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Current Controversies in Cancer

Should there be Mass Screening using Faecal Occult Blood Tests for Colorectal Cancer?

J. Faivre & M.A. Tazi | P. Autier | H. Bleiberg

Pro:

J. Faivre and M.A. Tazi

Registre des Tumeurs Digestives (Equipe associée INSERM-DGS and CRI 9505), Faculté de Médecine, 7 Boulevard Jeanne d'Arc, 21033 Dijon Cedex, France

INTRODUCTION

LARGE BOWEL cancer fulfils the conditions defined for mass screening. It is the second most frequent cancer in men and women in Europe, with an estimated 169 400 new cases in the 12 countries of the European Community in 1990 [1]. Despite advances in diagnostic techniques and treatment, the 5-year survival rate remains poor [2], but there is a stage when the disease is confined to the bowel wall (Dukes' A cancer) which can be cured by surgical resection. Unfortunately, most patients presenting symptoms (80–85%) have more advanced cancer and, therefore, lower survival rates. Furthermore, a precancerous lesion, the adenoma, can be removed using endoscopy, but it is generally asymptomatic. Considering the present state of knowledge, only the strategy of screening for intestinal tumours at their asymptomatic stage could reduce the mortality of colorectal cancer. Converging data from case–control studies and randomised studies, demonstrate that it is possible to reduce mortality from colorectal cancer in people who accept screening with faecal occult blood testing (FOBT), using the Hemoccult test. The purpose of this paper is to outline the basis on which the screening tools work and to consider the evidence for screening for colorectal cancer from published studies.

CHARACTERISTICS OF A MASS SCREENING TEST

This is an important point. Clinicians must understand that the properties required for a screening test are dramatically different from those of a diagnostic test [3]. We are addressing a healthy population not seeking health care and for whom we propose a test with the prospect of improving their health by detecting lesions which would otherwise only be discovered years later at an advanced stage. The objective of mass screening for colorectal cancer is to detect 50 subjects with colorectal cancer among 10 000 subjects over 50 years of age. Because of the size of the screened population, it is thus essential that the positivity rate of the selection test be as low as possible and that, for a positive test, a high proportion of subjects subsequently submitted to colonoscopy have one of the lesions that were screened for, i.e. the positive predictive value must be high. The test specificity, thus, has to be very high, whereas the test sensitivity is not the essential criterion. It is exactly the reverse for a diagnostic test: the test sensitivity must be high whereas the specificity is not the essential criterion. Another parameter is the pretest/post-test likelihood rate, which represents the chance of having large bowel cancer when one returns an abnormal test result. A test with 60% sensitivity and 98% specificity gives a post-test probability of having a large bowel cancer multiplied by 30.

From these considerations it can be understood that the main requirements of a screening test are: easy to perform; acceptable; without danger; cheap; with a demonstrated efficacy.

For this reason, mass screening for colorectal cancer must include two tests: a selection test which would actually be performed on a large part of the population, then a diagnostic test which would only be proposed for subjects with a positive initial test. The selection test's positivity rate must be low, around 2–3% and the diagnostic test's must be high.

One of the essential aspects to bear in mind is that the compliance rate has to be high both at the first screening and at rescreening. The experience in Nordic countries with screening for cervical cancer indicates that mortality due to this cancer decreased only in those regions where an acceptance rate of 40–50% was achieved [4]. If compliance is low, only a few subjects will actually benefit from it, but neither the health authorities nor the clinicians will be able to detect a significant improvement in colorectal cancer mortality. Furthermore, from an economical point of view, a screening campaign with a low compliance rate will just be a waste of money.

SCREENING METHODS

Several tests and procedures have been proposed to screen for colorectal cancer. The most commonly used test is FOBT. Most tests are guaiac-based tests which are intended to detect the peroxidase-like activity of haemoglobin. The most extensively evaluated test is the Hemoccult II (Smith Kline Diagnostic, California, U.S.A.). Two slides are prepared from three consecutive stool samples with or without dietary restrictions. This test is easy to perform, without great inconvenience to the individual and is inexpensive. If any slide is positive, a complete colonoscopy is usually recommended. Its sensitivity in detecting cancer with a non-rehydrated test and biennial screening in populations over 50 years of age is between 50 and 60% for cancers [5] and between 20 and 30% for adenomas more than 1 cm in diameter [6, 7]. The true positive rate ranges from 40 to 50%. Rehydration increases sensitivity, but decreases specificity and the predictive accuracy of a positive test becomes very low [5].

More complex FOBTs, particularly immunochemical tests specific for human haemoglobin, have been developed. They are more sensitive, but their specificity at a population level is not well established. They are more expensive and not so suitable for a mass screening procedure.

Periodic sigmoidoscopy has been recommended by some organisations, whereas colonoscopy is rarely considered for individuals at average risk. The theoretical advantages of endoscopic screening include its high diagnostic sensitivity and specificity. However, it is unpleasant to the individual, bears a risk of perforation, is expensive and its compliance is not known. It does not fulfil the criteria generally required for a screening procedure. The double contrast barium enema has the same drawbacks as endoscopy, as well as lower sensitivity and specificity. The rest of this article will be confined to results from FOBTs.

RESULTS OF CASE–CONTROL STUDIES

One possible method for the evaluation of screening is a case–control approach in an area where screening is already widely carried out. Screening histories in subjects who died of a colorectal cancer are compared with those of controls. Efficacy is suggested if a history of screening is less common among the cases than among the controls. As the results do not take participation into account, the results are valid for 100% compliance. Another limitation of case–control studies is that if individuals who comply with screening differ from non-compliers with respect to risk of cancer mortality, then these differences will bias estimates of efficacy.

In 1977, Germany introduced FOBT into a multiphasic cancer screening programme. The evaluation of this programme has been limited because of confidentiality problems [8]. Nevertheless, a case–control study in Saarland has shown that women dying of colorectal cancer are less likely to have been screened once or more in the time period 6–36 months prior to diagnosis than controls [9]. The results suggest a 57% reduction in the risk of death from colorectal cancer in controls compared with cases. Surprisingly, there was no protective effect from screening in men (odds ratio = 0.92). This discrepancy cannot be attributed to a lower participation in the screening programme in men. Case–control studies provide an absolute reduction in risk, i.e. the results are independent of compliance rate.

Another case–control study conducted among members of a health insurance plan in northern California suggests a 25% reduction in colorectal cancer mortality for people who have a Hemoccult test every 1–2 years [10]. For tests performed more than 2 years before diagnosis, little or no reduction in colorectal cancer mortality exists. The results of a case–control study performed in a Health Maintenance Organization in the State of Washington have, as it is stated by the authors themselves, to be interpreted with considerable caution [11]. Cases were less likely to have ever been screened than controls, with an odds ratio of 0.72, but it is difficult to understand why the effect of screening was lower when the test had taken place 3 years before diagnosis than when it had been performed more recently and that it was seen in individuals aged less than 70 years but not in those aged 75 years and older. A case–control study in Japan suggested that screening with an immunochemical test would reduce colorectal cancer mortality by approximately 60% for those screened annually or biannually compared with those not screened [12].

RESULTS OF CONTROLLED STUDIES IN VOLUNTEERS

In a prospective non-randomised controlled study performed in New York, U.S.A., colorectal cancer mortality was lower in subjects offered an annual rigid sigmoidoscopy and Hemoccult tests compared with those offered only sigmoidoscopy, but the difference was not significant [13].

More important are the results of a prospective randomised trial conducted among volunteers in Minnesota, U.S.A. [14]. The 13-year cumulative mortality from colorectal cancer was 5.88% in the annually screened group and 8.83% in the control group. This corresponds to a 33% reduction in mortality among those offered annual rehydrated Hemoccult tests as compared with controls. There was a non-significant reduction in mortality of 6% in those who where offered the test biennially. The significant reduction in mortality in the annually screened group was obtained with a compliance of 75% of the screening offered, 46% of the volunteers completing all the screenings and 90% completing at least one screening. Overall, 82.5% of the tests were rehydrated with a positivity rate of 9.8%. Among the annually screened group, a complete bowel examination was performed in 32.7%. It has been suggested that one-third to one-half of the mortality reduction observed in the annually screened group is attributable to chance selection for colonoscopy [15]. The authors of the Minnesota study have found that this estimation has been greatly overstated [16]. They estimated that chance detection of non-bleeding colorectal cancer accounted for only 14–26% of the 33% reduction in colorectal cancer mortality and that sensitive detection of bleeding cancers through Hemoccult testing accounted for 74–86%. This study demonstrates that it is possible to reduce mortality from colorectal cancer in those who accept annual screening with a rehydrated Hemoccult test. However, this strategy, applicable to those applying for individual check-ups, is not practical for a population-based programme. It would not be possible to perform an annual colonoscopy on nearly 10% of the population over 50 years of age. Furthermore, the cost of such a programme has not been seriously evaluated.

RESULTS OF POPULATION-BASED CONTROLLED STUDIES

In the Goteborg study, 63% of 27 700 subjects aged 60–64 years participated in the first screening and 60% in rescreen-

ing [17]. In the Funen study, compliance was 67% in the first screening campaign for 30 967 subjects, aged 45–74 years [18]. Only those who took part in the first screening round were invited for further screening [18]. Overall, 50% of the participants completed the five rounds. In the Nottingham study, 53% of participants completed the first screening out of nearly 76 466 subjects, aged 50–74 years. Those who refused the first invitation were re-invited and 6% accepted, thus 59% of the participants completed at least one screening. Overall, 38% completed all the tests they were offered. In the Burgundy study, the participation rate in the first screening campaign was 53% out of 91 000 subjects, aged 50–74 years. All study participants were invited to each screening campaign. The participation in the second to fifth screening campaigns varied between 54 and 58%. Overall, 69% of the population completed at least one screening test and 31% completed the five rounds.

The variation in the positivity rate between trials was related to the method of slide preparation. The positivity rate of the Hemoccult test on the initial screen was 1.1% in Odense when the test was Performed with diet restriction [18], 2% in Nottingham and in Burgundy [19, 20] without diet restriction and 6.7% in the Goteborg study where 80% of the tests were rehydrated [17]. The proportion of positive tests on subsequent screenings was between 1 and 1.5%, with the non-rehydrated Hemoccult test. The positive predictive value for subjects older than 45 years of age was approximately 10% for colorectal cancer (the detection rate being around 1%) and ranged between 30 and 40% for adenomas.

In all four trials, screen-detected cancers were detected at a less advanced stage than cancers in controls, with the proportion of Dukes' A cancers being around 40% [18, 19]. The non-responders presented at an even later stage than the controls. There was an intermediate situation for interval cases (diagnosed after a negative Hemoccult test) with a stage distribution between screen-detected cases and non-participants. The shift towards detecting a less advanced stage of the disease was maintained when the test group as a whole was compared with the control group. These data do not represent a sufficient argument in favour of the effectiveness of screening. There are a number of biaises. Slow growing cancers are more likely to be detected by screening (length bias). Screening hastens the diagnosis of incurable cancers, giving a longer lifespan to the disease without actually lengthening it (lead-time bias) and subjects who participate in screening can be at lower risk (selection bias). To exclude these confounding factors, the effectiveness of screening must be evaluated by controlled trials.

The effectiveness of a screening programme should be evaluated in terms of the number of cancer deaths prevented. The results of the Funen and Nottingham studies have recently been reported [18, 19]. They provide clear evidence that biennial screening with a Hemoccult test can significantly reduce mortality from colorectal cancer. The colorectal cancer mortality reduction was 15 and 18% in the Nottingham and Funen studies, respectively.

These findings can be extrapolated to screening of a general population if the conditions of the screening programme achieved in Denmark or the U.K. were to be reproduced. To be effective, a mass screening programme necessitates a rigid organisation with a call–recall system for individuals. This results in a high participation rate with the consequence of an intensive follow-up. Case finding in the general population is a difficult problem. It is difficult to organise and to evaluate. Such screening usually results in high marginal costs and the effect on mortality from colorectal cancer will probably be very small.

Screening must be shown to be not only clinically effective but also cost effective. To support the introduction of mass screening for colorectal cancer, it is necessary that the expected cost of screening be justified in the light of the benefits that the programme ultimately produces. Models have been constructed to estimate the potential health effects and health care costs of colorectal cancer screening strategies. Recently, five screening programmes were compared: annual FOBT alone, flexible sigmoidoscopy, flexible sigmoidoscopy and FOBT, one-time colonoscopy and air contrast barium enema [21]. The model shows that FOBT alone is the most cost-effective of these programmes. Screening of cost-effectiveness in terms of lives saved per year is encouraging. It has been suggested that mass screening for colorectal cancer using FOBT was slightly less costly than mass screening for breast cancer. The cost per year of saved lives was estimated to be between $10 000 and $13 500 in the U.S.A. [22]. The cost effectiveness of screening compares favourably with other health care strategies.

CONCLUSION

Currently, there is evidence that it is possible to reduce mortality from colorectal cancer in people who accept screening by FOBT. In practice, subject compliance is a critical issue that determines the effectiveness of screening. Recently, it has been demonstrated that it is possible, with biennial FOBT in average risk individuals, to reduce colorectal cancer mortality through organised screening at a population level. To achieve this goal, the conditions of screening achieved in randomised controlled studies have to be reproduced. Pilot studies at a population level are needed in countries in which the way to achieve a high compliance is not yet known. Now that FOBT screening has been shown to be better than no screening, work must continue in the development of FOBT with improved performance characteristics. The time has come to encourage colorectal cancer screening, despite its current limitations.

1. Esteve J, Kricker A, Ferlay J, Parkin DH. *Facts and Figures on Cancer in the European Community*. Lyon, IARC, 1993.
2. Berrino F, Sant M, Verdecchia A, Capocaccia R, Hakulinen T, Esteve J. Survival of cancer patients in Europe. The EUROCARE study. IARC scientific publications no. 132. Lyon, IARC, 1995.
3. Eddy DM. Secondary prevention of cancer: an overview. *Bull WHO* 1986, **64**, 421–429.
4. Laara E, Day N, Hakama M. Trends in mortality form cervical cancer in the Nordic countries: association with organized screening program. *Lancet* 1987, **i**, 1247–1249.
5. Young GP, St John DJB. Faecal occult blood tests: choice, usage and clinical applications. *Clin Biochem Rev* 1992, **13**, 161–167.
6. Bertario L, Spinelli P, Gennari L, *et al.* Sensitivity of Hemoccult test for large bowel cancer in high risk subjects. *Dig Dis Sci* 1988, **33**, 609–613.
7. Macrae FA, St John DJB. Relationship between patterns of bleeding and Hemoccult sensitivity in patients with colorectal cancer and adenomas. *Gastroenterology* 1982, **82**, 891–898.
8. Gnauck R. Screening for colon cancer in Germany. *Tumori* 1995, **80**(Suppl.), 30–37.
9. Warhendorf J, Robra BP, Wiebelt H, Oberhausen R, Weiland M, Dhom G. Effectiveness of colorectal cancer screening: results from a population-based case–control study in Saarland, Germany. *Eur J Cancer Prev* 1993, **2**, 221–227.

10. Selby JV, Friedman GD, Quesenberry CP, Weiss NS. Effect of fecal occult blood testing on mortality from colorectal cancer. *Ann Intern Med* 1993, **104**, 1661–1668.
11. Lazovich D, Weiss NS, Stevens NG, White E, McKnight B, Wagner EH. A case–control study to evaluate efficacy of screening for faecal occult blood. *J Med Screening* 1955, **2**, 84–89.
12. Saito H, Soma Y, Koeda J, *et al.* Reduction in risk of mortality from colorectal cancer by fecal occult blood screening with immunochemical hemagglutination test. A case–control study. *Int J Cancer* 1995, **61**, 465–469.
13. Winawer SJ, Fleminger BJ, Schottenfeld D, Miller DG. Screening for colorectal cancer with fecal occult blood testing and sigmoidoscopy. *J Natl Cancer Inst* 1993, **85**, 1311–1318.
14. Mandel JS, Bond JH, Church TR, *et al.* Reducing mortality from colorectal cancer by screening for fecal occult blood. *N Engl J Med* 1993, **328**, 1365-1371.
15. Lang CA, Ransohoff DF. Faecal occult blood tests: choice, usage and clinical applications. *J Am Med Assoc* 1994, **271**, 1011–1013.
16. Mandel JS, Ederer F, Church T, Bond J. Screening for colon cancer. Which test is best? *J Am Med Assoc* 1994, **272**, 1099 (letter).
17. Kewenter J, Brevenge H, Engaras B, Haglind E, Ahren C. Results of screening, rescreening, and follow-up in a prospective randomized study for detection of colorectal cancer by fecal occult blood testing. Results of 68,308 subjects. *Scand J Gastroenterol* 1994, **29**, 468–473.
18. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomized study as screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996, **348**, 1467–1471.
19. Hardcastle JD, Chamberlain JO, Robinson MHE, *et al.* Randomized controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996, **348**, 1472–1477.
20. Bedenne L, Durand G, Faivre J, *et al.* Résultats préliminaires d'une campagne de dépistage de masse du cancer colorectal. *Gastroentérol Clin Biol* 1990, **14**, 140–145.
21. Lieberman DA. Cost-effectiveness model for colon cancer screening. *Gastroenterology* 1995, **109**, 1781–1790.
22. Wagner, JL, Tunis S, Brown M, Ching A, Almeida R. Cost-effectiveness of colorectal cancer screening in average-risk adults. In Young GP, Rozen P, Leven B, eds. *Cost-effectiveness of Colorectal Cancer Screening in Average-risk Adults*. London, Saunders, 1996, 321–356.

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Contra:

P. Autier

[1]Division of Epidemiology and Biostatistics, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy

INTRODUCTION

Several methods for colorectal cancer screening have been proposed: digital rectal examination, faecal occult blood testing (FOBT, guaiac tests or immunochemical tests), double contrast barium enemas, rigid sigmoidoscopy, flexible sigmoidoscopy and full colonoscopy. Two recently published clinical trials conducted in the U.K. and in Denmark using FOBT showed evidence that population-based screening with FOBT could reduce mortality from colorectal cancer [1, 2]. At first sight, these results could be interpreted as positive signals for implementing large-scale screening programmes using FOBT. However, one should be cautious with the interpretation of results from these trials.

WHAT IS THE PUBLIC HEALTH RELEVANCE OF FOBT?

Reductions in colorectal cancer mortality achieved by the immense U.K. and Danish trials were modest, in the order of 15–18%, and more than 10 years were needed to see the emergence of statistically significant results. Translated in absolute terms, these figures indicate that for 1,000 persons invited for FOBT screening once every 2 years during 10 years, one death due to colorectal cancer would be avoided [3].

Another concern must be raised: in both trials, all the reduction in colorectal cancer mortality was not attributable to FOBT itself, but rather to better medical attention given to those subjects who complied with the screening test. In the two trials, because of its low sensitivity, FOBT detected less than 50% of all colorectal cancers diagnosed in subjects who were screened on one or more occasions during the entire study course. As a consequence, in subjects who accepted at least one FOBT, interval colorectal cancers were more numerous than screen-detected colorectal cancers. Interestingly, published data indicated that interval colorectal cancers were detected at an earlier stage than colorectal cancer diagnosed in the control group [1, 2]. This is surprising, since one would expect interval cancers not to be detected earlier than in the absence of a screening test. In theory, they could even be diagnosed at a later stage because subjects with a negative screening test would be re-assured and, thus, would tend to underestimate symptoms suggestive of an interval colorectal cancer. In the U.K. and the Danish trials, physicians (and perhaps many screened subjects) were aware that they were part of a clinical study and most physicians did not ignore the problem of interval cancers with a test known for its low sensitivity. Therefore, it is highly probable that among screened subjects, more attention was paid to early symptoms of eventual presence of interval colorectal cancer, prompting more precocious diagnosis of malignant lesions.

In reality, FOBT simply makes a triage between those subjects who should undergo a colonoscopy because of eventual presence of colorectal cancer and those who should not. A good triage technique ensures that subjects that tested positive actually have a colorectal cancer and those who tested negative actually have no colorectal cancer. In the two trials, more than half of colorectal cancers diagnosed in screened subjects were interval cancers. As a consequence, any individual to whom FOBT is proposed must be informed that he or she has more than a 1:2 chance that a colorectal cancer will be left undetected by the test and develop into a symptomatic disease in the following years. Hence, triage

performed by searching for blood in the faeces does not have great efficiency and may be perceived as a poorly reliable technology, even if not expensive. Indeed, increasing sensitivity of FOBT is possible, but then the recall rate for full colonoscopy is likely to rise: in the Minnesota study, a slight decrease in colorectal cancer mortality was obtained with an annual rehydrated guaiac test [4]. Rehydration improved sensitivity, but dramatically increased the false positive rate, resulting in colonoscopy in 38% of all participants (over 13 years of age). In that sense, the use of the rehydrated guaiac test was probably just another way to select randomly subjects for colonoscopy.

CAN SOCIETY AFFORD LARGE-SCALE SCREENING WITH FOBT?

Decision makers are confronted on the one hand with shrinking resources for the provision of health care services, and on the other hand with steadily increasingly health technologies for primary or secondary prevention of diseases, e.g. screening for breast cancer and cervical cancer, primary and secondary prevention of coronary heart diseases with statins, secondary prevention of coronary heart disease with various drugs, primary prevention of high blood pressure and so on. When all costs generated by one of these technologies are computed, they appear highly expensive. If some technologies may seem more cost-effective than others, the introduction (or more extensive use) of any technology represents a new competitor for each pound spent on health care.

For decision makers, the dilemma is how to choose between these health technologies. Cost-effectiveness calculations with data from the U.K. and the Danish trials will be informative on how colorectal cancer screening with FOBT compares with other medical technologies. However, even if screening with FOBT would appear to have an attractive cost-effectiveness ratio, increasing its utilisation will inevitably increase health care expenditures or require that money currently spent for other medical procedures be redirected in order to allow greater coverage with FOBT, mainly for paying for the full colonoscopies ensuing positive FOBT.

In the control groups of the U.K. and the Danish trials, death from colorectal cancer represented 3.4 and 3.9% of all deaths, respectively. Hence, gains in mortality to be expected thanks to widespread use of FOBT are marginal when compared with the burden of other life-threatening conditions that are (or will be) vulnerable to prevention methods. Thus, from a preventive medicine perspective, trying to slightly reduce colorectal cancer mortality by using FOBT could be regarded as a lesser priority than, for instance, increasing quality of and participation in mammographic screening in women aged 50–69 years, or achieving large blood cholesterol reductions in patients suffering from coronary heart disease. These two later types of health interventions are likely to yield more important reductions in mortality in shorter periods of time than screening with FOBT.

HOW GENERALISABLE ARE RESULTS FROM TRIALS WITH FOBT?

The U.K. and the Danish trials were conducted in countries with 'centralised' health care systems, succeeding in having 60–68% of the target population accepting at least one screening round. In countries with 'liberal' health care systems (most European countries), physicians are generally less aware of public health issues and the likelihood of having participation rates as high as 60% is not at all guaranteed. Therefore, it is not straightforward that modest gains in colorectal cancer mortality could be replicated in countries not equipped with instruments used in the U.K. and the Danish trials, among other things, invitation–re-invitation systems, standardised disease management procedures involving all those implicated in the detection, cure and rehabilitation of cancer patients, good quality cancer and mortality registers.

Given the important discrepancies in health care systems throughout Europe, cost and the cost-effectiveness ratio of FOBT may not be so favourable in countries with 'liberal' health care systems: lower participation rates, rarer standardised disease management procedures and differences in health care costs may greatly influence both the price and the effectiveness of colorectal cancer screening. This phenomenon has been well documented for breast cancer screening, a procedure capable of achieving reductions in cancer mortality larger than those obtained with FOBT, but for which considerable variations in cost-effectiveness performance exist between European countries [5].

COMPARISON WITH PAP-SMEAR TESTING FOR CERVICAL CANCER SCREENING

The Pap-smear test for cervix cancer screening also has the reputation of low sensitivity. Population-based screening programmes with the Pap-smear test have succeeded in decreasing mortality from that cancer [6], and it is well known that repetition of the Pap-smear test (say every 3 years) offers the best protection against cervical cancer occurrence. One could then assume that similar to what has been observed with cervical cancer, repetition of FOBT say, every 2 years, would result in marked reductions in mortality from colorectal cancer. There is unfortunately a considerable difference between FOBT and the Pap-smear test: FOBT essentially detects cancers. Since colorectal polyps rarely bleed, FOBT is not a good test for detecting large polyps which have the highest potential to develop into colorectal cancer. In contrast, the Pap-smear is used for detecting premalignant lesions of the cervix. Removing them eliminates the risk of a premalignant lesion eventually developing into an invasive cancer. Should one premalignant lesion go undetected by one Pap-smear test, a further screen will most probably detect it.

OTHER HEALTH TECHNOLOGIES FOR PREVENTION OR EARLY DETECTION OF COLORECTAL CANCER

A decreasing trend in mortality from colorectal cancer has already taken place in many parts of the world. A general decline in colorectal cancer mortality has been noticeable since the 1950s and 1960s in the U.K., Germany, France, the U.S.A. and Canada [7–9]. Reasons for the decline are multiple: changes in diet patterns, occasional removal of polyps, earlier diagnosis and improved management of colorectal cancer. It is difficult to know which of these factors accounts for the observed decline in mortality. Earlier detection encompasses various methods, from physicians and patients giving more attention to early symptoms of the presence of colorectal cancer, to sporadic screening tests in asymptomatic subjects, using one or a combination of the proposed screening methods. Perhaps widespread utilisation of FOBT would accelerate the decline in mortality, but it will be of more use

with more sensitive screening methods, which are able to detect the majority of cancerous lesions at an early stage, or lesions before they have evolved in cancer.

CONCLUSIONS

In our opinion, available data on colorectal cancer screening efficacy, including the U.K. and the Danish trials with FOBT, do not represent sufficiently strong arguments justifying the organisation of population-based screening programmes using any method proposed for colorectal cancer screening. FOBT is not yet the appropriate technology for colorectal cancer screening and, therefore, we do not think it would be relevant to mobilise millions of men and women to undergo a screening procedure that will have little impact on mortality from colorectal cancer. There is great hope that ongoing research will yield more effective methods for colorectal cancer screening and/or prevention. However, the ability of these methods to reduce mortality from colorectal cancer with a safety level comparable to mammography or the Pap-smear test must first be assessed by clinical trials and produce convincing results before proposing them as being part of the arsenal to fight cancers.

1. Hardcastle JD, Chamberlain JO, Robinson MHE, *et al.* Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996, **348**, 1472–1477.
2. Kronborg O, Fenger K, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996, **348**, 1467–1471.
3. Gotzsche P. Screening for colorectal cancer (Letter). *Lancet* 1997, **349**, 356.
4. Mandel JS, Bond JH, Church TR, *et al.* Reducing mortality from colorectal cancer by screening for fecal occult blood. *New Engl J Med* 1993, **328**, 365–371.
5. Ineveld BM van, Oortmarssen GJ van, Koning HJ de, Boer R, Mass PJ van der. How cost-effective is breast cancer screening in different EC countries? *Eur J Cancer* 1993, **29A**, 1663–1668.
6. Laara E, Day NE, Hakama M. Trends in mortality from cervical cancer in the Nordic countries: association with organised screening programmes. *Lancet* 1987, **i**, 1247–1249.
7. Canadian Cancer Society. *Canadian Cancer Statistiques*, 1997. Toronto, 1997.
8. Chu KC, Tarone RE, Chow W, Hankey BF, Reis LAG. Temporal patterns in colorectal cancer incidence, survival and mortality from 1950 through 1990. *J Natl Cancer Inst* 1994, **86**, 997–1006.
9. Coleman MP, Esteve J, Dameicki P, Arslan A, Renard H. Trends in cancer incidence and mortality. IARC Scientific Publications No. 121, Lyon, 1993.

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Arbiter:

H. Bleiberg

Gastroenterology Department, CHU Bordet, 1 rue Héger-Bordet, 1000 Brussels, Belgium

COLORECTAL CANCER is characterised by a rather slow growing pattern that allows approximately 50% of patients with clinical symptoms at diagnosis to be cured by surgery. It seems logical to assume that diagnosis and surgery at an earlier asymptomatic stage would allow more patients to be cured. Screening appears to be the simplest way of decreasing mortality due to colorectal cancer [1].

Faecal occult blood testing (FOBT) allows the detection of cancer in the entire colon. Guaiac gum remains the most widely used indicator for occult bleeding and, among many commercial tests using guaiac gum, the most popular and the most extensively used is the Hemoccult test.

A precise measurement of the accuracy of the Hemoccult test has been established only recently [2]. 1241 patients who had undergone resection of a colorectal cancer were followed for 3 consecutive years by annual Hemoccult tests and total colonoscopy. 12312 relatives were followed by an annual Hemoccult test and total colonoscopy, if the former test was positive. The sensitivity of the Hemoccult test was 26% and the predictive value of a positive test was 8.2% [2]. The chemical test for occult blood depends on an oxidation process that is catalysed by a number of naturally occurring peroxidases and catalases. Therefore, many non-haem compounds may be responsible for the high rate of false positive tests that may be observed. However, blood losses exceeding 20 ml per day are needed to give a positive reliable Hemoccult reaction, but even in symptomatic colorectal cancers blood losses less than 10 ml are generally observed [3, 4]. Moreover, even though bulky tumours often bleed, why should small, well-vascularised tumours do likewise?

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

Case–control studies appear to be an elegant method of evaluating the long-term usefulness of screening. 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 life style. Most of the studies suggest that case subjects undergo screening with the Hemoccult test less frequently than control subjects. The result of this type of study was used to recommend screening for cancer of the cervix [5]. In the case of colorectal cancer, the results of the screening are rather flimsy, and show a benefit of the procedure only if the screening was performed more than 3 years before diagnosis [6] or in individuals less than 70 years of age [7]. These results therefore, lose their capacity to convince us that the Hemoccult test is an efficient screening procedure.

Properly randomised studies are required to demonstrate the usefulness of the Hemoccult test and to minimise the risk

of biases. Three randomised studies [8–10] were published recently as described by Drs Faivre Tazi and Dr Autier.

In the U.K. and the Danish studies, reduction in mortality was modest, in the order of 15–18%, indicating that for 1,000 persons invited for screening once every 2 years during 10 years, one death due to colorectal cancer would be avoided [11]. As if this were not enough to convince us of the modest benefit of screening with the Hemoccult test, Dr Autier observed that in both studies, interval cancers were detected at an earlier stage than in the control groups and suggests that the small reduction in colorectal cancer mortality was not ascribed to the Hemoccult test itself but also to better medical attention for those subjects who were randomised in the screening group. Actually participants in the screened group were informed of the possible symptoms of colorectal cancer while in the control groups participants were not told about the study [12].

Trials investigating Hemoccult testing have reached full maturity and the benefits, if any, are small. Our efforts should now focus on other screening procedures. Endoscopy appears to be an obvious and incontestable means to detect intraluminal colorectal cancer. Both high sensitivity and specificity justify the use of the procedure as a gold standard for measuring the accuracy of FOBT [2]. Data from two case–control studies suggest that there could be a 70% reduction in mortality due to colorectal cancer in the distal colon [13, 14]. The validity of case–control studies for identifying a true effect of screening on colorectal cancer mortality is hampered, as for the Hemoccult test, by selection biases [15]. However, the potential reasons for this reduction with sigmoidoscopic screening include, not only the discovery of early curable cancers but, more importantly, the discovery of premalignant polyps that can be removed and the discovery of an index polyp (> 1 cm and/or villous structure) that prompts a full colon examination and subsequent surveillance. The negative association between screening sigmoidoscopy and subsequent advanced distal colon cancer remains strong for up to 10 years [13]. Nevertheless, 50% of patients with adenomatous polyps did not have an index adenoma in the sigmoid colon and could, therefore, not be detected with sigmoidoscopy [16].

The use of endoscopy as a screening technique has been hampered by a reputation of high cost and poor tolerance. However, cost will decrease with increasing year-life saved and tolerance will increase with operator skilfullness. Moreover, endoscopy is not required on a yearly basis and time intervals of 3, 5 and even 10 years have been recommended. Determination of the time interval between two endoscopies is crucial. Very little is known about the risk of developing cancer after a polyp is present and in patients who have no polyp. In a series of patients with polyps > 1 cm who refused resection [17], 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 [18]. In patients who had polyps resected at baseline, recurrent polyps were frequently found at follow-up examinations, but the risk of serious pathology (polyp > 1 cm and/or villous structure) was unusual [19]. For those who had small tubular adenomas at baseline sigmoidoscopy, only 0.5% developed cancer during a mean follow-up of 14 years without any intervention. Assuming that these patients have the same or higher risk of cancer as individuals with no polyps at sigmoidoscopy, it appears that the risk of developing cancer during this time period is extremely small [20]. These data suggest that efficacy could 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.

WHERE DO WE STAND? WHAT IS THE APPROPRIATE STRATEGY?

Screening based on FOBT is not advisable. Trials investigating this approach are fully mature with approximately 300 000 participants in well-designed randomised trials. They show that the reduction in mortality, if any, is too modest [10, 21]. Moreover, after correction for an observation bias, the reduction in colorectal mortality is no longer statistically significant [12]. The apparent easiness of the test cannot be an argument in favour of its generalised use. The data on endoscopic screening are not yet mature. Most are based on case–control studies [13, 14], retrospective studies [20] or comparisons with historical controls [19], i.e. methods that are not accepted in oncology for the evaluation of chemotherapy. A randomised trial to evaluate screening by a single flexible sigmoidoscopy at the age of 55–60 years with appropriate colonoscopic surveillance for the 3–5% of participants found to have high risk adenomas (> 1 cm or villous structure) has already started [22]. Screening with colonoscopy might have a greater impact on mortality and could be cost-effective if screening intervals could be extended to 10 years or more [16].

There is evidence that patients who develop colorectal cancer may have increased cell proliferation in normal-appearing colonic mucosa [23] and one may hope that genetic markers will soon be identified. Future strategies for screening could consist of a single endoscopy at the age of 50–55 years and, if no lesions are seen, a biopsy could be taken for biomarker analysis and used for risk stratification.

1. Faivre J, Tazi MA. Should there be mass screening using faecal occult blood tests for colorectal cancer? Pro. *Eur J Cancer* 1998, **34**, 773–776.
2. Ahlquist DA, Wieand HS, Moertel CG, *et al.* Accuracy of faecal occult blood screening for colorectal neoplasia. *J Am Med Assoc* 1993, **269**, 1262–1267.
3. Doran J, Hardcastle JD. Bleeding patterns in colorectal cancer: an effect of aspirin and the implications for faecal blood testing. *Br J Surg* 1982, **69**, 711–713.
4. Greegor DH. Detection of silent colon cancer in routine examination. *CA: A Cancer Journal for Clinicians* 1969, **19**, 330–337.
5. Clarke EA, Anderson TW. Does screening by 'pap' smears help prevent cervical cancer. *Lancet* 1979, **21**, 418–425.
6. Selby JV, Friedman GD, Quesentberry CP, Weiss NS. Effect of faecal occult blood testing on mortality from colorectal cancer. *Ann Intern Med* 1993, **118**, 1–6.
7. Lazovich D, Weiss NS, Stevens NG, White E, Knight MB, Wagner EH. A case–control study to evaluate efficacy of screening for faecal occult blood. *J Med Screening* 1995, **2**, 84–89.
8. Mandel JS, Bond JH, Church TR, *et al.* Reducing mortality from colorectal cancer by screening for faecal occult blood. *N Eng J Med* 1993, **328**, 1365–1371.
9. Lang CH, Ranschoft DF. Faecal occult blood screening for colorectal cancer. Is mortality reduced by chance screening colonoscopy. *J Am Med Assoc* 1994, **271**, 1011–1013.
10. Hardcastle JD, Chamberlain JO, Robinson MHE, *et al.* Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996, **348**, 1472–1477.
11. Gotzsche P. Screening for colorectal cancer (Letter). *Lancet* 1997, **349**, 356.

12. Autier P. Should there be mass screening using faecal occult blood tests for colorectal cancer? Contra. *Eur J Cancer* 1998, **34**, 776–778.
13. Selby JV, Friedman GD, Quesenberry CP, Weiss NS. A case–control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992, **326**, 653–657.
14. Newcomb PA, Norfleet RG, Storere BE, Surawicz TS, Marcus PM. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst* 1992, **84**, 1572–1575.
15. Wahrendorf J, Robra BP, Wiebelt H, Oberhausen R, Weiland M, Dhom G. Effectiveness of colorectal cancer screening: results from a population-based case–control evaluation in Saarland, Germany. *Eur J Cancer Prev* 1993, **2**, 221–227.
16. Lieberman D, Smith F. Screening for colon malignancy with colonoscopy. *Am J Gastroenterology* 1991, **86**, 946–951.
17. Stryker SJ, Wolff BG, Culp CE, Libb SD, Ilstrup DM, MacCarty RL. National history of untreated colonic polyps. *Gastroenterology* 1987, **93**, 1009–1013.
18. Morson BC, Bussey HJR. Magnitude of risk for cancer in patients with colorectaladenomas. *Br J Surg* 1985, **72**, S23–S28.
19. Winawer SJ, Zauber AG, O'Brien MJ, *et al.* and the National Polyp Study Workgroup. Randomised comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. *N Engl J Med* 1993, **328**, 901–906.
20. Atkin WS, Morson BC, Cuzick J. Long term risk of colorectal cancer after excision of rectosigmoid adenomas. *N Engl J Med* 1992, **11**, 658–662.
21. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996, **348**, 1467–1471.
22. Atkin WS, Cuzick J, Northover JMA, Whynes DK. Prevention of colorectal cancer by once-only sigmoidoscopy. *Lancet* 1993, **341**, 736–740.
23. Bleiberg H, Galand P. Cell proliferation in colorectal cancer, polyps and normal mucosa. *Cancer* 1985, **56**, 124–129.