Screening for colorectal cancer
Lijmer, J.G.; Bossuyt, P.M.M.

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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 their studied populations 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.

Brian Budenholzer
Corporate Center and Spokane District Office,
PO Box 204, Spokane, WA 99210, USA


Sir—The investigators in the two large randomised trials2,3 of screening for colorectal cancer conclude that it is time to consider screening for colorectal cancer. In their commentary Lieberman and Sleisinger1 write that the time has come 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 0·851 and 0·822). 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,4 the proportions of colorectal cancer death were 2·9% for the screened and 3·6% for the control group. If society benefits from screening for colorectal cancer if there is no effect on total mortality? Lieberman1 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,4 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 trials2,3 the 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.5 Both analyses5 are based on a 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-effectiveness 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.

*Jeroen G Lijmer, Patrick M M Bossuyt
Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, PO Box 22700, 1100 DE Amsterdam, Netherlands


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, 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.6

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 (>0·5 cm) test, 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.7 The results may be further improved by combination testing. Our findings add to Lieberman's5 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) by...
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.

*Markus R John, Heinrich Schmidt-Gayk, Andreas Sieg*

1 Department of Internal Medicine I, Medizinische Klinik, Ruprecht-Karls-Universität Heidelberg, 69120 Heidelberg, Germany; Laboratory Group, Heidelberg; and Internist and Gastroenterologen, Drossingen


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.

Guttmacher 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 offered screening. He also raises the issue of psychological side-effects; this has been studied and we were pleased to find that a false-negative 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 FOBT. However, improving test sensitivity may result in a reduction in specificity, thereby increasing costs.1 This was demonstrated by our comparison of Hemoccult with a more sensitive immunological FOBT in population screening.2

J D Hardcastle

Department of Surgery, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH, UK

The Delta trial

Sir—In his reply to my letter (Nov 2, p 1237), Sherer attacks my clarification of his commentary as “deceptive to clinicians making clinical decisions”. However, the data from the completed Delta2 and ACTG 175 trials and my 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 zalcitabine, 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 Nucomo, 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 zalcitabine 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 zalcitabine 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).3 For those with such experience of less than or equal to 12 months, a slight benefit in terms of disease progression or death resulted from

Ole Kronborg

Department of Surgery, Odense University Hospital, DK 5000 Odense, Denmark