Fecal Occult Blood Screening in the Minnesota Study: Role of Chance Detection of Lesions

Fred Ederer, Timothy R. Church, Jack S. Mandel*

Background: In the Minnesota Colon Cancer Control Study, annual fecal occult blood testing reduced mortality from colorectal cancer by at least 33.4%. Some attribute a large part of this reduction to chance detection of cancers by colonoscopies; rehydration of guaiac test slides greatly increased positivity and consequently the number of colonoscopies performed. This study was conducted to determine how much of the reduction resulted from chance detection. Methods: We used a mathematical model developed by Lang and Ransohoff to estimate the proportion of the 33.4% mortality attainable by chance alone. Applying the model requires the specification of five parameters: duration of follow-up, rate of compliance with fecal occult blood testing, rate of compliance with colonoscopy, positivity rate, and efficacy of colonoscopy in reducing colorectal cancer mortality. We took values for four of the five parameters directly from the Minnesota study. For the fifth parameter, efficacy of colonoscopy, we selected a value of 60%, based on the conclusions of another study. Whereas the Lang–Ransohoff model selects persons for colonoscopy by chance alone, those with bleeding cancers would also be selected by sensitive fecal occult blood testing. We therefore adjusted the result of the Lang–Ransohoff model for this dual detectability. Results: We found that 16%–25% of the reduction in colorectal cancer deaths effected by fecal occult blood testing in the Minnesota study was due to chance detection; the remainder was due to sensitive detection. Conclusion: Chance played a minor role in the detection of colorectal cancers by fecal occult blood testing in the Minnesota study. [J Natl Cancer Inst 1997;89:1423–8]
lower (by 33.4%) in the annually screened group than in the control group was attained after 13 complete follow-up years. The observed 33.4% effect is likely to underestimate the true potential of rehydrated fecal occult blood screening in this population because 1) 10% of the annual group did not complete any screens, and only 46% completed all screens; 2) some control group participants were screened by their physicians; 3) screening in the study was interrupted for 4 years; 4) 17% of the test slides were not rehydrated; and 5) 17% of the participants did not have a complete bowel examination after a positive test.

### Lang–Ransohoff Method

The Lang–Ransohoff method (5) is based on the idea that the reduction in mortality from colorectal cancer observed in the Minnesota study is attributable to the detection of both bleeding and nonbleeding cancers, with the discovery of nonbleeding cancers being due to the chance presence of fecal blood from other sources or the chance presence of other substances producing positive test results (e.g., certain digested foods). With the goal of estimating the proportion of the mortality reduction that was due to this chance effect, Lang and Ransohoff (5) constructed a mathematical model that simulates the 13-year experience of the annually screened group of the Minnesota study, with this exception: The screening test in this model is independent of (i.e., not associated with) the presence of cancer, so that selection for colonoscopy is purely by chance (“random colonoscopies”).

Underlying assumptions of the Lang–Ransohoff simulation are that the study population is aged 60 years at the outset, is followed long term, and is screened annually for occult blood during the first 5 years (phase I), is followed without screening for the next 4 years, and is then screened annually for the remainder of follow-up (phase II). Specification of the size of the population is unnecessary because results are expressed in percentages. Colonoscopies occur only after positive screens. The annual age-specific rates of mortality from colorectal cancer and from all causes are determined from U.S. life tables. After a colonoscopy, for a period of 5 years, or alternatively one of 10 years, screening is suspended, and risk of death from colorectal cancer is reduced by a specified amount (e.g., 60%). Additional parameters of the model are rate of compliance with fecal occult blood screening, rate of compliance with colonoscopy, and positivity rate (Table 1).

In that the Lang–Ransohoff model selects purely by chance, it simulates the manner of selection for colonoscopy of nonbleeding cancers in the Minnesota study. From the ratio of the chance reduction projected by the model to the reduction achieved in the Minnesota study (33.4%), one can determine the maximum role that chance could have played in the achieved mortality reduction. The model is limited to determining the maximum role of chance because, under the model’s constraints, all cancers that are discovered are discovered by chance alone. The model makes no provision for the real-life eventuality that in fecal occult blood screening some deaths prevented through chance selection for colonoscopy are also prevented through sensitive detection by the fecal occult blood test. Whereas the Lang–Ransohoff model simulates the manner of selection for colonoscopy under the theoretical construct that the blood found in all positive tests comes from sources other than cancer, in reality, cancer is present in the study population, some cancers do bleed, and bleeding cancers are detectable by both chance and sensitive fecal occult blood testing.

The effect of this dual detectability is illustrated in the Venn diagram (Fig. 1), in which the entire C circle represents the estimate from the Lang–Ransohoff model of the percent reduction in colorectal cancer mortality effected by chance detection. The entire S circle represents the reduction effected by sensitive fecal occult blood detection, and the overlap of the two circles represents the percent reduction effected by both sensitive testing and chance. The union of the two circles represents the entire reduction by screening in the Minnesota study. Thus, while the entire C circle represents the theoretical maximum reduction effect when chance is the only factor, in actual fecal occult blood screening, when chance and sensitive testing operate simultaneously, the theoretical maximum is diminished by the amount of overlap of the two circles (gray area). Were chance alone operative, sensitivity would be equal to the positivity of the test, which was 8.5% for the annually tested group in the Minnesota study. The actual sensitivity of that test, as shown by Church et al. (7), was about 90%, rather than 8.5%, indicating that the overlap between the circles in the Venn diagram is more than trivial and that the theoretical maximum chance effect, as estimated by the Lang–Ransohoff model, is likely to be a substantial overstatement of the true chance effect. The ratio R of the proportionate chance mortality reduction projected by the model to the 0.334 proportionate reduction effected in the Minnesota study is an estimate of the theoretical maximum proportionate reduction due to chance detection in that study. Thus, 1 − R represents the incremental effect of sensitive reduction (i.e., the increase in efficacy from adding fecal occult blood testing to chance selection for colonoscopy).

To assess the size of the overlap in Fig. 1, we assume the chance and sensitive detection effects to act independently. This assumption, like most simplifying assumptions, does not strictly hold for the following reasons: 1) The results of successive screens are interdependent, and 2) although the two mechanisms of detection (chance and sensitivity) are independent per se, their method of preventing death (e.g., by effective treatment of carcinoma) may be the same in particular cases. Nevertheless, the simplifying assumption leads to a useful approximation (7). The total mortality reduction R, under the assumption, can be expressed as

\[
R = C + S - CS, \tag{1}
\]

where C is the theoretical maximum reduction in mortality due to chance detection in the Minnesota study and S is the theoretical maximum reduction due to sensitive detection in the absence of chance. The sensitive detection effect S from equation 1 is

\[
S = (R - C)/(1 - C). \tag{2}
\]

Substituting the estimate of C from the Lang–Ransohoff model and the value of 0.334 for R yields an estimate of S. The extent to which chance inflates the effectiveness of screening over and above the effect of sensitive detection is the difference between the observed effect and the theoretical maximum effect of the fecal occult blood test. This marginal effect of chance in the presence of a sensitive detection effect of size S can be expressed by

\[
C_{adj} = R - S = R - (R - C)/(1 - C) = C(1 - R)/(1 - C). \tag{3}
\]

### Table 1. Annually screened group of the Minnesota study: differing parameter specifications for the two applications [our application and application by Lang and Ransohoff (5) of the Lang–Ransohoff model]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Our application (column 1)</th>
<th>Lang–Ransohoff application (column 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Duration of follow-up</td>
<td>13 y*</td>
<td>15 y</td>
</tr>
<tr>
<td>2) Rate of compliance with fecal occult blood testing</td>
<td>Phase I: 85%, 78%, 75%, 73%, 73%*†</td>
<td>Fixed at 80%</td>
</tr>
<tr>
<td>3) Rate of compliance with colonoscopy</td>
<td>Phase I: 86.5% (all screens)*</td>
<td>Fixed at 80%</td>
</tr>
<tr>
<td>4) Positivity rate</td>
<td>Phase I: 2.0%, 2.7%, 7.0%, 8.2%, 9.5%*†</td>
<td>Fixed at 10%</td>
</tr>
<tr>
<td>5) Efficacy of colonoscopy in reducing colorectal cancer mortality</td>
<td>50%–70%, with 60% as base case</td>
<td>50%–90%, with 70% as base case</td>
</tr>
</tbody>
</table>

*Actual values from the Minnesota study (1).
†By screen, in order, from the first to last screen; phase I had five screens, and phase II had six screens.
Hence, under the assumption of independence, adjustment of $C$ by the factor
\(1 - R/(1 - C)\) yields (approximately) the marginal effect of chance.

Application of the Lang–Ransohoff model requires the specification of values
for the five parameters shown in Table 1. As discussed earlier, the parameter
values specified in our application of the model (column 1, Table 1) differ from
those specified in Lang and Ransohoff’s application (5) (column 2). Our values
for the first four parameters are the observed values taken directly from the 13
years of follow-up experience of the group assigned to receive annual screening
in the Minnesota study (1): 1) duration of follow-up, 13 years; 2) rate of com-
pliance with fecal occult blood testing, year by year, as observed; 3) rate of
compliance with colonoscopy, by phase, as observed; and 4) positivity rate, year by
year, as experienced. The choice of the fifth parameter, the efficacy of colonos-
copy in reducing colorectal cancer mortality, rests on the assumption that the
relative efficacy of colonoscopy in preventing deaths from cancer of the entire
colorectum approximately equals the efficacy of rigid sigmoidoscopy in pre-
venting deaths from cancer of the distal colorectum detectable by the sigmoid-
oscope. Our “base case” (Lang and Ransohoff’s term) of this parameter, 60%,
is based on the odds ratio 0.41, which was adjusted for potential confounding
factors, provided in the report on the case–control study of sigmoidoscopy by
Selby et al. (8). The odds ratio 0.41 implies an efficacy of 1.00 – 0.41 = 0.59,
or 59%, which we rounded to 60%. In addition to 60%, we applied the values
50% and 70% for this parameter. For a sixth parameter, duration of colonoscopy
efficacy, we used the same values (5 and 10 years) as those used by Lang and
Ransohoff (5).

Results

Table 2 presents the results of our application and of Lang
and Ransohoff’s application of their model to the results for the
annually screened group of the Minnesota study. With actual
observed values from the Minnesota study as parameters, we
find that the theoretical maximum reduction in colorectal cancer
that is due to chance, expressed as a percent of all deaths pre-
vented in the Minnesota study, ranges from 27% to 39%; when
the adjustment is made for the overlap with sensitive detection,
the estimated range becomes 19%–30%; and when the efficacy
of colonoscopy is limited to our base case of 60%, the estimated
chance reduction adjusted for sensitive detection reduces further
to 16%–25% (Table 2). Thus, we estimate that between about
one sixth and one fourth of the deaths prevented by annual fecal
occult blood screening in the Minnesota study were prevented
by chance, and the rest were prevented by sensitive fecal occult
blood testing.

With Lang and Ransohoff’s approximate parameter values,
the estimates of chance reduction are larger. The theoretical
maximum reduction ranges from 25% to 54%. When adjusted
for overlap with sensitive detection, the range is reduced to
18%–44%. When the efficacy of colonoscopy is limited to the
Lang–Ransohoff base case value of 70%, the range is 26%–
44%.

<table>
<thead>
<tr>
<th>Efficacy of colonoscopy in reducing colorectal cancer mortality, %</th>
<th>Minnesota study parameter values*</th>
<th>Lang and Ransohoff’s approximations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Theoretical maximum (C) (column 1)</td>
<td>Reduction in colorectal cancer</td>
<td>Reduction in colorectal cancer</td>
</tr>
<tr>
<td></td>
<td>mortality due to chance, %</td>
<td>prevented in Minnesota study,</td>
</tr>
<tr>
<td></td>
<td>Adjusted approximately</td>
<td>% prevented by chance alone</td>
</tr>
<tr>
<td></td>
<td>for sensitive detection (C_{adj})</td>
<td>(column 2)</td>
</tr>
<tr>
<td>50</td>
<td>6.3</td>
<td>19</td>
</tr>
<tr>
<td>60</td>
<td>7.6</td>
<td>23</td>
</tr>
<tr>
<td>70</td>
<td>8.9</td>
<td>27</td>
</tr>
</tbody>
</table>

5 years of protection by colonoscopy

| 50 | 9.4 | 28 | 12.9 |
| 60 | 11.2 | 34 | 15.4 |
| 70 | 13.1 | 39 | 18.0 |

10 years of protection by colonoscopy

| 50 | 9.9 | 21 | 12.9 |
| 60 | 11.2 | 25 | 15.4 |
| 70 | 13.1 | 30 | 18.0 |

*Parameters 1 through 4 in Table 1.
Discussion

After the Minnesota study results were published, Ahlquist et al. (9) asked whether the colorectal cancer mortality reduction from annual screening achieved in the Minnesota study ‘... can be attributed to an artifact of the very high rate of false positive results (occurring in 10 percent of those screened each year) and consequent numerous colonoscopies. ... Perhaps the random performance of 10,000 colonoscopies in this group, irrespective of the test results, would have yielded a similar outcome.’’

Lang and Ransohoff (5) picked up on this theme: ‘... the benefit of colorectal cancer mortality reduction in the Minnesota study could occur either because fecal occult blood testing successfully identifies bleeding neoplasms, or because rehydration of slides in frequent positive tests and colonoscopy then detects nonbleeding neoplasms ... it is important to clarify how much each of these mechanisms may contribute to cancer mortality reduction. We constructed a simple mathematical model to assess the contribution of chance when fecal occult blood testing is performed annually with slide rehydration.’’

Lang and Ransohoff (5) estimated, from their base case analysis using their model (column 7, Table 2), that between 35% and 54% (‘‘between a third and a half’’) of colorectal cancer deaths prevented in the Minnesota study were the result of chance discovery of nonbleeding cancers by colonoscopy. Our estimate of that fraction, between 16% and 25% (between one sixth to one fourth) (column 4, Table 2), amounts to about half of their estimate. According to our estimate, a large majority (75%–84%) of the colorectal cancer deaths prevented by annual screening in the Minnesota study resulted from sensitive detection of bleeding cancers.

Three elements account for the difference between our results in column 4 of Table 2 and results obtained by use of Lang and Ransohoff’s application of their model in column 7: 1) the differences in values chosen for the screening parameters (first four parameters in Table 1); 2) the difference in base case values chosen for the efficacy of colonoscopy (60% versus 70%) (fifth parameter in Table 1); and 3) Lang and Ransohoff’s use of the theoretical maximum estimate versus our adjustment for the overlap with sensitive detection, which we will call the ‘‘method’’ element (Fig. 1).

Table 3 presents for both a 5-year and a 10-year colonoscopy effect the relative contribution of each of the three elements to the overall difference in the effect of chance. The contributions, expressed as percents, were determined as follows: Beginning with Lang and Ransohoff’s choice of parameter values (first two elements) and method (third element), we substituted arbitrarily, beginning with the first element and adding one element at a time, our own choice of values or method. We illustrate the method of calculation using 5 years of efficacy for colonoscopy. Lang and Ransohoff’s result for this case was 35% (Table 2, row 3, column 7), whereas our result was 16% (Table 2, row 2, column 4); the difference between the two results is 19%. To determine the fraction of this 19% that is accounted for by the first element, we substituted our own values of the first element only (leaving Lang and Ransohoff’s choices for the second and third elements unchanged), obtaining the value 27% from Table 2, row 3, column 3. The difference between the Lang–Ransohoff result, 35%, and this value is 8%, shown in Table 3, row 1, column 1. The ratio (expressed as a percent) of this difference to 19% (the total difference between Lang and Ransohoff’s and our results) amounts to 8%/19% = 42%. This value, shown in Table 3, row 1, column 3, is the relative contribution of the change in first element (the four screening parameter values). Coming to the second element (efficacy of colonoscopy), it was changed from 70% to 60%, while our values for the screening parameters were retained. This result (23%; Table 2, row 2, column 3) is subtracted from the result changing only the screening parameters (27%), and the difference (4%) is divided by the total difference of 19% to get the 21% in Table 3, row 2, column 3.

The results of the sensitivity analysis (Table 3) are discussed below (see elements 1–3).

For element 1, our choice of exact values of the Minnesota study for the first four parameters of Table 1 in place of Lang and Ransohoff’s approximate values accounts for 42% (5-year colonoscopy effect) to 52% (10-year colonoscopy effect) of the difference in the outcomes of applying the model. A particularly important parameter is the difference in positivity rates, which Lang and Ransohoff fixed at 10%, whereas we took actual values, rising from a low of 2% in the early years of the study when slides were not rehydrated to a high of 15% toward the end of screening, when all slides were rehydrated, and by which time the population had aged some 13 years.

<table>
<thead>
<tr>
<th>Element</th>
<th>Decrease in chance effect when change to element is added to prior changes, %</th>
<th>Relative contribution of element, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Choices of first four parameters of Table 1, column 1</td>
<td>8 15</td>
<td>42 52</td>
</tr>
<tr>
<td>2) Efficacy of colonoscopy = 60% versus 70%</td>
<td>4 5</td>
<td>21 17</td>
</tr>
<tr>
<td>3) Adjustment for overlap versus theoretical maximum estimate</td>
<td>7 9</td>
<td>37 31</td>
</tr>
<tr>
<td>Total change (approximate)</td>
<td>19 29</td>
<td>100 100</td>
</tr>
</tbody>
</table>

*Table shows the relative incremental contribution of each of three elements to the difference in the percentage of the colorectal cancer mortality prevented by chance alone.

1426 ARTICLES

Journal of the National Cancer Institute, Vol. 89, No. 19, October 1, 1997
For element 2, about 21% (5-year effect) to 17% (10-year effect) of the difference in results is explained by a difference in the choice of base case value for the efficacy of colonoscopy. Lang and Ransohoff’s choice of 70% was based on the odds ratio of 0.30, unadjusted for confounding, from the case–control study of sigmoidoscopy by Selby et al. (8); our choice of 60% is based on the adjusted odds ratio of 0.41 from that study, the value presented in the conclusion of the published report. The study by Selby et al. (8) on the relation of rigid sigmoidoscopy to mortality from colorectal cancers within reach of the sigmoidoscope (20 cm) was conducted among members of a health maintenance organization that had encouraged periodic sigmoidoscopic screening. The potential confounders that Selby et al. adjusted for are personal history of colorectal cancer or polyp, family history of colorectal cancer, and number of periodic health checkups. Taking into account additional potential confounding factors, either unknown or known [such as diet and physical activity (10)], for which Selby et al. (8) did not adjust, might further reduce the odds ratio and the estimated chance effect.

For element 3, about 37% (5-year effect) to 31% (10-year effect) of the difference is explained by the adjustment of the theoretical maximum for overlap with sensitive screening. The estimate produced by the Lang–Ransohoff model is a theoretical maximum reduction due to chance, a maximum that is reduced, as illustrated by the overlap in Fig. 1, by the fact that some cancers (e.g., some bleeding cancers) are detectable both by random colonoscopies in the Lang–Ransohoff model and by sensitive fecal occult blood screening.

Although the Minnesota study (1) found, as have a number of other prevention studies, that event rates and rates of mortality from all causes among members of the study’s control group are substantially lower than those of the general population (11), in our application of the Lang–Ransohoff model, we retained the general U.S. mortality statistics used by Lang and Ransohoff (5) because we found the Lang–Ransohoff model to be insensitive to even moderately large changes in mortality rates.

Lang and Ransohoff’s base case analysis led to the estimate that 40.8% of the annually screened subjects of the Minnesota study underwent one or more colonoscopic examinations (5), a proportion similar to the 38% actually reported for that group of subjects in the Minnesota study (1). In presenting the value of 38%, the authors neglected to clarify that this result pertained not to the first 13 years of complete follow-up (i.e., the period in which the 33.4% mortality reduction was attained) but to the first 17 years, the last four of which had incomplete (censored) follow-up. The proportion of the annually screened group with one or more colonoscopies was 31% after 13 years and only 16% after 9 years (Fig. 2). We mention the 9-year result because nonbleeding cancers that were discovered between years 10 and 13 could have contributed a small amount to the 13-year mortality reduction: 1) Discovery time for these tumors was short (4 years), 2) their follow-up was short (average of about 2 years), and 3) nonbleeding cancers are likely to be mostly in an early stage [i.e., Dukes’ stages A and B (12)], for which mortality rates are low. Thus, colonoscopies that could have contributed to the 33.4% colorectal cancer mortality reduction through the discovery of nonbleeding cancers were administered to only a small fraction of the annually screened population—perhaps about 16%.

Lang and Ransohoff (5) stated that the sensitivity of their random colonoscopy model is zero “...and all positive fecal occult blood test results are false positives.” As we have indicated, when colorectal cancers are present in the population, some will be discovered by random colonoscopies, which leads to a sensitivity greater than zero. In the Lang–Ransohoff model, positive tests are not associated with the presence of colorectal cancer, so that the sensitivity is minimal, but not zero, unless the prevalence of colorectal cancer in the screened population is zero, which is not the case for the Minnesota study population.

Although the Lang–Ransohoff model allows for prevention of colorectal cancer death by removal of adenomatous polyps, it is unlikely that substantial numbers of deaths were prevented by this method during the first 13 years of follow-up. A nonsignificant reduction in cumulative colorectal cancer inci-

Fig. 2. Of participants assigned to receive annual screening in the Minnesota study (1), the cumulative percentage who, after a positive fecal occult blood test, had 1) at least one adequate bowel examination and 2) at least one colonoscopy by follow-up year. Also plotted for the annually screened group is the percent reduction in cumulative mortality from colorectal cancer.
dence was noted in the annually screened group relative to the control group between the 9th and 13th years, suggesting a possible effect of polyp removal on incidence (1). Additional follow-up may clarify whether there is an effect of polyp removal.

The data in Fig. 2 lend support to our finding that the large number of colonoscopies did not contribute in a major way to the mortality reduction in the Minnesota study. Plotted in this figure, in addition to the cumulative percent with adequate bowel examinations (colonoscopy or sigmoidoscopy plus barium enema) and cumulative percent with colonoscopy for the annually screened group in the Minnesota study, is the reduction in percent cumulative mortality for that group. The percent with colonoscopy lags the percent mortality reduction until the 12th and 13th years, indicating that the decrease in mortality preceded by a number of years the colonoscopy of a commensurate fraction of the subjects; the cumulative percent mortality reduction would have lagged the cumulative colonoscopy rate had the many colonoscopies been a major contributor to the mortality reduction.

Cost assessment of fecal occult blood test screening will be important in formulating public health policy. In the Minnesota study, screening was not suspended after a false-positive screen (i.e., a positive fecal occult blood test leading to a colonoscopy that did not detect either cancer or adenoma). In such false-positive screens outside the study, follow-up screening would probably not have been needed for at least 5 years. This feature of the Minnesota study has obvious implications for cost–benefit analyses based on the Minnesota experience (13). From a mathematical model of continuous annual screening over a 10-year period (rather than with interrupted screening as it occurred in the Minnesota study), we estimate that a 5-year suspension of screening after a false-positive screen would have reduced the number of fecal occult blood tests and colonoscopies in the annual group of the Minnesota study by 13.5%.

We conclude that the 33.4% reduction in colorectal cancer deaths among subjects offered annual fecal occult blood test screening in the Minnesota study was predominantly (i.e., for 75%–84% of the subjects) because of sensitive detection of colorectal cancers by the test; chance detection played only a minor role. This finding is consistent with that of a sensitivity of about 90% for the Minnesota study, arrived at by various methods of estimation (7).

References


Notes

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1428 ARTICLES
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