MORBIDITY ANALYSIS

Fecal Occult Blood Testing and the Incidence of Colorectal Cancer

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Objective.—The objective of this abstract is to demonstrate by life table methodology a significant reduction in the mean annual incidence rate of colorectal cancer in randomized groups with annual or biennial screening for fecal occult blood, as compared with the annual incidence rate in the control group.

Background.—Testing for the presence of fecal occult blood has long been used for the early detection of colorectal polyps and potential cancers. The Minnesota Colon Cancer Study, in an earlier report, has shown that colorectal cancer mortality was significantly reduced, but a 12% reduction in incidence of colorectal cancer was not statistically significant. Follow-up in the Minnesota Study has now been extended to 18 years for augmented incidence results, which have now been reported in the source article and in this morbidity abstract.1

Results.—Subjects in Minnesota were recruited in 1975–1978 and randomized into annual or biennial screening for fecal occult blood, and a control group receiving “usual care.” Screening was continued 1976–1982, discontinued, then resumed 1986–1992. During 18 years of follow-up, about 235,000 person-years of exposure were accumulated in each randomized group, with 417 and 435 cases of colorectal cancer in each of the screening groups and 507 cases in the control group.

Conclusion.—Aggregate mean annual incidence rates of colorectal cancer were significantly lower in both screening groups than in the control group, as shown in Table 1. In the source article the same was true for the 18-year cumulative incidence rates, which were also significantly reduced (p < 0.001 for the annual screening group and p = 0.002 for the biennial screening group).

SUBJECTS STUDIED

During 1975 to 1978, 46,551 Minnesota residents were recruited for the Minnesota Colon Cancer Control Study and randomized into 3 nearly equal groups, 2 with annual or biennial screening with a standard test for fecal occult blood, and 1 with a control group receiving “usual care.” Subjects were adults in the approximate age range of 50 to 80 years; 48.1% were male and 51.9% were female. Persons with a history of prior colorectal cancer were excluded. The “Hemoccult” test kit was used for screening. This consisted of 3 sets of 2 guaiac-impregnated paper slides...
Table 1. Cumulative 18-Year Incidence of Colorectal Cancer in the Minnesota Cancer Control Study Randomized Groups With Annual or Biennial Screening for Fecal Occult Blood and a Control Group

<table>
<thead>
<tr>
<th>Screening Group</th>
<th>Number of Subjects</th>
<th>Exposure Person-Yrs.</th>
<th>Observed No. of Cancer Cases</th>
<th>Expected* No. of Cancer Cases</th>
<th>Morbidity Ratio 100 n/n'</th>
<th>Mean Annual Incidence Rate/1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (Usual care)</td>
<td>15,363</td>
<td>232,612</td>
<td>(507)</td>
<td>507</td>
<td>(100%)</td>
<td>(2.18)</td>
</tr>
<tr>
<td>Annual</td>
<td>15,532</td>
<td>235,584</td>
<td>417</td>
<td>514</td>
<td>81</td>
<td>1.8</td>
</tr>
<tr>
<td>Biennial</td>
<td>15,530</td>
<td>235,513</td>
<td>435</td>
<td>513</td>
<td>85</td>
<td>1.8</td>
</tr>
</tbody>
</table>

* Basis of expected cases of colorectal cancer: control subjects not regularly screened for fecal occult blood.

to hold a small portion of a stool specimen, so that 3 different stool specimens could be sampled. Specimens were returned to the University of Minnesota investigators for reading. Screening was carried out from 1976 to 1982, followed by a hiatus, and then screening was renewed from 1986 to 1992. In a 1992 report from this study, it was demonstrated that screening was associated with a significant reduction in colorectal cancer mortality. However, a 12% reduction in the incidence of colorectal cancer was not statistically significant. This led to a resumption of the follow-up observation.

Subjects with a positive test for occult blood were invited to undergo a diagnostic evaluation that consisted of a history, examination, routine laboratory studies, barium enema, flexible colonoscopy (or rigid rectosigmoidoscopy in the early part of the study), ECG and chest x-ray. If polyps were detected on colonoscopy, they were routinely removed and examined. Such diagnostic evaluation was continued through 1993.

FOLLOW-UP

All subjects were requested to complete an annual questionnaire on vital status, newly diagnosed colorectal polyps and cancers in the control group, and in the other groups when the lesions were not related to screening. In all 3 groups, colorectal cancers were confirmed by review of all medical records from the treating physicians or hospital. Slides were also reviewed to confirm the diagnosis and staging. From 1988 through 1994, cases of colorectal cancer were also identified through linkage to the Minnesota Cancer Surveillance System, which collects data on all newly diagnosed and pathologically confirmed cancer cases in Minnesota. A special committee whose members were not acquainted with the randomized grouping of the cases reviewed death records. Follow-up for vital status was over 95% complete through 17 years of follow-up and over 91% complete through 18 years. In Figure 1 of the source article, follow-up data are given through 18 years.

RESULTS

In the total period in which screening was offered, 11 annual and 6 biennial screenings were potentially possible. The rate of compliance was 75% for the annual and 78% for the biennial screenings. Of those with positive tests, about 84% accepted diagnostic evaluation, including complete colonoscopy, 11% had barium enema and proctosigmoidoscopy, and 5% declined to consult a physician. Overall, 75% of the subjects with positive screening tests were evaluated at the University of Minnesota Medical Center or clinics.

With life table methodology used during the 18 years of follow-up, approximately 235,000 person-years of exposure were recorded in each group (exact totals are given in Table 1). In the annual screening group, 417 cases of colorectal cancer developed, 435 cases in the biennial screening group and in the
control group 517 cases, as shown in Table 1. The mean annual incidence rate for colorectal cancer in the control group was 2.17 cases per 1000 per year. Significantly lower rates were found in the 2 screening groups, with a morbidity ratio of 81% for the annual and 85% for the biennial screening groups. By the Poisson distribution, 2 standard deviations (2 SD) for the 507 cancer cases in the control group are derived as \((1.96)(507)^{1/2}\), or \((1.96)(22.5)\), or ±44 cases. The lower 95% confidence limit would then be 507–44, or 463 cancer cases. It is clear that this limit is well above the observed numbers of 417 and 435 cases in Table 1.

In the source article the authors did not calculate \(r = 1000(n/e)\) as shown in Table 1. Instead, they calculated the annual cumulative incidence rates, \(R = 1 - P\), for all 3 groups and showed the results in Figure 1. The 18-year cumulative incidence \(R\) was 0.32 in the annual screening group, 0.33 in the biennial screening group, and 0.39 in the control group. On the basis of slightly different morbidity ratios, they determined \(P\) values for the differences from the control group of <0.001 for subjects screened annually and 0.002 for those screened biennially.

Table 2 of the source article gives the predictive value for adenomatous polyps >1 cm and for colorectal cancer, according to the number of positive tests (numbers 1 to 6). For these data and other details, the reader is referred to the source article.

**COMMENT**

I consider this study to be noteworthy for several reasons. Testing for occult blood in the stools is a useful, common, low-cost procedure often used in checkup examinations. Unusually large subject groups were randomized (over 15,000 in each group) for this clinical trial. After an initial cutoff date, the data were apparently sufficient to demonstrate a statistically significant reduction in mortality due to colorectal cancer. The mechanism for this was chiefly through the discovery of adenomatous colonic or rectal polyps and their removal, regardless of whether malignant changes were found or not. However, a 12% reduction in cancer incidence rate was not statistically significant. The investigators then made a decision to resume their screening and control follow-up, and this was done for a total duration of 18 years. A remarkable exposure of about 235,000 exposure-years and well over 400 cases of colorectal cancer were achieved in each group. The reduction in annual incidence rate in the screening groups below the control rate increased to 15% or 19%, reductions with a very high statistical significance. They state that this is the first randomized clinical trial showing a significant reduction in cancer incidence rates. They deserve a “well done” for their accomplishment.

**REFERENCE**