Letters to the Editor


Letter

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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 completely discredit this test is a great disservice to us all.

Kosaku Sakamoto, M.D.

Reference:

Letter

A. K. M. Shamsuddin
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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 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

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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
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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 polyps. 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

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