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REDUCING MORTALITY FROM COLORECTAL CANCER BY SCREENING FOR FECAL OCCULT BLOOD

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Abstract *Background.* Although tests for occult blood in the feces are widely used to screen for colorectal cancers, there is no conclusive evidence that they reduce mortality from this cause. We evaluated a fecal occult-blood test in a randomized trial and documented its effectiveness.

Methods. We randomly assigned 46,551 participants 50 to 80 years of age to screening for colorectal cancer once a year, to screening every two years, or to a control group. Participants who were screened submitted six guaiac-impregnated paper slides with two smears from each of three consecutive stools. About 83 percent of the slides were rehydrated. Participants who tested positive underwent a diagnostic evaluation that included colonoscopy. Vital status was ascertained for all participants over 13 years of follow-up. A committee determined causes of death. A single pathologist determined the stage of cancer for each tissue specimen. Differences in mortality from colorectal cancer, the primary study end point, were monitored with the sequential log-rank statistic.

Results. The 13-year cumulative mortality per 1000 from colorectal cancer was 5.88 in the annually screened group (95 percent confidence interval, 4.61 to 7.15), 8.33 in the biennially screened group (95 percent confidence interval, 6.82 to 9.84), and 8.83 in the control group (95 percent confidence interval, 7.26 to 10.40). The rate in the annually screened group, but not in the biennially screened group, was significantly lower than that in the control group. Reduced mortality in the annually screened group was accompanied by improved survival in those with colorectal cancer and a shift to detection at an earlier stage of cancer.

Conclusions. Annual fecal occult-blood testing with rehydration of the samples decreased the 13-year cumulative mortality from colorectal cancer by 33 percent. (N Engl J Med 1993;328:1365-71.)

IN 1993 there will be approximately 152,000 new cases of colorectal cancer in the United States and 57,000 deaths from this disease.[1] The cause of colorectal cancer is unknown, although associations have been reported with family history, diet, alcohol, and sedentary habits.[2] In the absence of definitive information to support primary-prevention programs, attention has focused on the use of screening to detect this cancer earlier, when intervention may reduce mortality.[3]

Although the concept of occult-blood detection has existed since 1864, there was little interest in its appli-

cation to the early detection of large-bowel cancer until 1967, when Greegor proposed a test for home use that involved guaiac-impregnated paper slides.[4] There has been no direct evidence, however, of the efficacy of screening with this test in reducing mortality from colorectal cancer.

Randomized trials of fecal occult-blood screening are ongoing,[5-12] but interim results of these studies have so far not provided conclusive evidence of the effectiveness of screening. Likewise, a nonrandomized study involving 21,756 participants systematically assigned to screening or to a control group reported a significant shift to an earlier stage of cancer at diagnosis and a significant increase in survival with colorectal cancer, but a nonsignificant reduction in mortality due to colorectal cancer in the screening group.[3]

In this article, we report the results of the Minnesota Colon Cancer Control Study and present conclusive evidence from a randomized trial of the effectiveness of fecal occult-blood screening in reducing mortality from colorectal cancer.

METHODS

Details of the study design have been reported elsewhere[13-15] and are summarized here. From 1975 through 1977, 46,551 participants 50 to 80 years of age were recruited from among volunteers for the American Cancer Society and fraternal, veterans, and employee

groups in Minnesota. Persons who at the time of enrollment reported a history of colorectal cancer, familial polyposis, or chronic ulcerative colitis and persons known to be bedridden or otherwise disabled were not enrolled in the trial. No effort was made to interview or examine prospective participants or to review their medical records. After stratification according to age, sex, and place of residence, the participants were randomly assigned to screening once a year, to screening once every two years (biennially), or to a control group.

The participants in the two groups assigned to screening were each asked to submit six guaiac-impregnated paper slides (Hemoccult); the slides contained two smears from each of three consecutive stools. The participants were instructed to abstain from red meat, poultry, fish, and certain raw vegetables and fruits and to stop taking vitamin C tablets and aspirin for 24 hours before and during the collection of the samples; adherence to this regimen was not verified. The slides were tested at the laboratories of the University of Minnesota Hospital according to a standardized, controlled procedure. The mailing of slides from areas throughout Minnesota delayed their processing for up to eight days. Because the drying caused by this delay may have decreased the sensitivity of the test, the procedure of rehydrating each slide with a drop of deionized water during processing was begun in 1977. All slides were rehydrated from 1982 through the end of screening in February 1992.

The participants were notified of the results of screening. Those with one or more slides testing positive in the set of six were urged to return for evaluation at the hospital. Initially, the diagnostic protocol included a history and physical examination, rigid proctosigmoidoscopy, single-column barium-enema radiography, complete blood count, urinalysis, routine tests of blood chemistry, upper gastrointestinal series, chest radiography, electrocardiography, and colonoscopy. In 1978, the use of single-column barium-enema radiography was discontinued, because this procedure missed 20 percent of the cancers detected by colonoscopy.[16] Thereafter, double-contrast barium enemas were administered to about 5 percent of the patients when colonoscopy was incomplete or suboptimal. The use of rigid proctosigmoidoscopy and upper gastrointestinal series was abandoned in 1982. Proctosigmoidoscopy was unnecessary with colonoscopy, and the upper gastrointestinal series did not uncover substantial disease requiring treatment.

During colonoscopy, biopsies of visible lesions were performed, and the lesions were removed when possible. All substantial abnormalities, particularly polyps and cancers, were treated, and the patients were followed by either their physicians or the university staff.

Some participants with positive guaiac tests who saw their own physicians for the diagnostic evaluation did not undergo colonoscopy. Detailed information on the results of the examination was obtained from the attending physician.

The participants in all three study groups received mailed questionnaires annually to ascertain their vital status, the occurrence of colorectal cancer and polyps in the control-group participants, and the detection of any colorectal lesions by other means than the study screening in members of the screened groups. Participants who did not return the questionnaire were telephoned and asked for this information. For all reported lesions, medical records concerning the diagnosis were obtained.

Death certificates were obtained for all patients who died. The uncoded death certificates, along with the relevant medical records, were submitted without study-group designation to a Deaths Review Committee consisting of two pathologists, an oncologist, and a gastroenterologist, none of whom were otherwise involved with the study, in order to determine whether colorectal cancer had been the underlying cause of death.

The study pathologist staged the slides of pathological specimens obtained from patients with colorectal cancer, using the Turnbull modification of the 1932 Dukes' staging system.[17,18] When neither lymph nodes nor adequately oriented sections of the tumor were available for staging, the cancer was categorized as unstaged. The cause of death as determined by the Deaths Review Committee and the stage as determined by the study pathologist were used in the present analyses.

A sample containing 15,000 participants in each group and 45,000 overall was initially determined.[13] The initial protocol specified five years of screening and five years of follow-up, with the screening phase to end in 1982. In 1985, the Policy and Data Monitoring Group recommended that screening be reinstituted, because the number of deaths from colorectal cancer in the control group was lower than had been initially projected.[19,20] Screening was reinstituted in February 1986, and it continued through February 1992.

Differences in mortality from colorectal cancer, the primary study end point, between each of the two screening groups and the control group were monitored in a group-sequential analysis by means of the sequential log-rank statistic as computed from life tables[21,22] through year 13, the last complete year of follow-up in this analysis. A one-sided type I error rate of 0.025 was applied to each comparison with 80 percent power against the alternative hypothesis of a 25 percent reduction in mortality from colorectal cancer. To adjust each sequential statistical test for multiple examinations of the data, stopping boundaries for rejecting the null hypothesis were computed[23] with use of a constant spending rate for the type I error and for accepting the null hypothesis by the stochastic curtailment method of Lan and Wittes,[24] with 95 percent confidence intervals for the rate ratios for mortality adjusted for sequential analysis.[25] Total mortality, the incidence of colorectal cancer, and the survival of patients with colorectal cancer were analyzed without monitoring by life-table methods.[21,22] The decision to publish results was made after a review of the most recent data on mortality from colorectal cancer showed that the stopping boundary had been crossed in the annually screened group. In a supporting analysis, proportional-hazards (Cox) regression was used to adjust for age, sex, and place of residence.[26]

The sensitivity of the screening test was determined with the assumptions that cases of colorectal cancer discovered within one year after positive screening were true positives (cases detected by screening) and that those discovered within one year after negative screening were false negatives.

RESULTS

Randomization was effective in creating a balance among the three study groups with respect to age and sex (Table 1) and place of residence (data not shown).

The annually screened group completed 75.2 percent of the screening offered, and the biennially screened group completed 78.4 percent (Table 2). Ninety percent of each group completed at least one screening. All the screenings were completed by 46.2 and 59.7 percent of the groups screened annually and biennially, respectively.

Seventy-five percent of the participants testing positive were examined at the University of Minnesota Hospital (Table 2), 20 percent were followed by their own physicians, and 5 percent declined to consult a physician. The proportion examined outside the university was higher in the case of women and increased with age for both men and women, from less than 10 percent for participants under 65 to approximately 40 percent for those over 80. Over 96 percent of those examined at the university underwent colonoscopy. Of those examined elsewhere, 44 percent had a colonoscopy, 42 percent had flexible sigmoidoscopy and barium enema but no colonoscopy, 11 percent had repeat stool blood tests, and 3 percent were told by their physician that no examination was necessary.

Of 12,246 colonoscopies performed at the university, 4 resulted in perforation of the colon (all requiring surgery), and 11 in serious bleeding (3 requiring surgery).

Vital status was determined for each study participant through 13 years of follow-up. Death certificates were obtained for 99.9 percent of the participants who

died, and medical records were available for 99 percent of the participants. Except for deaths from colorectal cancer, the distribution according to underlying cause of death as recorded on the death certificate was similar in the three study groups (Table 3).

Over the first 13 years of follow-up, there were 1002 cases of colorectal cancer, 10,097 deaths, and 320 deaths from colorectal cancer among the 46,551 participants (Table 4). Although the cumulative incidence of colorectal cancer was virtually identical in the three groups, the cumulative annual mortality rate from colorectal cancer was lower in the annually screened group (5.88 per 1000) than in the biennially screened group (8.33 per 1000) and the control group (8.83 per 1000). The rate ratio for mortality from colorectal cancer (the mortality rate in each screened group divided by the mortality rate in the control group) was significantly below 1 in the annually screened group (rate ratio, 0.67; 95 percent confidence interval, 0.50 to 0.87), but not in the group screened every two years (rate ratio, 0.94; 95 percent confidence

Table 1. Age and Sex of the Participants at the Time of Randomization, According to Study Group.

SEX AND AGE (YR)	STUDY GROUP			
	ANNUAL SCREENING	BIENNIAL SCREENING	CONTROL	ALL
	no. (%) of subjects			
Women				
<60	3201 (39.6)	3231 (39.7)	3155 (39.6)	9,587 (39.6)
60–69	3404 (42.1)	3430 (42.1)	3420 (43.0)	10,254 (42.4)
≥70	1476 (18.3)	1482 (18.2)	1385 (17.4)	4,343 (18.0)
All	8081 (100)	8143 (100)	7960 (100)	24,184 (100)
Men				
<60	3230 (43.1)	3171 (42.6)	3212 (43.2)	9,613 (43.0)
60–69	3010 (40.2)	3049 (41.0)	3027 (40.7)	9,086 (40.6)
≥70	1249 (16.7)	1224 (16.4)	1195 (16.1)	3,668 (16.4)
All	7489 (100)	7444 (100)	7434 (100)	22,367 (100)

interval, 0.68 to 1.31). These results reveal a significant reduction in mortality at 13 years of follow-up in the annually screened group as compared with the control group (Fig. 1). Adjustment for age, sex, and place of residence by Cox proportional-hazards regression[26] did not alter this conclusion.

Early in the study, the biennially screened group had a higher cumulative mortality and incidence of colorectal cancer than the control group (Fig. 1 and 2). By year 13, the trend had reversed, and there was a slight reduction in mortality as compared with the control group. The statistic for the biennially screened group did not cross the stopping boundary, however, indicating that the alternative hypothesis for the biennially screened group (a 25 percent reduction in mortality) was neither accepted nor rejected.

The results for cumulative survival from the time of diagnosis of colorectal cancer (Fig. 3) were consistent with the view that earlier detection by screening results in improved survival and reduced mortality from colorectal cancer (Table 4 and Fig. 1). Patients with disease detected by screening had higher 13-year sur-

Table 2. Compliance with Screening and Diagnostic Protocols and Results of Examinations, According to Study Group.

VARIABLE	ANNUAL SCREENING	BIENNIAL SCREENING
Percent of screenings completed*	75.2	78.4
	% of group	
Participants completing ≥1 screening	90.2	89.9
Participants completing ≥50% of screenings	77.2	82.4
Participants completing ≥75% of screenings	69.4	76.5
Participants completing 100% of screenings	46.2	59.7
Follow-up of patients testing positive		
Examination at the study clinic	75.0	73.8
Colonoscopy	80.9	81.7
Complete bowel examination	82.7	84.0
	% of examinations	
Findings		
Colorectal cancer	1.9	2.7
Polyps	27.5	29.5

*Calculated by dividing the total number of screenings completed by the total number of eligible screenings.

vival rates than those with disease not detected by screening in both screened groups (Fig. 4). The 13-year survival rate in the control group (59 percent) was similar to that of the patients with cancer not detected by screening in each of the screened groups (58 percent).

The cumulative 13-year incidence rates of colorectal cancer according to study group and Dukes' cancer stage showed changes in the incidence of Dukes' stage A and stage D cancers in the screened groups as compared with controls that were consistent with earlier detection of colorectal cancer by screening (Fig. 5). The percent distribution according to stage and group showed the same pattern of stage shifting that we observed in the cumulative incidence rates (data not shown).

Table 5 shows that there were twice as many Dukes' stage D cancers in the control group as in the annually screened group (65 vs. 33, respectively). These can-

Table 3. Distribution of Causes of Death According to Study Group, on the Basis of Death Certificates.*

CAUSE OF DEATH	STUDY GROUP		
	ANNUAL SCREENING	BIENNIAL SCREENING	CONTROL
	% of deaths		
Colorectal cancer	2.6	3.2	3.4
Other malignant neoplasm	25.1	25.9	25.7
Ischemic heart disease	32.1	31.6	30.7
Cerebrovascular accident	8.7	8.2	8.9
All other circulatory diseases	9.6	9.3	10.7
Respiratory disease	7.1	7.6	6.8
Digestive system disease	2.7	2.3	2.3
Accident	3.0	3.3	2.9
All other	8.1	7.7	7.7
Unknown	1.0	1.0	0.9

*Underlying causes of death were defined according to the Eighth Revision of the *International Classification of Diseases*,[27] as coded by a nosologist unaware of the study-group assignment. Percentages may not total 100 percent because of rounding.

Table 4. Mortality and Incidence of Colorectal Cancer per 1000,
According to Study Group, during the 13 Years after
Randomization.

VARIABLE	STUDY GROUP		
	ANNUAL SCREENING	BIENNIAL SCREENING	CONTROL
Person-years in the study	184,160	183,934	181,966
Colorectal cancer			
No. of cases	323	323	356
Cumulative incidence*	23	23	26
95% Confidence interval	21–26	20–25	23–28
Deaths from all causes			
No. of deaths	3361	3396	3340
Cumulative mortality*	216	218	216
95% Confidence interval	209–222	211–224	210–223
Deaths from colorectal cancer			
No. of deaths	82	117	121
Cumulative mortality*	5.88	8.33	8.83
95% Confidence interval	4.61–7.15	6.82–9.84	7.26–10.40
Cumulative mortality ratio	0.67	0.94	1.00
95% Confidence interval†	0.50–0.87	0.68–1.31	

*Rates shown for mortality and cancer incidence are per 1000. Numbers of deaths from colorectal cancer are based on determinations by the Deaths Review Committee.

†Adjusted for sequential monitoring.

cers accounted for 54 and 40 percent, respectively, of the deaths from colorectal cancer in these groups. The percent survival at five years was only 2.4 for patients with Dukes' stage D cancers, as compared with earlier-stage cancers, for which survival ranged from 94.3 percent (Dukes' stage A) to 56.6 percent (Dukes' stage C).

A notable feature of this study was the effect of rehydration of the slides on test results. Overall, 82.5 percent of the slides were rehydrated. As a result of rehydration, the rate of positive results increased more than fourfold, from 2.4 to 9.8 percent (Table 6). There was a marked increase in positivity with age, particularly for the rehydrated slides. The positivity rate for such slides increased from 8 percent in the case

Figure 1. Cumulative Mortality from Colorectal Cancer, According to Study Group.
Bars represent ±2 SE.

of participants 50 to 59 years of age at entry into the study to 16 percent in the case of participants 80 or over, and the rate was higher in men than in women (data not shown). The age trend was less marked in the case of slides that were not rehydrated; positivity rates increased slightly, from 1.8 percent for participants 50 to 59 years of age to 2.4 percent for those 80 or over.

Rehydration increased the sensitivity of the test for colorectal cancer from 80.8 to 92.2 percent and decreased the specificity from 97.7 to 90.4 percent (Table 6). With the loss of specificity, the positive predictive value decreased from 5.6 to 2.2 percent.

From the abstracted records for the cases of colorectal cancer, it was determined that in only 1.8 percent of the cases in the control group was the diagnosis
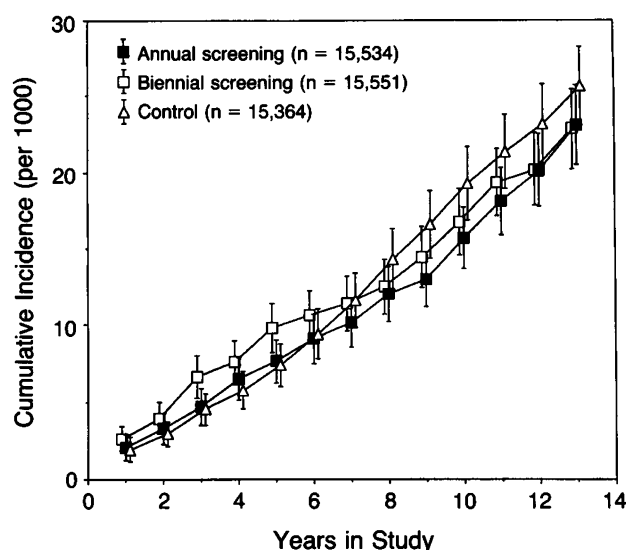

Figure 2. Cumulative Incidence of Colorectal Cancer, According to Study Group.
Bars represent ±2 SE. Participants in whom colorectal cancer was diagnosed before randomization are not represented in this figure.
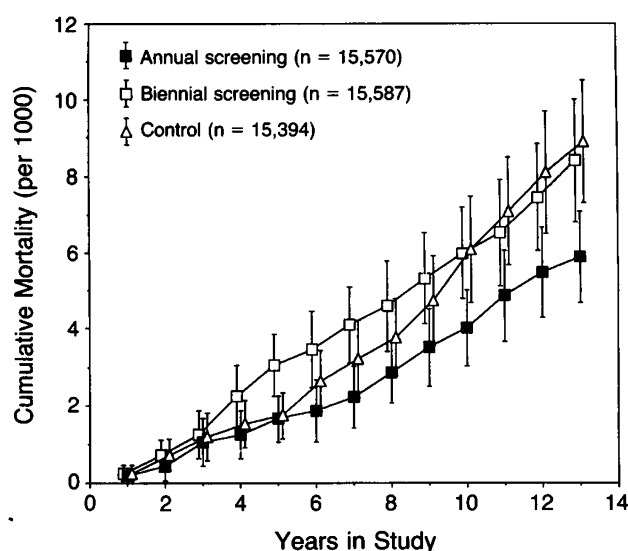
made after a positive fecal occult-blood test, as compared with 49.5 and 38.3 percent of those in the annually and biennially screened groups, respectively.

DISCUSSION

This randomized trial demonstrates a significant reduction in mortality from colorectal cancer as a result of screening with fecal occult-blood tests. A 33 percent decline in mortality was observed in the annually screened group as compared with the control group. The 6 percent reduction observed in the biennially screened group, though not statistically significant, was consistent with the finding in the annually screened group, in that cumulative mortality in the biennially screened group was intermediate between that of the annually screened group and the controls. Additional follow-up is necessary to evaluate the efficacy of screening every two years.

The survival data were consistent with the mortality data. Survival was better in the annually screened group than in the control group. The efficacy of screening was further supported by the fact that patients with disease detected by screening had significantly better survival than patients with disease not so detected and by the fact that patients with disease not detected by screening and controls had similar survival.

Staging of the cancers according to study group yielded results consistent with the mortality rates. There was a significantly higher 13-year incidence of Dukes' stage D cancers in the control group than in the screened groups. The reduction in these cancers in the annually screened group as compared with the control group was larger in the current study (48 per-
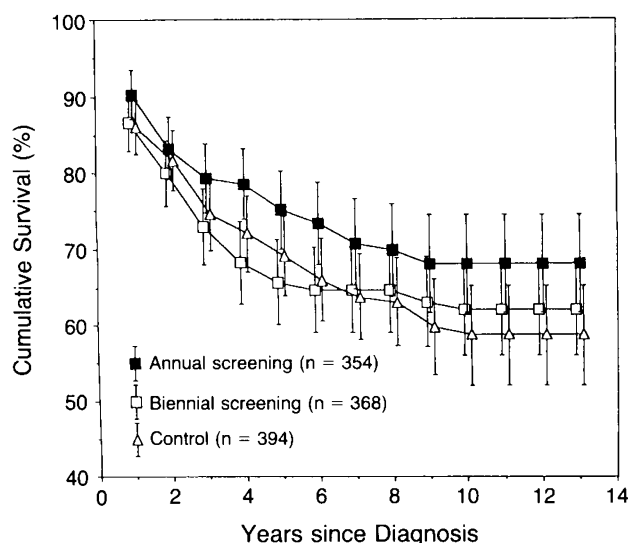

Figure 3. Cumulative Survival of Participants with Colorectal Cancer, According to Study Group.
Bars represent ±2 SE.

cent) than the reductions reported to date in the three European trials (10 to 38 percent).[5-12] The Swedish study, the only European study in which slides were rehydrated, had the largest reduction in Dukes' stage D cancers (38 percent).[5,6]

There were twice as many stage D cancers in the control group as in the annually screened group. The detection of a cancer before its development into a stage D cancer had a profound effect on mortality, since only 2.4 percent of patients with stage D cancers survived five years, whereas for patients with cancers in earlier stages, five-year survival ranged from 94 percent for stage A to 57 percent for stage C.

The 37 percent reduction in the incidence of Dukes' stage D cancers in the biennially screened group, as compared with the control group, did not result in a significant reduction in mortality from colorectal cancer. This may be due to the higher incidence of colorectal cancer and to the higher mortality from this
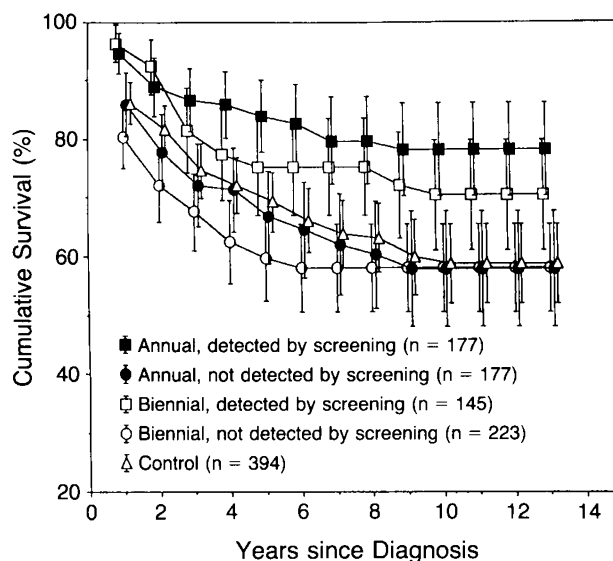

Figure 4. Cumulative Survival of Participants with Colorectal Cancer, According to Method of Detection and Study Group.
Bars represent ±2 SE.

cancer in the biennially screened group early in the study, which may have resulted from a chance imbalance in the randomization procedure. With continued follow-up, a significant reduction in mortality could emerge. It is not possible to determine the effect of the three-year hiatus in screening.

Most of the slides were rehydrated, resulting in increased positivity but also in an increased number of colonoscopies and in decreased specificity of the test.
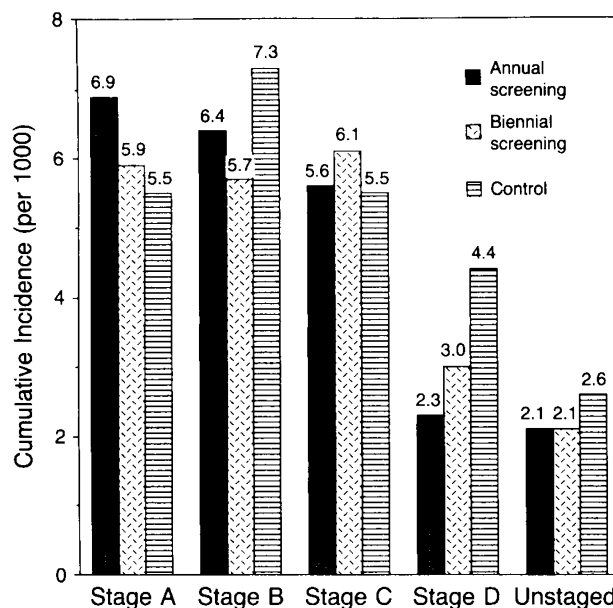

Figure 5. Cumulative 13-Year Incidence of Colorectal Cancer, According to Study Group and Dukes' Stage.
Numbers shown above the bars are numbers of cases of colorectal cancer per 1000. Participants in whom colorectal cancer was diagnosed before randomization are not represented in this figure.

Table 5. Colorectal Cancers, According to Study Group and Dukes' Stage, and Five-Year Survival According to Stage.

STAGE	STUDY GROUP				FIVE-YEAR SURVIVAL (%)
	ANNUAL SCREENING	BIENNIAL SCREENING	CONTROL	ALL	
	no. of cancers				
A	107	98	88	293	94.3
B	101	95	120	316	84.4
C	80	100	82	262	56.6
D	33	41	65	139	2.4
Unstaged	33	34	39	106	87.0
All	354	368	394	1116	70.0

The large number of false positive results clearly affects the assessment of cost and benefit. During the study, 38 percent of those screened annually and 28 percent of those screened biennially had at least one colonoscopy. The increase in positivity resulting from rehydration of the slides and the consequent increase in the use of colonoscopy may have increased the likelihood that nonbleeding cancers in earlier stages would be detected by chance in persons who tested positive for other reasons. This could partly explain the significant reduction in mortality in the group screened annually, the improvement in survival, and the shift to detection at an earlier stage of cancer. The extensive use of colonoscopy could also have contributed to the decline in mortality through the removal of polyps. The small differences among the study groups in the incidence of colorectal cancer suggest, however, that polyp removal has not yet contributed substantially to the reduction in mortality. During the first eight years of follow-up, the incidence of colorectal cancer was about the same in all three groups. During the next five years, the rate of increase in the cumulative incidence of this cancer was lower in each screened group than in the control group. The effect of polyp removal on the subsequent incidence of cancer may become clearer with additional follow-up. It is

Table 6. Positivity, Sensitivity, Specificity, and Positive Predictive Value of Testing for Colorectal Cancer, According to Rehydration Status of Slides, in Both Screening Groups Combined.*

VARIABLE†	REHYDRATION	No REHYDRATION
	percent	
Positivity	9.8	2.4
Sensitivity	92.2	80.8
Specificity	90.4	97.7
Positive predictive value	2.2	5.6

*Data are based on results from 1976 through 1982.

†Sensitivity was defined as the number of true positive results divided by the sum of true positive results and true negative results, specificity as true negative results divided by the sum of true negatives and false positives, and positive predictive value as true positive results divided by the sum of true positives and false positives.

also possible that polyp removal in the screened groups and the expected reduction in the subsequent incidence of cancer were offset by an increased discovery of cancers through screening. It is, of course, also possible that in this study the removal of polyps had little or no effect on mortality.

Had there been frequent fecal occult-blood testing performed outside the protocol in the control group, such testing could have diminished the difference in mortality. The small percentage (1.8 percent) of colorectal cancers in the control group that were associated with fecal occult-blood testing indicates, however, that these tests had little effect on the results.

Unequal ascertainment of cancers in the study groups could have biased the results. Because of colonoscopy, there was a higher likelihood of ascertaining cancers in the patients who were screened than in the controls. However, the nearly equal incidence rates in the three study groups argue against an ascertainment bias.

About 22 percent of the patients with colorectal cancer in the screened groups, but few of those in the control group, were treated at the University of Minnesota Hospital. A difference in treatment between the university and other hospitals could have resulted in a spurious difference in survival. When treatment procedures were analyzed according to sex, age, screening group, anatomical location, and Dukes' stage, no significant treatment differences were revealed between study groups.[28] The possibility of confounding was addressed by the Cox regression analysis, which showed that age, sex, and place of residence at enrollment did not affect mortality from colorectal cancer.

This study demonstrates that a 33 percent reduction in mortality from colorectal cancer can be achieved by annual fecal occult-blood testing with rehydrated slides and colonoscopic follow-up in patients with positive test results. Whether a similar result can be attained without rehydration — that is, with a test of lower sensitivity — is unknown at this time. The result was obtained with an annual screening program (with a three-year hiatus in screening) during which 10 percent of the screened group did not receive any study screening tests, only 46 percent had all 11 screening tests, and 17.5 percent of the slides were not rehydrated. A greater reduction in mortality might be obtained with more adherence to protocol.

In the formulation of public health policy for mass screening, cost is important. Fecal occult-blood testing with rehydrated samples should lead to a fourfold increase in the number of positive tests and diagnostic procedures involving colonoscopy. The increase in cost is substantial and will have to be weighed against the estimated benefit of a 33 percent reduction in mortality from colorectal cancer.

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