On the Sensitivity of Fecal Occult Blood Test Screening for Colorectal Cancer

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In this issue of the Journal, two publications (1,2) from the Minnesota Colon Cancer Control Study address the question of "how well" fecal occult blood test (FOBT) screening detects early colorectal cancer and how much of the "mechanism" of detection may be due to chance, as proposed by us 3 years ago (3). Our goals in a brief comment on a complicated subject are to identify the main issues and to discuss briefly how these new data relate to them.

In our simple mathematical analysis (3) of the data published from the Minnesota study (4), we estimated that one third to one half of the mortality reduction observed in that study could be accounted for by chance colonoscopy done for work-up of a FOBT result that was "falsely positive" in a person who had a neoplasm that was not bleeding. The hypothesis is plausible because rehydrated FOBT slides are positive in 8%-16% of persons each time a FOBT is done (4), and chance detection of lesions can occur when a diagnostic test has a high false-positive rate (5,6).

The Minnesota study investigators address these issues of sensitivity and specificity (i.e., false-positive rate) by providing new primary data from their study and a revised model (2), as well as a series of approaches about how to calculate test sensitivity (1) based on data from the original study.

The modeling exercise reported by Ederer et al. (2) provides several advances. Although we have not examined the model itself, we believe that the role of chance should be revised downward on the basis of these new data and the revised model. In our analysis, we used the summary data published in the original report (4); however, because some parameters vary over time (particularly the positivity rate of FOBT), the use of primary data instead of summary estimates should provide a better picture of how FOBT works.

Furthermore, the investigators have revised our model to add a concept of "dual detectability" to indicate that, for some neoplasms, the FOBT may be positive both because of bleeding and because of chance, and they suggest that these detections should not all be accounted to chance. Last, a lower rate is used for endoscopy efficacy in reducing mortality (60% versus 70%). With these revisions, the investigators calculate that the amount of mortality reduction due to chance in their study is about one sixth to one quarter, with the majority of that reduction being due to their use of primary data. On the basis of what is published here and without seeing the model itself, we believe that these new features are reasonable and that the role of chance should, quantitatively, be revised downward.

Biologically, this analysis suggests that FOBT screening is more specific than in our analysis, since specificity is the main driving force of the "chance detection" phenomenon (3). We would ask whether some of this apparent increase in specificity might have been due to the use of nonrehydrated (and less falsely positive) slides in the initial phases of the trial, inasmuch as mortality reduction in a screening trial tends to be related to earlier screens (7).

Church et al. (1) use several different arguments to suggest that FOBT sensitivity is very high. In the larger picture, the sensitivity of a screening test is critically important because it determines "how many" colorectal cancer deaths can be prevented. In other words, if a test cannot detect the precursors of fatal colorectal cancer, then it cannot reduce colorectal cancer mortality. The several approaches used in the report by Church et al. (1) conclude that "sensitivity" of FOBT screening is on the order of the 80% or 90% originally reported in the Minnesota study (4). We are not persuaded by these approaches for several reasons. First, several of the calculations (including the follow-up-adjusted screen sensitivity estimate, the truncated product-biomial model, and the comparative incidence by test results) utilize results from the Minnesota study in which sensitivity rates were based on detection of colorectal cancer at any stage. By the inclusion of advanced colorectal cancer in the calculations, FOBT sensitivity is inflated when the test is given credit for detection of advanced lesions that are not primary targets of screening, because they are not readily treatable compared with early colorectal cancer or large adenomas.

Furthermore, advanced lesions are more likely to have positive FOBT results than early lesions that are the targets of screening.

Moreover, if the sensitivity of a program of FOBT screening is 80%-90%, as these several approaches suggest, then it is not clear why colorectal cancer mortality reduction is only 33.4% (4). We agree with the Minnesota investigators that imperfect

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compliance with FOBT screening or follow-up explains in part the limited mortality reduction. However, we believe that FOBT sensitivity for curable neoplasms, even for a program of repeated application of FOBT, is as yet simply unknown, and we suspect it is substantially lower than the 80%–90% suggested here. Empirical data to shed light on this question may be available from recently completed clinical trials (8,9), including this one (4), if an analysis were done of colorectal cancer mortality reduction among compliant patients. While such an estimate is fraught with hazards of post-hoc analysis, it could arguably establish an upper bound of the efficacy of FOBT screening.

While the use of primary data clearly helps advance an understanding of this problem, the interpretation of the results is still complicated for clinicians and policy-makers. The relative sensitivity of nonrehydrated FOBT slides is increased by only a small amount by rehydration according to the Minnesota investigators’ own calculations (4), while the false-positive rate quadruples, suggesting large inefficiencies for a relatively small gain. The cost and effort incurred by rehydration are substantial and need to be considered by physicians and policy-makers (10) in making choices among various test options.

Finally, these analyses touch on some larger issues about the evaluation of diagnostic tests. First, the commonly used concept of “sensitivity” appears increasingly to be inadequate to think about certain kinds of medical problems, such as those in which the true state (e.g., the presence or absence of cancer) is not routinely assessed each time the screening test is done and in which a screening test is applied repeatedly over time in a program of screening. Confusion occurs when a term like “sensitivity” is applied to describe rates that are measured in very different ways. The analyses here highlight the challenges in understanding this larger problem; ultimately we will need to develop concepts that go beyond “sensitivity” (11).

Second, while FOBT screening reduces colorectal cancer mortality, it is yet uncertain what is the main “mechanism” of mortality reduction; i.e., is it detection of early colorectal cancers or of precursors such as large adenomatous polyps?

Furthermore, it is unclear what is the “maximum” mortality reduction achievable and how, perhaps with new test strategies (12), to increase mortality reduction. The answers to these questions ultimately depend on biologic features, such as how frequently early colorectal cancer may bleed over time. Thus, the Minnesota investigators assume (1) in the simulation used to reconcile the results of the Minnesota study with the studies by Ahlquist et al. (14) that bleeding is “independently distributed” (i.e., that each neoplasm has an “equal chance” of bleeding). Others have made the same assumption in building models of colorectal cancer screening (13). In contrast, it is at least theoretically possible, if clinically disturbing to consider, that some neoplasms while at a curable stage simply do not bleed (14), even when assessed repeatedly over time. In our view, the evidence available at this time is insufficient to resolve one way or another how often colonic neoplasms bleed enough to be detected before they become incurable (15).

The good news is that FOBT screening clearly reduces colorectal cancer mortality. The bad news—or the challenging news—is that the sensitivity and specificity of the test are still imperfect. We need to learn more about why that is so and about how to improve them further.

References

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