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 laboratory studies, which were based on biennial screening, which will also affect the cost-effectiveness ratio in a negative way. Most important, both assume an effect of screening on the mortality rate ratio of colorectal cancer, which has been shown (total mortality was shown (total mortality rate ratio 1.01 and 0.99, respectively). Therefore, reduction in mortality due to colorectal cancer has no effect on total mortality. In the Danish trial, mortality recorded (disease specific rate ratio 0.85 and 0.82, respectively). The conclusion on the reduction of the colorectal mortality was (disease specific rate ratio 0.85 and 0.82, 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. Would 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 randomised controlled trials, which were based on the findings of the randomised controlled trials, the rates of colorectal cancer (a benefit affecting less than 0.2 of the population) might well vanish.

Brian Budenholzer


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 Slesinger 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 0.85 and 0.82, respectively). 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. Would 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 randomised controlled trials, which were based on the findings of the randomised controlled trials, the rates of colorectal cancer (a benefit affecting less than 0.2 of the population) might well vanish.

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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 offered 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 FOBTS in population screening.

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**Author's reply**

Sir—It has never been shown that an offer of screening turns the world’s healthy citizens into fearful patients-to-be—on the contrary, there is no substantial evidence from other screening programmes to support Gøtzsche’s idea. Whether the benefits obtained justify the costs is a political matter. Long-term randomised studies including screening for many diseases have been done, and others are underway.

Budenholzer is right that no reduction in overall mortality was documented in our study, but it was not our intention to identify such a effect. The slight reduction in mortality could mean a substantial reduction in number of patients dying from colorectal cancer, because of the high frequency of the disease compared with other cancers. Death from colorectal cancer is not sudden, and is usually combined with high morbidity from complications, making even a slight reduction attractive. We will have to die, and reducing the risk of dying from CRC does not mean that other causes of death will be less common.

In reply Lijmer and Bossuyt, cost-effectiveness analyses with the data from the Danish trial was underway, and the preliminary figures suggest that the cost per added year of life without dying from colorectal cancer will be somewhat less than that from mammography, and much less than that from cervical cancer screening.

I agree with John and colleagues that it is important to improve performance of FOBTS, but so far, it has not been possible to achieve the same high specificity of Hemoccult-II with any other faecal test; the increase in sensitivity usually has to be paid for by a decrease in specificity. We certainly are looking forward to see the results of the combination test they suggest.

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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 “disservice 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 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 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 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). For those with such experience of less than or equal to 12 months of zidovudine, a slight benefit in terms of disease progression or death resulted from...