Screening for colorectal cancer
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wonder if the authors of the two studies published in The Lancet might be able to report the all-cause mortality rates of the groups in their studies, who were diagnosed with colorectal cancer—both in the screened and in the unscreened groups. If all cause mortality in those diagnosed with colorectal cancer is not reduced, the rather small benefit of reduced risk of death from colorectal cancer (a benefit affecting less than 0.2% of the population) might well vanish.

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Sir—The investigators in the two large randomised trials of screening for colorectal cancer conclude that it is time to consider screening for colorectal cancer. In their commentary Lieberman and Sleisinger write that there is time to encourage colon screening. We believe that these recommendations are premature. The investigators base their conclusions on the reduction of the colorectal mortality recorded (disease specific rate ratio 0.85 and 0.82). However, in both studies no reduction in total mortality was shown (total mortality rate ratio 1.01 and 0.99, respectively). An explanation could be that colorectal cancer is a small cause of death in comparison with others. Therefore, a reduction in mortality due to colorectal cancer has no effect on total mortality. In the Danish trial, the proportions of colorectal cancer death were 2.9% for the screened and 3.6% for the control group. Will society benefit from screening for colorectal cancer if there is no effect on total mortality? Lieberman et al states that the costs per added year of life do not exceed the costs of other well accepted treatments. He refers to a recently published cost-effectiveness analysis (CEA) of colorectal cancer screening, showing a cost per added year of life for an annual FOBT of US$12 570. These costs are based on a model in which a 100% compliance is expected. In the recent trials compliance was considerably lower (57% and 60%, respectively). The cost-effectiveness ratio will be much higher with lower compliance rates, as shown by another cost-effectiveness analysis. Both analyses are based on an annual screening strategy. The trials used a biennial screening, which will also affect the cost-effectiveness ratio in a negative way. Most important, both assume an effect of screening on the totally mortality, by contrast with the results of the trials. The results of existing cost-effective analyses cannot simply be combined with the findings of the recent trials to advocate screening for colorectal cancer. A new cost-effectiveness analysis based on the data of the recently published trials is necessary before a national screening programme for colorectal cancer can be recommended.

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Sir—Hardcastle1 and Kronborg2 and their colleagues show clear evidence that screening programmes based on faecal-occult-blood tests (FOBT) can reduce mortality from colorectal cancer by 15%.3,4 To reduce mortality further it is important to improve the performance of FOBTs. Our new combined quantitative immunological faecal occult-blood/protein test offers some advantages, which the 1995 International Union Against Cancer Colorectal Cancer Workshop set as specific goals for future FOBTs: improved sensitivity, fewer difficulties with specificity, and automated method for batch processing.5 In addition to measurement of haemoglobin (Hb) we tested faecal albumin (Alb)6 and carcinoembryonic antigen (CEA) with chemiluminescent CEA-bead assay. (method unpublished) and correlation to Abbott EIA: \( r^2 = 0.954 \); chemiluminescent bead assays for Hb and Alb are under development. The immunological tests do not need the patient to follow a special diet. Patients were instructed to take two samples from three consecutive bowel movements with special air-tight stool sample collection vials, providing a more representative amount of faeces (about 1 g) than paper smears. In the laboratory the samples were weighed, diluted and thoroughly mixed before analysis.

In early studies with diagnosed but untreated patients we evaluated the faecal Hb-Alb and a Hb-Alb-CEA combination test to determine sensitivity. Threshold values and specificity were defined in screening 80 healthy controls (age 6-81; mean 40, SD 23) with six faecal samples each, by taking the highest value of this series. Patients were regarded as positive if one result of the immunological tests was positive. The specificity of each test was set at 97.5% (table). Our test for faecal Hb has high sensitivity and specificity for colorectal cancer. For polyps (\( p<0.05 \))—as in gastric cancer (\( p>0.05 \))—the addition of Alb and CEA further improved sensitivity. By contrast, Hardcastle1 and Kronborg2 do not provide any data on gastric cancer findings after a positive FOBT. Comparing our results with published data for chemical faecal peroxidase testing, we conclude that the immunological test of Hb with proper specimens increases sensitivity, specificity, and patient compliance since no diet is necessary. The results may be further improved by combination testing. Our findings add to Lieberman’s3 conclusion that a faecal occult blood alone programme is more cost-effective than other screening programmes. We plan to examine the reliability of our combination test (Hb-Alb).
obtaining faecal samples from 1000 patients before scheduled colonoscopy, as well as from those in a screening study on 5000 healthy persons above 45 years of age.

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Author’s reply

SIR—Your correspondents mistakenly assume that we were looking for a difference in all cause mortality as an endpoint of this trial. The purpose of showing all cause mortality was to demonstrate that the randomisation process had resulted in study and control groups of comparable health status. It would be impractical to attempt to show a significant reduction in all cause mortality because of the sample size that would be necessary.

Colorectal cancer accounts for only 3% of all deaths; a 15% reduction in deaths from disease would thereafter be expected to reduce all cause mortality by only 0.5% which is included in the 95% CI of the observed risk. The same argument applies to all preventive interventions aimed at a single disease.

Gøtzsche combines the results of the UK and Danish studies, although the risk difference for colorectal cancer is one death prevented per 1000 invited, not screened as he suggests. Our own combined analysis shows a relative risk of 0.84 (95% CI 0.75-0.94) in the group subjected to screening. He also raises the issue of psychological side-effects; this has been studied and we were pleased to find that a false-positive finding did not result in long-term psychiatric morbidity. Those data will be published shortly.

John and colleagues are right that it is important to improve the performance of FOBTs. However, improving test sensitivity may result in a reduction in specificity, thereby increasing costs. This was demonstrated by our comparison of Hemoccult with a more sensitive immunological FOBT in population screening.

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The Delta trial

SIR—In his reply to my letter (Nov 2, p 1237), Sherer attacks my clarification of his commentary as a “false positive to clinicians making clinical decisions.” However, the data from the completed Delta 2 and ACTG 175 trials and his own commentary support my view: neither trial shows significant benefit in terms of relative risk of disease or death from two-drug combination anti-HIV therapy for experienced zidovudine users.

The overall summary of the Delta 2 trial, presented in table 5 (p 288), indicates no significant reduction of risk in any of the four categories of death, disease progression, or their combinations for those receiving either two-drug combination therapy, zidovudine and didanosine or zidovudine and zaltabine, compared with those receiving only zidovudine, when analysed separately or in aggregate. The Delta 2 trial result for the treatment effect of zidovudine and didanosine in experienced zidovudine users presented in figure 1 and given in the text (p 287), cited by Sherer, is one of multiple comparisons, and, therefore, with p=0.05 is of doubtful statistical significance.

The complete results of the ACTG 175 trial, published on Oct 10, 1996, were not available when I submitted my letter. The data of the ACTG 175 trial for individuals with CD4 cell counts of 200-500 per µL presented in table 4 (p 1085), indicates a modest effect from zidovudine and didanosine compared with zidovudine alone for experienced zidovudine users, and similarly for the endpoint of death alone. However, the modest effect is questionable. Multiple comparisons raise the question of its statistical significance, and, as Sherer noted, “unlike Delta and Nucombo, ACTG 175 had a high lost-to-follow-up rate and few events, so its findings should be interpreted cautiously.” The ACTG 175 trial finding indicated no significant benefit from zidovudine and zaltabine therapy compared with zidovudine alone for experienced zidovudine users in terms of progression to AIDS or death.

ACTG 175 report on effects of combination therapy on individuals with AIDS or CD4 cell counts less than 200 per µL indicates no benefit from combination therapy with either zidovudine and didanosine or zidovudine plus zaltabine compared with zidovudine alone in terms of disease progression or death for those with more than 12 months of previous zidovudine treatment (table 4, p 1104).* For those with such experience of less than or equal to 12 months of zidovudine therapy, a slight benefit in terms of disease progression or death resulted from

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