

## THE EFFECT OF FECAL OCCULT-BLOOD SCREENING ON THE INCIDENCE OF COLORECTAL CANCER

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**ABSTRACT**

**Background** Both annual testing for fecal occult blood and biennial testing significantly reduce mortality from colorectal cancer. However, the effect of screening on the incidence of colorectal cancer remains uncertain, despite the diagnosis and removal of precancerous lesions in many persons who undergo screening.

**Methods** We have followed the participants in the Minnesota Colon Cancer Control Study for 18 years. A total of 46,551 people, most of whom were 50 to 80 years old, were enrolled between 1975 and 1978 and randomly assigned to annual screening, biennial screening, or usual care (the control group). Those assigned to the screening groups were asked to prepare and submit two samples from each of three consecutive stools for guaiac-based testing. Those with at least one positive slide in the set of six were offered a diagnostic examination that included colonoscopy. Screening was conducted between 1976 and 1982 and again between 1986 and 1992. Study participants have been followed with respect to newly diagnosed cases of colorectal cancer and deaths. Follow-up has been more than 90 percent complete.

**Results** During the 18-year follow-up period, we identified 1359 new cases of colorectal cancer: 417 in the annual-screening group, 435 in the biennial-screening group, and 507 in the control group. The cumulative incidence ratios for colorectal cancer in the screening groups as compared with the control group were 0.80 (95 percent confidence interval, 0.70 to 0.90) and 0.83 (95 percent confidence interval, 0.73 to 0.94) for the annual-screening and biennial-screening groups, respectively. For both screening groups, the number of positive slides was associated with the positive predictive value both for colorectal cancer and for adenomatous polyps at least 1 cm in diameter.

**Conclusions** The use of either annual or biennial fecal occult-blood testing significantly reduces the incidence of colorectal cancer. (N Engl J Med 2000; 343:1603-7.)

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THREE randomized, controlled clinical trials have shown that both annual screening and biennial screening for occult blood in the stool significantly reduce the rate of death from colorectal cancer.<sup>1-4</sup> Several observational studies have had similar results.<sup>5-13</sup> The reduction in mortality is evidently a consequence of the earlier detection and surgical removal of malignant colorectal tumors. Fecal occult-blood screening may yield an additional benefit: a reduction in the incidence of

colorectal cancer, resulting from the detection and removal of premalignant adenomatous polyps. Fecal occult-blood tests are not very sensitive for the presence of polyps but will detect some, particularly large polyps, which are more likely to bleed<sup>14-16</sup> and also to become cancerous.<sup>17</sup>

Subjects in the National Polyp Study had a lower incidence of colorectal cancer than subjects in three historical control groups, which suggests that the incidence of this cancer is reduced by colonoscopic polypectomy and surveillance of persons with adenomatous polyps.<sup>18</sup> In the trials of fecal occult-blood screening, many polyps were detected and removed during bowel examination after a positive screening test. Thus, a reduction in the incidence of colorectal cancer in the screened groups might be expected. After 13 years of follow-up in the Minnesota Colon Cancer Control Study, the incidence of colorectal cancer was 12 percent lower in the screened groups than in the control groups (P not significant).<sup>1</sup> We now present data on the cumulative incidence of colorectal cancer after 18 years of follow-up.

**METHODS****Participants**

The Minnesota study was a randomized, controlled clinical trial conducted to evaluate the effectiveness of fecal occult-blood testing in reducing the rate of death from colorectal cancer.<sup>1,19</sup> Briefly, 46,551 people, the majority of whom were 50 to 80 years old when recruited between 1975 and 1978, were randomly assigned to annual screening, biennial screening, or usual care (control group). The annual-screening and biennial-screening groups will be referred to collectively as the screening groups. For each screening, participants assigned to the screening groups were asked to prepare two guaiac-impregnated paper slides (Hemoccult, Beckman Coulter, Palo Alto, Calif.) for each of three consecutive stools and submit them to the investigators. Screening was conducted between 1976 and 1982 and, after a hiatus, resumed in 1986. All screening was completed in 1992.

The institutional review board of the University of Minnesota reviewed and approved the study, and all participants gave written informed consent.

**Study Design**

Participants with at least one positive slide were invited to undergo a diagnostic evaluation, which initially included history taking and a physical examination, single-column barium enema, rig-

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id proctosigmoidoscopy, urinalysis, a complete blood count, routine tests of blood chemistry, an upper gastrointestinal x-ray series, chest radiography, electrocardiography, and colonoscopy. Single-column barium enema was discontinued in 1978. Double-contrast barium enemas were administered to participants who had at least one positive screening test and whose colonoscopic examinations were incomplete or suboptimal (about 5 percent of the subjects). Rigid proctosigmoidoscopy and the upper gastrointestinal series were discontinued in 1982. Throughout the trial, colonoscopy was the dominant diagnostic procedure used to identify colorectal polyps and cancers. During colonoscopy, all polyps detected were routinely resected.

Diagnostic evaluation of subjects with positive screening tests was completed in 1993. Follow-up has continued to the present time in order to ascertain the incidence of colorectal cancer and all deaths.

Beginning in 1976 and continuing to the present, all study participants received an annual questionnaire designed to ascertain vital status and identify newly diagnosed colorectal polyps and cancers in the control group and in members of the screening groups whose lesions were not detected by screening. Colorectal cancers reported in all three groups were confirmed by a review of relevant medical records from the diagnosing or treating physicians or hospitals, with the written consent of the participants. For colorectal cancers and for polyps reported in conjunction with colorectal cancers, slides of tissue were obtained for independent confirmation and staging by the study pathologist.

To validate the method of ascertainment, new cases of colorectal cancer were also identified by linkage of the cohort, from 1988 (the first year for which data were available) through 1994 (the last year for which data were available), to the Minnesota Cancer Surveillance System,<sup>20</sup> which collects data on all newly diagnosed and pathologically confirmed cancers in Minnesota.

For deaths occurring in the first 15 years after enrollment in the study, a deaths review committee, whose members had no knowledge of the group assignments, reviewed all records of selected subjects who had died to determine the underlying cause of death. Included in this review were all such subjects in whom a history of gastrointestinal disease or cancer could not be definitively ruled out.<sup>21</sup>

### Statistical Analysis

For the analysis of incidence, which included all cases diagnosed in the first 18 years of the study that were logged into the data base before January 1, 1999, the cumulative probability of survival free of colorectal cancer was estimated by the life-table method.<sup>22</sup> The cumulative incidence was obtained by subtracting this probability from 1. The 106 subjects in whom colorectal cancer was diagnosed before randomization were omitted from the analysis of incidence, leaving 46,445 subjects. The ratios of the 18-year cumulative incidence of colorectal cancer in the two screening groups to the incidence in the control group and the 95 percent confidence intervals for these ratios were computed as a measure of the extent to which screening affected incidence. Reported P values are two-sided, and no correction was made for multiple tests.

To evaluate the sensitivity of the fecal occult-blood test for the detection of large polyps, we used the following indirect method.<sup>23</sup> For all returned slide sets that contained all six specimens, the positive predictive value (for colorectal cancer, the fraction of subjects with a positive screening test who had colorectal cancer; for polyps, the fraction who had polyps) was estimated for each given number of positive slides. The positive predictive value was calculated in the screening groups separately and for each of two outcomes: colorectal cancer or polyps at least 1 cm in diameter but no colorectal cancer. Only positive tests that were followed by adequate examinations, defined as colonoscopy or a combination of flexible sigmoidoscopy and barium-enema radiography, were used in the computations.

To account for the potential correlation between repeated screenings in the same subject, we estimated the positive predictive value of each number of positive slides and for each screening group

in a single, generalized linear model with a logit-link function, using the generalized-estimating-equation approach.<sup>24-27</sup> Accounting for correlation in this manner corrects for the excessive weight that would be given to participants with multiple screenings if the positive predictive value were estimated as the simple ratio of the number of true positives to the total number of positive screening tests. Spearman's rho test<sup>28,29</sup> was used to measure the size and statistical significance of the association between the number of positive slides and the positive predictive value.

### RESULTS

A total of 46,445 people (22,323 men and 24,122 women) without a prior diagnosis of colorectal cancer were randomly assigned to one of the three study groups (Table 1). During the screening period, participants in the annual-screening and biennial-screening groups were offered 11 and 6 opportunities for screening, respectively. The mean rate of compliance per screening opportunity was 75 percent in the annual-screening group and 78 percent in the biennial-screening group. Of the subjects with a positive test, 83 percent in the annual-screening group and 84 percent in the biennial-screening group underwent diagnostic follow-up, including a complete examination of the large bowel by colonoscopy or the combination of double-contrast barium enema and flexible sigmoidoscopy. In each group, about 11 percent of the subjects with positive screening tests underwent flexible sigmoidoscopy or barium enema or underwent another fecal occult-blood test. Five percent of the subjects with positive tests declined to consult a physician. Overall, 75 percent of the subjects with positive screening tests were examined at the University of Minnesota Hospital and Clinics.

Follow-up for vital status through year 18 was complete for 91.3 percent, 91.7 percent, and 91.2 percent of participants in the annual-screening, biennial-screening, and control groups, respectively, and it was 95 percent complete through year 17 for all groups. Death certificates were obtained for all but 3 of the 15,873 people who were known to have died during the 18-year follow-up period. Because active surveillance has continued since the cessation of screening, including a successful linkage with the Minnesota Cancer Surveillance System (performed without knowledge of group assignment), the ascertainment of the incidence of colorectal cancer was nearly complete and did not vary significantly between the groups.

During the 18 years of follow-up, approximately 235,000 person-years were accrued for each study group, and 1359 new cases of colorectal cancer were ascertained: 417 in the annual-screening group, 435 in the biennial-screening group, and 507 in the control group (Table 1 and Fig. 1). The ratios of the cumulative incidence rates in the screening groups to that in the control group were 0.80 (95 percent confidence interval, 0.70 to 0.90;  $P < 0.001$ ) for the annual-screening group and 0.83 (95 percent confidence interval, 0.73 to 0.94;  $P = 0.002$ ) in the biennial-screening group (Table 1).

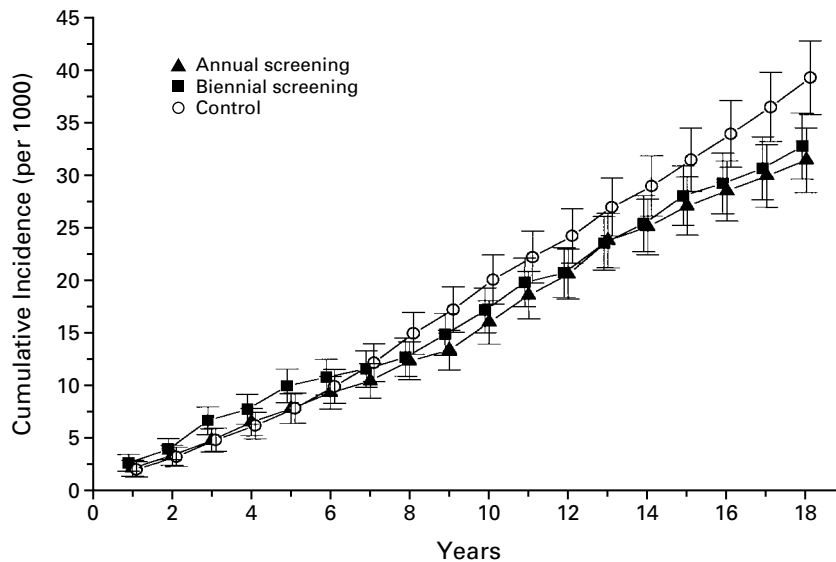
**TABLE 1.** RESULTS OF FECAL OCCULT-BLOOD TESTING ACCORDING TO STUDY GROUP AFTER 18 YEARS OF FOLLOW-UP.\*

VARIABLE	ANNUAL SCREENING	BIENNIAL SCREENING	CONTROL
Subjects — no.			
Total	15,532	15,550	15,363
Men	7,474	7,430	7,419
Women	8,058	8,120	7,944
Person-years of observation — no.	235,584	235,513	232,612
Cases of colorectal cancer — no.	417	435	507
Cumulative incidence/1000	32 (29–35)	33 (30–36)	39 (36–43)
Cumulative incidence ratio†	0.80 (0.70–0.90)	0.83 (0.73–0.94)	1.0
P value‡	<0.001	0.002	—

\*Values in parentheses are 95 percent confidence intervals.

†Values are the ratios of cumulative incidence in each screening group to that in the control group.

‡P values are for the comparison with the control group.



	NO. OF SUBJECTS									
Annual screening	15,532	15,364	14,991	14,538	14,022	13,451	12,763	11,983	11,157	9494
Biennial screening	15,550	15,386	14,984	14,507	13,989	13,407	12,716	11,988	11,155	9554
Control	15,363	15,202	14,835	14,382	13,851	13,218	12,598	11,827	11,021	9342

**Figure 1.** Cumulative Incidence of Colorectal Cancer, According to Study Group, during 18 Years of Follow-up.

Table 2 shows the positive predictive value of a positive test, according to the number of positive slides, for colorectal cancer and for adenomatous polyps at least 1 cm in diameter but no colorectal cancer. For both screening groups, there was a strong association between the number of positive slides and the percentage of subjects with colorectal cancer. For the annual-screening group, the positive predictive value

ranged from 0.87 percent for one positive slide to 4.53 percent for six positive slides (Spearman's rho = 0.94, P = 0.02). For the biennial-screening group, the positive predictive value ranged from 1.12 percent for one positive slide to 6.13 percent for six positive slides (Spearman's rho = 0.94, P = 0.02). For adenomatous polyps at least 1 cm in diameter, there was also an association between the number of positive

**TABLE 2.** PREDICTIVE VALUE OF FECAL OCCULT-BLOOD TESTING ACCORDING TO THE NUMBER OF POSITIVE SLIDES.\*

No. OF POSITIVE SLIDES IN SET OF SIX	No. OF SCREENING TESTS	POSITIVE PREDICTIVE VALUE FOR COLORECTAL CANCER	POSITIVE PREDICTIVE VALUE FOR ADENOMATOUS POLYPS $\geq 1$ cm
		percent (95 percent confidence interval)	
<b>Annual-screening group</b>			
1	2874	0.87 (0.59–1.29)	5.99 (5.18–6.92)
2	2448	1.55 (1.13–2.13)	6.08 (5.18–7.13)
3	1118	1.16 (0.68–1.99)	7.03 (5.69–8.66)
4	883	1.93 (1.20–3.07)	7.49 (5.92–9.43)
5	368	2.72 (1.47–4.97)	8.25 (5.85–11.50)
6	972	4.53 (3.38–6.04)	7.87 (6.29–9.79)
<b>Biennial-screening group</b>			
1	1695	1.12 (0.72–1.75)	6.86 (5.74–8.16)
2	1412	1.13 (0.70–1.84)	8.07 (6.73–9.64)
3	632	2.69 (1.68–4.29)	9.96 (7.79–12.65)
4	526	2.28 (1.30–3.97)	10.87 (8.47–13.86)
5	220	5.00 (2.79–8.82)	10.99 (7.49–15.84)
6	685	6.13 (4.56–8.20)	10.08 (8.03–12.59)

\*Only positive tests that were followed by adequate examinations, defined as colonoscopy or a combination of flexible sigmoidoscopy and barium-encephalography, were used in the computations.

slides and the positive predictive value; this value ranged from 5.99 percent to 7.87 percent for the annual-screening group (Spearman's  $\rho=0.94$ ,  $P=0.02$ ) and from 6.86 percent to 10.08 percent for the biennial-screening group (Spearman's  $\rho=0.83$ ,  $P=0.06$ ).

## DISCUSSION

Our findings demonstrate a significant reduction in the incidence of colorectal cancer after fecal occult-blood testing. This reduction occurred after both annual and biennial screening. The most plausible explanation is the identification and removal of the precursor lesions for colorectal cancer — that is, adenomatous polyps. In study participants who were examined at the University of Minnesota, polyps visualized during the examination were routinely removed. For patients with a positive slide who were examined elsewhere, the information on whether polyps were diagnosed and removed during follow-up was complete. However, the decision to remove polyps was made less consistently than at the University of Minnesota, especially during the early years of the study. Since the focus of the study was on colorectal cancer, information was abstracted only on polyps that were removed in the course of a diagnosis of cancer or a workup after a positive fecal occult-blood test. Thus, the attribution of the reduced incidence of colorectal cancer to the removal of adenomatous

polyps is based on the not unreasonable assumption that the removal of polyps was much more common in the screening groups than in the control group. The National Polyp Study found that the removal of adenomatous polyps, followed by colonoscopic surveillance, significantly reduced the incidence of colorectal cancer below the rates in the general population.<sup>18</sup> The sensitivity of fecal occult-blood tests for the detection of adenomatous polyps has been reported to be moderate but is greater for larger polyps, which are more likely to bleed, than for smaller polyps.<sup>14–17</sup> The positive predictive value increased with the number of positive slides in our study, which further supports the results of earlier studies<sup>14–17</sup>; our findings also provide evidence that polyp removal is the likely explanation for the decrease in incidence.

The failure of screening for fecal occult blood to lead to a clinically significant reduction in the incidence of colorectal cancer after early follow-up in some studies might be interpreted as an argument against the hypothesis that most cancers arise from benign adenomatous polyps.<sup>30,31</sup> Our study supports the theory of the adenoma–carcinoma sequence and emphasizes the importance of detecting and resecting advanced adenomas. To date, however, the European trials have involved less follow-up, making it difficult to show a reduction in incidence with screening. Lang and Ransohoff argued that the reduction in mortality from colorectal cancer in our trial was largely the consequence of chance detection of cancers as a result of many colonoscopies performed, rather than a result of the sensitivity of the fecal occult-blood test.<sup>32</sup> However, the reverse has been shown to be true; that is, the reduced mortality resulted primarily from the sensitivity of the fecal occult-blood test, with chance detection of cancer playing only a minor part.<sup>33</sup> It may similarly be argued that the reduced incidence of colorectal cancer in our trial is largely the result of the chance detection of non-bleeding adenomatous polyps by the many colonoscopies performed, rather than a result of the sensitivity of the fecal occult-blood test for the detection of bleeding polyps. However, the fecal occult-blood test was sensitive for larger polyps, as shown by the statistically significant association between the positive predictive value of a test and the number of positive slides.

The reductions in the incidence of colorectal cancer that we observed may underestimate the true reductions that could be achieved among persons who elect to participate fully in screening. Compliance with screening in our trial was less than complete, averaging about 75 percent for each screening occasion. About 50 percent of the screening subjects participated in all the screening tests they were offered; 10 percent participated in none.<sup>1</sup> In addition, subjects in the control group were not prevented

from undergoing screening through their personal physicians. Thus, noncompliance in the screening groups and participation in screening in the control group are likely to have attenuated the true effect. A hiatus in the screening program, which averaged 4.5 years for the annual-screening group and 3.6 years for the biennial-screening group, is likely to have further attenuated the effect.<sup>4</sup> Although subjects in the screening groups may have participated in some screening beyond that offered in the study, the data that were collected indicate that this occurred infrequently (data not shown). Finally, screening advances the date of diagnosis and thus leads to a temporary, artifactual increase in incidence. After screening ceases, this effect is diminished.

The use of either annual or biennial fecal occult-blood testing significantly reduces the incidence of colorectal cancer. Preventing colorectal cancers reduces morbidity and is likely to improve the cost effectiveness of screening for colorectal cancer by fecal occult-blood testing.

Supported by research contracts (N01-CB-95613, N01-CB-61005, N01-CB-53862, and R01CA65728) with the National Cancer Institute and by a cooperative agreement with the Centers for Disease Control and Prevention through the Association of Schools of Public Health.

*We are indebted to G. Mary Bradley, D. Engelhard, J. Cordes, and G. Watt for their contributions to this study.*

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