Hemoccult should no longer be used for the screening of colorectal cancer

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About 50% of the patients with colorectal cancer who are diagnosed on the basis of clinical symptoms could be cured by surgery. It may be assumed that diagnosis and surgery at an earlier asymptomatic stage would allow more patients to be cured. Therefore, screening appears to be the simplest way to decrease mortality due to colorectal cancer [1].

The most widely investigated screening procedures are faecal occult blood testing (FOBT) and sigmoidoscopy or total colonoscopy.

FOBT would allow detection of cancer in the entire colon. Guaiac gum remains the most widely used indicator for occult bleeding and of the many commercial tests using guaiac gum, the most popular and the most extensively studied is Hemoccult.

The chemical test for occult blood depends upon an oxidation process that is catalysed by a number of naturally occurring peroxydases and catalases. Therefore, many non-heme compounds can be responsible for the high number of false-positive tests often observed. In addition, blood losses exceeding 20 ml/day are needed to give a reliable positive Hemoccult reaction, and even in symptomatic colorectal cancer blood losses <10 ml/day are generally observed [2, 3]. Moreover, although one can understand why bulky tumours often bleed, why should small, well-vascularised tumours do likewise?

A series of 1241 patients who had a resection of a colorectal cancer, and 12 312 relatives, were followed for three consecutive years by annual Hemoccult test and sigmoidoscopy, and total colonoscopy if the test was positive. The sensitivity of Hemoccult was 26% and the predictive value of a positive test was 8.2% [4].

In the long-term, a screening program must lead to a decrease in cancer-related morbidity and mortality. Owing to various biases (selection bias, lead time bias and length time bias), studies comparing the mortality of patients whose cancer was detected by screening with that of patients in the general population or with clinical symptoms are difficult to interpret.

Case–control studies appear to be an elegant method for evaluating the long-term usefulness of screening. In these, the frequency of the screening procedure in patients with colorectal cancer is retrospectively compared with that of control subjects matched with the case subjects for age, sex and lifestyle. Most case–control studies suggest that case subjects have undergone screening with Hemoccult less frequently than control subjects. The results of the case–control studies led to the recommendation of screening for cancer of the cervix [5]; however, for colorectal cancer screening, some flimsiness is seen in the results of case–control studies. For example, a benefit of screening was identified only if it had taken place >3 years before the diagnosis [6], or in an individual <70 years of age [7], and therefore the studies do not convince us that Hemoccult is an efficient screening procedure.

Properly randomised studies are required to demonstrate the utility of Hemoccult test and minimise the risk of biases. Three randomised studies have been published. The Minnesota Colon Cancer Control Study, which assigned 45 551 participants, 50–80 years of age, to screening with Hemoccult once a year, every 2 years or to a control group [8]. Those with positive Hemoccult tests underwent bowel examination. The cumulative mortality rate in the annually screened group (5.88 per 1000), but not in the biennially screened group (8.33 per 1000), was significantly lower than that in the control group (8.83 per 1000). Reduced mortality in the annually screened group was accompanied by improved survival and a shift to detection at an earlier stage of cancer. The 13-year survival in the patients with cancer not detected by screening was similar to that of the patients in the control group. A notable feature of this study was the effect of rehydration of the slides on test results with a more than 4-fold increase, from 2.4% to 9.8%, in the number of positive results. As a consequence of this high positive number, 38% of the patients underwent total colonoscopy. A mathematical model simulating...
the cohort of screened patients in the Minnesota study suggests that one-third to a half of the mortality reduction observed from Hemoccult may be attributable to chance selection for colonoscopy [9]. After an 18-year follow-up period, Hemoccult (and/or colonoscopy) significantly reduces the incidence of colorectal cancer [10].

Two other randomised studies were published in the same issue of The Lancet [11, 12]. In both studies, participants were randomly allocated to Hemoccult screening or no screening. Controls were not told about the study and received no intervention. Hemoccult tests were not rehydrated. Participants with a positive test were offered colonoscopy. Screening was repeated every 2 years. The primary end point was colorectal cancer mortality. In the two studies, 152850 [11] and 137485 [12] persons were included. There were 205 [12] and 360 [11] deaths attributable to colorectal cancer in the screening groups as compared with 249 and 420, respectively, in the control groups. Both studies concluded that biennial screening by Hemoccult can reduce colorectal cancer mortality. In both studies the sensitivity of the screening test was low, with <50% of all colorectal cancers diagnosed as a consequence of a positive Hemoccult test. Reduction in mortality was modest, in the order of 15% to 18%, indicating that for 1000 persons invited for screening once every 2 years for 10 years, one death due to colorectal cancer would be avoided [13]. If this is not enough to convince us of the very modest benefit of screening with Hemoccult, interval cancers were detected at an earlier stage than in the control groups, suggesting that the small reduction in colorectal cancer mortality was not attributable to the Hemoccult alone but also to better medical attention in those subjects who were randomised to the screening group [14]. In fact, participants in the screened group were informed of the possible symptoms of colorectal cancer, while in the control groups participants were not even told about the study.

Endoscopy appears to be an obvious and incontestable means of detecting intraluminal colorectal cancer. Both sensitivity and specificity are high, justifying the use of the procedure as a gold standard for measuring the accuracy of FOB tests [4]. Data from two case–control studies suggest that screening by sigmoidoscopy can substantially reduce mortality from cancer of the rectum and distal colon [15, 16]. The validity of case–control studies for identifying a true effect of screening on colorectal cancer mortality is hampered, as for Hemoccult, by selection biases [17].

It has been suggested that patients with advanced distal neoplasia (defined as an adenoma that was 10 mm or more in diameter, a villous adenoma, an adenoma with high grade dysplasia or invasive cancer) would also be more likely to have proximal advanced neoplasia [18]. If this hypothesis is confirmed then sigmoidoscopy could be used as a screening procedure and colonoscopy performed only in those patients with distal advanced neoplasia.

Recent studies have shown that colonoscopy can detect colonic neoplasms in asymptomatic adults [19, 20], and although those who have polyps in the distal colon are more likely to have advanced proximal neoplasia (relative risk 6.7 for advanced distal neoplasms, 4.0 for distal tubular adenomas, 2.6 for hyperplastic polyps) than those without distal polyps [20], about half of the cases of advanced proximal neoplasia had no distal lesion [19, 20].

Determination of the time interval between two endoscopies is crucial. In a series of patients with polyps >1 cm who refused resection [21], the rate of progression to cancer was 2.5% at 5 years and 8% at 10 years. In patients with any type of adenoma the rate of cancer has been estimated to be 4% at 10 years [22]. In patients who have polyps resected at baseline, recurrent polyps are frequently found at follow-up examinations, but the risk of advanced neoplasia is unusual [23]. For those who have small tubular adenomas at baseline sigmoidoscopy, only 0.5% develop cancer during a mean follow-up of 14 years without any intervention [24]. These data would suggest that efficacy would be maintained by extending screening intervals to 5–10 years. If this is re-examined and further confirmed in more structured studies, the cost of screening would be dramatically reduced.

In conclusion, screening based on FOBT is not advisable. Trials investigating this approach are fully mature with about 300000 participants in well-designed randomised trials. They show that the reduction in mortality, if any, is modest [11, 12], and after correction for an observation bias, the reduction in colorectal mortality is no longer statistically significant [14]. The apparent simplicity of the test cannot be an argument in favour of its generalised use. The poor specificity of the test may lead a high proportion of patients being unduly submitted to repeated barium enema and colonoscopy. Although secondary colonoscopy may have a global impact on survival [9], the psychological impact and cost of such an inaccurate procedure has not been evaluated. Moreover, in current practice, Hemoccult testing is not followed by an adequate evaluation in a significant proportion of patients, and decision-making seems to be influenced more by the number of positive tests than by the positivity of a single one [25].

The data on endoscopic screening are now mature. Based on current published data, screening colonoscopy should be recommended in asymptomatic persons ≥50 years of age [19, 20]. The role of sigmoidoscopy remains to be determined in the frame of cost evaluation in large population-based screening and in further surveillance of patients with previous distal advanced neoplasm [26].

Other early detection strategies will be developed. K-RAS mutations and the presence of long DNA or microsatellite instability have been found in stool specimens of patients with colorectal cancer and advanced neoplasms [27]. Identification of other gene mutations including P53 and APC could further increase the sensitivity of this approach.
References