Letters to the Editor


Letter

Kosaku Sakamoto

Department of Surgery, Gunma University School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371, Japan

The paper by Kristal et al. (1) is of interest and curiosity for several reasons. To begin with, there is an inadequate description of the methodology. For instance, how were the test negative cases confirmed for adequacy of sample collection? In other words, if a patient was negative, was it because the mucus was biochemically negative, or because there was no rectal mucus at all? This would greatly affect the sensitivity of the assay (2). It is well known that following the “prep” there is very little mucus in the rectum.

In the first of the two studies, rectal mucus samples for colon cancer screening were taken from 608 subjects after they were prepared for colonoscopy. A screening test is to be performed before colonoscopy and not at the time of colonoscopy. Thus one cannot take this study seriously. The second study has a sample size (52 subjects) smaller than those of all the other reports they have criticized. In spite of that, it is better designed than the first one. Because of their study population of patients with colon or polyps or high risk, the study cannot evaluate specificity; it can only measure the sensitivity of the assay, which they show to be very high (92%), a figure consistent with all of the other published and unpublished reports.

Kristal et al. criticize our reports for either having (a) small numbers or (b) not adequately documenting normal subjects, thus conveniently ignoring our reports on 330 asymptomatic normal people showing >92% specificity (3). The study by Mackett et al. (4) showed a high sensitivity and specificity for 676 cases; simple arithmetic tells us that Mackett’s study alone had a larger sample size than the 608 + 52 cases from Kristal et al.

It is of interest that the data by Kristal et al. indicate 66.7 to 100% incidence of mucin strip test-positives in the subjects with a previous history of colon cancer or recurrent adenomatous polyps, even though they were diagnosed as “normal” at the time of colonoscopy, supporting the common knowledge that these subjects are at a high risk of developing colon cancer at a later date. Thus they cannot be categorized as “normal.” Ironically, this also provides support for the principle on which the test is based, i.e., that galactose-N-acetyl-galactosamine detected in rectal mucus is a marker not just for cancer but also for precancerous conditions and lesions. On that issue, why were patients with inflammatory bowel diseases who are also known to be at high risk for colon cancer excluded? Kristal et al. have neglected to discuss these important issues of colon carcinogenesis, which are vital to screening for colorectal cancer.

Evaluation of this new test should be continued with rational study designs and an open mind, for it already shows great potential in our strategies for early detection and prevention of colon cancer; any attempt to prematurely discredit this test is a great disservice to us all.

References

Letter

A. K. M. Shamsuddin

University of Maryland, School of Medicine, Baltimore, Maryland 21201

The assay used by Kristal et al. (1) is based on the principle that, as a result of the field effect of the carcinogen, the colonic mucus is abnormal in cancer and precancer (2). This abnormal mucus may be present in the rectum of patients having cancer, precancerous polyps, or inflammatory bowel diseases, conditions that predispose a patient to cancer of the colon and rectum. While the rectum is the site for the mucus sampling, the abnormal mucus is an indicator of the disease anywhere in the colorectum (2, 3). Since this is a rather novel approach, in evaluating this assay, its principle and concept must be understood.

Kristal et al. have failed to understand the fundamental principles of colon carcinogenesis and that of the assay. Such is evident from the design of the first study,
in which the rectal mucus was collected after preparation for colonoscopy. As conceded by the authors, that was a serious flaw, necessitating a supplemental study.

It is common knowledge that normal people do not undergo colonoscopy; the discomfort and the cost are prohibitive. On the other hand, patients who are undergoing surveillance colonoscopy are not normal; they are at a high risk for colon cancer, or else the health maintenance organization (of the clinics from which the patients are selected) would not pay for the study. Thus, contrary to their claim, Kristal et al. have not evaluated normal people, nor was their sample size of 52 larger than any of the other studies. Therefore, this study cannot assess the specificity, which some report to be as high as 100% (4). Since the patients in the study by Kristal et al. are all at a high risk for colon cancer, as expected, the assay showed a remarkably high (92%) sensitivity. This fact alone begs for further clinical trials.

Our current strategies for colorectal cancer screening depend on fecal occult blood tests, which have been in usage for nearly two decades despite their very poor performance. Better assays are urgently needed to combat this nuisance. Studies on >7,000 people done worldwide to date show great promise for this new rectal mucin assay. But, in order to prove its usefulness, this assay, like any others, must stand the test of time.

References

Reply

Alan R. Kristal
Fred Hutchinson Cancer Research Center, Cancer Prevention Research Program, Seattle, Washington 98104

We welcome the opportunity to respond to the comments of Drs. Sakamoto and Shamsuddin on our evaluation of the MST as a screening tool for colorectal cancer. We will first address the three points made in these letters, and then discuss how negative publication bias may in part account for the lack of other reports finding poor results when using the MST.

The first point is related to when and how we collected mucus samples. For practical reasons, principally to minimize interference with clinic procedures, we collected mucus samples after preparation for colonoscopy. We discussed this design with Dr. Shamsuddin, who worked with us in a small pilot study in which we demonstrated that mucus could be collected after colonoscopy preparation. The problems we experienced during the full study, described in detail in the report, were related to the very small size of the test strip and the difficulty of distinguishing mucus from lubricant when placing the sample on the strip. We did demonstrate, however, that after careful physician training we could collect mucus on 100% of all strips. For the main study of 608 participants, we acknowledged that some proportion of tests were negative or indeterminate because they had little or no mucus on the test strip. This would lead to underestimates of sensitivity and unpredictable errors in specificity; however, this would not bias the main study result that there were no differences in MST-positive rates among persons with cancer, adenomatous polyps, or no disease. A second related argument is that preparation for colonoscopy could have changed the biochemical composition of rectal mucus. Yet, in our supplemental study of 52 participants in which mucus was collected both before and after preparation for colonoscopy, we again found no differences in MST positivity by diagnosis.

The second point is related to the study population, described by Drs. Sakamoto and Shamsuddin as “high-risk.” We note that the purpose of our study was to determine whether a much larger study of the MST, such as a population-based screening evaluation, should be mounted. The population we chose for evaluating the MST was appropriate to answer this question for three reasons. First, we could test enough persons at high risk to estimate the sensitivity of the MST. Testing the MST on a random population sample would yield too few true positives (previously undiagnosed colon cancer) for a meaningful estimate of the MST’s sensitivity. Second, we also included persons at relatively low risk, that is, persons receiving colonoscopy due to rectal bleeding or positive hemoccult tests alone, allowing us to estimate the specificity of the MST among persons with no disease. Third, everyone in our sample received colonoscopy, so that true disease status could be determined for all participants. Table 1 in the original report gives the distribution of reasons for colonoscopy. Since these reasons are not mutually exclusive, we give here the percentages of participants in the main study whose indications for colonoscopy were exclusively: (a) hemoccult positive, 7.9%; (b) rectal bleeding, 0.9%; and (c) hemoccult positive and rectal bleeding, 15.9%. Since there are many reasons for hemoccult positivity and rectal bleeding not related to colon cancer, these 110 persons were not necessarily at elevated risk of disease. Furthermore, Table 2 gives results stratified by a priori risk of cancer, defined as a previous diagnosis of cancer, recurrent adenomatous polyps, single diagnosis of polyps, or no history of cancer or polyposis. Regardless of indication for colonoscopy or previous history of disease, we found no evidence that MST positivity rates were related to disease.

The third point is related to our necessarily brief discussion of previous reports, especially that of Mackett and colleagues. This study is difficult to interpret, principally because only persons who were hemoccult positive or MST positive were further evaluated. Thus, it is...

A K Shamsuddin


Updated version Access the most recent version of this article at: http://cebp.aacrjournals.org/content/1/7/603.2.citation

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.