ARTICLES

Colorectal Cancer Mortality: Effectiveness of Biennial Screening for Fecal Occult Blood

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Background: In 1993, a randomized controlled trial in Minnesota showed, after 13 years of follow-up, that annual fecal occult blood testing was effective in reducing colorectal cancer mortality by at least 33%. Biennial screening (i.e., every 2 years) resulted in only a 6% mortality reduction. Two European trials (in England and in Denmark) subsequently showed statistically significant 15% and 18% mortality reductions with biennial screening. Herein, we provide updated results—through 18 years of follow-up—from the Minnesota trial that address the apparent inconsistent findings among the trials regarding biennial screening. *Methods:* From 1976 through 1977, a total of 46 551 study subjects, aged 50–80 years, were recruited and randomly assigned to an annual screen, a biennial screen, or a control group. A screen consisted of six guaiac-impregnated fecal occult blood tests (Hemoccult®) prepared in pairs from each of three consecutive fecal samples. Participants with at least one of the six tests that were positive were invited for a diagnostic examination that included colonoscopy. All participants were followed annually to ascertain incident colorectal cancers and deaths. *Results:* The numbers of deaths from all causes were similar among the three study groups. Cumulative 18-year colorectal cancer mortality was 33% lower in the annual group than in the control group (rate ratio, 0.67; 95% confidence interval [CI] = 0.51–0.83). The biennial group had a 21% lower colorectal cancer mortality rate than the control group (rate ratio, 0.79; 95% CI = 0.62–0.97). A marked reduction was also noted in the incidence of Dukes' stage D cancers in both screened groups in comparison with the control group. *Conclusion:* The results from this study, together with the other two published randomized trials of fecal occult blood screening, are consistent in demonstrating a substantial, statistically significant reduction in colorectal cancer mortality from biennial screening. [J Natl Cancer Inst 1999;91:434–7]

Screening for fecal occult blood statistically significantly reduces colorectal cancer mortality. In 1993, the Minnesota Colon Cancer Control Study, a randomized controlled clinical trial, showed that after 13 years of follow-up, annual fecal occult blood testing reduced colorectal cancer mortality by at least 33%, a result that was statistically significant *(1)*. Subsequently, two published trials *(2,3)* in England and Denmark showed statistically significant mortality reductions of 15% and 18% from biennial (every 2 years) fecal occult blood testing. These results were obtained despite only about 50% compliance with screening and screening positivity rates of less than 2%. The Minnesota trial also evaluated biennial screening. In 1993, when the first results were published, the cumulative colorectal cancer mortality rate in the biennial group was only 6% lower than in the control group, an anomalous result thought to have resulted from a chance excess in the early years of the trial in colorectal cancer mortality in the biennial group relative to the control group. Although screening ended in 1992, the cohort has continued to be followed to ascertain new colorectal cancer cases and deaths. This article presents an update of colorectal cancer mortality through 18 years of follow-up.

METHODS

Detailed descriptions of the study design have already been published *(1,4–7)*. Briefly, during the period from 1976 through 1977, 46 551 men and women aged 50–80 years were recruited from Minnesota and randomly assigned, with stratification by age, sex, and residence, to annual screening, biennial screening, or a control (usual care) group. Participants in the screened groups were asked to prepare six guaiac-impregnated Hemoccult® (SmithKline Diagnostics, Palo Alto, CA) slides from samples obtained in pairs from each of three consecutive fecal samples. The slides were mailed for processing to a central laboratory; except for the initial 3 years of screening, the slides were rehydrated with a drop of deionized water prior to adding the reagent. Rehydration resulted in increased positivity and sensitivity *(7)*. Individuals with one or more positive slides out of a set of six were invited to the University of Minnesota for a diagnostic work-up that included colonoscopy. If colonoscopy was incomplete, a double-contrast barium enema was performed. This study was approved by the University of Minnesota Committee on the Use of Human Subjects in Research in accordance with U.S. Department of Health and Human Services assurance that written informed consent was obtained from every study participant.

The study was initially designed with a 5-year screening period during which five annual screens and three biennial screens were to be completed. The screening began in February 1976 and was completed by December 1982 (phase I). During the subsequent follow-up phase, it became apparent that the death rate in the control group was considerably lower than expected due to a large healthy volunteer effect *(8,9)*. This led to a recommendation from the study's Policy and Data Monitoring Group to reinstitute screening. A second phase of screening began in February 1986 and concluded in February 1992 (phase II). As a result of the hiatus between phases, screen group participants had an interval ranging from 3 to 5 years between the end of the last screening interval of phase I and the first screen attempt of phase II. Because subjects were randomly assigned over a 2-year period, the hiatus between phases varied from individual to individual. Furthermore, because phase I consisted of five 1-year screening intervals for the annual group and three 2-year screening intervals for the biennial group, the average hiatus duration in the annual group was about a year longer than in the biennial group. In all, 11 screens were offered to the annual group and six to the biennial group.

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See "Notes" following "References."

Throughout the study, participants were mailed an annual questionnaire to ascertain colorectal cancer cases among all control group participants, among those screened group participants not taking part in the screening program, and among those diagnosed with the disease between screens (interval cases). The questionnaire also served to identify participants who died since last contact.

Colorectal cancer cases reported in the annual survey have been processed through a validation procedure that included a review of medical and hospital records to verify the diagnosis. A tissue specimen has been obtained and reviewed by the study pathologists to verify the diagnosis and, if colorectal cancer, to classify the stage of cancer according to Dukes' *(10,11)*. To determine the underlying cause of death, a Deaths Review Committee reviewed, without knowledge of study group assignment, all autopsy reports and the medical and hospital records of all decedents in whom gastrointestinal disease was known or suspected to be present at the time of death *(12)*. Since screening ended in 1992, the cohort has continued to be followed by the annual survey to ascertain colorectal cancer incident cases and deaths.

Mortality data were analyzed in the same manner as in Mandel et al. *(1)*, with the exception that no further adjustment for group-sequential monitoring was done since analysis of the 13-year follow-up results. Cumulative estimates of mortality from colorectal cancer at the end of each follow-up year were made with the life table technique, with deaths from other causes censored *(13,14)*. Because sequential monitoring ended in 1992, the 95% confidence intervals (CIs) on 18-year cumulative mortality rates were not adjusted for the earlier group-sequential analyses and are thus nominal for the 95% confidence coefficients. Since these intervals are given for the purpose of estimation and not hypothesis testing, no further adjustment is necessary. It is expected that with further follow-up, the width of CIs will continue to decrease.

RESULTS

During the screening intervals (from 1976 through 1982 and from 1986 through 1992), about one million Hemoccult® tests were processed. Compliance with annual and biennial screening averaged 75% and 78% per screen, respectively *(15)*.

Ninety-five percent of the participants with a positive screen received diagnostic follow-up. Eighty-three percent of the positive screens in the annual group and 84% in the biennial group underwent a complete large bowel examination consisting of colonoscopy or double-contrast barium enema and flexible sigmoidoscopy. Some of the others had a flexible sigmoidoscopy or a barium enema or submitted another fecal occult blood test. Five percent of the participants declined to consult a physician. The annual screen group participants had an average of 3.7 screens in phase I and 4.0 screens in phase II; biennial screen group participants had an average of 2.3 and 2.1 screens per phase. The mean hiatus between phases was 4.48 years for annual group participants and 3.65 years for the biennial group participants, a difference of 0.83 years.

Follow-up for vital status through year 18 was complete for 88.8%, 89.1%, and 88.5% of annual, biennial, and control group participants, respectively. Death certificates were obtained for 99.7%, 99.8%, and 99.8% of known decedents in the three groups, respectively. Through 18 years of follow-up, there were 717 908 total person-years of observation, approximately equally divided among the three study groups (Table 1). There have been 15 635 deaths, representing about one third of the study cohort. Colorectal cancers account for 2.9% of the deaths.

As expected, the cumulative rates of death from all causes were the same in the three study groups, 342, 340, and 343 per 1000 population in the annual, biennial, and control groups, respectively. There were no notable differences in any major cause of death categories (Table 2). However, there was a statistically significant deficit of colorectal cancer deaths in each screened group relative to the control group (Table 1). The cumulative colorectal cancer mortality rate in the annual group was 33% lower than in the control group (rate ratio, 0.67; 95% CI =

Table 1. Screening for fecal occult blood: results through 18 years of follow-up

	Study group		
	Annual screening	Biennial screening	Control
No. enrolled	15 570	15 587	15 394
Person-years of observation	240 325	240 163	237 420
Deaths from all causes			
No. of deaths	5236	5213	5186
Cumulative mortality*	342	340	343
95% confidence interval (CI)†	334–350	333–348	336–351
Deaths from colorectal cancer (CRC)			
No. of deaths	121	148	177
Cumulative mortality*	9.46	11.19	14.09
95% CI†	7.75–11.17	9.39–12.99	12.01–16.17
Cumulative CRC mortality ratio	0.67	0.79	1.00
95% CI†	0.51–0.83	0.62–0.97	—

*Rates shown for mortality are per 1000.

†CIs are not adjusted for earlier group-sequential analysis and thus are nominal.

Table 2. Percent distribution of cause-specific mortality by study group

	Study group		
Cause of death*	Annual screening	Biennial screening	Control
Malignant neoplasms	27.2	28.5	28.3
Ischemic heart disease	29.4	29.8	28.6
Cerebrovascular accident	8.8	8.5	9.3
All other circulatory diseases	10.2	9.9	11.1
Respiratory diseases	8.2	8.0	8.1
Diseases of the digestive system	2.6	2.5	2.1
Accidents	2.8	3.2	2.9
All other causes	9.6	8.5	8.6
Unknown causes	1.0	1.1	1.0
Total	99.8	100.0	100.0

*Underlying cause of death from death certificate coded according to the International Classification of Diseases, 8th Revision *(18)*.

0.51–0.83). The biennial group had a 21% lower colorectal cancer mortality rate than the control group (rate ratio, 0.79; 95% CI = 0.62–0.97). Early in the study, the cumulative colorectal cancer mortality was greater in the biennial than in the control group (Fig. 1). The trend was reversed by the 11th year of follow-up and resulted in a 21% cumulative reduction by year 18.

A total of 1292 adenocarcinomas of the colon and rectum were diagnosed and validated over the 18-year period. A notable feature of the distribution of these cancers by stage is the incidence of Dukes' stage D cancer among the study groups (Fig. 2). Because the 5-year survival rate for Dukes' stage D cancer was only 2.5% compared with 94.3%, 84.4%, and 56.6% for stages A, B, and C, respectively, stage D cancers contribute substantially to the number of colorectal cancer deaths. The annual and biennial screening groups, respectively, had 47% and 32% fewer Dukes' stage D cancers than the control group. This pattern was also observed in the 13-year analysis, for which we reported a 48% and 37% reduction in Dukes' stage D cancer in the two screened groups compared with the control group *(1)*. Between years 13 and 18, when little screening was offered by the study, the percent reduction in Dukes' stage D cancer was 33% and 15%, respectively, for the annual and biennial groups relative to the control group.
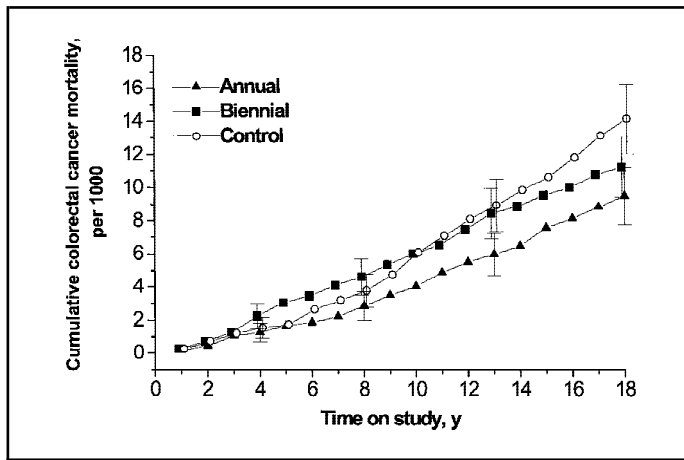
Fig. 1. Cumulative mortality by years since randomization (time on study) for each randomization group (annual, biennial, and control), with the bars at 4, 8, 13, and 18 years representing 95% confidence intervals. Early in the study, cumulative colorectal cancer mortality was greater in the biennial group than in the control group. The trend was reversed by the 11th year of follow-up and resulted in a 21% reduction by year 18.
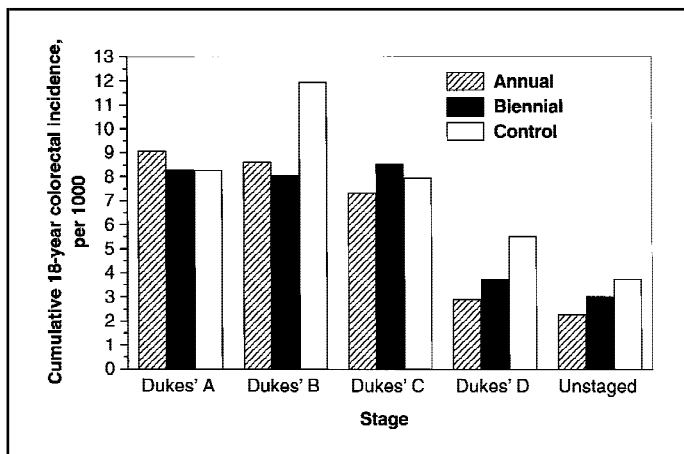

Fig. 2. Cumulative 18-year incidence rate per 1000 by Dukes' stage *(10)* of cancer and study group for all cases of colorectal cancer. A total of 1292 adenocarcinomas of the colon and rectum were diagnosed and validated over the 18-year period. A notable feature of the distribution of these cancers by stage is the incidence of Dukes' stage D among the study groups. Because the 5-year survival rate for Dukes' stage D cancer was only 2.5% compared with 94.3%, 84.4%, and 56.6% for stages A, B, and C, respectively, stage D cancers contribute substantially to the number of colorectal cancer deaths. The annual and biennial screening groups, respectively, had 47% and 32% fewer Dukes' stage D cancers than the control group.

DISCUSSION

At the end of 13 years, we reported that the cumulative colorectal cancer mortality rate was only 6% lower in the biennial group relative to the control group *(1)*. This appeared to be inconsistent with the large benefit found for annual screening and the 37% reduction in Dukes' D stage cancers in the biennial group compared with the control group. At the time, we stated that the higher colorectal cancer mortality rate in the biennial group compared with the control group in the early years of the study was probably due to chance and that additional follow-up might lead to a statistically significant reduction in mortality. This has proven to be the case. Despite the higher colorectal cancer death rate early in the study, the biennial group, through

18 years of follow-up, shows a statistically significant 21% colorectal cancer mortality reduction from the control group. This result is more consistent with the reduction in Dukes' D stage cancers observed earlier *(1)*.

Lang and Ransohoff *(16)* proposed that between 35% and 54% of colorectal cancer deaths prevented in the Minnesota trial resulted from the chance detection of nonbleeding cancers by colonoscopy. In a subsequent paper, Ederer et al. *(17)* using the Lang–Ransohoff model, but with actual rather than estimated data from the Minnesota trial, showed that only between 16% and 25% of the mortality reduction was due to chance detection. The remainder, 75%–84%, was due to sensitive detection by fecal occult blood testing.

Two European randomized trials *(2,3)* have also found statistically significant colorectal cancer mortality reductions from biennial screening with Hemoccult®. The Nottingham trial *(2),* involving 152 850 participants randomly assigned to biennial screening or a control group, evaluated a nonrehydrated Hemoccult® test with a relatively low positivity rate (2.1% on first screen and 1.2% on the three to six subsequent screens) and a low sensitivity (53.6%) but high specificity (98%) for cancer. This trial, despite low compliance with screening (about 50%) and relatively short follow-up (median, 7.8 years), reported a statistically significant 15% mortality reduction.

The Funen trial *(3),* involving 61 933 participants, found a statistically significant 18% mortality reduction. This trial also evaluated biennial screening with a nonrehydrated Hemoccult® test *(3)*. The positivity rate was 1% on the first screen and ranged from 0.8% to 1.8% on the four subsequent screens. Sensitivity of the test was 51% and specificity was 99%. Compliance with each of the five screens averaged about 56% and average follow-up was 10 years.

Three important conclusions emerge from the results of these three randomized controlled trials involving more than 250 000 participants. First, the results published to date are consistent in showing a statistically significant colorectal cancer mortality reduction from biennial screening. The differences in magnitude of the reduction, which ranged from 15% to 21%, may be due to differences in the characteristics of the trials, such as compliance, positivity, test sensitivity, and length of follow-up, or due to chance. Second, the actual benefit to those who comply with screening for fecal occult blood is likely greater than 33% and 21% for annual and biennial screening with rehydrated Hemoccult® and greater than 15%–18% for biennial screening with nonrehydrated Hemoccult® tests. The observed mortality reduction in the three randomized trials is diluted by noncompliance with screening in the screened groups and contamination by screening in the control group and diminished by the hiatus in screening in the Minnesota trial and the relatively short follow-up periods (8 and 10 years) in the European trials. Third, both annual testing and biennial testing for fecal occult blood are effective methods for statistically significantly reducing colorectal cancer mortality, with the benefit from annual screening appearing to be greater than for biennial screening.

It has been suggested that the results of the European trials have greater external validity than the Minnesota trial because, unlike the Minnesota trial, which enrolled volunteers, these studies randomly assigned all eligible members of the population to the screen or control groups, seeking consent only from the screening group, but including the experience of all individuals irrespective of group assignment or consent *(3)*. Compliance is usu-

ally lower in an unselected population than in volunteers. However, the low compliance with screening in the European trials may not represent future compliance, in that the individuals solicited for the trials did not have the incentive of knowing that screening would prove to be effective in reducing colorectal cancer mortality. Now that there is definitive evidence of the effectiveness of screening, compliance with screening might improve as public health education programs are implemented. The challenge is to develop effective strategies to increase screening rates in the average-risk population.

REFERENCES

(1) Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study [published erratum appears in N Engl J Med 1993;329:672]. N Engl J Med 1993;328:1365–71.

(2) Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472–7.

(3) Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sandergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348:1467–71.

(4) Gilbertsen VA, Church TR, Grewe FJ, Mandel JS, McHugh RB, Schuman LM, et al. The design of a study to assess occult-blood screening for colon cancer. J Chronic Dis 1980;33:107–14.

(5) Church TR, Mandel JS, Bond JH, Ederer F, Snover DC, Bradley GM, et al. Colon Cancer Control Study: status and current issues. In: Miller AB, Chamberlain J, Day NE, Hakama M, Prorok PC, editors. Cancer screening. Cambridge (U.K.): Cambridge University Press; 1991. p. 83–106.

(6) Mandel JS, Bond J, Snover D, Williams S, Bradley M, Walker C, et al. The University of Minnesota's Colon Cancer Control Study: design and progress to date. In: Chamberlain J, Miller AB, editors. Screening for gastrointestinal cancer. Toronto (Canada): Hans Huber; 1988. p. 17–24.

(7) Mandel JS, Bond JH, Bradley M, Snover DC, Church TR, Williams S, et al. Sensitivity, specificity, and positive predictivity of the Hemoccult test in screening for colorectal cancers. The University of Minnesota's Colon Cancer Control Study. Gastroenterology 1989;97:597–600.

(8) Ederer F, Church TR, Mandel JS. Sample sizes for prevention trials have been too small. Am J Epidemiol 1993;137:787–96.

(9) Church TR, Ederer F, Mandel JS, Watt GD, Geisser MS. Estimating the duration of ongoing prevention trials. Am J Epidemiol 1993;137:797–810.

(10) Dukes CE. The classification of cancer of the rectum. J Pathol Bacteriol 1932;35:323–32.

(11) Turnbull RB Jr. Cancer of the colon. The five- and ten-year survival rates following resection utilizing the isolation technique. Ann T Coll Surg Engl 1970;46:243–50.

(12) Ederer F, Geisser MS, Mongin SJ, Church TR, Mandel JS. Colorectal cancer deaths as determined by expert committee and from death certificates: a comparison. The Minnesota Study. J Clin Epidemiol. In press 1999.

(13) Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. J Chronic Dis 1958;8:699–712.

(14) SAS/STAT User's Guide. Vol. 2. Version 6. 4th ed. Cary (NC); SAS Institute. 1989.

(15) Thomas W, White CM, Mah J, Geisser M, Church TR, Mandel JS. Longitudinal compliance with annual screening for fecal occult blood. Minnesota Colon Cancer Control Study. Am J Epidemiol 1995;142:176–82.

(16) Lang CA, Ransohoff DF. Fecal occult blood screening for colorectal cancer. Is mortality reduced by chance selection of screening colonoscopy? JAMA 1994;271:1011–3.

(17) Ederer F, Church TR, Mandel JS. Fecal occult blood screening in the Minnesota study: role of chance detection of lesions. J Natl Cancer Inst 1997;89:1423–8.

(18) National Center for Health Statistics. International Classification of Diseases. Adopted for use in the United States. 8th Revision. Washington (DC): Govt Print Off; 1967. Report No: PHS Publ No. 1693.

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