Screening for Colorectal Cancer

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Colorectal cancer remains a major cause of mortality in the United States. Of all persons diagnosed with this tumor, less than 50 percent survive five years. Useful preventive measures have not been established. Screening programs, however, offer the prospect of detecting cancers early in their course, when the prognosis for survival is more favorable.

To date, no screening test has clearly demonstrated its effectiveness in reducing mortality from colorectal cancer. Periodic rigid sigmoidoscopy and stool occult blood testing have gained many advocates, but have yet to be proved worthwhile in adequately controlled clinical trials. Uncontrolled studies indicate that both these techniques discover approximately 2 cancers per 1000 screenees. There is suggestive evidence that the cancers discovered are more likely to be localized.

For the present, physicians should limit colorectal cancer screening to persons at relatively high risk: persons aged over 45 years, with a family history of bowel cancer, or with polyps. Protocols should be designed to ensure high specificity. The recommendations of the National Cancer Institute's consensus conference provide practical guidelines pending the outcome of randomized controlled trials.

Colorectal cancer is the second most common internal malignancy in the United States. In 1980, more than 110,000 new cases will be diagnosed, and 53,000 persons will die from the disease.[1] Although substantial progress was made in its treatment during the middle part of this century, five-year survival rates have improved only modestly over the past 20 years despite the introduction of combination chemotherapy, radiotherapy, immunotherapy, and improved surgical techniques.[1-3]

The overall five-year survival rate for colorectal cancer stands at about 43 percent,[2,3] but the prognosis depends markedly on the extent of disease at the time of surgery. Patients with localized Dukes' A and B lesions have five-year post-surgical survivals of 80 percent and 60 percent, respectively. Of patients with regional node involvement, however, only 30 percent are alive five years after operation.[4] Unfortunately, less than half of colorectal cancers are localized at the time of diagnosis.[5,6] Patients who come to operation for asymptomatic cancers rarely have metastases, and their five-year survival approaches 90 percent in some series.[7]

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Such statistics form the foundation for the widespread enthusiasm for colorectal cancer screening. Physician instituted screening programs might be expected to detect clinically silent tumors which have not yet metastasized, thereby making curative surgery possible. With therapy for advanced tumors still wanting, it appears that only early diagnosis can reduce overall mortality from this cancer. As a result, a variety of screening recommendations have been introduced over the past two decades. Their success in achieving their purposes will be the focus of this paper.

Principles of Screening

A careful distinction should be made at the outset between screening asymptomatic persons and evaluating patients with bowel complaints. Symptomatic patients are relatively likely to have serious disease. Furthermore, they have sought medical attention voluntarily. Such patients should have all appropriate diagnostic investigations. Persons without complaints, on the other hand, are at far lower risk. Moreover, as they feel well, they do not ordinarily seek medical services. Any program designed to make apparently well persons "healthier" through screening must be able to demonstrate clearly that its benefits outweigh any costs or harms.

Not all diseases are amenable to screening, and criteria for determining a condition's suitability for a screening program have been outlined.[8] First of all, the disease must have serious consequences, recognized not only by physicians but also by the population targeted for screening. The disease should be reasonably common. It should have an asymptomatic phase, during which time screening tests are capable of detecting it. A therapy must be available for the condition during the asymptomatic phase which will favorably alter its natural history, not simply by advancing the point in time at which the diagnosis occurs, but by improving survival, function, or both. Furthermore, the results of treatment during the asymptomatic period should be superior to those possible once the disease becomes symptomatic. Available health services must be adequate to follow up the expected number of positive screening results, provide diagnostic confirmation, and offer effective therapy. Colorectal cancer appears to satisfy all these criteria, and thus the search for a suitable screening protocol seems justified.

Choice of Screening Test

The selection of an appropriate screening test is more difficult. The screening instrument should be safe, inexpensive, accurate, easy to use, and acceptable to the persons being screened. Many screening tests for colorectal cancer have been proposed. Some, like the carcinoembryonic antigen (CEA) have been abandoned[9]; others, such as colonic mucin staining, are still being developed.[10] Two screening procedures, rigid sigmoidoscopy and the testing of stools for occult blood, have attracted the most serious attention.

Sigmoidoscopy

Sigmoidoscopy meets most of the criteria for a successful screening test, albeit with some difficulties. Bowel perforation occurs in only 0.002 to 0.07 percent of all procedures, and related mortality approaches zero, and thus it appears safe.[11] However, as a screening instrument it is not inexpensive and, in addition, requires considerable experience to perform well. Many examiners find it difficult to pass the scope beyond the acute flexure in the rectosigmoid area, and the mean length of bowel examined during the procedure is estimated to be only 20 cm.[12] Although one investigator claims the ability to perform ten examinations per hour (including history taking and paperwork),[13] most physicians accomplish the test at a far slower pace. Virtually no information exists on its accuracy in detecting colorectal cancers, as measured by sensitivity and specificity, but as only the distal bowel can be visualized, its sensitivity must be low. Finally, despite assertions to the contrary, the procedure is uncomfortable, and relatively unacceptable to the person who has no symptoms of bowel disease.

Testing for Stool Occult Blood

Because of the limitations of rigid sigmoidoscopy, most interest now focuses on the testing of stools for occult blood. This procedure was first promoted by Greegor, who, having had little suc-

cess in detecting asymptomatic colorectal cancers with sigmoidoscopy, found that virtually all persons with tumor had occult blood in at least one of three stool specimens.[14,15] The test, now institutionalized as the guaiac-impregnated Hemoccult Slide (Smith Kline Diagnostics), has gained widespread popularity and use. It is entirely safe, inexpensive, easy to use (usually performed by the patient in his home), and is aesthetically acceptable to patient, physician, and laboratory technician.

The accuracy of Hemoccult as a screening test has been the center of considerable debate. Ideally, a screening test should have 100 percent sensitivity (that is, it identifies all persons who have the disease) and 100 percent specificity (that is, it reassures all persons who do not have the disease). In the real world, such goals are never achieved. Although Greegor claims perfect sensitivity for colorectal cancer in ten years of personal experience with his Hemoccult protocol,[16] false negative tests appear to be common. One hospital series of colon malignancies showed a single test sensitivity of only 40 percent,[17] although the experience in outpatient screening programs using multiple slides ranges from 66 to 97 percent.[16,18-20] A carefully performed study using injected red blood cells labeled with ^{51}Cr found single Hemoccult slides to have a sensitivity of only 37 percent with low concentrations of blood in the stool, improving to more than 90 percent sensitivity when concentrations of more than 20 mg of hemoglobin per gram of stool were reached.[21] Although Hemoccult appears relatively insensitive compared to other guaiac or orthotoluidine tests, it does have the virtue of being much more specific.[21,22] Estimates of the test's specificity, while also variable, range from 89 percent to more than 99 percent in outpatient screening programs using multiple slides.[18,19,23-37]

Several factors can account for these discrepant estimates of sensitivity and specificity. Perhaps the most important for sensitivity is the intensity with which those persons with negative screening results are followed up. Only by ascertaining the later status of such persons can the number of false negatives, and hence the sensitivity, be determined. One trial of screening, using a three-slide protocol, attempted such follow-up and found sensitivity to be only 71 percent.[20] In addition, the number of Hemoccult slides used in the screening process affects the estimates of sensitivity and specificity. Given that colonic bleeding may be intermittent, the more stools per person that are tested, the more likely it becomes that at least one will be positive. Increasing the number of stools tested by the protocol results in greater sensitivity, but (because additional slides provide more opportunities for false positive errors as well) causes a simultaneous fall in specificity. Greegor's early suggestion, apparently empirical, that two slides be made from different portions of stool on each of three consecutive days, with any one slide's positive reaction making the series "positive," has been widely adopted, although its scientific basis has been questioned.[14,38,39]

Hemoccult screening also presents unique technical problems. Red meat in the diet has been found to greatly increase the number of false positive screens, with specificity falling as low as 77 percent; this has resulted in the adoption of a test diet eliminating meat but high in bulk (to stimulate bleeding).[15] Vitamin C has been reported to cause false negative reactions,[40] and recently cimetidine tablets have been postulated to cause false positives.[41] Delay of four or more days in developing the slides may result in false negative tests, especially if bleeding is slight.[42,43] "Rehydrating" such slides with water restores their sensitivity.[44,45] Finally, the recent introduction of Hemoccult II slides, while improving sensitivity over standard Hemoccult, adds further complexity to the issue, for rehydration of Hemoccult II drastically lowers specificity.[44,46] What initially appears to be a very simple screening test has, in fact, a number of subtle pitfalls (Table 1).[47]

Protocol Design

The physician deciding on a protocol for colorectal cancer screening in his practice must take these problems into account. Should all screenees be on a special three-day diet? Should three or six slides be used? If the slides are mailed in after four days, should they be rehydrated? Depending on how such questions are decided, the sensitivity and specificity of the screening protocol may fluctuate markedly.

To a major extent, sensitivity and specificity are inversely related; as one improves, the other worsens. The physician designing a screening program must decide where to strike the balance. If high sensitivity is desired (eg, six slides, rehydra-

Table 1. Technical Problems in the Use of Hemoccult Slides for Screening

Factors Yielding False Positive Screening Results:
Diet: inclusion of red meat, peroxidase containing vegetables, eg, horseradish, beets
Concurrent use of aspirin
Misreading of color change (green should be considered nonreactive)
Rehydration of Hemoccult II
Cimetidine tablets (FDC blue lake No. 2)
Factors Yielding False Negative Screening Results:
Delay of four or more days in developing slides
Concurrent vitamin C supplements
Low bulk diet
Inadequate number of slides in protocol

tion, no diet) virtually all cancers will be detected, but large numbers of nonaffected persons will be asked to undergo expensive and uncomfortable diagnostic procedures. On the other hand, if specificity is set high (eg, three slides, meat-free diet, no rehydration), the number of unnecessary workups will be reduced, but some cancers will be missed. The physician's decision should depend on the likelihood of disease in the persons he will screen, the availability of resources for follow-up and treatment, and the attitudes of his patients.[8]

Clinical Trials of Screening

Sigmoidoscopy Trials

Clinical trials provide some estimates of the benefits and costs resulting from different screening protocols. Trials of sigmoidoscopy have largely been performed in uncontrolled "annual checkup" programs. Although sigmoidoscopy permits immediate recognition of malignant lesions, its yield as a screening procedure appears small. One series of 1,020 examinations in asymptomatic patients aged over 40 years discovered one polyp with carcinoma in situ but no invasive cancers, and a second series of more than 2500 examinations gave identical results.[14,48] Other studies indicate that 1 to 3 cancers will be found per 1,000 examinations in asymptomatic persons.[7,11,19,49] Gilbertsen found 27 adenocarcinomas in 21,150 initial screening sigmoidoscopies; 64 percent of the patients with cancer survived five years. During 92,650 subsequent examinations on this initial cohort, he found only 13 more persons with cancer, 11 of whom survived five years.[50] His claim of having reduced the predicted number of cancers through repeated examinations with polypectomy is unconvincing, because the basis for his calculation of expected cancers—the general population incidence—cannot be applied to a group selected on the basis of a previously normal examination and then repeatedly examined. However, the favorable course of the cancer patients so discovered suggests that early diagnosis was beneficial.

The only randomized controlled trial of periodic sigmoidoscopy was carried out at the Kaiser-Permanente Hospital in Oakland, California, as part of a larger study of periodic health examina-

tions.[51] Ten thousand subjects were randomly assigned to study or control groups, and persons in the study group were offered annual sigmoidoscopy as part of a comprehensive general examination. During an 11-year follow-up, study group subjects received about 56 percent more sigmoidoscopic examinations than did control subjects, and suffered a mortality from colorectal cancer of 1.0/1,000 (5 deaths) vs 3.3/1,000 (18 deaths) in controls ($P<.05$). Sixty percent of the 20 cases of colorectal cancer diagnosed in the study group were staged as in situ or Duke's A, vs 48 percent (of 25) in the control group. However, before entry into the study, 14 persons in the control group had had a previous history of colorectal cancer, compared to only 6 in the study group. This imbalance might at least partially account for the results reported.

Proponents of sigmoidoscopy argue that the removal of polyps found during examinations provides an additional benefit further justifying the procedure. This premise assumes that some polyps are premalignant, and that their removal prevents later degeneration to invasive cancer. The validity of this view remains controversial.[52] At present, the only clear value of routine sigmoidoscopy lies in the detection of early rectal cancers.

The present evidence indicates that a small proportion of routine sigmoidoscopic examinations uncovers curable invasive lesions. Although some lives can probably be saved by the procedure, physicians and their patients have not accepted it with enthusiasm despite its promotion by the American Cancer Society and others.[1] The advent of flexible sigmoidoscopy may, however, result in a reappraisal of its benefits.[12]

Trials of Hemoccult Screening

Numerous uncontrolled trials of screening with Hemoccult have been reported in the past six years. In comparison to screening by sigmoidoscopy, the diagnostic process with Hemoccult is complex. After selecting an appropriate group to be screened, the physician must provide slides individually and explain their use. The persons screened must be compliant in preparing their slides and in returning them. The slides must be interpreted accurately, which, as discussed previously, requires some sophistication. Those with positive screens must be reappointed for further diagnostic tests; contact with the physician must actually be made, and the workup completed. Those with detected cancers must agree to surgery before any impact on mortality can be expected. Clearly, there are many opportunities for the screening process to go awry.

The many reported uncontrolled trials of Hemoccult screening offer a wide variety of protocols. Some of the larger and better described trials are summarized in Table 2. Although these trials have major differences in design, there is remarkable uniformity in their most important finding: about one or two colorectal cancers were discovered per 1,000 persons identified for screening. Many of these studies report the discovered cancers by pathological stage, and suggest that the distribution is skewed towards earlier, localized lesions. None of them, however, has as yet followed its cancer cases for five-year survival.

Early results of a controlled trial of Hemoccult screening in combination with sigmoidoscopy have been published.[49,53,54] In this trial, nearly 22,000 persons were divided (nonrandomly) into "screened" and "control" groups. All subjects were aged 40 years or more, and 93 percent were asymptomatic for bowel disease. Virtually all 22,000 received sigmoidoscopy, as well as a physical examination. In addition, the "screened" group performed the six-slide protocol for fecal occult blood while on a red-meat–free, high roughage diet. Those with at least one positive Hemoccult slide underwent air-contrast barium enema and colonoscopy. Of 13,127 persons screened with Hemoccult for the first time, 74 percent returned their slides, and of these, 2.5 percent were positive. After several years of screening, 43 colon cancers had been diagnosed with the aid of Hemoccult (0.33 percent of the screened group), and another 16 cancers in this cohort were discovered only by other means. Cancers diagnosed in the screened group had more favorable clinical staging than those found in the sigmoidoscopy only control group. This latter group suffered only 12 cancers (0.14 percent of control subjects) during the same period, a rate of diagnosis less than one third that of the screened group. This discrepancy in diagnostic rates suggests either that the control group currently harbors a large number of occult cancers, or that the cohort receiving Hemoccult testing was chosen on the basis of high risk for cancer. Unfortunately, data published on this trial to date do not include baseline comparisons of the two

Table 2. Uncontrolled Trials Of Screening With Hemoccult Slides

Investigator	Number of Slides	Diet	Persons Enrolled	Number Returning Slides (%)	Number Screening Positive (%)	Number Receiving Diagnostic Evaluation (%)	Number with Colorectal Cancer Found By Hemoccult	Colorectal Cancers / Persons Enrolled
Kurnick et al[19]	4	No	5,595	5,450 (96.9)	120 (2.2)	NS	9	0.16%
Richardson[23]	6 (?)	Yes	1,038	885 (85.3)	54 (6.1)	27 (50.0)	0	—
Sterchi[24]	1	Yes	1,204	770 (64.0)	29 (3.8)	18 (62.1)	0	—
Miller et al[25]	3	No	2,332	2,278 (97.7)	64 (2.8)	11 (17.2)	1	0.04%
Glober et al[26]	6	No	1,682	1,539 (91.5)	400 (26.0)	32 (8.0)	3	0.18%
Withers et al[27]	6	Yes	NS	1,050 (–)	112 (10.7)	28 (25.0)	4	≤0.38%
Hardcastle et al[28]	3	No	1,638	742 (45.3)	29 (3.9)	29 (100)	2	0.12%
Goodman[29]	3	Yes	2,500	1,749 (70.0)	9 (0.5)	9 (100)	0	—
Hastings[30]	3	Yes	3,450	2,625 (76.1)	159 (6.1)	86 (54.1)	5	0.14%
Heeb et al[31]	3	Yes	5,740	3,956 (68.9)	79 (2.0)	64 (81.0)	5	0.09%
Goodman[32]	6	Yes	3,200	2,000 (62.5)	137 (6.9)	107 (78.1)	4	0.13%
Bralow et al[33]	NS	Yes	3,798	3,008 (79.2)	328 (10.9)	126 (38.4)	7	0.18%
McDougal et al[34]	3	No	6,943	3,788 (54.6)	37 (1.0)	12 (32.4)	2	0.03%
Helfrich et al[35]	NS	No	NS	8,930 (–)	157 (1.8)	23 (14.6)	3	≤0.03%
Ross et al[36]	3	No	1,187	1,103 (92.9)	70 (6.3)	30 (42.9)	4	0.34%
Frühmorgen et al[37]	3	Yes	6,007	5,016 (83.5)	136 (2.7)	117 (86.0)	13	0.22%

NS=not stated. For diet, a "yes" entry indicates a meat-free, high bulk diet was recommended. Except for the final column, percentages are calculated using data from the left adjacent column as denominators. "Diagnostic evaluation" is defined as at least a barium contrast study or sigmoidoscopy

study groups, or information on the number of screenings performed in each group. A full report, including follow up for mortality, is anticipated.

Studies such as these leave the efficiency of Hemoccult screening in doubt. Present data indicate that only 1 or 2 cancers will be found per 1,000 examinees, or approximately the same yield as rigid sigmoidoscopy. Although there is a suggestion that discovered cancers are more likely to be surgically curable, no mortality data have yet been reported. The ultimate verdict on fecal blood screening will probably rest on the findings of the Colon Cancer Control Study now underway at the University of Minnesota.[45] During a two-year period, 48,000 asymptomatic persons aged 50 to 80 years were enrolled in this trial, and randomized by age, sex, and geographic area into three groups: one screened annually, one biannually, and one given "routine care." The screening consists of the three-day, six-slide Hemoccult protocol on a meat-free high fiber diet, with all slides mailed to a central laboratory for rehydration before testing. Those persons with at least one positive slide will be worked up with sigmoidoscopy, barium enema, and colonoscopy. All groups will receive a health survey annually, and mortality from colorectal cancer over a ten-year period will be measured. Early results show a 74 percent compliance with the slide protocol; 2.4 percent of the returned slides are positive. Of the positive screenees, about 88 percent complete diagnostic workups. Of the first 75 gastrointestinal cancers detected, 65 percent were Dukes' A and 13 percent Dukes' B.[55] The results of this large, well-designed trial may finally establish or discount the value of screening for fecal occult blood.

Hidden Costs of Screening

Inasmuch as screening has not yet been shown to reduce mortality from colorectal cancer, its total cost should be considered. In addition to the monetary expense of administering large numbers of screening tests, there are other, less obvious costs. False positive screening results, which invariably constitute more than half of all positive results, occasion diagnostic workups which

would not otherwise have been performed. These workups may produce unwarranted anxiety in subjects and their families. Rarely, they may even result in procedure related morbidity (eg, bowel perforation during endoscopy). Physicians may be diverted away from their sick patients to work up many asymptomatic persons who are, in fact, well. Those few persons with tumors that go undetected by the screening process may be harmed by false reassurance, which may delay their presentation for medical care once symptoms do occur. Hidden costs such as these often are not considered by screening proponents. Even large costs might be easily outweighed, however, by a screening protocol which could demonstrate its effectiveness in reducing colorectal cancer mortality.

Present Alternatives: A Practical Approach

As the benefits of screening for colorectal cancer, although suggestive, are still unproved, practicing physicians should use present techniques with discretion. An important goal of cancer screening is to make the process as efficient as possible. To this end, the screening protocol's predictive value (that is, the proportion of positive screening results that are true positives) should be maximized, largely by reducing the number of false positive tests. The most effective strategies to improve predictive value are to choose a group for screening that has a high prevalence of disease, and to select a screening instrument with high specificity.

By choosing screenees who are known to be at relatively high risk for colorectal cancer, disease prevalence in those undergoing testing can be maximized. As age is a major risk factor for this cancer, persons selected for screening should be at least 45 years of age. Persons of any age with a personal or family history of colorectal cancer, or with a history of colorectal polyps should also be screened. Planning a protocol with high specificity, for example by enforcing a strict diet, using only three Hemoccult slides, and not rehydrating slides, will also reduce the number of false positive results and improve predictive value. Although some sensitivity is sacrificed with such decisions, the overall benefits in time and money may outweigh the losses, and even allow screening to proceed where a less efficient protocol would prove impractical.

These principles are inherent in two recently published consensus reports on screening for colorectal cancer. In June 1978, a group of gastroenterologists, internists, epidemiologists, oncologists, surgeons, family physicians, economists, and pathologists met as a committee at the National Cancer Institute to formulate screening guidelines.[56] Among their recommendations were that Hemoccult testing be limited to asymptomatic persons over the age of 40 years, unless there are additional personal or familial risk factors. The diet should be free of meat and high in fiber, and the slides tested within four days of their preparation. Hemoccult II slides should not be rehydrated, and "doubtful" reactions should be considered negative. Persons with at least one positive slide should receive air-contrast barium enema and/or colonscopy, although recent studies indicate that some cancers may be missed on barium enema alone.[37,55] The committee also urged the continuation of controlled trials examining the benefits and costs of Hemoccult screening. Late in 1979, the Canadian Task Force on the Periodic Health Examination also published guidelines for colorectal cancer screening. While endorsing the use of Hemoccult in persons aged 45 years or older "not more frequently than annually," they urged research to "determine the sensitivity, specificity, acceptability, side effects, and appropriate frequency" of such screening, as conclusive evidence for its benefit has not been attained.[57]

Conclusion

Colorectal cancer remains an important cause of mortality, and satisfies the criteria for a screenable disease.[8] Although there is evidence that routine sigmoidoscopy may occasionally detect early curable cancers, this procedure has not gained acceptance as a screening instrument despite its widespread promotion for decades. Likewise, the data for Hemoccult testing are inconclusive; it is hoped that the well-designed trials now in progress will clarify this issue. Newer techniques, such as flexible sigmoidoscopy, immunologic markers, and colonic mucin stains may become established in the future,[10,12,17] but for now, physicians should use the available tests efficiently in order to maximize their impact. Until prevention of this cancer becomes feasible, early detection will remain the best weapon in reducing its mortality.

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