decreased polyp occurrence in a large population. It also will examine questions such as if and how the biomarkers vary over time, whether they appear differently in different places in the colon, and if the biomarker response to treatment varies in people with different vitamin D receptors or in those taking nonsteroidal anti-inflammatory medications.

Just a little finger prick

Bostick is ready to take the next steps toward development of an effective biomarker screening test. That step involves a large prospective study of people who have never had a polyp, much less any sign of colon cancer, to determine if biomarkers can predict who will develop colon problems. As a part of this process, Bostick wants to develop a simple and easy test, such as identification of biomarkers in blood, urine, or mucosal tissue.

Nanotechnology may enable him to make such tests fast and cheap. Working with the quantum dot technology available at Emory and Georgia Tech, he is creating software that automatically scans slides to quickly and accurately quantify the presence and quantity of biomarkers in mucosal tissue. What used to take a researcher six hours can now be done by a machine in 15 minutes.

If Americans followed the American Cancer Society's recommendations for regular colonoscopies, gastroenterologists would be unable to meet the demand. While the finger prick screening test that Bostick envisions would not do away with colonoscopies, a cheaper, easier biomarker test would more likely be accepted and used by more people. The biomarker screening will provide better information on who needs a colonoscopy when and how often, and will provide additional motivation for those who most need a colonoscopy to get one, says Bostick.

So get ready to hold out your finger. ●