SCREENING FOR COLORECTAL CANCER – NEW EVIDENCE IN THE LAST 10 YEARS

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Abstract
The evidence base for screening for colorectal cancer has expanded at a rapid pace in the last 10 years. Faecal immunochemical tests for haemoglobin have been proven to be superior to guaiac-based faecal occult blood tests in terms of acceptability to screenees and analytic and clinical sensitivities for cancer and advanced adenomas. In addition, flexible sigmoidoscopy has been proven to reduce incidence and mortality from colorectal cancer, demonstrating that structural detection of preinvasive lesions will reduce its incidence. Both methods are now proven screening tool options and should be considered for implementation in screening programs. The requirements of screening programs are also much clearer. The monitoring and reporting outcomes of screening programs have been subject to consensus processes and have been clearly enunciated. They include quality, population acceptance, costs, adverse effects and measures of disease burden. The data needed to measure these should be an obligatory aspect of organised screening programs. The evidence base supporting communication strategies has expanded. These, combined with strategies proven to increase participation, should be part of all screening programs. Australian society is clearly benefitting from colorectal cancer screening and guidelines need revision to reflect the new evidence.

The last 10 years have seen considerable advances in screening for colorectal cancer (CRC), not only in terms of tests used, but in understanding of how to execute and how to judge the outcomes of population-based organised screening programs, including our own National Bowel Cancer Screening Program. Furthermore, the latest research points to newer technologies that seem likely to change the screening scene in the next 10 years. This short review will focus primarily on the new evidence base and what it means for Australia at this point in time.

Nature of screening and WHO principles
Screening is a multi-step and multidisciplinary process. The World Health Organisation (WHO) guidelines address the need for an evidence base for the test and its impact, issues around the screening process, the importance of the cancer for the community in question, and the need for community engagement. For the screening process to work, a significant proportion of the population should engage in the screening test, the screening test should be performed appropriately and correctly, colonoscopy must be undertaken with skill, and any therapy, whether colonoscopic, surgical, chemotherapeutic or radiological, must be done well. Each of these steps is crucial if we are to achieve a reduction in population mortality from CRC or in its incidence. Quality assurance at each step is vital. A screening program should seek to ensure all these aspects are in place, and should be monitored carefully for quality and to demonstrate value and feasibility.

Principles of the WHO, while promulgated in 1968, continue to be the basis for this approach, although two aspects of the original standard need comment – reduction of cancer incidence, and the nature of the screening test.

The WHO principles always envisaged screening being undertaken using a simple screening test with follow-up of a ‘positive’ by diagnostic verification (in the case of CRC this would be colonoscopy). In some countries, CRC screening with the diagnostic test (colonoscopy) is underway and being performed with careful attention to quality and good population acceptance. However, we still do not have randomised control trials (RCT) of average-risk populations assessed on an intention-to-screen basis to support such ‘one-step’ screening. Such trials are underway, but it will be a decade before the information is available.

The WHO principles also focused on reducing cancer mortality, with little attention paid to incidence reduction. Clearly the latter will lead to the former. Given we now have evidence, discussed below, showing CRC screening can reduce incidence, we need to consider whether we should target not just early stage cancer, but also pre-invasive lesions, especially ‘advanced adenomas’.

Targeting adenoma detection has a risk of leading to overdiagnosis, although there has been no evidence to emerge that suggests over-diagnosis is an issue for CRC. Over-diagnosis refers to detection of inconsequential disease that will not shorten one’s life-span if left untreated. Overdiagnosis will occur when we focus on detection of adenomas, but it should be noted that the vast majority of these will be simply treated at colonoscopy.

Screening contexts and outcomes
Organised screening programs are the preferred basis for implementing screening programs. This ensures all
elements of the screening process are in place, that quality assurance is addressed systematically, or resourcing of key aspects such as colonoscopy are appropriately dealt with, population engagement can be addressed and improved and benefit to the community is readily understood. Screening by case-finding is ad hoc and quality assurance, as well as equitable population coverage, are difficult since screening is more than simply carrying out the screening test and referring people for diagnosis where indicated.

Invitation processes must be developed and carefully tested in the target population. The program should then ensure that a high level of compliance with diagnostic follow-up occurs. Practice standards for diagnosis, treatment and surveillance must be set. While we have done this most recently for CRC through the National Health and Medical Research Council guidelines of 2005, new approaches in aspects of CRC have emerged since the National Bowel Cancer Screening Program began in earnest in 2006.

Global standards have now emerged for monitoring CRC screening at the population level. These generally cover the following categories of measurable events:

1. Population acceptance
2. Screening pathway adherence by screenees and health professionals
3. Test performance and lesion detection, including missed (or interval) lesions and technical aspects of the screening test
4. Quality measures (at all levels)
5. Adverse events
6. Cost-effectiveness
7. Burden of disease at the population level:
   - Cancer and advanced adenoma detection rates
   - Down-staging of cancer (a useful surrogate for mortality in the case of CRC screening)
   - CRC-specific mortality
   - CRC incidence.

Complete and accurate recording of relevant data on each person and every screening and diagnostic test performed is crucial. This places major demands on all involved in the screening pathway, and on data systems and processes for collating and monitoring data. Incorporating evaluation of the program into the protocols adopted for the screening process must be in place at the start. In this context of oversight, ‘safety-net’ systems can also be implemented. For example, nurse pathway coordinators serve to ensure program adherence and improvement in quality.

**New evidence base for screening tests**

Two key developments in simple screening tests have changed or are in the process of changing the nature of screening programs. The first relates to the revolutionary changes in faecal tests for occult blood (FOBT) brought about by faecal immunochemical tests (FIT) for haemoglobin. It should be noted that FIT is the preferred abbreviation for the latter since the technology, clinical performance, and population acceptance is very different from the original guaiac-FOBT (gFOBT).

As background, the relatively insensitive gFOBT Hemoccult offered biennially, reduced CRC-mortality by 15-20% on an intention-screen basis. This improves to 33% with rehydration of Hemoccult offered annually, a process that increases sensitivity, but results in considerable deterioration in specificity. The increased sensitivity achieved with rehydrated Hemoccult is also associated with a 20% reduction in CRC incidence when followed up for 18 years, presumably resulting from increased detection and removal of adenomas. Together with this benefit on CRC mortality, the associated parameters regarding screening participation, test accuracy and cancer down-staging have been demonstrated. For CRC screening, we can be confident down-staging will translate into survival benefit and reduced population mortality.

It is now clear that FIT provides better accuracy, including improved sensitivity for advanced adenomas as well as CRCs, and better acceptability when evaluated on an intention-to-screen basis. When evaluated in a program involving repeated testing, two-thirds to three-quarters of cancers are detected by FIT. Population-based and case-control studies support the value of this technology. Further studies from the Netherlands confirm the value of FIT in a population RCT when analysed on an intention-to-screen basis relative to Hemoccult II. While that study showed that FIT resulted in twice as many colonoscopies as gFOBT, more than twice as many advanced neoplastic lesions were detected, meaning that the number needed to colonoscope to detect one lesion was largely unchanged. All this evidence has led to recommendations that FIT replace gFOBT. FIT technology has significantly better capacity to detect adenomas than gFOBT, and repeated testing improves detection. In other words, when using this FOBT technology, there is capacity to reduce incidence as well as mortality.

Publications are now calling for the use of quantitative FIT, not just the qualitative versions, since these allow flexibility, including choice of preferred test performance characteristics and adjustment of the cut-off triggering colonoscopy, such that programs can be carefully matched to colonoscopic resources. These tests are also readily automated and the endpoints are objectively ascertained, improving quality assurance in the laboratory.

Finally, FIT tests have now been shown in the absence of bias to lead to down-staging on an intention-to-screen, as well as a participant basis in the National Bowel Cancer Screening Program. They have also been associated with down-staging in an extensive cancer register. We can be confident of their value in reducing CRC mortality.

More recently, the results of three sigmoidoscopy screening RCTs consistently showed that endoscopic excision of colorectal adenomas is associated with a substantial reduction in CRC incidence (18%-23%) and mortality (26%-31%) on an intention-to-screen basis. Considering subjects who were actually screened, the reduction in CRC incidence ranged between 31% and 33%, and CRC-specific mortality was reduced by 38%-43%. The observed protective effect refers to a follow-up of 11 years and was mainly limited to the distal colon. The
reduction in CRC incidence in the proximal colon was small and not statistically significant either in the UK (3%) or in the Italian (15%) trials.\textsuperscript{35, 34} A statistically significant 14% reduction in CRC incidence in the proximal colon was documented only in the Prostate, Lung, Colorectal and Ovarian cancer screening trial,\textsuperscript{35} but there was no mortality reduction in the trial.

Based on the effect observed for flexible sigmoidoscopy, it can be concluded that structural detection (i.e., visualisation at endoscopy) of lesions brings significant benefit in terms of reduced incidence, morbidity and CRC mortality. But it should be noted that the majority of adenomas would not progress to cancer during a person’s life time if left in situ.\textsuperscript{36}

Whether the benefit of polypectomy extends to the proximal colon is not yet certain. This uncertainty is underscored in observational studies that showed use of colonoscopy was not associated with a reduction in the risk of dying from right-sided CRC.\textsuperscript{37-40} Only one case-control study has shown a reduction in proximal CRC incidence associated with self-reported use of colonoscopy in the preceding one to 10 years, and only in subjects older than 60 years.\textsuperscript{41} These findings underscore how crucial the quality of diagnostic examinations is to maximising effectiveness in screening and to optimise the balance between potential harms and benefit. They also suggest effectiveness of one-step colonoscopic screening in practice might not be as great as is often assumed.

Therefore, even though colonoscopy improves detection of both invasive lesions and pre-invasive lesions (adenomas), adding the potential to prevent cancer, the benefit of colonoscopic screening, either in terms of CRC mortality, or incidence reduction, has not been assessed by mass population RCTs in the setting of mass population screening.\textsuperscript{42} Such studies are, however, underway.\textsuperscript{3} New guidelines for CRC screening need to specify FOBT technology and the superiority of FIT over gFOBT.

**Emerging tests**

Molecular tests using multi-target DNA markers are being developed using faecal samples. They continue to improve, with promise of very good sensitivity and specificity for cancer and advanced adenomas. Their adoption will depend on logistics and cost. Blood based molecular markers also show promise, although at this stage they do not seem superior to FIT in terms of performance, and are limited in capacity to detect advanced adenomas.\textsuperscript{43} Nonetheless, qualitative studies show that the concept of a blood test would be preferred by the majority.

**Communication and program**

The target population should receive relevant information to enable them to make an informed decision about screening. CRC screening is more complex than for breast or cervix, especially in view of the more complex risk groups and wider range of test options. Communications need to address the anxiety this can raise.

The screening process needs to be clearly explained, as well as the fact that a positive test in two-step screening should be followed by colonoscopy. Similarly, programs must explain that screening tests are not perfect. While many innovative studies are underway to address how best to do this, and some guidelines are providing guidance,\textsuperscript{2} programs should clearly enunciate communication standards needed for the community context.

Communicating the value and appropriateness of screening aids participation as it moves people through the stages of pre-contemplation and contemplation to action. An advance letter improves uptake in the Australian environment and in many others, but this needs support from a wider media-based awareness campaign.\textsuperscript{44} FIT tests help to overcome some of the faecal sampling barriers due to their simpler sampling devices (compared to gFOBT) and removal of dietary restriction barriers inherent in gFOBT.\textsuperscript{10} FIT also avoids the high false-positive rate of gFOBT in certain ethnic populations.\textsuperscript{46} A trusted advocate, specifically a person’s own general practitioner, increases screening participation rates and adherence to screening over multiple rounds.\textsuperscript{46} It makes sense to develop methods to demonstrate to invitees that GPs are supportive. While most screening guidelines have traditionally restricted themselves to addressing tests, it is now time that guidelines for communication and proven participation-enhancing strategies are incorporated.

**Conclusions**

In the last 10 years, FIT has been proven to be superior to gFOBT in terms of acceptance and analytic and clinical sensitivities for cancer and advanced adenomas. In addition, flexible sigmoidoscopy has been proven to reduce incidence and mortality from CRC, demonstrating that structural detection of pre-invasive lesions will reduce incidence. Both need to be specifically included as proven screening tool options and should be explored for implementation in screening programs.

The outcomes of screening programs that should be monitored and reported have been subject to consensus processes and have been clearly enunciated. These should be obligatory aspects of organised screening programs. Some of the inadequacies of colonoscopy in CRC detection have been highlighted, and RCTs to help guide us are underway. The evidence base supporting communication strategies has expanded and the standards of such are being established. These, combined with strategies proven to increase participation, should be presented along with guidance about the screening tests themselves. CRC screening clearly brings benefit to Australian society. But given the advances over the last 10 years, the guidelines for screening need revision to reflect the expanding and more informative evidence base.

**References**

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**FORUM**


