Effect of faecal occult blood screening on mortality from colorectal cancer: results from a randomised controlled trial

J H Scholefield, S Moss, F Sufi, C M Mangham, J D Hardcastle

Background: Three large randomised trials have shown that screening for colorectal cancer using faecal occult blood (FOB) tests can reduce the mortality from this disease. Two national pilot studies have recently been launched in the UK to investigate the feasibility of population screening for colorectal cancer in the National Health Service. The largest of the randomised trials was conducted in Nottingham and randomised 152 850 individuals between the ages of 45 and 74 years to receive biennial Haemoccult (FOB) test kit (intervention group) or to a control group.

Aims: We have compared the mortality in the intervention group compared with the control group.

Methods: The 152 850 randomised individuals were followed up through local health records and central flagging (Office for National Statistics) over a median follow up period of 11 years.

Results: At a median follow up of 11 years there was a 13% reduction in colorectal cancer mortality (95% confidence interval 3–22%) in the intervention group despite an uptake at first invitation of only approximately 50%. The mortality reduction for those accepting screening was 27%. The reduction in mortality was independent of sex and site of tumour. There was no significant difference in mortality from causes other than colorectal cancer between the intervention and control groups.

Conclusions: Although the reduction in colorectal cancer mortality was sustained, further follow up of this population is required to determine whether a significant reduction in the incidence of colorectal cancer will be achieved.
rates reflect the decreasing completeness of follow up with increasing time since randomisation. In addition therefore Nelson-Aalen estimates of cumulative mortality were calculated from the number of deaths (or cases) in each year since randomisation divided by the number of person years observed during that year and summing these individual rates.12

CRC incidence and mortality rates were calculated as the number of cases of and deaths from CRC divided by the total person years. A standard “intention to treat” analysis was performed with the control group data as the denominator to calculate estimates of relative incidence and mortality. Poisson regression, offset by the natural logarithm of person years of observation, was used to calculate incidence and mortality rate ratios relative to the control group and also to provide 95% confidence intervals for these estimates. The variation in these rate ratios with age and sex was also investigated using Poisson regression. Poisson models were compared using the likelihood ratio test. Proportions were compared using the \( \chi^2 \) test.

In the standard “intention to treat” analysis, mortality rates in the whole of the intervention group are compared with the control group. It is also possible to estimate the mortality reduction in those accepting screening, relative to the control group. However, when those accepting screening are at different underlying risk from non-acceptors of screening the standard method of analysis will underestimate or overestimate the relative risk (depending on whether non-acceptors are at higher or lower risk than the control group), and also produce confidence intervals which are too narrow. An additional method of analysis described by Cuzick and colleagues4 allows for differences in underlying rates in the acceptors and non-acceptors of screening in order to produce a less biased estimate of relative risk (assuming that the underlying rate in acceptors is equivalent to that in the control group adjusted for the rate in the non-acceptors). The confidence intervals are also increased so that the level of significance is not greatly changed. This method has been used to provide an estimate of CRC mortality in those accepting the first screening test relative to the control group.

Cause specific mortality has been investigated in subjects in the control and intervention groups, the latter subdivided according to whether they had accepted at least one test. In order to study the risk of ischaemic heart disease following a positive test/colonoscopy, mortality rates were calculated for unscreened subjects in the intervention group using deaths and person years up to the date of a first test. After a first negative test, events and person years of follow up were allocated to the “negative” category until the date of a first positive test; all subsequent follow up was included as following a positive test. In addition, mortality in the first 12 months since date of entry for those with a positive test at first invitation was compared with that in the control group.

RESULTS

Of the 152 850 individuals recruited, 76 466 were randomised by household to the intervention group and 76 384 to the control group; 547 (0.4%) could not be traced by ONS or had emigrated and were therefore excluded from the mortality analysis. Of the remaining 152 303 study participants, 76 224 were allocated to the intervention group and 76 079 to the control group. Median follow up was 11.7 (range 8.4–18.4) years. The total person years of observation in each group was 844 419

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Colorectal cancer (CRC) incidence, mortality rates, and mortality ratios in the intervention and control groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (per 1000 person years)</td>
</tr>
<tr>
<td></td>
<td>Intervention group</td>
</tr>
<tr>
<td>No recruited</td>
<td>76 224</td>
</tr>
<tr>
<td>Person years</td>
<td>844 419</td>
</tr>
<tr>
<td>CRC cases</td>
<td>1 268</td>
</tr>
<tr>
<td>Deaths from verified CRC</td>
<td>593</td>
</tr>
<tr>
<td>Deaths from all causes</td>
<td>20 421</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex.
groups were well matched in terms of age and sex.

and 843,463, respectively. Both intervention and control groups were well matched in terms of age and sex.

Cumulative CRC incidence at the end of the follow up period was similar in the intervention group and the control group (1.51 v 1.53 per 1000 person years; p=0.76) (table 1). Adjusting for age and sex did not alter this estimate. Figure 1 shows the cumulative incidence in the screening and control groups after 18 years of follow up. During the earlier part of the study (up to five years) the incidence of CRC was higher in the intervention group compared with the control group due to the advance in date of diagnosis by screening. This pattern was reversed at eight years after which the cumulative incidence of CRC in the control group exceeded that in the intervention group. At no point was the difference in incidence of CRC between the intervention and control groups statistically significant.

Overall, 20,421 (26.8%) subjects in the intervention group and 20,336 (26.7%) in the control group have died during the study period. The rate of verified deaths from CRC was lower in the intervention group compared with the control group due to the advance in date of diagnosis by screening. This increase occurred in all of the major specific mortality rates by acceptance of FOB testing have been reported, the most serious of which are cardiovascular.

Table 2: Verified colorectal cancer (CRC) mortality rates by age and sex

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Control group</th>
<th>Rate (per 1000 person years)</th>
<th>Mortality ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>261</td>
<td>304</td>
<td>0.58</td>
<td>0.68</td>
</tr>
<tr>
<td>Males</td>
<td>332</td>
<td>380</td>
<td>0.85</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Age at entry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 y</td>
<td>300</td>
<td>348</td>
<td>0.50</td>
<td>0.58</td>
</tr>
<tr>
<td>≥65 y</td>
<td>293</td>
<td>336</td>
<td>1.20</td>
<td>1.37</td>
</tr>
</tbody>
</table>

*Interaction p=0.87. †Interaction p=0.87.

Table 3: Verified colorectal cancer (CRC) mortality rates by site of cancer*

<table>
<thead>
<tr>
<th></th>
<th>Intervention group</th>
<th>Control group</th>
<th>Rate (per 1000 person years)</th>
<th>Mortality ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site of cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal to the sigmoid colon</td>
<td>212</td>
<td>251</td>
<td>0.25</td>
<td>0.30</td>
</tr>
<tr>
<td>Distal cancers</td>
<td>368</td>
<td>420</td>
<td>0.44</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*Cancers of unknown site excluded. †Interaction p=0.75.

Table 4: Incidence and mortality ratios in acceptors of faecal occult blood screening compared with controls (adjusted for non-acceptance of the first test)

<table>
<thead>
<tr>
<th></th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>0.98 (0.83–1.13)</td>
</tr>
<tr>
<td>Deaths from verified CRC</td>
<td>0.73 (0.57–0.90)</td>
</tr>
<tr>
<td>Deaths from all causes</td>
<td>1.01 (0.96–1.05)</td>
</tr>
</tbody>
</table>

CRC, colorectal cancer.
The causes of death other than CRC were broadly similar in the test and control groups. In common with other screening studies, it is notable that the “non-responders” generally had a higher mortality for all causes than either the “acceptors” or “controls”. Consideration of the introduction of population screening has led to concern over the possible disbenefits of screening in both physical and psychological terms. No colonoscopy related deaths have been observed in the Nottingham trial although complications of colonoscopy have occurred. Although concerns have been expressed over the potential psychological harm caused by screening for cancer, earlier studies of the Nottingham trial population have failed to show anything other than a transitory rise in the anxiety score.

The results of the Nottingham trial at a median follow up of 7.8 years showed a reduction in mortality from CRC in the intervention group of 15% (95% CI 0.74–0.98).7 Long term follow up of the Minnesota trial8 showed a reduction in CRC mortality in the group offered biennial screening in 21% at 18 years of follow up whereas at 13 years only a 6% reduction had been observed. Compliance in the present study was only 57%, estimated mortality reduction in acceptors of the first test was 27%. Although compliance in the present study was only 57%, one might speculate that compliance would be greater in a national population screening programme once screening had been shown to be effective. There was no significant influence of age or sex on mortality in this study.

A major concern for any CRC screening programme is the number of colonoscopies generated. The cumulative colonoscopy rate in the Nottingham study was 1.9% of the intervention group using a biennial screening process. This compares with a cumulative colonoscopy rate of 38% in the Minnesota study using an annual regimen.7 As colonoscopy is expensive in terms of manpower and facilities, it is encouraging that the colonoscopy rate in the Nottingham study was 1.9% of the intervention group compared with 38% in the Minnesota study. The causes of death other than CRC were broadly similar in the intervention and control groups. In common with other screening studies, it is notable that the “non-responders” generally had a higher mortality for all causes than either the “acceptors” or “controls”. Consideration of the introduction of population screening has led to concern over the possible disbenefits of screening in both physical and psychological terms. No colonoscopy related deaths have been observed in the Nottingham trial although complications of colonoscopy have occurred.9 Although concerns have been expressed over the potential psychological harm caused by screening for cancer, earlier studies of the Nottingham trial population have failed to show anything other than a transitory rise in the anxiety score for the intervention group.

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around the time of testing (M Parker, 2000, personal communication). In the present mortality analysis there was no excess of suicide in the acceptor or test groups. Although it has been suggested that there may be an excess of cardiovascular deaths following colonoscopy in screening programmes such as this,15 16 our data showed similar rates of cardiovascular deaths in the control and intervention groups. In order to examine this question more closely, the authors specifically investigated cardiovascular deaths occurring within one year of accepting the first test offered to them (the period in which most individuals would undergo a colonoscopy), and again found no suggestion of an excess.

While the data from this study continue to show a reduction in disease specific mortality from FOB screening, despite a compliance rate of only 57%, it is reassuring that there was no significant excess of deaths following the screening process. Further follow up data are awaited to determine the effect of the screening process on the incidence of this disease.

REFERENCES

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