Debate

Fecal occult blood screening for colorectal cancer: open issues

C. La Vecchia*

Istituto di Ricerche Farmacologiche 'Mario Negri', & Istituto di Statistica Medica e Biometria, Università degli Studi di Milano, Milan, Italy

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Data from seven case–control and—mainly—three randomized clinical trials consistently indicate that biennial fecal occult blood screening (FOBT) can reduce colorectal cancer (CRC) mortality by ∼20% after 10–18 years. The reduction may be greater in compliant subjects. In the long-term, incidence also appears to be reduced. There are suggestions that the effect of annual screening may be greater, although data are inadequate to quantify the potential advantages of annual versus biennial screening. The issue of the effectiveness of FOBT in the general population and, more important, of comparative cost-effectiveness with other possible screening tests for CRC, however, remain open to discussion.

Key words: colorectal cancer, fecal occult blood tests, screening

Colorectal cancer (CRC) mortality rates have been declining in males and, mostly, in females from developed countries over the last decade. In the European Union the overall fall in age-adjusted rates was >12% for males and >20% for females between 1988 and 1997 [1]. At least in part these favourable trends may be attributable to improved diagnosis of the disease, including through the use of fecal occult blood testing (FOBT). The evidence that FOBT reduces the incidence and mainly the mortality from CRC comes from observational (case–control) studies, and mainly, from randomized intervention studies.

The main results from seven case–control studies providing data on FOBT and CRC mortality are given in Table 1 [2–8]. Of these, one was conducted in Germany [2], two in the USA [3, 4], one in Japan [5], two in Italy [6, 8] and one in France [7]. Although the estimates are somewhat variable, possibly also on account of random variation, all of these gave relative risks (RRs) below unity, and most estimates were ~0.7, thus being compatible with a 30% reduction of CRC mortality in subjects undergoing FOBT screening over the few years preceding diagnosis.

There are, however, possible biases in case–control studies of screening effectiveness, specifically related to the inclusion or exclusion of the examination from which diagnosis is made, which may lead to positive or negative bias, respectively [9, 10]. The best evidence on the issue, therefore, has to come from randomized controlled studies.

At least three randomized controlled trials are available and have been published as full papers on FOBT and CRC incidence and/or mortality. Their main results are summarized in Table 2 [11–14].

Of these, one was conducted in Nottingham, UK, and included 76 465 subjects aged 45–79 allocated to biennial un-rehydrated FOBT, and 76 384 controls recruited between 1981 and 1997, and followed-up to 1995 for a median of 7.8 years [11]. Incidence of CRC was similar in subjects offered FOBT screening (893 cases, 149/100 000 person-years) and in the control group (856 cases, 144/100 000 person-years). Mortality from CRC was 15% lower in the screening group: 360 deaths from CRC were observed versus 420 in the comparison group, corresponding to an RR of 0.85 [95% confidence interval (CI) 0.74 to 0.98]. Only 236 of 893 (26%) cancers in the FOBT screening group were detected at screening, pointing to a relatively low compliance (only 38% of individuals who attended screening completed all the tests) and/or limited sensitivity, which was estimated to be ~54%. Only 4% of all individuals who completed FOBT underwent colonoscopy [11].

A Danish study [12] considered 137 485 individuals aged 45–75 in the town of Funen over the period 1985–1995. Of these, 30 967 were offered biennial un-rehydrated FOBT (screening group), 30 966 no intervention (control group) and 75 552 were not enrolled. For the screening group, compliance was ~67% for the first round, and >90% for repeated screening in those who had first-round FOBT screening. During the 10-year period of the study, 481 CRCs were diagnosed in the screened group compared with 483 in the comparison group. There were 205 deaths from CRC in the screening group compared with 249 in the control group, corresponding to an RR of 0.82 (95% CI 0.68 to 0.99). Of the 20 632 participants screened at least once, only 4% underwent colonoscopy. As expected, screening detected cases had considerably longer survival.
The Minnesota Colon Cancer Control Study [13], included 46,551 subjects, mainly aged 50–80 years, recruited between 1975 and 1978, and randomly assigned to annual (about 83%) rehydrated FOBT screening (n = 15,570), biennial screening (n = 15,587) or control (n = 15,394). The 13-year cumulative mortality [13] was 5.88 in the annually screened group, 8.33 in the biennially screened group and 8.83 in the control group. The conclusion was that FOBT with rehydration decreased 13-year cumulative mortality from CRC by ~33% in the annually screened group, but by only 6% in the biennially screened group.

The same dataset was followed up at 18 years for CRC mortality [14] and incidence [15]. At 18 years, 121 deaths from CRC were registered in the annual screening, 148 in the biennial screening and 177 in the control group. The corresponding RRs were 0.67 for the annual (95% CI 0.51 to 0.83) and 0.79 for the biennial (95% CI 0.62 to 0.97) screening group. Compliance was between 75% and 78% per screening, as compared with 50% to 56% in the European [11, 12] trials. Thus, the actual advantage in mortality for compliant subjects is likely to be higher than the 18% to 33% estimated in various studies.

Table 1. Main results from selected case–control studies of FOBT screening for CRC

<table>
<thead>
<tr>
<th>Study, year, location [ref. no.]</th>
<th>No. of CRC deaths</th>
<th>No. of controls</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahrendorf et al. 1991</td>
<td>163 males</td>
<td>694 males</td>
<td>0.92 (0.61–1.75)</td>
</tr>
<tr>
<td>Saarland, Germany [2]</td>
<td>209 females</td>
<td>846 females</td>
<td>0.43 (0.27–0.61)</td>
</tr>
<tr>
<td>Selby et al. 1993</td>
<td>485</td>
<td>727</td>
<td>0.69 (0.52–0.91)</td>
</tr>
<tr>
<td>California, USA [3]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lazovich et al. 1995</td>
<td>248</td>
<td>496</td>
<td>0.7 (0.5–1.0)</td>
</tr>
<tr>
<td>Washington, USA [4]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saito et al. 1995</td>
<td>193</td>
<td>579</td>
<td>0.4 (0.2–0.9) &lt;1 year</td>
</tr>
<tr>
<td>Amobi, Japan [5]</td>
<td></td>
<td>0.5</td>
<td>0.5 (0.3–0.9) &lt;3 years</td>
</tr>
<tr>
<td>Zappa et al. 1997</td>
<td>206</td>
<td>1030</td>
<td>0.6 (0.4–0.9)</td>
</tr>
<tr>
<td>Florence, Italy [6]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faivre et al. 1999</td>
<td>178</td>
<td>712</td>
<td>0.64 (0.46–0.91) &lt;3 years</td>
</tr>
<tr>
<td>Burgundy, France [7]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bertario et al. 1999</td>
<td>95</td>
<td>475</td>
<td>0.64 (0.36–1.15)</td>
</tr>
</tbody>
</table>

Table 2. Main results of randomized trials of fecal occult blood screening for CRC

<table>
<thead>
<tr>
<th>Study, year, location [ref. no.]</th>
<th>No. of subjects screened</th>
<th>No. of controls</th>
<th>Duration of follow-up</th>
<th>No. of CRC for screened</th>
<th>No. of CRC for controls</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardcastle et al. 1996</td>
<td>75,253</td>
<td>74,998</td>
<td>7.8 years (median)</td>
<td>360 deaths</td>
<td>42 deaths</td>
<td>0.85</td>
<td>0.74–0.98</td>
</tr>
<tr>
<td>Kronborg et al. 1996</td>
<td>30,967</td>
<td>30,966</td>
<td>10 years</td>
<td>205 deaths</td>
<td>249 deaths</td>
<td>0.82</td>
<td>0.68–0.99</td>
</tr>
<tr>
<td>Mandel et al. 1999</td>
<td>15,570 annual</td>
<td>15,394</td>
<td>18 years</td>
<td>121 deaths annual</td>
<td>177 deaths</td>
<td>0.67</td>
<td>0.51–0.63 mortality/annual</td>
</tr>
<tr>
<td></td>
<td>15,587 biennial</td>
<td></td>
<td></td>
<td>148 deaths biennial</td>
<td></td>
<td>0.79</td>
<td>0.62–0.97 mortality/biennial</td>
</tr>
<tr>
<td>Mandel et al. 2000</td>
<td>15,532</td>
<td>15,363</td>
<td>18 years</td>
<td>417 cases annual</td>
<td>507 cases</td>
<td>0.80</td>
<td>0.70–0.90 incidence/annual</td>
</tr>
<tr>
<td></td>
<td>15,550</td>
<td></td>
<td></td>
<td>435 cases biennial</td>
<td></td>
<td>0.83</td>
<td>0.73–0.94 incidence/biennial</td>
</tr>
</tbody>
</table>

FOB, fecal occult blood; CRC, colorectal cancer.

CRC, colorectal cancer; CI, confidence interval.
With reference to incidence [15], at the 18 year follow-up, 417 cases of CRC were detected in the annual screening group and 435 in the biennial screening group, compared with 507 in the control group. The corresponding RR s were 0.80 (95% CI 0.70 to 0.90) for the annual, and 0.83 (95% CI 0.73 to 0.94) for the biennial screening group.

Another study compared sigmoidoscopy with or without FOBT, and was conducted in New York City with 21 759 subjects randomized to sigmoidoscopy plus FOBT (n = 12 974) or sigmoidoscopy alone (n = 8782) [16]. A total of 92 CRC cases and 36 deaths were registered at 10 years in the sigmoidoscopy plus FOBT group, compared with 53 cases and 28 deaths in the sigmoidoscopy alone group. The RR of death in the group including FOBT plus sigmoidoscopy was 0.87 (95% CI 0.53 to 1.43).

Two other randomized studies of FOBT have been described, one from Göteborg, Sweden [17], and one from Burgundy, France [18]. Preliminary data on CRC mortality are only available for the first of these, however, and show a RR of 0.88 (95% CI 0.69 to 1.12).

A meta-analysis of available data from the four randomized trials on FOBT [11, 12, 14, 17] shows a 16% relative reduction in mortality (RR 0.84, 95% CI 0.77 to 0.93), which becomes a 23% reduction (RR 0.77, 95% CI 0.57 to 0.89) after allowance for attendance for screening [19].

There is therefore substantial consistency between available data from observational studies and randomized intervention trials. It is consequently now clear that biennial FOBT in a screening setting can reduce CRC mortality by ∼20% after 10–18 years. Using intention-to-screen analysis, there are suggestions that the impact of annual screening may be greater, although the data are inadequate to quantify the potential advantages of annual versus biennial screening. It is also reasonable to assume that the impact is greater for compliant subjects. The efficacy may also be greater for immunochromical tests, which appear to have greater sensitivity compared with standard guaiac based FOBT. In a case–control study from Florence, Italy [20], the RR of interval cancer was 2.6 (95% CI 1.3 to 5.4) for guaiac compared with an immunochromical test based on reverse passive hemagglutination. In the Minnesota Colon Cancer Study, however, sensitivity of the guaiac test approached 90% [21].

Thus, the consistency of available evidence from observational studies [2–8, 22], but mainly from randomized trials [11–15], indicates that FOBT has a proven screening effect, and can appreciably reduce CRC mortality. The issues of effectiveness of various types of FOBT in the general population and, more important, of comparative cost-effectiveness with other possible screening tests for CRC (mainly sigmoidoscopy and colonoscopy) [23–25], however, remain open to discussion, and are very sensitive to different assumptions made and models adopted [26–29].

Frazier et al. [26], for instance, compared 22 strategies for CRC screening in the general population and estimated a cost-effectiveness ratio of US$26 000 per year of life gained for annual FOBT, and of US$92 000 for annual FOBT plus sigmoidoscopy every 5 years, assuming an 80% reduction in CRC mortality. These figures compare well with those of other commonly adopted screening procedures, including annual pap smears beginning at 20 years and annual mammographies at 55–64 years of age, although the general public health instructions are now to start pap smears at 25–30 years and adopt a 3 year interval, and to adopt a biennial or 3-year interval for mammography on the basis of cost–benefit analysis [23]. More importantly, the cost-effectiveness for a simple sigmoidoscopy at age 55 was estimated at US$1200, but with only a 16% reduction in CRC mortality. This indicates the wide range of options that remain to be investigated and quantified for defining the optimal policy for CRC screening at a population level [27, 29]. Furthermore, there is the issue of defining an appropriate work-up with a positive screening FOBT [30], and the ultimate impact of such a screening policy on CRC mortality remains therefore to be assessed.

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References