

L Döbrössy*, A Kovács and A Budai

Chief Medical Officer's Office, Budapest, Hungary

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*Corresponding author: Dr. Lajos Döbrössy, Albert Flórián út 2-6, Budapest, H-10976, Hungary. E-mail: dobrassy.lajos@oth.antsz.hu

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Review Article

Conflicts between Clinical and Public Health Viewpoints: Colorectal Screening

Summary

In Hungary, the mortality rates from colorectal cancer are dramatically high, therefore the reduction by population screening as a public health measure is considered as one of the priorities of the National Public Health Programme. The aim of screening is to reduce the burden of cancer on the population by discovering latent disease in its early stage and treating it more effectively than if diagnosed later in a symptomatic stage. In the beginning, a human-specific immunological test was applied in the "model programmes", as a screening tool to detect the occult blood in the stool; compliance was 32% in average. However, the objectives of the model programmes have not been achieved, because – among other reasons – a debate on method of choice and the strategy to follow have divided the professional public opinion. In this paper the debated issues are critically discussed, being convinced that – at present – population screening seems to be the most promising way to alleviate the burden of colorectal cancer.

Introduction

Colorectal cancer is the second most common newly diagnosed cancer and the second most common cause of cancer death in both sexes in the European Union. Average-risk individuals account for 70%–75% of patients with colorectal cancer. Many of the fatal outcomes, however, could be avoided through early detection, by making effective use of screening tests followed by appropriate treatment. The Council of the European Union advises the member countries to introduce organized screening programmes for colorectal cancer using detection of occult blood in the stool (FOBT), as screening method [1]. The importance of colorectal screening is emphasized by the "Brussels Declaration", which was signed by several MPs of the European Union, in addition to representatives of scientific organizations, foundations and health insurance funds; the Declaration urges the European Council to prepare an action plan on how to alleviate the colorectal cancer burden, and to support the governments of Member States in developing organized screening programmes [2]. A similar declaration was published in Budapest on the occasion of the Hungarian Presidency of the Council of the European Union [3]. In 2011, the European Commission – in cooperation with the WHO International Agency for Research on Cancer (IARC) – published guidelines for quality assurance in colorectal screening and diagnosis [4].

In 2002, the government of Hungary, in the frame of the National Public Health Programme, took aim "to develop an organized colorectal screening programme based on detection of human-specific faecal occult blood, and in this way, to reduce the colorectal cancer mortality by 20% by the year 2010" [5]. This objective has been approved by the Parliament [6]. In 2008, the National Audit Office declared that "the aim of reducing colorectal mortality by screening has not been realised" [7].

The reason for the non-achievement had generated a heated debate on the strategy and methodology of colorectal screening

which divided the professional community, whether the "two-steps" strategy (when the first step is the detection of occult faecal blood, and after this, as a second step, colonoscopy for further assessment of those with positive test result is applied) or, as a "one step" strategy, i.e. colonoscopy alone should follow, as method of choice for a nationwide mass screening programme.

The task of this paper is to scrutinize this dilemma, and take a stand on these debated issues.

Methods for colorectal screening

Nowadays, a substantial amount of information is available on the natural history of colorectal cancer and its precursors, i.e. the adenoma-carcinoma sequence through which approximately 75% of tumours of colon and rectum go through ("sporadic cancers"). There could be alternative pathways to development of right colon cancer from serrated polyps [8]. The aim of colorectal screening is to prevent the development of advanced cancers through detection and, if possible, removal of the premalignant adenomatous polyps and localized cancers, from which the large majority of advanced cancers arise.

Although the methodological arsenal seems to be abounding, in fact, we do not have such screening methods that would meet all the requirements. Screening methods for colorectal cancer can generally be divided into two categories: endoscopic examinations (i.e. flexible sigmoidoscopy, colonoscopy), and detection of occult blood in the stool (FOBT). There are some other methods under evaluation. The methods differ in many aspects such as invasiveness, burden of the procedure, the sensibility and specificity of the methods, required screening frequency etc. Most importantly, the acceptance by the public of various methods also differs. These aspects of the different screening methods will be discussed below.

Endoscopy in colorectal screening

Flexible sigmoidoscopy (FS) with a 60 cm endoscope allows examination of the sigmoid colon and rectum up to the splenic flexure where 60% of cancers and adenomas are located; this means that approximately one-third of lesions are out of the scope of sigmoidoscopy. It is a safe and practical test. The effectiveness of sigmoidoscopy has been tested in case-control and randomized controlled trials [9-11]. The results of these epidemiological studies suggest that - if performed in an organised screening programme with careful monitoring of the quality and systematic evaluation of the outcomes, adverse effects and costs - patients screened with sigmoidoscopy have reduced incidence and mortality rates of distal colorectal cancer by roughly 40-60% [12], and from rectosigmoid cancer by 76% compared with the controls [13]. It can detect only 70% of cancers and polyps but it does not detect proximal neoplasms [14]. The sensitivity and specificity of sigmoidoscopy were 77% and 83%, respectively; combining FOBT with FS would not significantly improve the results of sigmoidoscopy [15]. Polypectomy is usually not performed during screening sigmoidoscopy. If any significant pathology is discovered, patients are usually referred for complete colonoscopy [16]. In the United Kingdom, in order to establish the role of flexible sigmoidoscopy, a multicentre randomized controlled trial is in progress [9].

Colonoscopy is the most reliable method of testing the colon and rectum, and the “*gold standard*” for colorectal cancer diagnosis. With colonoscopy, the total length of colon up to the ileo-coecal flexure can be examined by the control of the “naked eye”. Simultaneously, it makes possible the removal of polypoid lesion and obtaining biopsy specimens.

Colonoscopy is a hospital-based examination, however, in some countries it is also used as a primary screening tool for colorectal cancer. All those with positive screening tests in all programmes (FOBT, FS) need to undergo clinical colonoscopy to verify the screening result; therefore, the effectiveness of all screening examinations in practice is dependent on the quality of colonoscopy that is operator-dependent, and such, may be subject to bias [17].

Until recently, there has been no randomized trial investigating the efficacy of *colonoscopy screening*. Large multicentre trials are currently underway in several countries, comparing the efficacy of a once-only colonoscopy to no screening. However, there is indirect clinical evidence and observational studies to support the efficacy, feasibility, and accuracy of colonoscopy in screening for colorectal cancer; its sensibility is near 100% [18]. In the average-risk cohorts and prospective observational studies, colorectal cancer incidence and mortality were reduced after screening colonoscopy. These results provide additional evidence for the effectiveness of colonoscopy as a primary screening modality [19]. A nationwide colonoscopy screening program that uses highly qualified endoscopists can detect a significant number of adenomas and early-stage carcinomas [20,21].

Detection of faecal occult blood

These methods are based on the assumption that early cancer and its precursor conditions are intermittently bleeding and the small amount of blood which would not see by naked eye can be detected by suitable method in the stool. As the bleeding is intermittent,

samples are taken from 2-3 consecutive motions to increase the chance of detection. The test is qualitative: to localize the source of the bleeding, endoscopic examination needs to be done. Chemical and immunochemical methods are at disposal for this purpose.

The *chemical detection* method, the guaiac-based faecal occult blood test (gFOBTs) is a simple colorimetric test; it acts by detecting the intact haem molecule from haemoglobin. Two or three small samples from stools obtained on two or three consecutive bowel movements are applied to a piece of paper impregnated with guaiac gum. Upon application of a developing solution, the presence of trace amounts of haem results in a blue colour change due to the pseudo-peroxidase actions of haem. The accuracy of gFOBTs can be affected by some medications, diet and excessive amounts of reducing agents in faecal samples (eg, vitamin C) and they therefore require dietary restrictions during the days prior to the test. There are a number of such commercially available tests, collectively named “haemoccult tests” [22,23].

Until recently, the only test for which there has been robust evidence of efficacy from randomized controlled trials (RCTs) was the *guaiac-based faecal occult blood test (gFOBT)*. It has been proved that yearly or biennial examinations can reduce colorectal cancer mortality by 15-33% [24-27]. The effectiveness of gFOBT has been confirmed by meta-analyses [28,29]. However, gFOBTs have several weaknesses, including limited sensitivity even when used biennially [30,31]. Effectiveness of the gFOB test requires compliance with testing over many years, as its sensitivity is only 30-60% for one time use, but may be as high as 90% if 3 tests are performed, and when it is used every 1-2 years over a long period of time (programme sensitivity) [32]. Low sensitivity leads to a high number of false negative test results and the effect of false reassurance [33]. Its specificity is far from optimal, as blood identified in faeces may be due to several reasons unrelated to cancer, thus a proportion of cases identified by fecal occult blood testing as false-positive will be subjected to unnecessary tests by colonoscopy before a clinical decision is taken. This may cause people unnecessary stress and expose them to possible harm.

Immunochemical detection of faecal blood tests (iFOBT, or FIT) involves the use of an anti-human monoclonal antibody, targeted at intact human blood-borne proteins (usually haemoglobin). These tests therefore have the theoretical advantage of not being affected by haem, peroxidases or anti-oxidases in the diet or medication, therefore these tests are specific to human blood, and do not require dietary or medication restrictions. They are generally more expensive than the guaiac tests and require laboratory processing [34]. Both quantitative and qualitative FITs have been developed. Qualitative tests require a visual interpretation of test results as positive or negative; quantitative FITs are analysed automatically, providing a value for the amount of haemoglobin found in the stool sample [35].

The immunochemical tests are considered as evidence-based screening tests for colorectal cancer. Case-control studies evaluated the efficacy of iFOBT, and found a significant reduction in colorectal cancer mortality from iFOBT screening, ranging from 23% to 81%, depending on the study and years since the last iFOBT [36,37]. The evidence shows that the immunochemical FIT tests have a higher cancer detection rate, and are less prone to false positive tests than

gFOBTs [38]. On this basis, the immunochemical detection of occult blood is now considered an acceptable screening option by various bodies [4,39]. Its sensitivity and specificity are increased as compared to gFOBT. In a well-organised high-quality iFOBT screening programme, the risks of adverse effects are limited.

There have been efforts to make the immunochemical tests more sensitive by means of applying a second marker, such as lactoferrin [40], and alfa-1-antitripsin [41]. To date, most experiences have accumulated with the addition of albumin to haemoglobin as a marker of blood proteins [42,43]. Such “double” immunological screening tests had been used in our previous pilot programmes; we found it more sensitive in detecting polypoid adenomas as compared with the “single” hemoglobin test [44], however, due to the lack of validation, we would discontinue using the Fecatwin test. The validation of the test is in progress.

The use of molecular biology techniques to identify cancer-related faecal DNA [45], or protein biomarkers - used singly or as a panel - shows promise but it is in its infancy.

Other methods: Several new technologies are under development for colorectal screening. However, currently there is no evidence on the effect of new screening tests under evaluation on colorectal incidence and mortality; new screening technologies are therefore not recommended for screening the average-risk population.

Virtual colonography: An imaging procedure which uses x-ray and computers to produce tree-dimensional images of the large intestines, does not show as much detail as a conventional colonoscopy, so polyps smaller than between 2 and 10 mm in diameter, and flat polyps may not show up on the images. However, it is favored by some professionals because it permits complete visualization of the entire colon, hence providing more opportunity to identify precancerous polyps and cancer [46]. Another disadvantage that it is a hospital-based procedure and requires a number of equipment and personnel to perform. Studies on the impact of this method of screening on colorectal cancer incidence or mortality have not yet been conducted.

Capsule endoscopy: Capsule endoscopy involves swallowing a small capsule, which contains a colour camera, battery, light source and transmitter; it can visualise the lumen of the bowels. It has not yet been applied for colorectal screening purposes. No studies have yet reported on CRC incidence and mortality reduction from capsule endoscopy [47,48].

Compliance with screening tests

Participation, an indicator of acceptance and effectiveness of screening programmes, varies widely in clinical trials and population-based colorectal cancer screening programmes. High participation rates are necessary for a screening method to be successful, beneficial and cost-effective. Compliance is affected by the test acceptability to the population [49].

Colorectal screening is underused. Unfortunately, the uptake of screening for colorectal cancer remains low in comparison with other screening modalities such as mammography for breast screening, or a smear test for cervical screening and PSA screening for prostate

cancer [50]. The reported compliance of colorectal cancer screening in the general population varies widely, and is generally low. The reported participation rate for fecal occult blood tests (FOBT) ranges from 30% to 70% in community-based programs and from 12% to 27% for screening with endoscopy [51].

Understanding of the influencing factors that affect screening choices is essential to develop future screening strategies. Factors associated with low compliance have been widely investigated. Such factors include physician recommendation, patient demographics, financial enablers (such as income and insurance coverage), health care system interactions (personal invitation), and colorectal cancer risk. Furthermore, the rate of participation is influenced by various psychological, cognitive and behavioural factors, as well. Male gender, younger participants, low level of education, lower income, ethnic minorities and not having a spouse, were the most frequently reported barriers. All these factors have been identified in previous studies to influence patient adherence to colorectal cancer guidelines [52].

Opportunistic vs organized screening

According to the state-of-the art of cancer screening, examination of healthy or apparently healthy individuals may take place in two different ways: opportunistically or in an organised manner. The former is part of medical practice; the latter is a public health measure.

Opportunistic screening happens when someone asks their doctor or health professional for a test suitable for detection of symptomless target condition or such a test is offered by a doctor or health professional as part of everyday medical practice. By contrast, *organised screening programmes* are implemented at national or regional level, if there is such a national policy, i.e. if the relevant health authority expresses a political will to run such a programme. It is initiated by the provider health services, financed from public sources. The individuals are personally identified, invited, recalled if necessary, and followed up. Most importantly, every phase of organised screening is monitored and evaluated. There is high quality evidence that the screening programme is effective in reducing death rate from the target disease in the target population. Finally, there is consideration of social and ethical issues: everyone who takes part is offered the same information on benefits and potential harm, enabling him/her to arrive at an informed decision to participate.

Implementation of colorectal screening

As to colorectal screening, there is general consensus concerning the efficacy of it, thus its implementation in an organized way is recommended. However, there is a lack of agreement about which screening strategy and which screening test should be routinely applied. In fact, insufficient evidence is available to recommend one screening test over the other [53]. There is an obvious difference in recommendations for implementation of colorectal screening between the United States and Europe.

In the United States, a joint committee of several professional bodies has released a guideline that divided colorectal cancer screening tests into two groups: cancer *prevention tests* and cancer *detection tests*. Cancer prevention tests should be offered first. The

preferred prevention test is colonoscopy every 10 years. Cancer detection test should be offered to patients who decline colonoscopy or another cancer prevention test. The preferred cancer detection test is annual FIT for blood [41,54]. However, colonoscopy is the gold standard for colorectal screening and the most common method. In 2008, the US Preventive Services Task Force (USRSTF) recommended colonoscopy in every 10 years (or “once in a lifetime”) as the standard method, but annual-biannual screening with a sensitive FOBT, flexible sigmoidoscopy every 5 years with a half-time sensitive FOBT from age 50 to 75 years men and women at average risk is also mentioned as a possible option. There are no personal invitation-based organized nationwide screening programmes in operation [55-57].

On the other hand, most European programmes currently offer faecal occult blood testing as a single screening method, since it is recommended as the only screening strategy with sufficient evidence for a reduction in colorectal cancer mortality; in non-negative tests results need to be verified by colonoscopy. The relevant European authorities promote nationwide mass screening programmes for development in the member states [1]. In their view, in order to maximise the impact of intervention and ensure high coverage and equity of access, only organized screening programmes should be implemented - as opposed to case-finding or opportunistic screening - as only organized programmes can be properly quality assured. According to the European guidelines published by the European Commission in cooperation with WHO/International Agency for Research on Cancer [4], for mass screening purposes only “detection tests” (gFOBT, iFOBT or FIT) should be undertaken. According to the report on the implementation of the Council recommendations, colorectal screening is running or being established in 19 of 28 European Union member countries. In the majority of countries faecal occult blood testing was used as the only screening method. Colonoscopy was the only screening method used in one country; in some countries iFOBT and flexible sigmoidoscopy, or gFOBT and colonoscopy are the offered choice [56,57].

New technologies under evaluation are not yet recommended for colorectal screening, only after they have been evaluated for efficacy in randomized controlled trials, and after other relevant aspects such as cost-effectiveness in the different health care systems have been taken into account.

Status of colorectal screening in Hungary: a conflict between clinical and public health standpoints

In 2004, the Hungarian government decided to establish pilot programmes for the early detection of colorectal cancer in selected counties before organised population screening would be gradually extended countrywide. The early experiences have been published [44].

The programme management has decided to use the immunochemical detection of occult blood in stool samples (iFOBT: OC Sensor) as the screening test, considering that the social acceptance of these non-invasive tests is more favourable in comparison to that of endoscopic tests. According to screening protocol, colonoscopy as a verification test needs to be performed in all iFOBT positive cases (about 6% of all those screened). This is what is referred to as the “two-steps strategy” of colorectal screening.

In the meantime, alternative recommendations have emerged from the clinical community proposing colonoscopy to apply as a single test for primary screening [58-60]. Scientific societies argued that the primary goal of colorectal screening was the detection and removal of precancerous polyps, and in this way, prevention of colorectal cancer from development, thus the “one step strategy” is at the same time therapeutic intervention, therefore the most promising way of colorectal screening.

At this point, a conflict between clinical and public health standpoints had emerged that set back the implementation of population screening and the “clinical” standpoint seemed to discredit the other one. No doubt, colorectal screening is a public health exercise. The intention of a national mass screening programme is to apply the screening test to the entire population or, at least, to as large a segment of the population at average risk in certain age range as possible. To bring about reductions in mortality, a substantial proportion of the population must participate in the screening programme. Programmes with low uptake can be ineffective and can promote inequalities in health-service provision. The essence of the problem lies in the *compliance of the invited population* with the offered screening.

Each of the screening test has advantages and disadvantages. Colonoscopy is more uncomfortable and unpleasant for the participants than any others. Nearly all patients find preparation for colonoscopy, i.e. complete emptying and purification of the bowels to be far worse than the procedure itself [61]. Most patients either do not experience significant discomfort while colonoscopy is performed or do not remember it because of the amnesic effects of medication used for sedation. It requires costly equipment, which is not available in every clinical setting because of economic limitations. It is an invasive procedure, with a small but real risk of perforation and bleeding. The high demand for expertise, skillful and competent endoscopist to perform endoscopy needs also to be taken into account. High quality colonoscopy is time-consuming [62]. On the other hand, colonoscopy needs to be performed much less frequently, only every 10 years, for average-risk individuals. Over this long period, interval cancers were found to arise from a missed lesion in 52% of cases, a new lesion in 24%, and an incompletely removed lesion in 19% [63].

However, it is important to realize that not all eligible persons are willing to undergo colonoscopy; most people decline to accept it. Furthermore, in some countries, such as Hungary, the greatest impediment is limited colonoscopic capacity. The nationwide extension of FOBT-based colorectal screening, with an anticipated 50% participation of invitees and a 6% recall rate, means the existing volume of screening colonoscopy is not enough to meet the needs.

On the other hand, faecal occult blood tests meet all the requirements of an “ideal” mass screening test, more acceptable to the public. They are simple to perform, non-invasive, relatively inexpensive, requiring an annual or biannual assessment. In spite of the fact that the sensitivity and specificity of these tests are limited, FOBTs can be offered to patients as colorectal screening tests alternative to colonoscopy.

The greatest difficulty is winning the cooperation of the eligible population. As the participation is not compulsory, compliance with the recommended screening depends on the health consciousness of the patient. Low participation rates have implications on cost-effectiveness, as well. It is a general experience that the population is reluctant to accept even the blood test, but colonoscopy is seen as a much more disagreeable intervention. Therefore, conceding that - in a clinical setting - colonoscopy is the method of choice, and indispensable to further assessment of cases with positive test results, yet may not be considered a screening method for the population at average risk. It means that the "one-step" strategy must not be applied as a mass screening method for the invitation-based population screening because of its low attendance rate.

Conclusion

The burden of colorectal cancer is high and increasing in many countries, among others in Hungary. The available evidence strongly suggests that there is a large but widely underused potential for colorectal screening in reducing the burden of incidence and mortality of colorectal cancer. According to current evidence, colonoscopy, flexible sigmoidoscopy, and faecal occult blood tests - preferably faecal immunochemical tests - are prime candidates for an effective and cost-effective screening option. Colonoscopy is likely to remain the "gold standard" and, as such, the most attractive screening modality for the immediate future, although its shortcomings will continue. However, occult blood tests prove to be the most practicable for mass screening purposes. In this respect, *social acceptance is a key issue*. Furthermore, quantitative FITs offer the opportunity to provide tailored screening by adjusting the positivity cut-off level. This can be used to adjust screening to available resources and colonoscopy capacity (which is rather limited in the country). Recent studies suggest that the impact screening with FIT can approach that of colonoscopy if the adherence to multiple rounds is high.

Only the FOBT for men and women aged 50-74 years has been recommended for CRC screening by the European Union, to date. In Hungary, a consensus has been reached to apply „two steps” strategy, i.e. non-invasive, immunological stool tests (iFOBT or FIT) in the organized colorectal screening programme, as first step, and colonoscopy, as second step, for further assessment, if necessary. FIT screening is generally associated with higher participation and higher detection rates of adenomas and colorectal cancer compared with gFOBT screening. It calls for the timely implementation of organized screening programmes where they are not yet in place and for the continuous improvement of existing offers, where such programmes exist. This should be considered an obligation that is not to be postponed: the time to act is now.

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