

## SCREENING FOR COLORECTAL CANCER WITH FAECAL-OCCULT-BLOOD TESTS : TRIAL EVIDENCE AND BEYOND. J. Faivre. Dijon, France.

Colorectal cancer is one of the most common cancer in developed countries. Despite advances in diagnosis and therapeutic methods, its prognosis remains relatively poor. Faced with this disquieting situation, considerable research efforts have been made over the last 20 years to evaluate the ability of screening procedures to decrease the mortality or incidence of colorectal cancer. Currently, the simplest and most evaluated screening method for colorectal neoplasia is periodic stool testing for occult blood, followed by a colonoscopy in those screening positive. The most extensively evaluated test is a guaiac test intended to detect peroxidase-like activity of hemoglobin. The test is easy to perform (two small samples are collected from three consecutive stools), without great inconvenience to the individual and inexpensive. There are three European population-based trials and a US study among volunteers which compare colorectal cancer mortality within a study group and a control group. They provide very similar results. They reported a 14% to 18% reduction of colorectal cancer mortality in the general population with non-rehydrated Hemoccult II repeated at least every 2 years in asymptomatic adults aged 50 to 74 and with a medium follow-up of 10 years. In participants or volunteers mortality reduction varied from 33% to 39%. A decrease in colorectal cancer incidence was reported in the US study after 18 years of follow-up. Available data suggests that the degree of reduction in mortality depends mainly on the compliance to the screening test, the number of screenings that the subjects participate in and of compliance of positive screens with the diagnostic follow-up colonoscopy. If compliance is low, no reduction of colorectal cancer mortality will be seen, even with a very effective test. In Nordic countries and in England, a high compliance rate was obtained with the mailing of the test with eventually one or two reminders. In France, this strategy resulted in low compliance. It has to be combined with the participation of primary care physicians who give the test to their patients over a period of 4-6 months. It is then mailed to non-consultants. The active participation of primary care physicians can be a major determinant of effectiveness in many countries. It has also been shown that this colorectal cancer screening strategy meets commonly accepted criteria for cost-effectiveness. The Advisory Committee on Cancer Prevention of the European Union and the European Commission have recently recommended the implementation of colorectal cancer screening with faecal occult blood tests. They also concluded that immunological tests, flexible sigmoidoscopy and colonoscopy cannot, at present, be recommended for population screening. Colorectal cancer screening was also included in the European Code against cancer. An organisation with a call-recall system and quality assurance evaluation is necessary in order to achieve effectiveness. The benefits of a screening programme are achieved only if compliance to the screening test is over 50% initially and during successive screens and if a colonoscopy is performed in case of positive test. The positivity rate of the non rehydrated Hemoccult test without diet restriction is 2% on initial screen and 1 to 1.5% in subsequent screenings. The specificity of the test is 98%, the sensitivity estimated to be between 50 and 60% and the positive predictive value is around 10% for cancer and ranges between 30 and 40% for adenomas. Taking into account the EU recommendations, a national policy was decided in France. It was concluded that there was unequivocal evidence that repeated faecal occult blood testing reduces colorectal cancer mortality in asymptomatic subjects over 50. Organisation rules were proposed by the Ministry of Health and 22 areas, covering 25% of the population, were selected on their ability to organise the screening programme. A rigid organisation with a call-recall system and quality insurance was set up in each administrative area. The time has come to implement well-organised population-based faecal occult blood screenings despite current limitation of available tests. Efforts should be continued to improve faecal occult blood tests.

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## Faecal occult blood test as a screening test for colorectal cancer

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### Abstract

Screening for colorectal cancer with faecal occult blood test (FOBT) has been shown in randomised controlled trials to decrease mortality from this disease. The time has come to implement well-organised FOBT screening of the average-risk population. In order to have a high level of uptake, this program requires a substantial amount of initial planning and resource allocation, including defining roles of the different health professionals, training of the community of general practitioners together with proper education and information of the public on the risk factors for CRC and the alternative screening tools. The strengths and weaknesses of the available FOBT's are discussed and arguments are advanced to their use for screening in the average-risk population. (*Acta gastroenterol. belg.*, 2005, 68, 244-246).

### Introduction

Screening for the presence of blood in the stool is based on the fact that most cancers and some polyps bleed. The bleeding is intermittent and blood is unevenly distributed throughout the stool. Additionally, the amount of bleeding is dependent on the size of the polyp or cancer. Screening for the presence of blood in the stool is far less sensitive for polyps than for cancer (3,4).

Guaiaic-based tests for peroxidase activity are the most commonly used means of testing for blood in the stool. False positive results stem from other causes of gastrointestinal blood loss or other substances in stool that may cause a positive guaiac reaction. Avoiding non-steroidal anti-inflammatory medications, vitamin C intake, red meat and some fresh fruits and vegetables (radishes, turnips, broccoli) is often suggested to prevent false positive testing, although there is little evidence these maneuvers are required. Some reports suggest that delaying development of Hemoccult cards for at least three days will decrease the number of false positives caused by plant peroxidases and obviate the need for diet restriction of fruits and vegetables (5,7).

False negative FOBT results occur because colorectal neoplasia bleeds intermittently and blood is not always present throughout the entire stool (7). It's important to remember that screening for colorectal cancer with FOBT should not be done with stool samples obtained at a digital rectal examination (sensitivity : 4, 9%, specificity : 97%) (8,9,11).

Current recommendations are that testing be conducted on two samples for three different stool specimens on consecutive days as multiple, consecutive samplings

increase the likelihood of detecting blood (sensitivity : 24%, specificity : 98%).

Patients with one positive result on FOBT should have an examination of the entire colon and rectum, preferably by colonoscopy (1,2,3,4,5,7,16).

The sensitivity of the test is improved if the test is performed as part of a program of testing over a period of several years (annually or biennial) instead of a one-time test, as this offers several opportunities to detect intermittent bleeding (sensitivity : 72-78%, specificity : 98%, positive predictive value : 10-17%). The sensitivity of this test is also dependent on the hydration status of the developed sample cards. Rehydration of the samples with a few drops of distilled water prior to the addition of the developing reagent increases the sensitivity at the expense of the specificity (sensitivity : 88-92%, specificity : 90-92%, positive predictive value : 2-6%) and is not recommended (3,4,5).

### Discussion and review of the literature

To date, four randomised controlled studies have investigated fecal occult blood testing for colorectal cancer screening. These tests all incorporate a program of screening with multiple, consecutive tests on an annual or biennial basis.

Using data from the four randomised controlled studies, a systemic review including a meta-analysis was performed and published in the Cochrane Library.

This analysis showed an overall significant reduction in colorectal cancer mortality with screening by fecal occult blood testing of 16% (RR 0.84 ; CI 0.77 to 0.93). When the relative risk is adjusted for attendance for screening in individual studies, the mortality reduction is 23%. Overall, if 10000 persons were offered screening and approximately two-thirds attended for at least one fecal occult blood test, there would be 8.5 deaths (CI 6.5 to 13.5) from colorectal cancer prevented over 10 years. Stating this in another way, in order to prevent one death from colorectal cancer over 10 years, 1173 persons would need to be screened. However, the screening program would also result in 2800 participants having at least one colonoscopy. If harmful effects of screening from the Minnesota trial are considered, there

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would be 3.4 colonoscopy complications. If harmful effects of screening from the Goteborg trial are considered, approximately 600 participants would need at least one sigmoidoscopy and double contrast enema, resulting in 1.8 perforations or hemorrhage.

The estimate of mortality reduction from the randomised controlled trials of fecal blood tests is now well quantified and the confidence intervals are narrow enough to allow the conclusion that FOBT is likely to be beneficial in a program of colorectal cancer screening.

Other benefits of fecal occult blood testing are emerging. Most notably, a reduction in the incidence of colorectal cancer of 20% in subjects screened annually has been observed in the Minnesota trial. Additionally, treatment of early stage colorectal cancers may involve less invasive surgery. In all three randomised studies evaluating the effectiveness of fecal occult blood testing, a favourable stage shift to earlier stage disease, which has better outcome, was seen. In the Nottingham study, 90% of the screened group had Dukes' A or B compared with 40% of the control group. A similar shift was seen in the other two randomised controlled trials described (3,4).

Recently, a controlled trial in France showed also a significant reduction in colorectal cancer mortality from biennial FOBT. These results, along with those of the previous studies, were considered sufficiently convincing by the French health authorities to decide to start a pilot program in France in subjects age 50-74 years, covering about 20% of the population, as the first of a national policy (1,2).

Available data suggest that the degree of reduction in mortality depends mainly on the compliance of the screening test, the number of screenings that the subjects participate in and of compliance of positive screens with the diagnostic follow-up colonoscopy (17). A recent survey of patients shows that follow-up testing after a positive result on home-based testing is deficient. Current practice guidelines recommend colonoscopy after positive results on FOBT. The reason for this aggressive follow-up is the high frequency of advanced colonic neoplasia after positive results on a screening test : 4.2% of patients with these results have colorectal cancer, 6.5% have high-grade dysplasia, 10.2% have adenomas with villous feature, and 10.7% have an adenomatous polyp at least 1 cm in diameter. The patient survey showed that the follow-up of home-based FOBT fell far short of the recommended intensity. Of the patients reporting positive FOBT results, 31.6% reported that they did not have any follow-up imaging procedure of the colon (colonoscopy, sigmoidoscopy, or contrast radiography). Half of these patients reported receiving repeated FOBT. These findings imply that the physician stopped the diagnostic work-up of positive results on the first FOBT after negative results on the repeated test (8,9). Automatic gastrointestinal consults and reminder systems are to be organized in order to improve CRC screening follow up.

Table 1. — Choice of available FOBT by population characteristics and resources

Colonoscopy resources	Recommended FOBT
Limited	Guaiac test with high specificity : Hemoccult II, Laméris (0,56 €/test) or Immunochemical test (ICT) : Instant-View, International Medical (2 €/test)
Readily available	Guaiac test with high sensitivity : Hemoccult Sensa, Laméris (0,59 €/test) or Immunochemical test (ICT) : Instant-View, International Medical (2 €/test)

The World Health Organisation and the World Organisation for Digestive Endoscopy have published their recommendations for choice of fecal occult blood test for colorectal cancer screening (5,10). Their recommendations are based on the performance characteristics of the FOBTs in population studies and also take into consideration the different circumstances around the world in terms of colonoscopic resources, willingness to comply with dietary restrictions, and ability to pay for the cost of the initial FOBT (Table 1). When colonoscopy resources are readily available and population compliance with diet and drug restrictions is unreliable or uncertain, an Immunochemical FOBT may be advised (5,6,10,12,13,14,15).

Advantages of an immunochemical test compared with a guaiac test include :

- Improved specificity : immunochemical tests will not react with non-human haemoglobin, vitamins, drugs, or peroxidase from food sources. The ICT has also been shown to be non-reactive with blood from the upper gastrointestinal tract when bleeding is occult (5,6).
- Potential increase in patient compliance. Since no dietary restrictions are needed, it may be more acceptable to the consumer than current FOBT tests (5,6) .

Disadvantages of an immunochemical test compared with a guaiac test include :

- Limited clinical testing. It has not been tested in a large screening population of average-risk individuals. The ICTs efficacy in decreasing colon cancer mortality has not been tested in randomised controlled trials. However, if the ICTs are truly more accurate than Hemoccult II, their effectiveness need not be confirmed by randomised controlled trials because Hemoccult II's ability to save lives from colorectal cancer has already been shown (5,6).
- The same sensitivity limitations. While immunochemical tests have advantages over guaiac tests, they are still tests for occult blood, which may leak inter-

mittently and may occur from sources in the colon and rectum other than cancers or large adenomas. Data indicate that the problem for detection created by intermittency is less marked with immunochemical than with guaiac tests because higher test sensitivity is not accompanied by significant degradation of specificity, as is the case with guaiac tests.

In addition, because bleeding from adenomas occurs infrequently, the potential for CRC prevention through adenoma detection and removal is likely to be lower with this and all FOBT methods than with endoscopic and imaging screening modalities. However when used annually, as recommended, the program sensitivity of FOBT is very high (5,6).

## Conclusion

In conclusion, the results of several randomised population-based studies have shown that screening for colorectal cancer by FOBT can reduce colorectal cancer mortality. The time has come to implement well-organised FOBT screening of the average-risk population. In order to have a high level of uptake this program requires a substantial amount of initial planning and resource allocation, including defining roles of the different health professionals, training of the community of general practitioners together with proper education and information of the public on the risk factors for CRC and the alternative screening tools.

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