Colorectal cancer

Faecal occult blood screening for colorectal cancer

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WHAT ARE THE ESTABLISHED BENEFITS OF SCREENING WITH EXISTING FOB TESTS SUCH AS HAEMOCCULT?

A recent analysis of the Nottingham trial of faecal occult blood (FOB) testing confirmed the previously reported mortality reduction from colorectal cancer (CRC) in those offered screening.

The trial in Nottingham randomised 152 850 people aged 45–74 by household to a control group or to an intervention group offered 2 yearly screening by FOB testing. Structured case note reviews were carried out of deaths in registered colorectal cancer cases to obtain more reliable information on cause of death. The trial showed a reduction in mortality from CRC in the intervention group at 7.8 years of follow up of 15%. These results have now been updated and show a reduction at a median 11 years of follow up of 13% (RR 0.87, 95% CI 0.78–0.97) (fig 1).[1] There was a 16% reduction in mortality for cancer proximal to the sigmoid colon (RR 0.88, 95% CI 0.70–1.01) and a 12% reduction for distal cancers (RR 0.88, 0.76–1.01). Mortality from all causes other than colorectal cancer was similar in the intervention and control groups.

Five case control studies[2–6] and four randomised trials [7–10] have now shown a reduction in the risk of dying from colorectal cancer using faecal occult blood screening. The reduction in mortality is consistent across all the randomised trials despite the variation in the selection and age of the populations studied. The most recent results from these studies are summarised in figure 2; a meta analysis gives a pooled estimate of mortality reduction in the intervention group of 16% (RR 0.84, 95% CI 0.78–0.91).

All four randomised trials have used Haemoccult—a guaiac based test for the haem moiety of the haemoglobin molecule. In all these trials, an Intention to Treat (ITT) analysis dilutes the estimated effectiveness of screening because however good the screening programme some people do not wish to participate. In the Nottingham trial, the reduction in mortality amongst those accepting screening adjusted for the difference in rates between acceptors and non-acceptors was 27% (RR 0.73, 95% CI 0.57–0.90).[1]

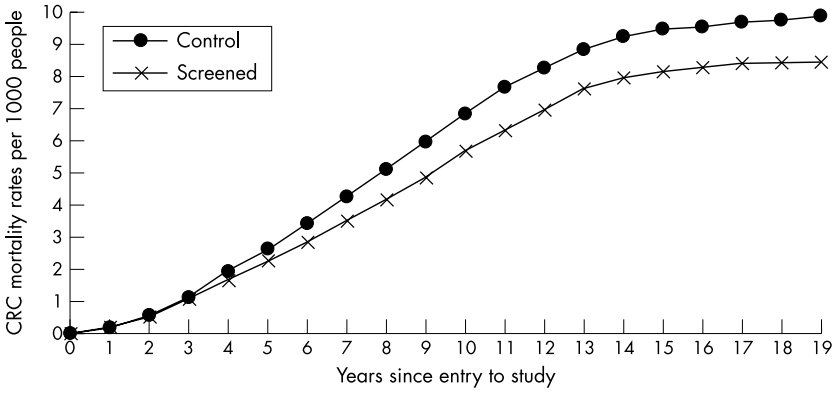

Figure 1 Cumulative mortality from verified CRC in Nottingham trial.

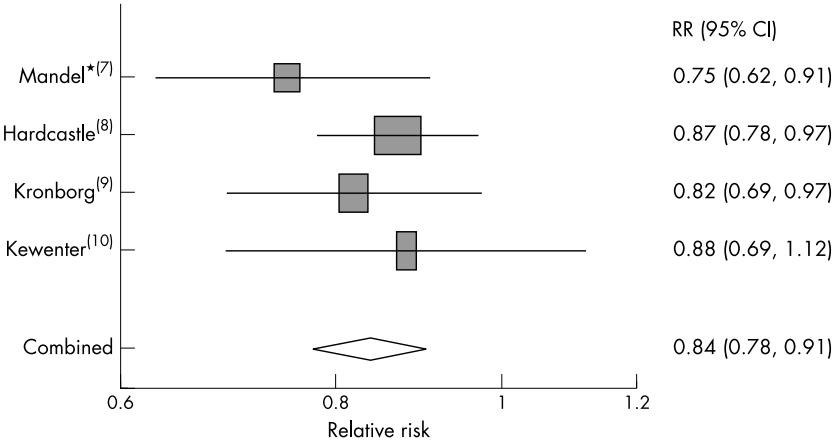

Figure 2 Summary of effect on mortality from colorectal cancer in randomised trials of FOB screening for colorectal cancer. *Annual and biennial combined.

HOW CAN THE RESULTS OF FOB SCREENING BE IMPROVED?

Compliance with a screening programme is a major factor in determining the reduction in mortality from colorectal cancer. In the randomised studies compliance ranged between 56% in Burgundy (Faivre) to 80% in Minnesota.[11] Age and sex do not appear to be significant predictors of compliance. Compliance is determined by many factors; some of these, such as the information provided with the tests and about the screening programme, facilitating return of the tests, can be influenced by the screening programmes themselves, while others cannot.

The sensitivity of FOB tests such as Haemoccult for cancer is only of the order of 50%. This relatively low sensitivity is a major concern in developing CRC screening programmes. Sensitivity may be increased by rehydrating the FOB tests but this markedly increases the positivity rate and more than doubles the colonoscopy rate. A better way to increase yield of the Haemoccult test may be to use annual rather than biennial testing.

The Minnesota study randomised the population to annual or biennial screening. After 18 years of follow up the mortality reduction was 33% in the annual group and 21% in the biennial group, although a significant reduction in the latter took longer to emerge.[11] Given the relatively low sensitivity of the Haemoccult test an annual FOB testing programme may be more appropriate than a biennial regimen. This would also reduce the high rate of interval cancers seen in the Nottingham and Funen studies.

So far, only one trial has shown that FOB screening leads to a reduction in the incidence of CRC as opposed to mortality from colorectal cancer (as a consequence

of colonoscopy and polypectomy in those with positive FOBs). Evidence of a divergence between incidence of colorectal cancer in the intervention and control groups has begun to emerge from the Minnesota trial. However, this was not observed until 13 years of follow up.[11] In view of the prolonged follow up required it is perhaps not surprising that in the Nottingham study the cumulative incidence in the intervention and control groups does not appear to be diverging, but follow up is ongoing.

A major concern for any colorectal cancer screening programme is the number of colonoscopies generated. The cumulative colonoscopy rate in the Nottingham study is 1.9% in the intervention group using a biennial screening process; this compares with a cumulative colonoscopy rate of 38% in the Minnesota study using an annual regime and hydrated FOB tests.[11] Since colonoscopy is expensive in terms of manpower and facilities it is encouraging that a significant mortality reduction has been achieved with a low overall colonoscopy rate.

Consideration of the introduction of population screening has led to concern over the possible harms of screening, both physical and psychological. No colonoscopy related deaths have been observed in the Nottingham trial, although complications of colonoscopy have occurred in this and the other studies.[1] 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 around the time of testing.[12] It is reassuring to find that there is no significant excess of deaths following the screening process.

Improved FOB tests

Immunologically based FOB tests are specific for human haemoglobin in stool. This reduces the false positive results seen with Haemoccult which are caused by breakdown of animal haemoglobins from meat or from peroxidases in some vegetables. The possibility of automated quantitative reading of these tests opens up new possibilities for manipulating the sensitivity of the test. These theoretical advantages have yet to be tested in population based studies.

FOB tests combined with flexible sigmoidoscopy?

Results of the UK multicentre flexible sigmoidoscopy (FS) trial that such screening is feasible and has a high yield of neoplasia.[13] It is likely to be another three or four years before mortality data are available, but preliminary data from this study and from similar programmes in the United States suggest that FS is more effective at preventing cancer (by detecting polyps) than FOB testing and because of its high sensitivity may be ideally suited to a one off screening process. Reluctance among the asymptomatic population to undergo invasive procedures has reduced the overall compliance to around 40% but the yield of polyps and cancers is greater than for FOB screening.

The major difficulty with FS screening is the current lack of facilities and skilled workforce required not only to complete the screening procedures but also to accommodate the large colonoscopy workload such a programme will generate.[14]

Concerns about only screening one half of the colon remain and may be addressed by combining FS screening with FOB screening.

The risk of complications from the endoscopic procedures should be manageable through better staff training and by provision of tailored patient information.

While the available evidence shows that both FOB testing and flexible sigmoidoscopy are effective screening tests in detecting colorectal adenomas and cancers, only FOB testing has so far been shown by randomised trials to reduce mortality from the disease. If the effectiveness of "one-off sigmoidoscopy" is demonstrated, a programme combining this with FOB testing might be considered. In either case, the introduction of a national screening programme would require a large investment in infrastructure and in particular in colonoscopy facilities.

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