POPULATION SCREENING FOR COLORECTAL CANCER

Working Party on Screening for Colorectal Cancer

NATIONAL HEALTH COMMITTEE

NATIONAL ADVISORY COMMITTEE ON HEALTH AND DISABILITY

HUNGA KAITITIRO I TE HAUORA O TE TANGATA

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FOREWORD FROM THE NATIONAL HEALTH COMMITTEE

The National Advisory Committee on Health and Disability (National Health Committee) has undertaken a series of reviews of screening for those common cancers - such as prostate, breast and colorectal cancers - which cause a significant proportion of deaths in New Zealanders. This report on screening for cancer of the colon and rectum (large bowel) is the result of an 18-month project to examine the role of screening and other measures to reduce mortality from this important disease. The results of two randomised controlled trials in Europe, published in December 1996, which demonstrated a statistically significant but modest reduction in colorectal cancer mortality following screening with faecal occult blood tests, prompted this review.

The review was undertaken by an independent working party. Members of the Working Party were nominated by involved medical colleges and societies and the Cancer Society of New Zealand, and included consumer and Māori representatives. The Working Party adopted an evidence-based approach, critically evaluating the literature on the benefits, risks and adverse effects of screening for colorectal cancer using a variety of screening modalities.

Several randomised controlled trials of screening with newer faecal occult blood tests and other modalities are presently underway throughout the world, and it is recommended that all new evidence of benefit from screening modalities should be similarly reviewed as it becomes available.

The report of the Working Party is endorsed by the National Health Committee. The Working Party's recommendations have been passed to the Minister of Health for a decision on the health policy implications of the report. A number of questions have been included in the back of this report (page 112), and we welcome your responses.

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RECOMMENDATIONS

The National Health Committee Working Party on Screening for Colorectal Cancer, having reviewed the published scientific evidence up to May 1998, advises that:

1 Given the modest potential benefit, the considerable commitment of health sector resources and the small but real potential for harm, population-based screening for colorectal cancer with faecal occult blood tests is not recommended in New Zealand.

2 Population-based screening for colorectal cancer with other modalities, such as flexible sigmoidoscopy, colonoscopy or double-contrast barium enema, is also not recommended as there is not yet evidence from randomised controlled trials that screening with any of these modalities produces a reduction in colorectal cancer mortality.

3 These decisions should be reviewed as evidence of benefit from new faecal occult blood tests and other screening modalities becomes available.

4 Colorectal cancer is recognised as an important cause of morbidity and mortality and it is recommended that New Zealand participate in international research in this area.

5 Wider consultation and further consideration should be undertaken to develop appropriate advice on surveillance recommendations for groups identified to be at increased risk of colorectal cancer.

EXECUTIVE SUMMARY

1 The Working Party on Screening for Colorectal Cancer was established after a reduction in colorectal cancer (CRC) mortality was demonstrated with faecal occult blood testing (FOBT) in two population-based randomised controlled trials (RCTs) in Nottingham, England, and Funen, Denmark.

2 Colorectal cancer is an important cause of morbidity and mortality in New Zealand, being the second most common cancer registered for both men and women. Each year about 2,000 New Zealanders will be diagnosed with colorectal cancer and about 1,000 will die from the disease.

3 There is moderately consistent evidence that a diet high in animal fat and low in vegetables and fibre is associated with an increased risk of colorectal cancer. No primary prevention strategy has yet been demonstrated to reduce deaths from colorectal cancer. Therefore screening (secondary prevention) is a strategy which merits consideration.

Screening for colorectal cancer

4 Screening is the process of testing people with no symptoms to identify early signs of disease.

5 A population screening programme is a strategy to reduce the impact of disease on a whole population within a given age range. It is a complex process that involves more than just a screening test. It includes identifying and inviting potential participants, investigating abnormal results, treating disease that is detected and ensuring the entire process is properly coordinated and carried out to a high standard.

6 The World Health Organization screening principles (page 13) and an evidence-based approach (greatest weight being given to evidence from randomised controlled trials) were used to assess whether to recommend population screening for colorectal cancer in New Zealand.

7 Three randomised controlled trials (Funen, Nottingham, and Minnesota in the USA) have provided evidence that screening with FOBT can reduce mortality from colorectal cancer. Two of these RCTs, Funen and Nottingham, are population-based and therefore are the most relevant to the Working Party's terms of reference (page 12). Screening with FOBT was offered to men and women aged 50 to 74 years in Nottingham and 45 to 75 years in Funen.

8 A meta-analysis of the two population-based trials reveals a 16 percent reduction in CRC mortality (95% CI 6%-25%) in the population offered screening over an eight- to 10-year period.

9 This means that one out of six CRC deaths could be prevented in people offered screening; the other five deaths would not be prevented.

10 The sensitivity of the FOBT in the Nottingham and Funen trials was approximately 50 percent; therefore, half of the colorectal cancers present in the screened population in each screening round were missed (see Table 1, page 10).

11 The specificity of the FOBT in the Nottingham and Funen trials was 96 to 98 percent; therefore, 2 to 4 percent of people screened who did not have CRC had a positive FOBT and underwent additional unnecessary investigations.

12 People who have a positive FOBT require further investigation. In the RCTs, colonoscopy (use of a flexible telescope by a specialist to examine the large bowel under sedation) was the standard diagnostic procedure. About 2 percent of people screened in the first screening round required colonoscopy.

13 Based on results from the Nottingham RCT, for every 10 people proceeding to colonoscopy on the basis of a positive FOBT, one will have CRC and three will have an adenoma greater than 10 mm. Six will have no significant abnormality, yet will have been exposed to the rare but significant risks of colonoscopy, which include: bleeding, perforation of the bowel wall and occasionally death.

14 Double-contrast barium enema (DCBE) is a safer procedure than colonoscopy. However, many of the abnormalities identified with this examination will require follow-up colonoscopic investigation. There is no published evidence from randomised controlled trials of the effectiveness of screening by FOBT followed by DCBE (a fourth RCT, in Göteborg Sweden, used DCBE and flexible sigmoidoscopy to follow up positive FOBTs and is due to report mortality data in 1999).

15 To prevent one cancer death in the Nottingham RCT, 1,250 people (95% CI 690-9090) had to be offered screening over about an eight-year period.

Implications for New Zealand

16 It is estimated that if New Zealanders currently aged 50 to 74 years were offered FOBT screening, about 512 deaths (95% CI 68-887) from CRC may be averted over an eight-year period (based on the results of the Nottingham RCT).

17 It is uncertain whether New Zealand could achieve in a population screening programme even the modest mortality reduction demonstrated in the research settings of the Nottingham and Funen trials. These uncertainties relate to achieving similar levels of participation, quality control and adequate resources, particularly to meet the increased colonoscopy demand. These uncertainties must be weighed, along with the small but real potential for harm.

18 In the Nottingham and Funen trials, of those invited to participate in FOBT screening for CRC, 60 and 67 percent respectively participated in the first screening round (38% of those offered screening in Nottingham and 46% of those offered screening in Funen completed all screening rounds). The likely levels of participation in FOBT screening in New Zealand are unknown.

19 In the Nottingham and Funen trials, the eligible populations were identified from population listings. Without such listings or accurate general practitioner registers, the levels of participation reached by these trials may not be achievable in New Zealand.

20 The resource implications for colonoscopy are significant - approximately 4,045 people undergoing colonoscopy each year in the first two years of screening if the Nottingham protocol were followed (see Table 2, page 10). A constant subsequent colonoscopy demand, allowing for adenoma surveillance, of 3,300 procedures, per year has been estimated.

21 The annual number of colonoscopies currently performed nationally in the public sector has been estimated at 10,000 procedures. The additional colonoscopy load that would result from a population screening programme with FOBT could not be met within the public health system at present.

22 A population screening programme involves the commitment of considerable health sector resources. There is insufficient information to estimate precisely the costs of a national screening programme. A model based on the Nottingham protocol (biennial FOBT screening for those aged 50-74 years and assuming 54% population participation), and taking information from existing screening programmes in New Zealand, yields estimates of approximately $24 million for the first screening round, reducing to $22 million for subsequent rounds.

23 Given the modest potential level of benefit, the considerable commitment of health sector resources, and the small but real potential for harm, the Working Party does not recommend population screening for CRC with faecal occult blood tests in New Zealand. For the same reasons, the Working Party does not recommend pilot CRC screening programmes in New Zealand.

24 The Working Party does not recommend FOBT as a screening test for CRC in average-risk individual cases outside a population screening programme. Those requesting screening by FOBT should be given information about the potential risks and benefits. Follow-up bowel investigations in the public health system cannot be guaranteed without an increased allocation of resources.

25 The Working Party also does not recommend population screening for CRC with other modalities, such as flexible sigmoidoscopy, colonoscopy or double-contrast barium enema, as there is as yet no RCT evidence that screening with any of these modalities produces a reduction in CRC mortality.

26 These decisions should be reviewed as evidence of benefit from new types of FOBTs and other screening modalities becomes available.

27 The Working Party recognises that CRC is an important cause of morbidity and mortality and recommends that New Zealand participate in international research in this area.

28 The Working Party recognises the need for better information in New Zealand on CRC incidence and mortality according to ethnicity.

Increased-risk groups for colorectal cancer

29 Increased-risk groups for developing colorectal cancer are identified. Namely those with:

- a family history of the hereditary CRC syndromes (familial adenomatous polyposis [FAP] and hereditary non-polyposis colorectal cancer [HNPCC])
- a first-degree relative with CRC, particularly if the relative developed CRC under the age of 55 years, or if there are two first-degree relatives with CRC
- a personal history of CRC, colorectal adenoma or long-standing extensive inflammatory bowel disease.

30 The Working Party recommends wider consultation and further consideration be undertaken to develop appropriate advice on surveillance recommendations for groups identified to be at increased risk of CRC.

Table 1 Predicted outcome of 1,000 FOBTs in the first screening round

Sensitivity of FOBT (%)	53.6
Specificity of FOBT (%; estimated)	98.0
Number of colorectal cancers detected per 1,000 screened	2.1
True positives	2
False negatives	2
True negatives	978
False positives	18
Number of people proceeding to colonoscopy follow-up	20
Number of people diagnosed to have cancer	2
Number of people diagnosed to have an adenoma >10mm	6
Number of people with no significant abnormality detected	12

Table 2 Estimated figures for the first two years of a national screening programme in New Zealand

New Zealand eligible population (adults aged 50-74)	727,224
Exclude those with existing CRC (13,750 people, approx 2%)	713,474
Identification of eligible people using GP age-sex registers (90%) and invitation to FOBT screening	642,127
Participation in screening (60%)	385,276
Number of colonoscopies for positive FOBTs (2.1% of those screened)	8,090
Perforations resulting from colonoscopy (0.045%-0.17%)*	4-14
Serious bleeding resulting from colonoscopy (0.03%)*	2
Deaths resulting from colonoscopy (0.02%)*	2

** See Chapter 6.1, pages 43-5.*

Sources: Based on data from Hardcastle et al*, Randomised controlled trial of faecal occult blood screening for colorectal cancer,* Lancet *1996; 348: 1472-7; Habr-Gama & Waye, Complications and hazards of gastrointestinal endoscopy,*Wld J Surg *1989; 13: 193-201; Waye, Kahn & Auerbach, Complications of colonoscopy and flexible sigmoidoscopy,* Gastrointest Clin Nth Am *1996; 6: 343-77; New Zealand Health Information Service,* Cancer: New Registrations and Deaths 1993*, Wellington: Ministry of Health, 1997; and Statistics New Zealand,*1996 Census*, Wellington: Statistics New Zealand, 1996.*

Table 3 Estimates based on Nottingham RCT for a cohort of New Zealanders aged 50-74 undergoing FOBT screening over eight years

New Zealand eligible population (adults aged 50-74)	727,224
Exclude those with existing CRC (13,750 people, approx 2%)	713,474
Identification of eligible people using GP age-sex registers (90%) and invitation to FOBT screening	642,127
Participation in screening at first round (60%)	385,276
Number of FOBTs (adjusted for declining participation after first screening round)	1,100,000
Number of colonoscopies for positive FOBTs in 8 years (4.6% of those screened); excludes surveillance colonoscopies for those diagnosed with CRC or polyps	17,723
People diagnosed with CRC*	7,619
Deaths from all causes	107,719
Deaths from CRC	3,072
Expected number of deaths from CRC averted by screening	512 (95% CI 68-887)

** Includes diagnoses made outside the screening programme.*

Sources: Based on data from Hardcastle et al*, 1996; New Zealand Health Information Service, 1997 and Statistics New Zealand, 1996.*

1. INTRODUCTION

Reducing the burden of disease

Cancers of the colon and rectum are the second most common cause of cancer-related deaths among New Zealand people, particularly those of European descent. Only lung cancer (in men) and breast cancer (in women) are more frequent causes of cancer death in New Zealand. Reducing deaths from colorectal cancer (often referred to as large bowel cancer or abbreviated to CRC) could have a major impact on premature death and on life expectancy for both men and women in this country. Approximately 2,000 people are diagnosed with colorectal cancer and over 1,000 people die as the result of colorectal cancer each year.

At present there are no proven primary prevention strategies to reduce the incidence of and mortality from colorectal cancer. In the absence of major mortality reductions from primary prevention or advances in treatment, the focus for reducing mortality has turned to possible secondary prevention by population screening.

CRC usually develops within a pre-existing adenomatous polyp, typically over quite a long course, between five and 10 years. Cancers detected at an early stage have a better prognosis than cancers detected later. There is also likely to be benefits from detecting and removing pre-cancerous polyps before malignant change occurs.

The natural history of the development of CRC, usually within a pre-existing polyp, typically follows quite a long course, between five to 10 years. Cancers detected at an early stage have a better prognosis than cancers detected later. There may also be benefits from detecting pre-cancerous polyps and removing them before malignant change to CRC can occur.

The screening technology discussed in this report is not new. Faecal occult blood tests (FOBT) have been available since the 1860s, and have been variably used in a number of countries to screen for cancers of the colon and rectum. Although it is known that both cancers and polyps bleed episodically, evidence that screening for blood in the faeces results in a definite but modest reduction in CRC mortality among average-risk people in populations screened using FOBT has only been available since late 1996.

Comparing the effectiveness of population screening with ad hoc screening or case finding

A concern of the Working Party was to assess the benefits and risks of screening for CRC. Screening of people with average CRC risk in New Zealand is currently carried out on an ad hoc basis, initiated by patient request or health professional recommendations. FOBTs are used most commonly. The review of screening for CRC took into account the wider implications of introducing a population screening programme, as described in Chapter 2 (pages 13-16).

This report

In response to new research evidence from randomised controlled trials (RCTs) that population-based FOBT screening could reduce CRC mortality, in January 1997 the National Health Committee convened an expert working party to review the implications for New Zealand. The Working Party was asked to advise the Minister of Health, through the National Health Committee, and to make recommendations on the advisability of introducing a publicly funded population screening programme based on FOBT screening, similar to the programmes trialled in research studies in Nottingham and Funen (see Chapter 6, pages 31-63, for a full discussion of these and other CRC screening trials). In doing so, the Working Party was asked to consider all the health implications of CRC, all possible screening methods, and the likely impact on publicly funded follow-up diagnostic and treatment services. The composition of the Working Party is detailed in Appendix 1 (page 106).

The report has two major themes:

- a balanced review of the evidence for population screening
- an investigation into the implications for the New Zealand public and for the public health system if population CRC screening for all New Zealanders of a particular age range were to be introduced.

The terms of reference for the Working Party are shown in Figure 1.1 below.

Figure 1.1 Terms of reference

The Working Party is asked to:

1 review the evidence for benefits and risks from the introduction of population screening for colorectal cancer

2 identify the economic and resource implications of introducing a CRC screening programme and its likely acceptability

3 report to the National Health Committee on issues surrounding population screening for CRC and make recommendations on the introduction of a screening programme in New Zealand or other actions that should be taken to reduce deaths from CRC in New Zealand.

The Working Party focused as far as possible on the evidence from reliable research for benefits and risks of screening populations at average risk of developing CRC. Population screening was considered in the context of the balance of evidence for benefits and risks, taking into account possible opportunity costs and the likely impacts of screening.

The Working Party took care to differentiate screening of the whole population at average risk, on the basis of age, from surveillance of the sub-populations at increased risk of developing CRC. The identification of individuals with increased risk of CRC is discussed in Chapter 12 (pages 94-100). Elsewhere in this report the Working Party's opinions relate to those in the population of average risk.

The Working Party submitted this report to the National Health Committee in July 1998, and the Committee and Minister of Health have now published the report for wider circulation and comment. Information on how to make submissions on this report are given on the back page of the report (page 112).

2. CRITERIA FOR INTRODUCING A POPULATION CRC SCREENING PROGRAMME

Characteristics of an acceptable population screening programme

In its policy guidelines for national cancer control programmes, the World Health Organization identified the following policy approaches to the early detection of cancer:[1]

- support of organised screening programmes as a means of reaching a high proportion of the at-risk population
- retention of cancer detection as part of routine medical practice
- advice to people to seek specific tests at regular intervals.

The WHO concluded that only organised screening programmes have a significant impact on the national cancer burden, and that the success of such programmes depends on a number of fundamental principles:

- the target disease should be a common form of cancer, with high associated morbidity and/or mortality
- effective treatment, capable of reducing morbidity and mortality, should be available
- the test procedures should be acceptable, safe and relatively inexpensive.

Screening programmes should be organised to ensure that a large proportion of the target group is screened and that appropriate diagnosis and treatment is provided to those in whom abnormalities are found. The WHO notes that 'screening which concentrates solely on "high-risk groups" is rarely justified, as identified risk groups usually represent only a small proportion of the cancer burden in a country. However, in planning the coverage of screening programmes, measures must be introduced to ensure that all those at high risk are included.'

Principles for population screening

Internationally agreed criteria for introducing a population screening programme were first published by Wilson and Jungner[2] in 1968 and subsequently adopted by the World Health Organization (see Figure 2.1).

Figure 2.1 Principles for the introduction of a population screening programme[1]

1. The condition should be an important health problem.
2. There should be a recognisable latent or early symptomatic stage.
3. The natural history of the condition, including the development from latent to declared disease, should be adequately understood.
4. There should be an accepted treatment for patients with recognised disease.
5. There should be a suitable test or examination for screening.
6. The test should be acceptable to the population who would be screened.
7. There should be an agreed policy of whom to treat as patients.
8. Facilities for diagnosis and treatment should be available.
9. The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case finding should be a continuing process and not a 'once and for all' project.

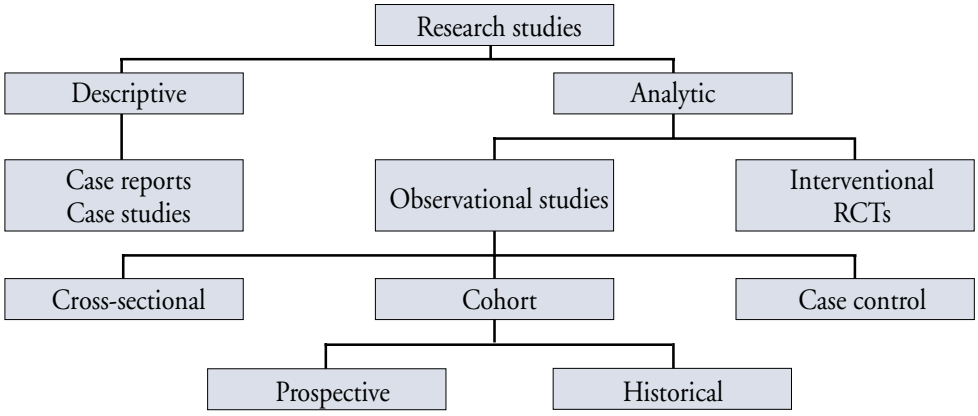
Assessment criteria for research evidence

In addition to evidence from the two major randomised controlled trials (RCTs) referred to in Chapter 1, the Working Party conducted a literature review of all evidence relating to the efficacy, effectiveness and acceptability of all current and potential screening methods for CRC. A very helpful source was a literature review of a number of CRC screening papers conducted by the Australian Health Technology Advisory Committee (AHTAC);[3] the Working Party is grateful to the authors for permission to use their draft report during the New Zealand review.

At the outset, the Working Party had no predetermined view on whether population screening for CRC should be introduced in New Zealand. Possible opportunity costs and the likely impact of screening on current services also had to be considered. The Working Party decided that it would be convinced only by evidence of benefit that significantly outweighed the risks from screening, and where such a screening programme was safe, acceptable and affordable. Although the initial evidence which led to the establishment of the Working Party related to screening using faecal occult blood tests (FOBT), the review extended to all other test modalities that might be used to screen for CRC.

The AHTAC literature review was a helpful but not the sole source of information. In many cases, the Working Party contacted authors and researchers directly for more information or clarification. Relevant new articles appearing during the review were discussed by the group. The evidence from published research was given appropriate weightings dependent on the study design, and the quality of the studies. The types of study that may be reported in the clinical literature are shown in Figure 2.2.

Figure 2.2 Choice of research methodologies



The results from various research methodologies do not contribute equally to the weight of evidence for the efficacy of an intervention, such as screening for CRC. This is because issues such as the quality of the research, and the likelihood that bias, confounding and/or chance could have affected the results, have to be taken into account. Certain study designs have particular advantages when the efficacy of screening is being evaluated.

Assessing the quality of the evidence on screening for CRC

Randomised controlled trials (RCTs) generally provide the best evidence about causal association and about the efficacy of screening for colorectal cancer. In RCTs, subjects are randomly allocated into study and control groups, and only those in the study groups are offered screening. The results are assessed by comparing rates of death (or other end points) from the disease in those offered screening with those not offered screening. RCTs are generally regarded as the most scientifically rigorous method of assessing screening, because they are less likely than other study designs to be affected by bias and confounding. These biases are described below.

Lead-time bias Screening advances the date of diagnosis, and thereby extends the interval between diagnosis and death, even if the time of death is unchanged. The survival time for people with CRC is measured from time of diagnosis until death. In screened individuals, the diagnosis is made earlier than it would have been in the absence of screening; this is known as the 'lead time' obtained by screening. Because of this lead time, these individuals will have longer survival times, even if screening had no effect on their time of death. The true effect of screening on CRC mortality cannot be assessed merely by comparing the survival times for screened and unscreened people because longer survival times in the screened group will be at least partly due to lead time.

Length bias Tumours grow at different rates and therefore remain for differing periods in the presymptomatic screen-detectable phase. With each screening round, the probability of detecting slow-growing tumours is greater than the probability of detecting fast-growing tumours, because slower growing tumours remain in the presymptomatic screen-detectable phase for longer. There will be fewer fast-growing tumours in a screened group compared with an unscreened group. Since slow-growing tumours tend to have a better prognosis, this may account for differences in outcome between the groups.

Overdiagnosis bias Screening detects very early lesions. It is possible that some of the detected cancers would not affect a person in his or her lifetime (with the person remaining asymptomatic and dying from some cause other than CRC). Because these cancers are more likely to be found in a screened group than in an unscreened group, comparisons of outcome could favour the screened group irrespective of any real effect of screening.

Selection bias Screening is offered to a particular group of people, not all of whom decide to accept. It may be that people who choose to take part in a screening programme have a different underlying risk of developing or dying from CRC. People who take up the offer of screening may differ in their underlying risk of disease and/or mortality so that their prognosis would have differed from non-participants even in the absence of screening. For instance, those with a family history of CRC may decide to take part because they perceive themselves to be at higher risk. A particular problem with selection bias is that it can operate in two directions: if low-risk people are more likely to be screened, then CRC mortality is likely to be lower in this group anyway, and the effect of screening will be overestimated; if high-risk people are more likely to be screened the effect of screening could be underestimated.

The only study design that is not affected by these biases is a *randomised controlled trial* with *colorectal cancer mortality* as the outcome measure. Thus, the Working Party placed more weight on evidence from RCTs of screening for CRC than on evidence derived from other study designs. There is a generally accepted ranking scheme for the grades of evidence derived from different study designs and, although the numbering of the hierarchies may vary between schemes, their relative positions are consistent across all schemes, as shown in Figure 2.3.

Figure 2.3 Evidence-grading hierarchy

Grade of evidence	Description	Comments
Grade 1	Randomised controlled trials (RCTs)	Only RCTs can control for various forms of bias
Grade 2	Non-randomised controlled trials	Randomisation is needed to minimise bias and confounding
Grade 3	Non-randomised historical cohort studies	Compares current outcomes due to intervention with previous outcomes, which may permit inappropriate groups to be compared
	Case-control & other population studies	
Grade 4	Case series	Data is derived from a group of unselected patients, and is limited in value
Grade 5	Expert (consensus) opinion	Not evidence *per se*, but may have value where evidence is not likely to be or become available

In assessing evidence relating to population screening, the sensitivity and specificity of the proposed screening test for detecting the disease in question is crucial.

Sensitivity is the ability of the test to correctly identify those with the disease. It has been measured in screening programmes in different ways. A common method of estimating sensitivity is to divide the number of cancers detected on screening by the sum of screen-detected cancers plus interval cancers detected in the following 12 months. Interval cancers are cancers which are diagnosed after a negative screening test.

Specificity is the ability of the test to correctly identify those without the disease. It measures the proportion of those without disease who are correctly identified as negative by the screening test. If a test has high specificity it means that only a very small proportion of people have false positive tests. Achieving high specificity is important in order to minimise the number of people undergoing unnecessary investigations as a result of false positive tests.

Evaluation of the evidence for and against screening

When making its recommendations on the introduction of a population CRC screening programme based on FOBTs or other screening modalities, the Working Party took into account the WHO criteria (Figure 2.1, page 13). In addition to these general screening criteria, the Working Party considered a number of questions about the nature of the evidence and its implications for screening for CRC in New Zealand. This required some modelling of the likely benefits and costs/risks implicit in the kind of programme that would be most likely to be acceptable to New Zealanders; the assumptions used for this are stated where appropriate.

There was no doubt that CRC is, and will continue to be, an important disease, the prevention and treatment of which should be supported by the publicly funded health service in New Zealand.

The major questions addressed by the Working Party when reaching its decisions (Figure 2.4) related to the relevance and impact of the available research evidence in support or otherwise of the value to New Zealand of introducing a population screening programme for CRC.

Figure 2.4 Questions about evidence

- Is significant benefit from screening established in the population under study?
- Is there the potential for similar benefits in the New Zealand population?
- Is there a suitable test and testing regimen?
- Are the risks of screening acceptably low?
- Has the age group for screening been identified from the RCTs?
- Does the evidence prove that the intervention is cost-effective?
- Would a screening programme in New Zealand achieve the same benefits as in the study populations?
- Could this be achieved at similar costs to those in the study?
- What are the costs of this type of CRC screening programme relative to others?

The findings of the Working Party on the evidence for and against screening interventions are discussed in Chapter 6 (pages 31-63).

References

1 World Health Organization. *National Cancer Control Programs. Policies and Managerial Guidelines*. Geneva: World Health Organization, 1995.

2 Wilson JMG, Jungner G. *Principles and Practice of Screening for Disease*. Geneva: WHO Public Health Papers No. 34, 1968.

3 Australian Health Technology Advisory Committee. *Colorectal Cancer Screening*. Canberra: Australian Government Printing Service, 1997.

3. EPIDEMIOLOGY OF CRC IN NEW ZEALAND

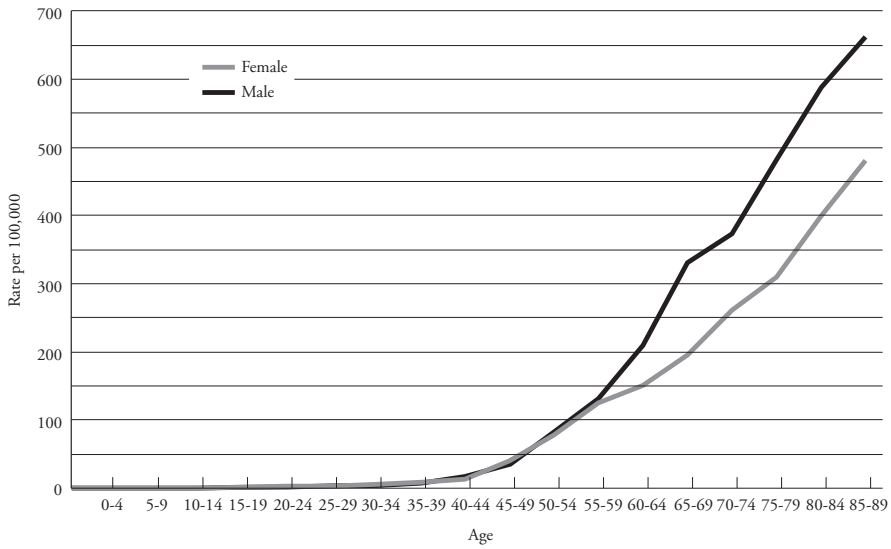
- Overall, the CRC incidence and mortality rates in New Zealand are among the highest in the world.
- However, New Zealand has a heterogeneous population with sub-populations who appear to have lower incidence rates.
- The stage distribution of CRC at diagnosis in New Zealand is similar to that in Denmark and Britain, where randomised controlled trials have been conducted, suggesting that similar reductions in mortality could be achieved by FOBT screening in New Zealand.

Colorectal cancer is an important cause of morbidity and mortality in New Zealand. Each year about 2,000 New Zealanders are diagnosed with CRC and about 1,000 die from it. It is the second most common cancer registered for both men and women.[1] In 1993 the age-standardised incidence rate (standardised to Segi's world population) for New Zealand men was 49.5 per 100,000 and for women was 37.4 per 100,000.[1] CRC incidence rates for Māori and non-Māori differ (see Table 9.1, page 76), with rates being considerably lower in Māori. CRC incidence in Pacific Islands people living in New Zealand is similarly low.[2] However, these differences in rates may be partly due to differences in assignment of ethnic group in the denominators (census data) and numerators (cancer registry and mortality data) of the rates. Only since 1997 has there been reasonable consistency among the census, cancer registry and mortality data in the assignment of ethnic group. (The issues associated with ethnicity reporting are discussed in more detail in Chapter 9, pages 76-9.)

The incidence of CRC increases with age (Figure 3.1); in New Zealand more than 90 percent of CRC registrations are in people over 50 years old. From 1984 to 1993 there was a 5.8 percent decrease in age-standardised CRC registrations in men, and a 12.9 percent decrease in age-standardised CRC registrations in women. During the same period age-standardised CRC mortality rates declined by 8.5 percent in women and 5.0 percent in men.[1]

CRC is the second major cause of death from cancer in New Zealand men (after lung cancer), accounting for 14 percent of cancer deaths in males. It is also the second most common cause of death from cancer in women, after breast cancer, and causes 16 percent of all female deaths from cancer. Mortality rates for Māori are lower than for non-Māori;[1] however, the problems with assignment of ethnic group should be taken into account.

Figure 3.1 The incidence of CRC in New Zealand, by gender



Source: New Zealand Health Information Service, 1997.[1]

Colorectal cancer and gender

In general, males and females have similar rates for colon cancer, but older men have higher rates of rectal cancer. In England women have slightly lower colon cancer incidence at all ages; and rectal cancer incidence increases rapidly in men over 70 years, so that the rate for men over 70 is about twice that for women over 70.[3] In New Zealand a similar pattern is seen for rectal cancer, but for colon cancer women under 55 years have slightly higher rates than men.[1]

Increased-risk groups

In general, the risk increases with age. For instance, the risk of CRC for a 70-year-old New Zealander is about 100 times that of a person aged under 30 years, and about 20 times that of a 40 year old.[1] Factors other than age can also elevate an individual's risk for CRC. The rare inherited conditions familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC), a family history of 'sporadic' CRC, a past history of CRC or colorectal adenoma, and a diagnosis of inflammatory bowel disease are all associated with increased risks of developing CRC. The degree of increased risk varies across these groups. It is important to identify individuals belonging to these groups as the surveillance strategies advised for such individuals to prevent or detect early CRC will be different from the CRC screening advice given to those individuals considered to be at average risk of developing the disease. Increased-risk groups are reviewed in Chapter 12 (pages 94-100).

Ecological data

Countries where there is a high fat intake also have high CRC incidence and mortality rates.[4] New Zealand has both a high fat intake and high CRC incidence and mortality rates; however, this pattern appears to be reversed in Māori, who have low CRC incidence and mortality rates despite a high fat intake.[4, 5, 6] The explanation for this is not clear, although lactase deficiency and the protective effect of a high fibre intake have been suggested as important factors as well as the possibility of data collection inaccuracies.[4]

Projections for CRC incidence and mortality in New Zealand

It has been projected that there will be an increase in both incidence and mortality from CRC in New Zealand during the late 1990s, followed by a decline early next century.[7] These projections take into account historical trends in CRC incidence and mortality, the contribution of an ageing population, and the declining incidence in recent generations of New Zealanders[6] (see also Chapter 5, page 29).

International comparisons

There are striking international differences in CRC incidence (Table 3.1, page 19), with rates in the highest risk countries being six or more times the rates in countries with the lowest risk. New Zealand has among the highest CRC incidence and mortality rates in the world.[8] Migrant studies suggest that international differences are environmental rather than genetic, as the risk for migrants approaches that of the host-country population within one to two generations.[8] Since the 1950s, a pattern has emerged where the incidence in most of the high-risk countries has been declining, the incidence in many low-risk countries has been increasing rapidly, and the rates for countries at intermediate risk have stabilised or increased slightly.[4]

Subsite comparisons

Colon cancer and cancer of the rectum are often combined as colorectal cancer, since their incidence rates in different populations are correlated, and since they are both associated with adenomatous polyps.[4] The incidence of colon cancer varies more by country than the incidence of rectal cancer.

However, there appear to be some clear differences between colon and rectal cancer with respect to anatomical site. Cancers occurring in the caecum, ascending colon, hepatic flexure, and transverse colon can be described as 'right-sided', or proximal, cancers; those occurring in the splenic flexure, descending colon, sigmoid, rectosigmoid, and rectum can be described as 'left-sided', or distal, cancers. Rectal cancer is usually separately distinguished. In countries with the highest risk of CRC, there is a higher proportion of sigmoid cancers and the incidence of colon cancer is about twice that of rectal cancer. These characteristics also apply to New Zealand.[1] In countries with a low risk of CRC, the incidence of rectal cancer may exceed the incidence of colon cancer because of a deficit in sigmoid cancers.[8]

Table 3.1 The incidence of colon and rectal cancer in men in selected countries, 1988-92

Country	Colon cancer*	Rectal cancer*
Canada, Newfoundland	31.4	15.9
New Zealand, non-Māori	31.2	20.1
USA, California (Black)	30.9	12.1
USA, Connecticut (White)	30.4	16.1
Germany, Saarland	25.5	17.3
Japan, Miyagi	24.9	16.7
England, Birmingham	23.7	17.5
Canada, Alberta	22.2	15.7
Norway	22.2	15.7
New Zealand Māori	21.5	12.8
Denmark	20.6	17.0
Iceland	19.2	6.1
Sweden	17.7	12.1
Puerto Rico	14.8	8.5
Finland	12.8	10.5
Colombia, Cali	6.6	5.4
India, Bombay	2.4	3.1

** Age-standardised (world population) rate per 100,000.*

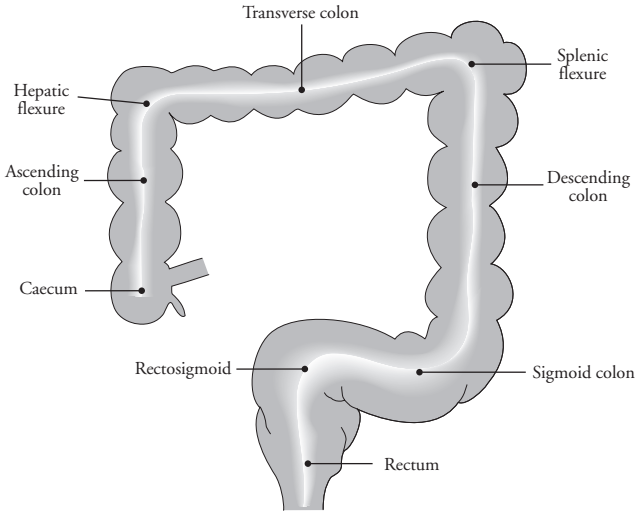
Source: Parkin DM, Whelan SL, Ferlay J, et al (eds). Cancer Incidence in Five Continents *Vol VII, IARC Scientific Publications No. 143. Lyon: IARC, 1997.*

Consistent with this pattern, there is a reported decline in the proportion of left-sided cancers, and a concomitant increase in the proportion of right-sided cancers in high-risk countries where the overall incidence is declining, including New Zealand.[8,9] Right-sided cancers appear to be more common in older people (those aged 70 and over) and in those under 50.[10] This has also been reported for New Zealand:

> It is known that the distribution of cancer within the colon and rectum varies with age, with cancer of the right colon becoming more frequent in the elderly. Colorectal cancer is uncommon under the age of 50 years. However, by examining the distribution of bowel cancer in 15,395 New Zealanders registered for colon cancer between 1974 and 1983, it was possible to show a significant excess of right sided bowel cancer in the young as well as in elderly members of the population.[11]

It has been suggested that hereditary colon cancer is more likely to occur in the right side of the colon and sporadic cancer is more likely to be left sided, and that the excess of right-sided cancers in the young is because the incidence

Figure 3.2 The colon



of hereditary cancers has remained stable in younger people while sporadic cancer has declined.[10, 11] However, the decline in the incidence of CRC in younger generations of New Zealanders has occurred for both right- and left-sided cancers.[6]

Table 3.2 shows the subsite distributions for CRC at all ages, and at 50 to 74 years (similar to the age range for which CRC screening using FOBT has been tested in randomised controlled trials). The table shows that approximately one-third of CRCs in New Zealand arise proximal to the splenic flexure (and are therefore beyond the reach of flexible sigmoidoscopy). In the 50-to-74 year age group, although there was a greater proportion of left-sided cancers, the difference is slight (63.5% versus 61.7%). In the United States between 1976 and 1987, 64 percent of CRCs were left sided;[12] in England and Wales between 1987 and 1992, 72 percent were left sided.[3]

Table 3.2 Subsite distribution of CRC in New Zealand

(a) **All ages**

Site	Male		Female		Total	
	Number	*%*	*Number*	*%*	*Number*	*%*
Right	255	24.9	370	37.8	595	30.0
Left	684	66.9	573	54.9	1,222	61.7
Unspecified	90	8.8	71	7.3	161	8.1

(b) **Ages 50-74**

Site	Male		Female		Total	
	Number	*%*	*Number*	*%*	*Number*	*%*
Right	152	23.5	192	36.0	344	29.0
Left	444	68.6	307	57.4	751	63.5
Unspecified	51	7.9	36	6.7	87	7.4

Source: New Zealand Health Information Service. Cancer: New Registrations and Deaths 1992. *Wellington: Ministry of Health, 1995.*

Stage distribution

Table 3.3 compares the stage at diagnosis in New Zealand in 1984[13] with the stage at diagnosis in the control groups of the RCTs in Nottingham,[14] Funen[15] and Minnesota[16] and with the North American National Survey of the Commission on Cancer[17]. To enable valid comparison of the different staging systems, the matrix for staging system conversion established by the 1990 World Congress of Gastroenterology Working Party in Clinicopathological Staging[18] has been used to convert each to Dukes' stage[19] (see page 23 for a discussion of the Dukes' classification system).

Although both Dukes' A and B lesions can be combined under the heading 'localised disease', Dukes' A disease has a significantly better prognosis than Dukes' B (approximately 90% versus 60% 5-year survival) and it is therefore appropriate to separate these out wherever possible. Table 3.3 shows that the stage distribution in New Zealand is similar to that in Nottingham and Funen, but differs from that of the USA. Even excluding patients with carcinoma *in situ*, the proportion of patients presenting with Dukes' A in the United States is at least double.[16, 17] One explanation for this may be a higher level of awareness of health issues in America, leading to earlier investigation and diagnosis. However, the correlation between symptom duration and disease stage in CRC is poor.[20] It may be that there is significant baseline screening of asymptomatic individuals outside the clinical trials in the USA population.

Any reduction in CRC mortality brought about by screening must be effected through a shift in stage distribution at diagnosis. RCTs in countries with stage distribution similar to New Zealand (Britain and Denmark) or better than New Zealand (USA) have demonstrated reduced CRC mortality with FOBT-based screening. It is therefore not unreasonable to assume that screening in New Zealand would have the potential to achieve a similar reduction in mortality.

Table 3.3 Stage distribution of CRC at diagnosis in New Zealand compared with other countries

Stage	A %	B %	A & B %	C %	D %	Not stated %
Colon & rectum						
NZ (1984)	n/a	n/a	42	33	19	6
Nottingham (1981-89)	11	33	44	31	21	4
Funen (1985-95)	11	37	48	23	24	5
Minnesota (1975-92)	22	30	52	21	16	10
USA (1993)	23 (27)	28	51 (55)	22	19	4
Colon						
NZ (1984)	n/a	n/a	41	33	20	6
Nottingham (1981-89)	n/a	n/a	44	28	29	1
USA (1993)	21 (25)	30	51 (55)	22	20	3
Rectum						
NZ (1984)	n/a	n/a	45	32	18	5
Nottingham (1981-89)	n/a	n/a	44	39	27	3
USA (1993)	27 (33)	23	50 (56)	22	17	5

Note: Bracketed figures include carcinoma in situ.

Source: Based on data from New Zealand Health Information Service, 1997;[1] *Hardcastle* et al, *1996;*[14] *Kronborg* et al, *1996;*[15] *Mandel* et al, *1993;*[16] *Beart* et al, *1995.*[17]

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4. NATURAL HISTORY AND TREATMENT OF COLORECTAL POLYPS AND CANCER

- CRC develops as a result of genetic mutations in colonic epithelium expressed phenotypically, usually as progression through the adenoma-carcinoma sequence.
- Many polyps do not progress to cancer; however, multiplicity, size greater than 10 mm, villous architecture and increasing epithelial dysplasia are all associated with a greater cancer risk.
- Detection and removal of adenomatous polyps reduces the subsequent risk of developing CRC.
- The prognosis of CRC depends on the stage of the disease. Surgery remains the major treatment modality at all stages, except for successful endoscopic removal of malignant polyps.
- Detection at an earlier stage may simplify treatment, reduce the need for a stoma, and increase the prospect of cure.
- Treatment variables have been shown to affect survival from CRC. The importance of providing appropriate treatment and access to such treatment must be taken into account when the implications of population screening are considered

Relevance to screening

The aim of screening for CRC is to detect disease at an early stage when cure is more likely to be achieved. The opportunity for early detection and treatment of CRC depends on its natural history. This chapter outlines the natural history of the disease, its treatment and prognosis.

The adenoma-carcinoma sequence

Molecular events

Understanding of the molecular basis of colorectal carcinogenesis has increased markedly in the last 10 years. It has been shown that mutations in a number of genes are associated with the development of adenomatous polyps, malignant transformation and invasive cancer.[1] Individuals with germ-line mutations are at very high risk of developing the disease (FAP and HNPCC), whereas individuals with a first-degree family history of CRC are at moderately increased risk.[2] The germ-line mutations in both FAP and HNPCC are inherited in an autosomal dominant fashion; however, these specific syndromes probably account for no more than 5 percent of all CRCs.[3] Seventy percent of people who develop CRC have no family history or other known risk factors.[2] The majority of cases, therefore, occur in so-called 'average-risk' individuals who would not be reached by targeting screening to increased-risk groups.

Whether sporadic or familial, tumour progression is associated with a stepwise accumulation of genetic mutations in the tumour. In FAP, affected individuals inherit a germ-line mutation in the FAP gene that predisposes to development of multiple polyps.[3] Progression to cancer is the result of subsequent somatic mutations in individual polyps. In HNPCC the germ-line mutation impairs the DNA repair mechanism, thus permitting accumulation of somatic mutations in the colonic mucosa, reflected by rapid progression through the adenoma-carcinoma sequence.[3, 4]

Environmental factors, such as dietary fibre and saturated fat content, are thought to act, at least in part, by modulating the underlying genetic events.

Morphologic changes

The hypothesis that the majority of CRCs begin as adenomatous polyps and progress through the adenoma-carcinoma sequence is supported by a large amount of circumstantial evidence.[5] This evidence is summarised as follows:

- In FAP there are hundreds of polyps, and cancer invariably develops in one or more unless the large bowel is removed.
- The subsite distribution of large bowel polyps is similar to the subsite distribution of CRC.
- Changes in subsite distribution of polyps and cancer over time tend to occur in tandem.[6]
- All stages in the evolution from benign polyp to invasive cancer have been observed histologically.

- Many carcinomas retain clear histological evidence of a polyp remnant.
- The mutations identified in adenomas and cancers suggest a stepwise accumulation of genetic defects which roughly parallels progressive phenotypic changes.[10]
- The risk of CRC is increased in people with known adenomas.[7]
- Polypectomy reduces the subsequent risk of CRC.[8, 9]

The major risk factors for malignant transformation of polyps have been identified as: villous architecture; multiplicity; large size, and increasing age.[10, 11] The appearance of dysplasia is a constant feature of the process.[11] The risk of malignancy in an adenoma less than 10 mm in diameter is very small, whereas over 20 mm the risk of malignancy is around 20 percent. The rate of progression from adenoma to cancer is usually slow, occurring over many years.[12] One study found a cumulative risk of cancer of 25 percent at 20 years for adenomas greater than 10 mm.[7] Although the majority of adenomatous polyps probably never progress to cancer,[13] others can do so more rapidly, particularly in HNPCC.[4]

The majority of CRCs develop from pre-existing adenomatous polyps; however, a minority can arise either *de novo*, or from small flat adenomas. Flat adenomas have been observed in members of families with a high incidence of CRC, suggesting an autosomal dominant inheritance,[14] and may represent an attenuated form of FAP. Sporadic cases have also been documented.[15, 16] *De novo* malignancy generally occurs in a background of predisposing disease, such as ulcerative colitis, where dysplasia of the colonic epithelium evolves in the absence of polyps. In inflammatory bowel disease the risk of CRC increases in proportion to the time the disease has been present and the extent of colonic involvement.[17, 18]

Non-neoplastic polyps

There is no proven link between hyperplastic polyps (small lesions which occur predominantly in the rectosigmoid region) and CRC; however, hyperplastic polyps may be a marker for increased risk of adenomatous polyps. Hyperplastic polyps are difficult to differentiate from small adenomatous polyps macroscopically and therefore require histological confirmation. Malignant transformation has occasionally been associated with other, less common, non-neoplastic polyp syndromes, including juvenile polyposis and Peutz-Jeghers Syndrome.

Disease stage & prognosis

The prognosis for CRC depends on the disease stage. A number of staging systems have been devised, all of which have at least three common elements: the depth of invasion of the bowel wall; the presence or absence of lymph node metastases, and the presence or absence of distant metastases (eg, tumour deposits in the liver or organs distant from the colon). The oldest, and probably most widely used, staging system is the unmodified Dukes' classification.[19] Although devised originally for rectal cancer, it holds equally well for colon cancer. The Dukes' classification is also the simplest, and all other classification systems can be converted to Dukes' stage.[20]

Figure 4.1 Dukes' classification

Dukes' A	Tumour confined to the bowel wall with no lymph node metastases
Dukes' B	Tumour penetrating through the bowel wall to serosa or perirectal fat with no lymph node metastases
Dukes' C	Lymph node metastases present
Dukes' D*	Distant metastases present

**Not in Dukes' original description; added subsequently.*
Source: Dukes, 1932.[19]

At least 90 percent of disease-related events (recurrence and death) occur within five years of treatment, so five-year survival figures are commonly reported. Following surgery, five-year survival for Dukes' A disease is around 90 percent, for Dukes' B 60 to 70 percent, and for Dukes' C 30 to 40 percent.[21] Five-year survival for patients with distant metastases (Dukes' D) is rare and the median survival in patients receiving palliative care for incurable disease is less than 12 months.

In addition to stage, histological grade also affects prognosis.[22] Presentation as an emergency, particularly with perforation, worsens the prognosis.[23] Surgeon-related factors also exert a significant influence on long-term outcome.[24, 25] In rectal cancer the risk of local recurrence is directly related to tumour stage.[26]

The stage distribution of CRC at diagnosis is discussed in Chapter 3 (page 20), but the evidence from trials shows that the stage distribution can be altered by screening asymptomatic individuals. Screen-detected cases are more likely to have earlier stage disease than cases detected after the onset of bowel symptoms.[27, 28, 29] There is no evidence that earlier diagnosis made after the onset of symptoms improves survival.[30] However, once symptoms of concern are identified, delays in diagnosis should be avoided as they cannot advantage the patient.

Treatment

Benign adenomatous polyps can be treated by polypectomy, done at the time of colonoscopy or flexible sigmoidoscopy, using diathermy to either destroy the entire polyp ('hot' biopsy) or snare the polyp base (snare polypectomy). Polyps that are too large or too numerous to remove endoscopically may necessitate surgical resection. Surgery is also occasionally required to deal with the principal complications of endoscopic polypectomy: bleeding and perforation.

As long as benign polyps are histologically confirmed and completely excised, no further treatment is necessary apart from ongoing surveillance for detection of metachronous lesions. In FAP it is not possible to manage the entire colon and rectum endoscopically because the polyps are too numerous and tend to recur rapidly. In HNPCC the polyps occur at a younger age, have a propensity for the right colon, and are more likely to progress to cancer in a shorter time interval.[4, 31] Therefore FAP and HNPCC require different follow-up and management strategies (see Chapter 12, pages 94-100, which deals with increased-risk groups).

The treatment of malignant polyps depends on the stage, gross (appearance) and histological morphology of the polyp, and the patient's fitness and willingness to undergo surgery.[32, 33, 34] Malignant polyps with early invasion can often be adequately treated by polypectomy alone. However, if histology of the polyp specimen shows features associated with a high risk of cancer recurrence, surgery may need to be considered. These features include:

- invasion into the deeper layers of the bowel wall (which contain a rich network of blood vessels and lymphatics)
- tumour close to or at the resection margin
- poor histological differentiation
- invasion into vascular channels.

Various criteria have been devised, based on these pathological features, to direct the need for further treatment;[32, 34] however, the risk of cancer recurrence has to be weighed against the risks of surgery for each individual.[33]

For CRC that cannot be managed endoscopically, the standard treatment is surgical removal of the involved segment of bowel together with the mesentery containing the regional lymph nodes. In Dukes' A and B diseases this is the only treatment that is currently recommended. In Dukes' C disease the addition of post-operative adjuvant chemotherapy has been shown to reduce recurrence rates and improve survival.[35, 36, 37] Some higher risk Dukes' B patients may also benefit from adjuvant chemotherapy;[36] several large international trials are in progress to evaluate this further. Selected patients with rectal cancer also benefit from adjuvant radiotherapy, given either pre- or post-operatively, to reduce the risk of local recurrence.[38]

CRC treatment is also affected by the mode of presentation and the site of the disease. The surgical management of patients presenting as emergencies (obstruction, perforation or bleeding) is more complicated, has a higher morbidity and mortality rate, and is more likely to involve the need for a temporary or permanent stoma.[39] The need for a temporary or permanent stoma is also affected by the site of disease. Distal rectal cancer requiring excision of the anal canal mandates a permanent stoma; however, modern surgical techniques now enable the removal of most rectal cancers without the need for a permanent stoma.

Treatment-related variance in CRC

Variance in a range of outcome measures is a well-recognised phenomenon in surgical practice.[40] CRC is no exception. The most important outcome measures in the surgical treatment of CRC are perioperative morbidity and mortality, local recurrence rates (particularly for rectal cancer), and long-term survival. There are some data available which demonstrate variability in these outcome measures, independent of disease- or patient-related factors.[24, 25, 26, 39, 41, 42] This variability is considered to be related to variance in surgical practice.

Variance in other aspects of treatment may also exist; for example, in the use of adjuvant therapy. There are many reasons why practice and outcomes vary from surgeon to surgeon. Exactly what these are, and what constitutes best practice in the treatment of CRC, are well beyond the scope of this discussion. However, in considering the benefits and risks of CRC screening, treatment-related variables which directly affect those identified with the disease may need to be addressed.

Recurrence

Patterns of disease recurrence are related to disease stage and the site of disease. Rectal cancer is associated with a higher risk of local recurrence than colon cancer, due to the difficulty of obtaining adequate excision within the anatomical confines of the pelvis. Adjuvant radiotherapy can reduce the risk of local recurrence in tumours extending through the rectal wall into perirectal fat,[38] and improvements in surgical technique may also result in fewer local recurrences.[26]

Occasionally, patients who present with local recurrence or metastastic disease can be treated with a prospect of cure.[43] This is only a possibility when all of the disease can be removed surgically with microscopically clear margins. Unfortunately, many patients present with advanced disease that is beyond the possibility of cure, either because of unresectable local disease, distant metastases, or both. Treatment in this group is tailored towards alleviating and preventing suffering, and maintaining quality of life for as long as possible. In some cases the best palliation requires active intervention, including surgery, radiotherapy, or chemotherapy; in others supportive care alone is more appropriate.

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5. PRIMARY PREVENTION STRATEGIES

- The strongest and most consistent evidence in relation to the potential for primary prevention of CRC lies in the traditional western diet.
- Many studies show a positive relationship between the probability of developing colorectal adenomas and cancer with dairy/animal fat intake, and a negative correlation with diets high in fibre sources such as fruit and vegetables.
- Other modifiable characteristics that may influence the risk of a person developing CRC include alcohol use, cigarette smoking, physical inactivity and socio-economic status.

Prevention can be categorised as primary, secondary, and tertiary. In Last's *Dictionary of Epidemiology*,[1] it is acknowledged that 'authorities on preventive medicine do not agree on the precise boundaries between these levels'. In this report, the following definitions of prevention are used:[1]

- *Primary prevention* is the protection of health by personal and community-wide effects (eg, preserving nutritional status, physical fitness and emotional well-being; immunising against infectious diseases, and making the environment safe).
- *Secondary prevention* can be defined as the measures available to individuals and populations for the early detection and prompt and effective intervention to correct departures from good health.
- *Tertiary prevention* consists of the measures available to reduce or eliminate long-term impairments and disabilities, minimise suffering caused by existing departures from good health, and to promote the patient's adjustment to irremedial conditions.

Secondary prevention includes screening for CRC, and this will be covered in detail in later chapters. This chapter examines the potential for primary prevention of CRC in New Zealand.

Primary prevention of CRC

In Chapters 3 and 4, a number of factors that influence the risk of a person developing CRC were identified. The most significant of these are family history, offering little opportunity for risk-factor modification, and ethnicity, where Māori and Pacific Islands people appear to have significantly lower CRC risk. Modifiable characteristics include diet, alcohol use, physical activity, sedentary occupation, socio-economic status, and cigarette smoking.

The strongest and most consistent evidence in relation to the potential for primary prevention lies in the traditional western diet. There is moderately consistent evidence from observational studies for an association between a high-fat diet and risk of CRC, and the consistency of the evidence for an association between dietary fibre intake and CRC is moderate to good. Observational studies have shown inverse associations between fruit and vegetable consumption and CRC, and physical activity and CRC.[2] Other modifiable lifestyle factors, including alcohol intake and cigarette smoking, may also play a role.

It has been suggested that some therapeutic agents may exercise a prophylactic role in preventing the development of adenomas and cancers in the colon and rectum. These include aspirin, calcium, carotene, and antioxidants, notably vitamins A, C and E. A summary of factors influencing CRC risk and levels of evidence is shown in Figure 5.1 (over).

Evidence for the effectiveness of primary prevention

The levels of evidence for a positive or negative association with CRC risk for a variety of factors is relatively low, and the findings show a reasonable level of consistency only for dietary fibre.

Diet

Many studies show a positive relationship between the probability of developing colorectal adenomas and cancer with dairy/animal fat intake,[3] and a negative correlation with diets high in fibre sources such as fruit and vegetables.[4] The

protective effect of vegetables and fruit may occur from factors other than their increased fibre content, and the precise biological mechanism is not fully understood. It has been suggested that the effects of diet are mediated through effects on bile acid secretion, although the mechanism leading to mutagenicity is unknown.[5]

Table 5.1 Summary of factors influencing CRC risk

	Grade of evidence	Consistency of evidence
Protective factors against CRC		
Fruit & vegetables	3	Moderate
A diet low in fat	3	Moderate
Dietary fibre	3	Moderate to good
Calcium	3	Poor
Carotene & vitamins A, C & E	3	Poor
Aspirin	3	Moderate
Physical activity	3	Moderate
Risk factors for CRC		
Alcohol	3	Poor
Cigarette smoking	3	Moderate
High socio-economic status	3	Poor

Source: Australian Health Technology Advisory Committee. Colorectal Cancer Screening. *Canberra: Australian Government Printing Service, 1997.*

The size of any effect from either dietary constituent group has been impossible to measure, and studies have not consistently shown a beneficial effect. As a result, it is not possible to quantify the benefits, in terms of reduced CRC risk, that might be achieved by modifying the amounts of animal fats and fruits/vegetables in the diet.

However, a number of public and personal health benefits may accrue from dietary modifications that increase the proportional intake of fruit and vegetables to animal products. Dietary changes of this nature have been occurring in New Zealand (which historically had a high intake of animal products) and this has been associated with a fall in CRC risk in younger cohorts with such diets.[6] Although clearly, these have some benefits in terms of a variety of health endpoints, the level of evidence that dietary modification alone is an effective intervention to reduce CRC risk is incomplete.

Most case control studies have shown a proportional decrease in CRC risk in relation to dietary fibre intake.[7] This appears to occur irrespective of the source of fibre, whether as part of the fruit and vegetable intake or as a dietary supplement such as bran fibre added to other foods. A mechanism for this may include the reduced transit time of faecal material in the colon and rectum, as well as absorption of potential carcinogens.

The evidence on diet is sometimes inconsistent and does not always achieve statistical significance. This may be because there are methodological difficulties associated with measuring the effect of diet on CRC, and studies differ with respect to the validity of the questions used and the characteristics of the populations studied.[8] In observational studies it is possible that confounding could partly explain an association between diet and CRC; those who differ in eating habits may also differ in other factors which are related to the risk of CRC. The results from RCTs, where the potential for confounding is minimised, will be important.

Since the mechanism and magnitude of any beneficial effect of modifying the diet as a way of reducing CRC risk is not understood, it could not be recommended as a specific intervention, except that it appears to be good for health generally.

Alcohol

There is some evidence that alcohol consumption increases the risk of developing both adenomas and carcinoma of the colon and rectum. A recent review concluded that alcohol probably increases the risk of CRCs.[9] Although the association between alcohol and CRC is probably only moderate, these cancers are common, so even a small risk from alcohol drinking may have important public health implications.[10] The size of the effect is such that confounding

factors cannot be excluded, and although alcohol consumption has a number of important public health impacts, it is not possible to make any recommendations based on current data.[11]

Food supplements

There is conflicting evidence concerning the benefits of calcium[12] and vitamins,[13] and while the current studies undertaken in the United States by the Women's Health Initiative Dietary Modification Trial[14] and the National Cancer Institute Polyp Prevention Trial[15] are incomplete, it is not yet possible to comment on any potential benefits.

Non-steroidal anti-inflammatory drugs

Some prospective and case control studies have demonstrated a reduction in the probability of developing adenomas, and possibly CRC, in people taking non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin.[16, 17] The possible benefits in terms of reduced CRC mortality must be quantified and compared with the risks of gastrointestinal haemorrhage before any recommendation can be made.

Physical activity/sedentary occupation

There are a number of studies showing that levels of recreational and occupational physical activity are inversely proportional to adenoma[18] and cancer[19, 20] risk. There may be spin-offs from public health initiatives to reduce obesity, hypertension and cardiovascular disease, but the size of the effect does suggest that this is a primary prevention opportunity for reducing mortality from CRC specifically. There are potential confounding factors in that CRC risk appears to be marginally higher in some socio-economic groups unrelated to exercise at home or at work.[21]

Cigarette smoking

Most case control studies have shown an increased risk for adenoma (especially for recurrent adenomas post-polypectomy) among smokers, although similar evidence for increased incidence of CRC itself is weak and inconsistent. It is therefore not clear whether current programmes to promote non-smoking will have any impact on the epidemiology of CRC.

Conclusion

There has been a 40 to 50 percent decline in the incidence of CRC in recent generations of New Zealanders born between 1943 and 1953 compared with those born about 1933.[6] These people are still relatively young at 45 to 55 years, and are therefore at low risk of CRC; it is not known whether the reduced incidence of CRC will persist in this group as they age. However, it is probable that the reduced incidence will persist since the shape of the incidence by age curves is similar for each cohort; the curves for younger cohorts merely shifted downwards.[22] This pattern has also been observed in other countries including Italy,[6] and England and Wales.[23] It has been suggested that dietary changes may explain the falling incidence of CRC which started 20 years ago in young people in England and Wales.[23]

At present, there is a lack of evidence from intervention studies on the preventive potential of diet and exercise, but a large RCT – the Women's Health Initiative Dietary Modification Trial – is currently underway in the United States.[14] The intervention includes explicit advice to increase consumption of fruit and vegetables, and the endpoints to be measured in the trial include heart disease, cancer (including breast cancer and CRC) and osteoporosis. The results of the trial will not be available for several years.

It has been suggested that, with the present level of evidence from observational studies, it is reasonable to advocate a 'prudent' diet, especially given that a diet low in fat and high in fruit and vegetables is also likely to have beneficial effects on other diseases such as cardiovascular disease.[23] Such a diet is consistent with general advice on good nutrition outlined in the *New Zealand Food and Nutrition Guidelines*.[24]

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6. SCREENING TEST OPTIONS

6.1 Faecal occult blood testing

- Three RCTs have provided Grade 1 evidence that screening for CRC with guaiac FOBTs can result in statistically significant reductions in mortality from CRC.
- A meta-analysis of the two population studies relevant to New Zealand reveals a 16 percent mortality reduction (95% CI 6%-25%) in the population offered screening. This means that one out of six deaths could be averted in people offered screening; the other five deaths would not be averted.
- The sensitivity of the FOBT in the Nottingham and Funen trials was approximately 50 percent: therefore, half of the CRCs present in the screened population were missed in each screening round.
- The specificity of the guaiac FOBT in the Nottingham and Funen RCTs was 96 to 98 percent: therefore, 2 to 4 percent of those without CRC had a positive FOBT.
- For every 10 people proceeding to colonoscopy on the basis of a positive FOBT, one will have CRC and three will have an adenoma greater than 10 mm. Six will have no significant abnormality detected, yet will have been exposed to the rare but significant risks associated with colonoscopy.
- The resource implications for colonoscopy are significant: approximately 8,090 people would undergo colonoscopy to investigate a positive FOBT in the first two years of screening if the Nottingham protocol were followed in New Zealand. A constant subsequent colonoscopy demand, allowing for adenoma surveillance, of 3,300 procedures per year has been estimated.
- To prevent one cancer death in the Nottingham RCT 1,250 people (95% CI 690-9090) had to be offered screening over about an eight-year period.
- The acceptability of FOBTs and the likely participation rate in a population screening programme utilising FOBT in New Zealand is unknown.
- It still remains to be determined which FOBT, in the context of population screening, will achieve the optimal balance of sensitivity, specificity and cost.

Faecal occult blood testing to detect CRCs is predicated on the observation that CRCs bleed intermittently. Approximately two-thirds of cancers will bleed in the course of a week, blood lost in this manner being unevenly distributed in the stool. Large polyps greater than 20 mm also bleed. Follow-up investigations of a positive FOBT will therefore lead to both the detection of CRC and colorectal polyps (the latter being more common).

Types of faecal occult blood tests

In 1864 Van Dien used gum guaiac as an indicator reagent for bloods,[1] and it remains the most widely used indicator for occult bleeding. However, it was only about 20 years ago that Greegor stimulated interest in screening healthy populations using guaiac-impregnated slides.[2, 3] The FOBT requires collection of a faecal sample or sequential faecal samples, which are applied to a test kit that can detect blood. The rationale for the test is that CRCs are friable and can bleed into the lumen of the bowel. It is known, however, that cancers may only bleed intermittently. Furthermore, benign and other precancerous lesions of the bowel may also bleed into the lumen and there is also a physiological blood loss into the lumen of the bowel. In addition, blood pigments may reach the lumen of the bowel from external sources such as ingested meat. Other substances may also produce false-positive readings.

As blood passes through the digestive system, the original red pigment (haemoglobin) is digested; haem (heme), the main initial by-product, is produced, and subsequent digestive action results in further breakdown to substances called porphyrins. Various types of FOBTs can detect one or more of haemoglobin, haem or porphyrins. The more proximal the bleeding site in the digestive tract, the more advanced the breakdown of blood present in the faeces.

There are two main groups of faecal occult blood tests in common use. The guaiac tests are the most widely used; immunochemical tests are more modern. Guaiac tests detect haem and haemoglobin; immunochemical tests detect

intact human haemoglobin only. There are numerous proprietary guaiac and immunochemical tests available; different proprietary brands may not be identical in sensitivity and specificity.

A third category of tests are the heme-porphyrin assays, which detect all three components of faecal blood - that is, haemoglobin, heme-derived porphyrins and intact haems.

Guaiac tests

The guaiac-based tests for faecal occult blood are the simplest and least expensive tests available. They detect both intact haem and haemoglobin and, because they do not detect porphyrins, are relatively specific for large bowel blood loss. The test relies on the pseudoperoxidase activity of haem or haemoglobin, which converts colourless guaiac to a blue colour in the presence of hydrogen peroxide in the developing agent. These tests are the most widely evaluated in trials of faecal occult blood screening with the Haemoccult, Hemoccult, Hemoccult II and, more recently, the Hemoccult II SENSA being the most extensively studied.[4]

The sensitivity of the tests can be increased by rehydration of the slide prior to testing, but this is accompanied by a decrease in specificity.[1, 5, 6, 7, 8] False-positive tests can be generated by ingestion of red meats, plant peroxidases and aspirin ingestion,[9, 10] and false-negative tests by Vitamin C.[11] Dietary restrictions clearly modify the (false) positivity rates of these type of tests (eg, from 3.4% positive to 1.3% positive in one study[12]) but also affect the acceptability of the tests.

Immunochemical tests

Immunochemical tests are based on the production of antibodies specific to intact human haemoglobin. Various systems are used to detect antibodies bound to haemoglobin in the faecal sample.[13]

Quantitative assays are confined to laboratories but non-quantitative, relatively simple slide assays are now available, and automated processing has been developed. Theoretically, these types of tests eliminate false-positives from dietary causes and, because human haemoglobin is the only substance being detected, are more specific for lower gastrointestinal bleeding. Non-specificity for human haemoglobin has been reported in some assays,[14] and predictably other causes of lower gastrointestinal bleeding may produce positive results.

Heme-porphyrin assays

These tests are designed to detect intact haemoglobin, heme-derived porphyrins and intact haems. They are not widely used, particularly in screening programmes, because they detect upper as well as lower[15, 16] gastrointestinal bleeding, plus dietary porphyrins and animal haems.

Self interpretation of FOBTs

There has been interest in self-interpreted tests (or throw-in-the-bowl tests) that reduce or eliminate the need to handle stool as well as providing an instant result. However, such tests (guaiac-based) have shown substantive and unsatisfactory reductions in the accuracy of the tests; in one study 33 percent of patients did not feel comfortable in interpreting the results and 29 percent found it difficult to interpret the colour change.[17]

Combined tests

A different approach has been proposed to increase sensitivity and decrease the rate of false-positive results. The idea is to use a two-step approach in which one stool specimen is collected on each of three days and samples are prepared for Hemoccult II SENSA (guaiac) and HemeSelect (immunochemical) testing. The more sensitive Hemoccult II SENSA test is developed first and, if the result is positive, the more specific HemeSelect test is then developed. The overall results of the screening are considered positive only if the results of both Hemoccult II SENSA and HemeSelect are positive. If the Hemoccult II SENSA test results are negative, then the samples that were collected for the HemeSelect tests are discarded. This approach may be substantially better than the widely used guaiac-based tests.[18, 19]

Procedures for testing

The currently accepted procedure for the Hemoccult II test (which was used in the Funen RCT) involves preparing one slide with two windows each day and sampling two sites from three stool specimens.[20] This procedure was established by historical precedent rather than empirical research; it is based on the concerns that colorectal neoplasms may bleed intermittently and that blood may not be homogeneously distributed in a specific bowel movement.

Positive screening results have commonly been defined as one or more positive reactions out of the six windows prepared when assessed for a blue-colour reaction at 30 to 60 seconds.

The reason for using slides collected over several days and interpreting the test result as positive if any window is positive is to maximise the sensitivity of the test for CRC and precursor neoplasms. Obtaining a faecal sample for an occult blood test during a rectal examination, although commonly done, is not recommended; data are insufficient to allow the interpretation of a positive test result obtained. One concern is that false-positive results may be induced by trauma from the rectal examination itself.[13, 20]

Number of windows and definition of positive results

The sensitivity and specificity of guaiac-based tests may be influenced by the number of samples used and the number of windows needed to yield positive results before the overall test results are considered positive. Even the decision about whether a window has enough blue colour to be interpreted as positive has been debated.[21, 22]

Although various strategies have been considered (eg, using more or fewer slides or different criteria for positivity), the evidence needed to assess such strategies is lacking. Until better data are available, the preferred method should continue to include the preparation of two-window slides from three separate faecal specimens, and the definition of a positive result as one or more positive windows.[20]

Diet and drug interactions

Diet may affect the results of FOBTs.[13, 20] For example, false-positive results (positive results that occur when no bleeding is present) on guaiac-based FOBTs may result from intake of foods that contain peroxidase activity. It is not clear whether low doses of aspirin or even warfarin cause clinically significant blood loss and false-positive results, but higher doses of aspirin may cause problems.[20] False-negative results may be due to intake of vitamin C.[11]

In most of the clinical trials, people being screened were encouraged to abstain from red meat, poultry, fish, some raw vegetables, vitamin C, and aspirin. Although compliance with diet restriction has not been reported in detail, recommending a strict regimen may decrease overall compliance with screening. The topic of compliance deserves further research because its effect on test results and subsequent mortality rates may be substantial.[20]

Rehydration of samples

Perhaps the most controversial, unresolved issue about the method of screening for CRC with guaiac-based FOBTs is whether to rehydrate the slide by adding a drop of water to the slide window before development with the peroxide-containing reagent. The goal of rehydration is to increase test sensitivity and the rate of positive results, which decline over time from slide preparation to development.[23] Rehydration has been used in RCTs,[5, 6, 7] and in the Minnesota study resulted in a four-fold increase overall in test positivity, from about 2 percent without slide rehydration to about 10 percent with rehydration (the range was from 8% in younger patients to 16% in older ones), and reported sensitivity increased from 80 to 92 percent.[5]

The decision about rehydration is controversial because it involves a potential trade-off between missed cancer if rehydration is not done and an increased number of more extensive work-ups (generally colonoscopy) if rehydration is done. If a large number of colonoscopies are performed because of false-positive tests, neoplasms that did not bleed enough to cause the positive result may be detected by chance. Such chance detection may reduce mortality rates.[20] Combined rehydration and annual testing dramatically increased the rate of colonoscopy to a cumulative 38 percent for a period of about 13 years in the Minnesota study compared with rates of around 4 percent for eight to 10 years of biennial, non-rehydrated screening in Funen and Nottingham.[5, 20, 24, 25] Recent reviews have not advocated rehydration because of the loss of specificity.[13, 20]

Timing of development of test samples

Seemingly mundane practical decisions, such as the delay between sampling and development of the FOBT samples, may substantially affect test results and interpretation. For example, after specimen collection, the rate of true-positive results (detection of blood) and the rate of false-positive results (detection of vegetable peroxidase) begin to decrease over time; however, the decrease of true- and false-positive results occur at different rates because vegetable peroxidases degrade more rapidly.[20] Because the goal is to maximise true-positive results and minimise false-positive results, these different rates of decrease become important in considering when (ie, how many days after stool sampling) to develop cards for FOBTs. Test manufacturers and clinical investigators are largely silent on the issue of timing.

Alternative tests

Although potential screening tests other than FOBTs have been developed or are under investigation, as yet none of them has supplanted FOBTs and none has been studied as extensively.[4, 26] These tests include the use of tumour markers,[27, 28, 29, 30] other markers of faecal bleeding or exudation (albumin,[31, 32] haptoglobin,[33] calprotein,[34] and α_1-antitrypsin[35]), and molecular detection techniques on tumour cell shedding.[13, 36, 37] Some of these tests may eventually replace FOBTs, but insufficient data are currently available to assess their role, if any, in population screening programmes.

Table 6.1 Comparison of three RCTs using FOBT for CRC screening

	Minnesota	Funen	Nottingham
Eligible population	volunteers	population based	population based
Size	3 groups of 15,000	2 groups of 31,000	2 groups of 76,000
Age range	50-80	45-75	50-74
Screening method	a) annual FOBT* b) biennial FOBT*	biennial FOBT	biennial FOBT
Dietary restrictions	yes	yes	no (except for retests after positive FOBTs)
Participation at first screen (%)	a) 90 b) 89	67	53†
Mean follow-up	13 years	10 years	7.8 years
Sensitivity (%)‡	92.2 (rehyd) 80.8 (non-rehyd)	51	53.6
Specificity (%)	90.4 (rehyd) 97.7 (non-rehyd)	98 (est)	96-98 (est)
Positive predictive value (%)	2.2 (rehyd) 5.6 (non-rehyd)	9-17	12
Colonoscopy rate (%)	a) 38 b) 28	4.3	4
Mortality rate in control group	67 per 100,000 PY	89 per 100,000 PY	70 per 100,000 PY
Mortality rate in intervention group	a) 45 per 100,000 PY b) 64 per 100,000 PY	73 per 100,000 PY	60 per 100,000 PY
Relative risk (95% CI)	a) 0.67 (0.50-0.87) b) 0.94 (0.68-1.31)	0.82 (0.68-0.99)	0.85 (0.74-0.98)
Mortality reduction (%)	a) 33 b) n/a	18	15
Absolute risk reduction	a) 22 per 100,000 PY b) n/a	16 per 100,000 PY	10 per 100,000 PY
NNT§	a) 4,545 b) n/a	6,250	10,000
NNS//	4,545	3,125	5,000
NINS#	350	625	1,282

* *From year 3 all FOBTs were rehydrated before analysis.*

† *The entire intervention group was invited at each round (including those who had not participated in round 1); 60% participated in at least one screening round.*

‡ *Sensitivity is calculated as true positive tests divided by the sum of true positive tests and interval cancers detected in the first year after a negative FOBT.*

§ *Number of people in the eligible population needed to prevent one death from CRC during the follow-up period in the population offered screening.*

// *Number of screens to be offered to prevent one death from CRC during the follow-up period in the population offered screening.*

\# *Number of individuals needed to prevent one death from CRC during the follow-up period in the population offered screening.*

Sources: Based on data from Hardcastle et al, *1996;*[25] *Kronborg* et al, *1996,*[24] *and Mandel* et al, *1993.*[5]

Has screening with FOBT been shown to bring significant benefits in other populations?

Towards the end of 1996, the results of two large RCTs of FOBT screening for CRC, one from Nottingham in Britain,[25] and the other from Funen in Denmark,[24] were reported. Both showed statistically significant reductions in CRC mortality. A previously reported RCT of FOBT in a volunteer population from Minnesota in the USA had also shown a significant reduction in CRC mortality,[5] and non-randomised and case control studies had reported results in the same direction.

This review will focus on an analysis of these three randomised controlled trials. A fourth RCT currently in progress in Göteborg, Sweden is due to report mortality data in 1999.

COMPARISON OF THE THREE RCTS OF FOBT SCREENING

Study design
These three trials were RCTs designed to assess the efficacy of FOBT in reducing mortality from CRC.[5, 24, 25] In assessing the efficacy of screening for CRC, a RCT with CRC mortality as the outcome measure is the only way to control for the particular biases (lead time, length, selection and overdiagnosis biases; discussed in Chapter 2, pages 14-15) associated with the evaluation of screening. Table 6.1 (opposite) summarises the three trials, which are described in more detail .

Eligible population
The three trials were all field trials, in that they took place in the community. However, the criteria for eligibility and exclusion differed.

Minnesota Volunteers from the American Cancer Society and fraternal, veterans, and employee groups in Minnesota, aged 50 to 80 years, were eligible. People who reported a history of CRC, familial polyposis or chronic ulcerative colitis, and those who were bedridden or otherwise known to be disabled were excluded. Medical records were not checked.

Funen Those on the population register for Funen, aged 45 to 75 years, were eligible. People with known CRC, precursors of CRC (adenomas), and distant spread from all types of malignant disorders were excluded (identified by record linkage). Those who had taken part in a pilot study were also excluded. Any study participants who were diagnosed with adenomas or CRC between randomisation and the first screening invitation were also excluded (although they were included in the follow-up analysis, as all analyses were on an intention-to-treat basis).

Nottingham Individuals living in Nottingham, registered with a general practice and aged 50 to 74 were eligible (a pilot study had included people aged 45 to 74). Family doctors excluded people with serious illness, including those with a diagnosis of CRC within the previous five years.

Randomisation
In all three trials allocation to groups was random. Without the intervention, the control and intervention groups in each trial could be reasonably expected to have had similar colorectal mortality rates. When differences in CRC mortality are found it may therefore be assumed that these are due to the effect of screening.

Minnesota Randomisation was by individual after stratification by age, sex, and place of residence. Randomisation produced three similar groups (15,000 per group) with respect to age, sex and place of residence.

Funen Randomisation was by individual (using ID numbers) with married couples allocated to the same group. Randomisation produced two similar groups (31,000) with respect to age and sex.

Nottingham Randomisation was by household so that all eligible household members were randomised to the same group. Randomisation produced two similar groups (76,000 per group) with respect to age and sex.

Invitation method

Minnesota Volunteers. The annually screened group completed 75.2 percent of screens offered (90% completed the first screen), and the biennially screened group completed 78.4 percent (89% completed the first screen). All screenings were completed by 46.2 and 59.7 percent of the annual and biennial groups respectively.

Funen Invitations with two reminder letters. Only those who took part in the first round continued to be invited. All five screening rounds were completed by 46 percent, with 67 percent having attended the first screening round and reinvited thereafter.

Nottingham Invitations were sent to individuals registered at general practices participating in the trial. Only those who took part in the first round were invited subsequently, until five years after the trial began when invitations were sent every two years to all individuals who had not previously responded. In the first screening round 53 percent attended. Overall, 59 percent completed at least one screening, and 38 percent completed all screening rounds.

Screening methods

Minnesota Two groups: (a) annual FOBT screening, and (b) biennial FOBT screening. Each individual was asked to submit six paper slides (Hemoccult) with two smears from each of three consecutive stools. Advice on avoidance of certain foods, aspirin, and vitamin C tablets was given. All FOBT slides were rehydrated for the last 10 years of the trial. Follow-up was by annual mailed questionnaires to those in all three groups. The medical records of those reporting diagnoses of CRC and polyps were checked.

Funen Every two years the intervention group was asked to provide two samples (Hemoccult II) from each of three consecutive stools. Advice was given on dietary restrictions, avoidance of aspirin, NSAIDs, and vitamin C. Slides were not rehydrated. Controls were not told about the trial. Follow-up was through the Funen patient database, the county public health officer, the Danish National Patient Registry, and the Danish Cancer Society.

Nottingham Every two years the intervention group was asked to provide two samples (Haemoccult) from each of three consecutive stools. A cohort (size not given) within the intervention group was asked to test six consecutive stools. No dietary advice was given. The slides were not rehydrated. Controls were not told about the trial. Follow-up information was obtained from general practitioners, hospital databases, the regional cancer registry, the National Health Service Central Registry database, and the Office of Population Censuses and Surveys.

Sensitivity and specificity of the screening test

The relatively low sensitivity in the Funen and Nottingham trials meant that about half of those diagnosed with cancer in the screened group had false-negative tests. Specificity was higher, but because far more people in a screening programme do not have disease, even more people had false-positive tests, with the resulting anxiety and unnecessary investigations.

Minnesota The sensitivity of the FOBT was 92 percent (rehydrated) and 81 percent (not rehydrated). Specificity was 90 percent (rehydrated) and 98 percent (not rehydrated).

Funen Sensitivity was 51 percent, and specificity was estimated at 98 percent.

Nottingham Sensitivity was 53.6 percent, and specificity was estimated at between 96 and 98 percent.

Assessment of people with positive screening results

Minnesota If one or more tests were positive, people were referred to the University of Minnesota Hospital (75%), some consulted their own physicians (20%), and 5 percent declined to consult a physician. During the trial, 38 percent of those screened annually and 28 percent of those screened biennially had at least one colonoscopy.

Funen Those with one or more positive tests were invited for assessment. During the trial 4.3 percent of those who were screened at least once underwent colonoscopy.

Nottingham Those with up to four positive tests were sent a repeat test (with dietary advice). Only those with five or more positive tests initially or one or more positive tests at retesting were assessed. During the trial, 4 percent of those screened had colonoscopy once or more.

Key results

Minnesota After 13 years CRC mortality was 45 per 100,000 person-years in the annually screened group, 64 per 100,000 person-years in the biennially screened group, and 67 per 100,000 person-years in the control group. The relative risks were 0.67 (95% CI 0.50 to 0.87) in the annually screened group and 0.94 (95% CI 0.68 to 1.31) in the biennially screened group.

Funen After 10 years the CRC mortality was 73 per 100,000 person-years in the intervention group, and 89 per 100,000 person-years in the control group. The relative risk was 0.82 (95% CI 0.68 to 0.99).

Nottingham After 7.8 years the CRC mortality was 60 per 100,000 person-years in the intervention group, and 70 per 100,000 person-years in the control group. The relative risk was 0.85 (95% CI 0.74 to 0.98).

There was no significant difference in all-cause mortality rates between intervention and control groups in the three trials (the trials were not designed with the power to detect differences in all-cause mortality).

Other results

- **Percentage positivity FOBT**

Minnesota	9.8% rehydrated; 2.4% non-rehydrated
Funen	First screen = 1%. Rescreen: round 2 = 0.8%; round 3 = 0.9%; round 4 = 1.3%; round 5 = 1.8%
Nottingham	First screen = 2.1%. Rescreen within 27 months = 1.2%

- **Detection rates adenoma and CRC /1,000 screened**

Nottingham	
Overall	First screen = 2.1 cancer, 7.7 adenoma
	Rescreen within 27 months = 1.4 cancer, 3.8 adenoma
Over 65 years	3.4 cancer, 7.7 adenoma
Under 65 years	1.1 cancer, 4.4 adenoma

- **CRC and Dukes' A stage of CRC in screened and control groups**

Funen	Dukes' A: screened = 105 (22%); control = 54 (11%); P<0.01
	Total: screened = 481; control = 483
Nottingham	Dukes' A: screened = 181 (20%); control = 95 (11%); P<0.001
	Total: screened = 893; control = 856

- **Positive predictive value FOBT for cancer**

Minnesota	2.2% rehydrated; 5.6% non-rehydrated
Funen	First screen = 17%; final screen = 10%
Nottingham	First screen = 9.9%; rescreen within 27 months = 11.9%

- **Positive predictive value FOBT for adenoma**

Minnesota	Not reported
Funen	Adenoma >10 mm: first screen = 32%; final screen = 21%
Nottingham	Neoplasia (cancer + adenoma): first screen = 47.1%; rescreen within 27 months = 44.8%
	Adenoma <10 mm: screened = 253 (25%); control = 129 (35%)
	Adenoma 10-19 mm: screened = 481 (48%); control = 140 (38%)
	Adenoma >20 mm: screened = 267 (27%); control = 100 (27%)
	Total adenomas: screened = 1,001; control = 370

Internal validity

Statistically significant reductions in CRC mortality were seen for annual screening in the Minnesota trial, and for biennial screening in the Funen and Nottingham trials. The likelihood of finding reductions in CRC mortality of the magnitude found in these trials by chance, if screening really had no effect on CRC mortality, was less than 5 percent. Sample size and power calculations had been performed for all three trials, taking into account CRC mortality at the time that the trials began (screening was continued for longer than originally planned in the Minnesota trial and the sample size was increased in the Nottingham trial, because of lower than expected CRC mortality in the control groups in both trials).

Confounding should have been minimised by randomisation in the three trials. All three showed that randomisation had resulted in similar groups with respect to age and sex (and place of residence in the Minnesota trial), but there is no information given about other risk factors for CRC. With the relatively large numbers in these trials it is likely that randomisation would have produced similar groups with respect to other factors as well as age and sex. The Nottingham trial was randomised by household, which reduces the likelihood that the two groups would have been similar; however, this trial had very large numbers (76,000 in each group) and, presumably, the cluster randomisation was taken into account in the analysis, although this is not stated.

Selection bias was minimised by carrying out intention-to-treat analyses (stated for Funen trial, and assumed for Minnesota and Nottingham). An intention-to-treat analysis is essential to avoid selection bias, but it *underestimates* the efficacy of screening because it includes those who were offered screening but did not participate. This is appropriate, because in population screening programmes not everyone chooses to take part. The reduction in CRC mortality among those who take part in screening is actually greater than the reduction for the whole intervention group.

All three trials used CRC mortality as the outcome measure. Information bias was minimised in all the trials by blinding those reviewing death certificates to the intervention- or control-group status of individuals in the trial. Determination of cause of death was carried out by independent panels (with case-note review in the Nottingham trial).

In the Minnesota trial, 38 percent of those in the annual screening group underwent colonoscopy at least once. It has been argued that a large part of the reduction in CRC mortality was due to chance detection of cancers by colonoscopy, but mathematical modelling has determined that 16 to 25 percent of the reduction in CRC mortality was due to chance detection,[38] and the remainder was due to sensitive detection. High colonoscopy rates also carry risks.

In all three trials there was a shift towards an earlier stage at diagnosis and improved survival in the intervention groups compared with the control groups. This is not a measure of efficacy, as it can be influenced by lead-time, length, and overdiagnosis biases. Only the Nottingham trial found an increase (of only 4.3%) in CRC incidence in the intervention group compared with the control group. This suggests that FOBT screening detects existing tumours at an earlier stage, but with a relatively short lead-time. It was suggested in the Minnesota and Funen reports that colonoscopy may (by removing precursor lesions) lead to a decline in incidence of CRC in the intervention group over a longer time period than has been reported to date.

External validity

Minnesota The Minnesota trial was carried out among volunteers. This group may be different in several ways from the general population, including their participation rates, adherence to screening and assessment protocols, and their underlying risk of developing and/or dying from CRC. These differences could make the results less applicable to other populations.

Funen The Funen trial was population-based. It excluded those with known CRC and people with diagnosed adenomas, which meant that the trial population was likely to be at lower risk of CRC that a general population.

Nottingham The eligible population in the Nottingham trial was identified through general practice age-sex registers. Only those with serious illness or a diagnosis of CRC in the previous five years were excluded. This is likely to be similar for a population screening programme, and general practitioners are likely to identify those who should be excluded.

Meta-analysis of the RCTs

This was performed by the AHTAC Working Party to provide a greater precision of the estimates of mortality reduction; the results are recorded in Table 6.2 (opposite).[2]

The meta-analysis of the two trials considered most similar to the New Zealand situation - the Nottingham and Funen studies - yielded an odds ratio of 0.84 (ie, a 16% relative reduction in mortality in the screened versus the control group).

The Swedish trial

The fourth RCT of population screening with FOBT was begun in Göteborg, Sweden, by Kewenter and colleagues in 1982.[7] There are a number of differences between this trial and the three trials outlined above; these will be important to note when the mortality data from this trial is published in 1999 (interim data suggests a 10% relative reduction in mortality in the screened group[39]).

Table 6.2 Meta-analysis of the RCTs

1. Combined Nottingham and Funen studies

Study	*Number of deaths/number of patient years*		*OR*
	Screened	*Control*	
Funen	205/281,883	249/281,328	0.822
Nottingham	360/597,944	420/596,369	0.855

Overall OR (& 95% CI) 0.842 (0.75-0.94)
Test of homogeneity X^2 = 0.11, 1 df, p = 0.738

2. Nottingham and Funen studies + Minnesota biennial data

Study	*Number of deaths/number of patient years*		*OR*
	Screened	*Control*	
Funen	205/281,883	249/281,328	0.822
Nottingham	360/597,944	420/596,369	0.855
Minnesota	117/183,934	121/181,966	0.957

Overall OR (& 95% CI) 0.860 (0.78-0.95)
Test of homogeneity X^2 = 0.92, 2 df, p = 0.633

3 Nottingham and Funen studies + Minnesota annual data

Study	*Number of deaths/number of patient years*		*OR*	*Weight*
	Screened	*Control*		
Funen	205/281,883	249/281,328	0.822	84.442
Nottingham	360/597,944	420/596,369	0.855	139.762
Minnesota	82/184,160	121/181,966	0.669	44.517

Overall OR (& 95% CI) 0.812 (0.72-0.91)
Test of homogeneity X^2 = 2.34, 2 df, p = 0.311

4 Nottingham and Funen studies + all Minnesota data

Study	*Number of deaths/number of patient years*		*OR*	*Weight*
	Screened	*Control*		
Funen	205/281,883	249/281,328	0.822	84.442
Nottingham	360/597,944	420/596,369	0.855	139.762
Minnesota	192/368,094	121/181,966	0.784	74.178

Overall OR (& 95% CI) 0.831 (0.75-0.92)
Test of homogeneity X^2 = 0.42, 2 df, p = 0.812

Source: Australian Health Technology Advisory Committee, 1997.[26]

The age range of the subjects (all inhabitants of Göteborg, born between 1918 and 1931) was narrowed to between 60 and 64 at the time of entry. Hemoccult II tests with dietary restriction were used. Except for those from subjects born between January 1918 and July 1920, all slides were rehydrated because the investigators considered the number of false-negative results with non-rehydrated slides to be too high: the rate of interval cancers in the non-rehydrated group was 77 percent compared with 11 percent in the rehydrated group.

The intervention group was offered only one rescreen after 18 to 24 months.

The number of positive tests increased successively within the different cohorts, reaching 14.2 percent in the 1992 rescreening. The reasons for this are not clear, but a similar increase was reported in the Minnesota study.

To reduce the number of follow-up investigations, the subjects in the last cohort who tested positive at either the first or second screening were reinvestigated using the Hemoccult II test. This strategy of retesting before a work-up to increase the specificity of the test remains largely unassessed.[20]

Only those who had a positive second test were invited for follow-up investigation. This consisted of proctoscopy, rectosigmoidoscopy (60 cm) and double-contrast barium enema.

The number of cancers detected in the screening group (117) was significantly higher ($p<0.001$) than the number detected in the control group (44). Significantly ($p<0.03$) more Dukes' A carcinomas were diagnosed in the test group than in the control group during the screening period. A total number of 563 adenomas were detected in 419 subjects in the test group (258 subjects had at least 1 adenoma >10mm) compared with 64 adenomas in 51 subjects in the control group (24 subjects had at least 1 adenoma >10mm).

Could the New Zealand population potentially benefit similarly?

The results from the Nottingham and Funen trials are likely to have the greatest relevance to New Zealand, since they were carried out in a general population rather than volunteers. CRC incidence and mortality are lower in Denmark and England than in New Zealand, but the stage distribution at diagnosis (in the absence of screening) is similar. Therefore, the potential for a similar shift in stage distribution as in the Funen and Nottingham trials exists for New Zealand.

The Nottingham RCT (as was the Funen RCT) was carried out in a 'closed' cohort, in that people could enter during the recruitment phase of the trial if they were in the eligible age range, but they did not leave when they reached 75, so that by the time the RCT ended some of these people were aged 80 or more. In a population screening programme for people aged 50 to 74, the cohort would be 'dynamic' in that people would become eligible when they turned 50 and would no longer be eligible for screening once they turned 75. Because the risk of CRC increases with age, FOBT screening in the RCT (where, as time passed, the population being screened included an increasing proportion of people aged over 75) might have resulted in higher CRC detection rates and higher colonoscopy rates than in a population screening programme over an equivalent time period.

The Minnesota trial was carried out among volunteers and this could make the results less generalisable to New Zealand. However, CRC tends to be diagnosed at an earlier stage in the United States than in New Zealand (even in the general population rather than volunteers); consequently, it may be that the potential for FOBT screening to effect a shift in stage distribution is even greater in New Zealand than in the United States.

Is the FOBT a suitable screening test?

The sensitivity of a FOBT to detect early CRC or its precursor lesions is the most important determinant of its benefit as a screening test. However, a FOBT cannot detect cancers or large polyps that do not bleed, and thus the bleeding biology of CRC and precursor neoplasms determine the upper limit of screening efficacy for the test. Ransohoff and Lang speculate that the sensitivity of a single test of any FOBT for curable CRC is less than 50 percent and may be as low as 30 percent.[20] However, if target lesions remain at least intermittently detectable for years before they progress to incurable disease, repeated testing using a test with low sensitivity could still produce a large benefit. Calculating an absolute sensitivity for the detection of asymptomatic cancer in a screening population by FOBT is almost impossible: cancers occur in screening populations at the rate of 1 to 2 per 1,000, and 100 to 200 patients with screen-detected cancers would need to be studied to ensure narrow confidence intervals of the sensitivity measures.[40]

The specificity of a FOBT (rate of negative tests in the absence of disease) is a principal determinant of the effort and cost of screening, because false-positive tests account for most of the colonoscopic examinations performed. A small change in test specificity (eg, from rehydrating test slides) can make a significant impact on the number of follow-up investigations. False-positive tests also impact on screenees, generating anxiety and follow-up bowel investigations. Determining the actual specificity for FOBTs would be extremely difficult, because adequate large numbers of asymptomatic screenees are unlikely to undergo definitive investigation to prove normality in those testing negative.[40]

The guaiac test is the only FOBT used in the RCTs that reported a significant reduction in CRC mortality. The sensitivity of the non-rehydrated test was 51 percent in the Funen study and 53.6 percent in the Nottingham study, with an estimated specificity of 98 percent and 96-to-98 percent respectively.

The newer guaiac Hemoccult II SENSA test has improved sensitivity but specificity has been a problem in certain populations (Japan and California) who consume high peroxidase diets. Immunochemical tests (detecting only intact

human haemoglobin) are promising, but there is variation between tests; Young considers only Immudia-HemSp and HemeSelect meet the criteria for improved sensitivity but acceptable specificity.[40] The combined approach of Hemoccult II SENSA followed by HemeSelect (if the initial Hemoccult II SENSA is positive) may also increase sensitivity and decrease the rate of false positive results. However, the performance of these tests within a population screening programme has yet to be demonstrated. It remains to be determined, in the context of population screening, which FOBT will achieve the optimal balance of sensitivity, specificity and cost. Young comments that the process of demonstrating the superiority of the newer FOBTs to those used in the three RCTs discussed need not include mortality as an endpoint but must involve a direct comparison in large numbers of screenees (say 20,000) with cancer yields, apparent specificity and compliance determined for each test.[40]

How should a positive FOBT be investigated?

The investigative options generally considered here are colonoscopy or double-contrast barium enema (DCBE), either alone or in conjunction with rigid or flexible sigmoidoscopy. In the Minnesota, Nottingham and Funen trials, colonoscopy was chosen as the follow-up investigation, with DCBE being performed if colonoscopy was incomplete or suboptimal. The initial diagnostic work-up in the Minnesota study consisted of rigid proctosigmoidoscopy and single-column barium enema; use of the latter procedure was discontinued in 1978 because it missed 20 percent of the cancers detected by colonoscopy. In the case of the Göteborg study, the diagnostic work-up consisted of proctoscopy, sigmoidoscopy and DCBE.

Colonoscopy is regarded as the gold-standard investigation of the large bowel. Rex *et al* found the sensitivity of colonoscopy for CRC to be 95 percent compared with 82 percent for DCBE, with an odds ratio of 3.83 for a missed cancer by DCBE compared with colonoscopy.[41] Cancers detected by colonoscopy were more likely to be Dukes' A (24.9%) than cancers detected by DCBE (9.8%). However, this is a retrospective study; the actual sensitivities of both DCBE and colonoscopy are considered to be overestimated. In the Göteborg study, the combination of DCBE and rectosigmoidoscopy (60 cm) overlooked 2 percent of the carcinomas in the work-up of subjects with a positive FOBT.[42] Prospective studies of the performance of DCBE have found lower sensitivities in detecting both CRC and large polyps in symptomatic patients (64-75%),[43, 44, 45] and in asymptomatic patients with positive FOBT results (50-75%).[46, 47, 48, 49, 50] The strengths and weaknesses of these studies and DCBE are discussed at length in Chapter 6.4 (pages 61-3).

With respect to adenoma detection by colonoscopy, a recent back-to-back study revealed that 6 percent of lesions greater than 10 mm were missed whereas 27 percent of adenomas under 5 mm and 13 percent of adenomas 6 to 9 mm in size were missed.[51] The sensitivity of colonoscopy for the detection of cancer and adenomas is discussed further in Chapter 6.3 (pages 56-60).

With the reported differences in sensitivities of the two procedures, particularly for small lesions, and the fact that lesions detected during colonoscopy can be either biopsied or removed at the time (lesions identified by DCBE examination require a follow-up colonoscopy), colonoscopy is widely advocated as the initial investigation of choice in FOBT-positive individuals. The results of the three RCTs confirm the effectiveness of colonoscopy used in this way. There is no published evidence from RCTs of the effectiveness of screening by FOBT followed by DCBE. Interim data from the Göteborg RCT of population screening with FOBT in which positive FOBTs (Hemoccult II slides rehydated) were investigated with proctoscopy, rectosigmoidoscopy (60 cm) and DCBE, suggests a 10 percent relative reduction in mortality in the screened group.[39]

However, colonoscopy is expensive and currently is only performed by specialist physicians or surgeons with training in endoscopy. If resources, cost and accessibility are issues, then DCBE with flexible sigmoidoscopy is considered an alternative by many professional bodies.[52] However, at the present time, flexible sigmoidoscopy is seldom performed in New Zealand except for follow-up after polyp removal.

Concurrent upper gastrointestinal investigation

There is some debate as to whether concurrent upper gastrointestinal investigation should be performed as part of the diagnostic work-up for a positive FOBT, particularly if no abnormality is detected at colonoscopy. In the Minnesota study this practice was discontinued in 1982 because it did not detect substantial disease requiring treatment. Upper gastrointestinal investigation was not routinely performed in the Funen and Nottingham trials. Thomas and Hardcastle followed 447 patients with a positive FOBT.[53] No colon cancer was detected in 283, but 14 of these patients had

upper gastrointestinal symptoms. Investigation in this group revealed significant findings in six, including one gastric cancer. In the remaining 269 patients followed for two to eight years, only five developed upper gastrointestinal disorders (all benign), suggesting that routine upper gastrointestinal investigation in individuals with a positive FOBT and no upper gastrointestinal symptoms is not worthwhile.

Management after a complete colorectal evaluation for a positive FOBT

In a position paper on FOBT by the American College of Physicians, it was considered that 'if complete colonoscopy revealed no colorectal adenoma or only a single small (<10mm) tubular adenoma, further screening for CRC may reasonably be deferred for five or more years'.[54] This was not standard practice in the Funen and Nottingham trials.

What is the screening interval?

The Nottingham and Funen studies both reported significant reductions in CRC mortality with biennial screening with FOBT. The biennial FOBT screening arm of the Minnesota study did not - even with the use of rehydrated tests, a 28 percent colonoscopy rate and a follow-up period of 13 years (as opposed to almost 8 years in Nottingham and 10 years in Funen). The reason for this is not clear. The Minnesota study was based on volunteers (unlike the other two studies) and the cumulative mortality and incidence of CRC were initially higher in the biennially screened group compared with the control group. By the end of the 13-year follow-up period, this trend was reversing. According to the AHTAC report, ongoing follow-up of participants in the Minnesota trial has shown a reduction in mortality of approximately 20 percent in the biennially screened group and 35 percent in the annually screened group.[26] Because the Nottingham and Funen studies are considered more relevant to the New Zealand situation, evidence from these trials would support a biennial screening interval initially. Although annual testing is likely to result in greater mortality benefits, the incremental costs and resource requirements may offset these.

What age group should be screened?

On the basis that the incidence of CRC begins to increase more significantly from the age of 50, most recommendations concerning screening for CRC recommend a starting age of 50 years. In considering screening of the population aged between 40 and 50 years, the AHTAC Working Party considered 'that cost effectiveness should be taken into account, as the prevalence of occult lesions in this group is likely to be comparatively low. As age increases, occult lesions become more prevalent but potential years of life saved through screening diminish.[26] However, in an environment of rationed health care, the question of cost-effectiveness should be taken into account for each age group for whom screening is considered (this is addressed in Chapter 11, pages 82-93).

The age groups screened in each of the RCTs were as follows:

- Minnesota 50-80 years
- Nottingham 50-74 years
- Funen 45-75 years
- Göteborg 60-64 years.

The Nottingham study reported the detection rate of carcinomas and adenomas to be higher in individuals over 65 years of age: 3.4 cf 1.1/1000 screened for cancer; and 7.7 cf 4.4 /1000 screened for adenomas.

Data from the Funen group published in 1989 revealed only one carcinoma in people aged between 45 and 54 years detected by FOBT, but more than half of the screen-detected carcinomas were in those aged 65 to 74 or older.[55]

However, there was no significant difference in the CRC mortality ratio between individuals over 60 years and those under 60 in the Funen study, nor between those over 65 years and those under 65 years in the Nottingham study. It has to be considered that this may be purely a reflection of sample size.

The results of the Göteborg study, where only those aged between 60 and 64 years were entered into the screening, will be interesting.

On when to cease screening, the American Clinical Guidelines state,

> . . . there is no direct evidence relating to the time at which screening should stop, but indirect evidence supports stopping screening tests in people nearing the end of life. Polyps take about 10 years to progress to cancer and

screening to detect polyps may not be in the patients' best interest if they are not expected to live at least that long. Also, screening and diagnostic tests are in general less well tolerated by elderly people. Therefore, there will come a time in most people's lives when the rigours of screening and diagnostic evaluation are no longer justified by the potential to prolong life.[52]

Country-specific community consultation would be pertinent in deciding on this issue, as well as cost-effectiveness data.

Are the risks of the screening programme acceptable?

The risks of the screening programme can be classified as physical and psychological.

Physical

The risks here relate predominantly to the complications that may arise as a result of having a colonoscopy in the course of investigating a positive FOBT. Colonoscopy is generally a safe procedure with significant complications being considered rare. Where complications may arise, they are the result of:

- sedation
- cardiopulmonary events
- the procedures and interventions performed.

The complications of most concern are those associated with the procedure itself or the interventions performed during the procedure, namely polypectomy. Surgery may subsequently be necessary, and in rare instances death results.

Reviewing the literature on complication rates of colonoscopy is difficult. The majority of studies are retrospective with limited statistical significance, and bias is a problem in the collection and reporting of complications.[56] These biases include sampling/selection bias, confounding bias and measurement bias. Examples of these in relation to endoscopy are outlined in Table 6.3 below.

Table 6.3 Bias in reporting complications

Bias		
Sampling selection bias	1	Non-responders
	2	Specialist centres may have different patient populations than general population
	3	Expert endoscopists may have a lower complication rate than less expert endoscopists
Confounding bias	1	Some procedures carry a higher risk
	2	Emergency vs elective procedures
Measurement bias	1	Non-standard definitions of complications
	2	Incomplete reporting of delayed complications
	3	Non-independent observer

Source: Based on data from Baillie, 1994,[56] modified from: Newcomer MK, Brazer SR, Complications of upper gastrointestinal endoscopy and their management, Gastrointest Endosc Clin Nth Am *1994; 4: 551-70.*

The first three studies described in Table 6.4 (over) were generated when colonoscopy was in its infancy.[57, 58, 59] Waye *et al* reported the overall perforation rate for diagnostic colonoscopy from three prospective studies between 1987 and 1994 to be 0.045 percent,[60] but the majority of cases and both perforations came from the largest study (8/12,876 = 0.06%).[61] The decrease in perforation rate for diagnostic colonoscopy (from 0.17% in the earlier pooled study) was attributed to better training of physicians and improvement in the performance characteristics of the endoscopic instruments. The perforation rate was higher after polypectomy (0.41% for 12 pooled studies[60], 0.83% in a recent prospective study[61]).

In order to estimate the mortality rate from perforation, Waye combined the studies of diagnostic and polypectomy cases for a number of studies dating back to 1974. Five deaths were reported out of 83,725 procedures, a mortality

rate of 0.006 percent.[60] This is lower than the mortality rate of 0.015 percent for the recent pooled diagnostic and therapeutic prospective study from a training centre of 12,876 partial and total colonoscopies,[61] and lower than the 0.02 percent mortality rate previously reported for diagnostic procedures.[60] The need for large, well-designed prospective studies to address these questions is clear.

Table 6.4 summarises the complication rates of colonoscopy as reported in a number of studies

Table 6.4 Diagnostic colonoscopy complications

Study	No.	Perforation	Haemorrhage	Infection	Cardio-pulmary	Death
Berci *et al,* 1974	3,850	7 (0.18%)	-	-	-	1 (0.025%)
Macrae *et al,* 1983	5,000	4 (0.08%)	1 (0.02%)	2 (0.04%)	5 (0.1%)	3 (0.06%)
Habr-Gama & Waye, 1989*	100,773	173 (0.17%)	28 (0.03%)	-	-	21 (0.02%)
Waye *et al,* 1996†	17,734	8 (0.045%)	-	-	-	-

* *Pooled analysis of eight studies, including data from Berci* et al*, 1974,[57] and Macrae* et al*, 1983,[58] reported above.*
† *Pooled analysis of three prospective studies, 1987-94.*

Complication rates also vary with the level of expertise of the operator.[62]

There is little New Zealand data available on the complication rates for colonoscopy, although this information should be available via audits of the main centres. From the time of the establishment of the ACC Medical Misadventure Unit in 1992 until 30 June 1997, there had been 39 accepted claims relating to injuries following colonoscopy and polypectomy: 37 were related to perforation and two were deaths.[63]

Quality controls would have to be in place for any colonoscopy performed as part of a screening programme. Currently, New Zealand – unlike Australia – does not formally credential colonoscopists. If a screening programme were introduced, this situation would need to be reviewed.

The complications reported above are largely for diagnostic procedures performed in patients who had symptoms or blood test abnormalities. Screening procedures are performed in well people, and it has been postulated that the complication rates for colonoscopy in this situation may be less. Colonoscopy complications do occur in the context of population screening, but the size of these studies does not allow us to know whether the mortality from such complications is lower than expected in the usual clinical setting. The reported colonoscopy complications from the screening trials are outlined in Table 6.5.

Table 6.5 Reported colonoscopy complications

	Screening trials		
	Nottingham	Funen	Minnesota*
No. procedures	1,778	1,000	12,246
Perforation, diagnostic	1	n/r	4
Perforation, therapeutic	4	n/r	0
Bleed, major	1	n/r	11
Snare entrapment	1	n/r	0
Death	0	1	0

** Diagnostic and therapeutic procedures performed at university hospital.*

Sources: Personal communication JD Hardcastle to S Parry, 19 September 1997; personal communication, O Kronborg to S Parry, 23 September 1997; Mandel et al*, 1993.[5]*

The denominator is small for such infrequent events as perforation and death. To rule out a risk of death of 0.02 percent, according to the formula described by Hanley and Lippman-Hand,[64] 0 deaths in 15,000 consecutive colonoscopies would be required.

On the basis of the results of the Nottingham and Funen trials, the majority of colonoscopies within a CRC screening programme would be performed in individuals with false-positive test results. Of every 10 people proceeding to colonoscopy because of a positive FOBT one will have cancer, and three will have an adenoma greater than 10 mm (considered to be significant as cancer risk increases with adenoma size), which will be removed during the procedure. Smaller lesions may also be removed, especially if they are multiple, to differentiate between hyperplastic and adenomatous polyps. Polypectomy is associated with the higher perforation rate but this increased risk is mostly carried by those with significant pathology. The six people investigated for false-positive results will have been exposed to the inconvenience and discomfort of a procedure with a perforation risk of 0.045 percent to 0.17 percent and a mortality rate of possibly 0.02 percent.

The risk of complications resulting from colonoscopy has to be weighed against the benefits of the screening programme.

Double-contrast barium enema (DCBE) is a safer procedure than colonoscopy, but many of the abnormalities identified with this examination will require follow-up colonoscopic investigation. There is no published evidence from RCTs of the effectiveness of screening by FOBT followed by DCBE. Interim data from the Göteborg RCT of population screening with FOBTs (using rehydrated Hemoccult II slides) in which positive results were investigated with proctoscopy, rectosigmoidoscopy (60cm) and DCBE, suggests a 10 percent relative reduction in mortality in the screened group.[39]

The level of public support for screening programmes is likely to be affected by the accuracy of the tests and by their possible adverse consequences.

Psychological

Any screening programme has positive and negative psychological sequelae. However, there are two particular areas of concern with regards to population screening for CRC with guaiac-based FOBT.

1 Approximately half of the cancers occurring in the screened population will be missed. People with missed cancers may have been falsely reassured by a negative test result that they did not have CRC.
2 The positive predictive value of FOBTs is approximately 10 percent for CRC and 30 percent for adenomas greater than 10 mm. Of 10 people proceeding to colonoscopy on the basis of a positive FOBT, six will have no significant abnormality detected. These six people could be considered to have had an unnecessary procedure with exposure to associated risks and to have suffered inconveniences, such as time off work and bowel preparation. Anxiety with regards to outcome of the procedure would also have been generated. A negative result may influence future compliance with follow-up investigations after a positive FOBT.

These concerns are discussed in more detail in Chapter 8 (pages 71-5).

Could New Zealand achieve the expected benefits?

Participation

The participation rate is one of the most important determinants of the success of a population screening programme. Recruitment strategies and the acceptability of the screening test largely determine these rates.

For New Zealand to achieve the expected benefits, an overall level of participation at least equal to that in the Nottingham and Funen trials would need to be obtained. Population screening is likely to require even greater effort to recruit and retain participants. In most studies the participation level declines with time, particularly among younger participants.

Participation rates in the RCTs of population screening with FOBT and the factors influencing participation are discussed in Chapter 7 (pages 64-70).

Resource availability

The work force and resource implications of a population screening programme are enormous. Resource availability will influence whether the level of benefit seen in the RCTs can be achieved in New Zealand and has to be considered for each step of the 'screening pathway'. This is reviewed in Chapter 11 (pages 82-93).

The involvement of general practitioners is critical to the success of cancer screening through all phases of a programme, including recruitment, delivery of screening, assessment and management of results. Screening has a recognised impact on workload and practice organisation and experience with other cancer screening programmes in general practice could benefit the introduction of screening for CRC.

Colonoscopy resources

A major area of concern would be the resources required to expedite the number of colonoscopies generated by the screening programme. This concern relates not only to the number of colonoscopies initially generated by a positive FOBT, and the need to perform the procedure within three months of the positive test, but also to the incremental number generated by follow-up of polyps detected by colonoscopy in the course of investigating a positive FOBT. The positive predictive value of a FOBT for adenomas greater than 10 mm in the Nottingham trial for first-round screening was 33 percent (273/837) and 32 percent in the Funen trial. The majority of adenomas greater than 10 mm are likely to require follow-up colonoscopic surveillance. The percentage requiring polyp follow-up would be greater if it is not generally accepted that those people with a single simple tubular adenoma less than 10 mm are not at increased risk for developing CRC in the age group being screened, if there is no family history of CRC.[65, 66, 67]

In order to begin to address the impact of population screening for CRC by FOBT on the colonoscopic resources of New Zealand, two steps were taken:

1 An informal survey of the number of colonoscopies performed annually in each of the four main centres, in both the public and private systems, was carried out. These numbers are listed in Table 6.6 below.
2 An estimate of the number of colonoscopies that would be generated by the first and subsequent screening rounds for (a) the New Zealand population and (b) the Auckland population aged from 50 to 75 years over eight years, if the Nottingham protocol were followed. The calculations and figures are outlined in Tables 6.7 and 6.8 (pages 47 and 48).

Table 6.6 Number of colonoscopies performed in New Zealand's four main urban centres, 1996/97

Centre	Public	Private	Total
Auckland	2,474	3,420	5,894
Wellington	840	1,440	2,280
Christchurch	800	1,499	2,299
Dunedin	712	n/a	712
Total	**4,826**	**6,359**	**11,185**

Sources: Based on figures supplied to the Working Party by all public and private facilities performing colonoscopies in the four main centres.

National data on the total number of colonoscopies performed in New Zealand in the public and/or private sector is not available (the 3,053 colonoscopies purchased by the Health Funding Authority in 1996/97 clearly being exceeded in the public sector). In the four main centres, approximately 11,500 colonoscopies are performed each year: 5,000 being in the public sector and 6,500 in the private sector. Data from the 1996 Census reveals that 51.3 percent of New Zealanders of all ages are usually resident outside the four main urban centres.[68] The total number of colonoscopies being performed in New Zealand could therefore be estimated by doubling the total number of colonoscopies being performed in the four main centres. These numbers may be overestimates because, although colonoscopy is performed outside the main centres, these centres tend to serve populations in adjacent areas.

Estimated number of colonoscopies performed in New Zealand annually

- performed in the public sector 10,000
- performed in the private sector 13,000
- total performed in both sectors 23,000

Table 6.7 Screening with FOBT: annual colonoscopy predictions for New Zealand, estimated mean procedures per year

Model		54% coverage of eligible population*			60% coverage of eligible population†		
	years	*diagnostic*	*surveillance*	*total*	*diagnostic*	*surveillance*	*total*
I	1-2	4,045	-	4,045	4,495	-	4,495
	3-8	1,820	1,396	3,217	2,022	1,552	3,574
II	1-2	4,045	-	4,045	4,495	-	4,495
	3-8	1,963	1,426	3,389	2,181	1,585	3,766
III	1-2	4,045	-	4,045	4,495	-	4,495
	3-8	1,960	1,418	3,377	2,177	1,575	3,753

* *This assumes 90 percent of the eligible population are invited for screening (identified using GP age-sex registers) and that of those invited 60 percent participate in screening, resulting in 54 percent coverage (60% of 90%).*

† *This assumes all the eligible population are invited for screening and 60 percent participate, resulting in 60 percent coverage.*

I *Model assumes a constant rate of drop-out to rescreen, calibrated to the Nottingham RCT colonoscopy rate (4.6 per 1,000 accepting screening).*

II *Model assumes a constant proportion of the population fails to return for rescreening at each round.*

III *Model incorporates the drop-off rates for breast cancer screening in Edinburgh (Roberts MM, Alexander FE, Anderson TJ,* et al. *Edinburgh trial of screening for breast cancer: mortality at seven years.* Lancet *1990; 335: 241-6).*

The limitations of the figures in Table 6.7 are stated. It was assumed that all people identified as having an adenoma greater than 10 mm in size as a result of colonoscopic follow-up of a positive FOBT would have two further follow-up colonoscopies over a subsequent eight-year period. This presumes complete polyp removal at the initial colonoscopy, no adenomas at repeat colonoscopy in three years, and a subsequent colonoscopy five years later. This surveillance regime is in line with the polyp guideline produced by the Practice Parameters Committee of the American College of Gastroenterology in 1993.[69] No colonoscopic follow-up was presumed for tubular adenomas less than 10 mm. These assumptions provide a conservative estimate of the actual numbers of colonoscopies that would result from adenoma surveillance.

As Table 6.7 shows, nationally, assuming 54 percent of the eligible population participate, the number of additional colonoscopies that would be generated is around 4,000 annually for the first two years (see Table 2, page 10) and 3,300 per year subsequently. Although the numbers of colonoscopies generated at rescreening decrease in years three to eight (positivity of FOBT falls from 2.1% to 1.2% at rescreen), the number of polyp surveillance colonoscopies increase over this time.

% annual increase resulting from 4,000 additional colonoscopies in New Zealand

- if performed within the public sector 40%
- if performed within the private sector 30%
- if performed within both sectors 17%

% annual increase resulting from 3,300 additional colonoscopies in New Zealand

- if performed within the public sector 33%
- if performed within the private sector 25%
- if performed within both sectors 14%

This estimated 33 to 40 percent increase in the total number of colonoscopies being performed in the public sector would not be feasible at present, particularly since a number of public hospitals are already struggling to meet the colonoscopic demands of symptomatic patients (see Chapter 6.2, pages 53-4). This estimated percentage increase in colonoscopies performed per year in the public sector is likely to be conservative because, as already stated, the number of colonoscopies performed nationally may have been overestimated. In addition, if 100 percent of the eligible population were able to be invited, and thus 60 percent rather than 54 percent participated, the number of colonoscopies generated per year would be higher still: 4,500 for the first two years and 3,700 for years three to eight.

Table 6.8 Screening with FOBT: annual colonoscopy predictions for Auckland, estimated mean procedures per year

Model		54% coverage of eligible population*			60% coverage of eligible population†		
	years	*diagnostic*	*surveillance*	*total*	*diagnostic*	*surveillance*	*total*
I	1-2	1,113	-	1,113	1,236	-	1,236
	3-8	501	384	885	556	427	983
II	1-2	1,113	-	1,113	1,236	-	1,236
	3-8	540	392	932	600	436	1,036
III	1-2	1,113	-	1,113	1,236	-	1,236
	3-8	539	390	929	599	433	1,032

* *This assumes 90 percent of the eligible population are invited for screening (identified using GP age-sex registers) and that of those invited 60 percent participate in screening, resulting in 54 percent coverage (60% of 90%).*

† *This assumes all the eligible population are invited for screening and 60 percent participate, resulting in 60 percent coverage.*

I Model assumes a constant rate of drop-out to rescreen, calibrated to the Nottingham RCT colonoscopy rate (4.6 per 1,000 accepting screening).

II Model assumes a constant proportion of the population fails to return for rescreening at each round.

III Model incorporates the drop-off rates for breast cancer screening in Edinburgh (Roberts et al, *1990).*

Auckland has approximately 200,000 people aged between 50 and 74 years,[68] and the numbers of colonoscopies performed there are more accurately known (in 1996/97, 2,474 in the public sector and 3,420 in the private sector, totalling 5,894 procedures). If the numbers of colonoscopies generated by a FOBT screening programme are adjusted accordingly, assuming 54 percent of the eligible population participate, then 1,100 extra colonoscopies would be generated each year for the first two years, and subsequently approximately 900 additional procedures per year.

% annual increase resulting from 1,100 additional colonoscopies in Auckland

- if performed within the public sector 44%
- if performed within the private sector 32%
- if performed within both sectors 19%

% annual increase resulting from 900 additional colonoscopies in Auckland

- if performed within the public sector 36%
- if performed within the private sector 26%
- if performed within both sectors 15%

There are around 20 colonoscopists in Auckland – the 1,100 additional procedures would represent 52 additional colonoscopies, or nine to 13 additional colonoscopy lists, per colonoscopist per year. The 900 additional procedures would represent 45 additional colonoscopies, or seven to 11 colonoscopy lists, per colonoscopist per year. However, in practice, the colonoscopy load would not be evenly distributed among colonoscopists.

These figures are in line with the estimated increases for a national programme and, if confined to the public sector, could not be resourced currently.

The Minnesota trial, with annual FOBT using rehydrated slides, reported a 38 percent colonoscopy rate (compared with 4.3% in Funen and 4.0% in Nottingham). It is clear that this colonoscopy rate would not be feasible in New Zealand.

At the outset of any screening programme, resources are likely to be inadequate (eg, mammography and follow-up assessment services for breast cancer screening). The likely benefit of a screening programme has to be weighed against the risks of the programme and whether screening could be implemented without reducing access to critical diagnostic services, such as colonoscopy and large bowel radiology, for people with gastrointestinal symptoms. Provision of adequate colonoscopic resources for a population screening programme for CRC using FOBTs, according to the

Nottingham protocol, would significantly impact on current resource provision. Colonoscopy is a highly technical procedure performed by specialists. Trainee colonoscopists are required to perform at least 75 to 100 procedures under appropriate supervision. The supervision of an increased number of trainee colonoscopists would initially reduce the current capacity for colonoscopy.

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6.2 Flexible sigmoidoscopy as first-line screening

- In the absence of RCT evidence for reduction in mortality through CRC screening, a national programme based on flexible sigmoidoscopy screening would not be justified. However, this conclusion should be reviewed once the results of the two RCTs in progress are known.
- Flexible sigmoidoscopy is a potential screening tool, but many issues about its use are not resolved; for example, the age at which screening should be offered, and rational algorithms for the follow-up of screen-positive and screen-negative subjects are not agreed.
- Participation rates in flexible sigmoidoscopy screening, and its efficacy and cost-effectiveness in average-risk populations, have not been assessed sufficiently.
- In addition, currently there are inadequate endoscopic services within the public health system to deal with symptomatic lower gastrointestinal disease in New Zealand.

The concept of reducing mortality from CRC by endoscopic screening of the asymptomatic general population was first proposed in the 1960s and 1970s. All the early studies used rigid sigmoidoscopy, which can only examine to a maximum of 25 cm from the anal verge. Large descriptive follow-up studies[1, 2] and retrospective case control studies[3, 4, 5] were performed and indicated reductions in CRC incidence and mortality in the screened groups; these protective effects could last for five to 10 years after screening. Some of the early studies were criticised for faulty design, but the underlying concept remains intact.[6]

Is flexible sigmoidoscopy a suitable screening test?

With the development of medical fibre optics, flexible sigmoidoscopy (FS) superseded rigid sigmoidoscopy as a CRC screening tool. FS allows visualisation of the rectum and the left side of the colon to a maximum of 60 cm from the anal verge, and it permits biopsy and fulguration of colorectal lesions if bowel preparation has been adequate. FS can be used as a single screening test for 'one-time' or repeated screening. Alternatively, it can be used in combination with other screening modalities such as FOBT.[7, 8]

Is there any evidence of benefit for population screening with FS?

Efficacy

One RCT, the Norwegian Telemark Polyp Study, showed a reduction in CRC mortality at 10 years in the group screened by FS.[9] Because this was a small study and the screened and control groups were not strictly comparable, conclusions about the efficacy of FS as a screening test must await the outcomes of the large RCTs currently underway in Britain[10] and the USA[11]; these results will not be available for a number of years.

Any reduction of mortality from CRC by screening with FS must be largely achieved by: detection of CRC at an early stage when treatment will have a significant effect, and by prevention of CRC by removal of premalignant polyps.

Detection of early CRC

There are few data on the distribution of asymptomatic CRC. The proportion of such CRC within the reach of the FS can therefore only be estimated at between 50 and 60 percent of the total.[10] In practice, it is likely that the proportion will be smaller, as complete endoscopic examination to the splenic flexure will not be achieved in all subjects. It is expected, however, that many of these CRCs will be at an early stage and therefore will respond well to treatment.

Although FS cannot detect cancers proximal to the splenic flexure, 23 percent of patients with such lesions also have adenomas or synchronous cancers in the left side of the colon.[12] Therefore, if all subjects with adenomas detected by FS screening were offered a full colonic evaluation (usually by colonoscopy, but conceivably by double-contrast barium enema), it is estimated that up to 70 percent of all asymptomatic CRCs could be detected.[6]

Prevention of CRC by polypectomy

It is generally agreed that adenomas greater than 10 mm and those with villous histology or severe dysplasia are likely to progress to cancer. Furthermore, there is evidence that removal of these adenomas may reduce the subsequent risk of malignant change.[13, 14] FS screening detects adenomas in 10 to 15 percent of subjects, which represents about half the detection rate of colonoscopy screening.[6]

Screening algorithms

There are no generally agreed algorithms for the management of subjects with and without polyps detected on FS screening. Three main factors complicate the construction of such algorithms: the complete colon is not examined; colorectal adenomas are common in persons over 50 years but only a small proportion become malignant; and new polyps continue to form even after a negative screen.

Missed polyps because of incomplete colonic examination

The prevalence of proximal, undetected adenomas is reported as follows:

- when no distal polyps found – between 3.4 and 28 percent
- when distal hyperplastic polyp(s) found – between 14 and 32.5 percent
- when distal adenomatous polyp(s) found – between 29 and 51 percent.[6]

Because so many proximal polyps are missed on FS screening, some authorities have recommended a full colonic evaluation in all subjects with distal adenomas.

Predicting the malignant potential for colorectal adenomas

Although it is not possible to accurately assess the malignant potential of an individual polyp, three factors have been shown to have predictive value: polyp histology, size, and number.

Hyperplastic polyps are thought to have little or no malignant potential. Unfortunately, they cannot be reliably distinguished from neoplastic polyps on their endoscopic appearances alone.[15] Furthermore, they are frequently associated with the presence of proximal adenomas (see above). Therefore, it is not agreed whether all subjects with distal polyps detected by FS screening should go on to have a full colonic evaluation or whether only those with biopsy-proven adenomas should be so managed.

Small (<10mm) single, distal tubular adenomas are associated with advanced pathology (ie, adenomas >10mm, villous adenomas, high-grade dysplasia, or cancer) throughout the colon and rectum in only 3 percent of cases.[16] Furthermore, patients with such polyps appear to have a subsequent, long-term risk of CRC which is no greater than the average.[17] For these reasons, some authorities do not recommend full colonic evaluation for persons with polyps less than 10 mm. However, because data from the National Polyp Study indicate that removing all adenomas could reduce the subsequent rate of CRC,[14] a full colonic evaluation for subjects with only small, single distal adenomas is recommended by others.

Where there are large adenomas (>10mm), multiple adenomas, villous adenomas, or cancer, the frequency of advanced pathology elsewhere in the colon is much higher (8-18%[16]). Not only do patients with distal adenomas greater than 10 mm and villous adenomas have an increased risk of CRC, excess risk persists for years after such lesions have been removed.[18] It is therefore generally agreed that all subjects with such lesions detected on FS screening should go on to have a full colonic evaluation.

Current studies are attempting to improve the definition of risk factors for advanced neoplasia.[6] In this way, more rational algorithms for the management of subjects with distal polyps on FS screening can be constructed.

Follow-up after negative FS screening

With a well-run FS screening programme, the frequency of missing significant lesions should be low. The reason for repeated FS as part of the screening programme would therefore be to identify new lesions. After a negative FS, the rate of polyp formation is low (6% of subjects at a mean of 3.4 years) and the types of polyp found are not associated with a high risk of CRC.[19] Therefore, if the negative screening group were to be offered a second FS screening, an interval of five to 10 years between the two procedures would be appropriate.

What age group should be screened and at what intervals?

There are no conclusive data on the optimum age or frequency of CRC screening by FS in an average-risk population. Most authorities favour either a 'one-time' examination at around age 60 years or offer screening to everyone in the age-range of 55 to 64 years.[20] Others suggest screening every five to 10 years from age 55 to 70 years.[21] The British study is currently addressing questions on age and frequency of screening, and answers should be available in 1999.[20]

Are the anticipated risks acceptable?

FS is an invasive procedure that carries the risks of colorectal perforation and bleeding.[22] The frequency of these complications are variously reported. For example, a postal survey of consultant members of the British Society of Gastroenterology gave frequencies of 0.06 per 1,000 procedures for both complications.[23] Other reports suggest perforation rates of 0.02 percent for diagnostic procedures and slightly higher rates where polypectomy is performed.[24] It is anticipated that, where polypectomy and fulguration are not performed at the initial screening procedure, such complication rates would be small in a screening programme. Unlike with colonoscopy, sedatives and analgesics are not usually administered to people having FS.

As with the use of all clinical endoscopes, there is a risk of transfer of infection between subjects, if cleaning and disinfection procedures are inadequate.[25]

Could New Zealand achieve the expected benefits?

Participation

FS screening is described as an office procedure. It requires less bowel preparation than colonoscopy but may not be more acceptable. Discomfort, bloating, pain, and embarrassment are frequently reported.[26, 27] One study suggested that colonoscopy was preferred to FS because sedatives were used with the former but not the latter.[28] In two other studies, only 1 to 1.4 percent of subjects indicated that they would refuse to have a repeat FS should it be requested.[26, 29]

A number of recent studies on participation rates with screening FS programmes have produced variable results:

- an academic general internal medicine practice (USA) – 75%[26]
- general practices (Melbourne) – 49%[27]
- a hospital-based study (Dunedin) – about 65%[28]
- general practice-based feasibility and pilot studies (Britain) – 47% & 44%[30]

In a recent single general practice-based randomised study in Britain, participation was highest in a group screened by FS (46.6%) compared with a group screened by FOBT (31.6%) and another group screened by both FOBT and FS (30.1%).[8] FS detected polyps in 19.3 percent of cases, but only 6.8 percent had adenomas and 2.4 percent had 'high-risk' adenomas. FOBT was positive in 0.8 percent, but in the group screened by both modalities FS detected more cases with CRC and adenomas than FOBT.

A community-based pilot study from Western Australia had a participation rate of only 12 percent.[29] This result may reflect the degree of participation that could be expected in New Zealand. The Australian study identified some of the reasons for non-participation. Should a similar screening FS programme proceed here, participation problems ought to be addressed in the programme design, and a campaign of public education should precede its introduction.

Resources

FS and colonoscopy utilise some of the same equipment but, overall, FS requires less resources. It is a quicker procedure and the recovery time is shorter because sedation is not routinely given. Consequently, only minimal recovery facilities are needed. In addition, some claim that the procedure can be performed satisfactorily by specifically trained nurses[31] or GPs[29]. To investigate these claims, more data are needed on the effect of endoscopic expertise on screening sensitivity, specificity and costs. A hospital-based screening programme in Dunedin estimated that screening by FS cost 60 percent less than by colonoscopy; this cost advantage was reduced to 20 percent per subject, however, when follow-up colonoscopies were included.[28]

Currently, New Zealand does not have all the resources needed to introduce a large-scale FS screening programme for the middle-aged, average-risk population; indeed, present endoscopic services to deal with symptomatic lower gastrointestinal disease are inadequate. (For example, in June 1998, waiting times in Christchurch public hospital for

colonoscopies for patients with lower gastrointestinal symptoms were up to eight weeks for urgent cases, and up to nine months for semi-urgent cases; non-urgent cases were not being done at all. At Middlemore Hospital, in June 1998, 482 patients were on the waiting list for out-patient colonoscopies; this is in the context of an annual demand for out-patient colonoscopies of 1,040 and an annual contract for 372 such procedures.)

Has screening been shown to be cost-effective in any population?

FS is only a part of any CRC screening programme. To improve sensitivity, it may be repeated or used in collaboration with FOBT. Also, many of the lesions detected by FS will necessitate further evaluation and treatment, usually by colonoscopy and polypectomy. Clearly, various combinations are possible, leading to a number of different screening programmes.

To date, there is no published evidence from RCTs on the effectiveness of screening by FS. Therefore, there is no firm information on cost-effectiveness. Models have been used to compare the efficacy and cost-effectiveness of some of the different screening programme options. One model addressed the screening of asymptomatic subjects from age 55 to 65 years.[32] The following test frequencies were modelled over the 10-year screening period: FOBT annually, FS twice in 10 years, and colonoscopy once. All positive tests were evaluated by colonoscopy. The model predicted that screening colonoscopy was the most effective option in preventing CRC and CRC-related deaths.

Table 6.9 Efficacy of CRC screening programmes: 100% compliance over 10-year screening period

Screening test	% of CRC prevented	% of deaths prevented
FOBT alone, annual	22.5	47.0
FS alone, 5 yearly	37.5	52.5
FOBT plus FS	50.0	66.0
Colonoscopy once	70.0	80.0

Source: Lieberman, 1995.[6]

Key variables that affected cost-effectiveness were identified. For screening with either FS or colonoscopy these included: participation, procedure costs, complications, and the frequency of surveillance after polyp detection.

Other mathematical models have indicated that CRC screening by FS could be cost-effective when compared with accepted management approaches to other common disorders. Colonoscopy screening would only be cost-effective in comparison with other screening options if its frequency were low.[33, 34] These models have limitations, which are discussed in Chapter 11 (pages 82-93).

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6.3 Colonoscopy as first-line screening

- In the absence of RCT evidence for reduction in mortality through CRC screening, a national programme based on primary colonoscopic screening would not be justified.
- There are concerns regarding safety, levels of participation and availability of resources for primary colonoscopic screening of average-risk individuals in New Zealand.
- Currently, primary colonoscopic screening is the screening option that offers the greatest potential for prevention, in addition to early detection, of CRC.

Is colonoscopy a suitable screening test?

Sensitivity

Sensitivity of colonoscopy for detection of all neoplasms (polyps and cancers) has been reported to be as high as 95 percent.[1] However, it is not always possible to visualise the caecum; and missed cancers are usually caused by failure to reach the right colon, failure to recognise this and failure to arrange a back-up double-contrast barium enema examination to complete visualisation of this region. Some lesions, such as 'flat' adenomas and carcinomas, may be missed unless other procedures (including dye-spraying techniques) are utilised.[2, 3] Cancers appearing within three years of a colonoscopy may be 'missed' early cancers at the time of the colonoscopy.[4] The sensitivity of colonoscopy, as with other modalities, is also operator dependent.

Missed pathology

Tandem colonoscopy studies have shown that it is very unusual to miss significant pathology (cancers and large polyps). Less than 5 percent of polyps over 10 mm and up to 25 percent of polyps under 10 mm may be missed.[5, 6] However, small polyps are not thought to impose a significant risk since studies have shown that growth of adenomas under 5 mm is slow and many polyps under 10 mm in size actually stop growing or regress.[7]

Collateral evidence from FS screening

It is reasonable to assume that case control studies[8, 9, 10] showing a protective effect of FS screening (60-85% reduction in rectal or distal colon cancers) can be extrapolated to full colonoscopy. If FS screening is effective for the region examined, then complete colonoscopy should be equally as effective for the entire colon. However, FS screening studies have been criticised on the basis of bias[11] and RCTs of population screening by FS are only now taking place.

The Norwegian Telemark Polyp Study began with 799 men and women aged 50 to 59; those with polyps on FS were followed up with colonoscopy which was repeated at two and six years. None of the subjects who attended for follow-up had CRC within 10 years compared with four in the unscreened group.[12] The poor yield of polyps at follow-up in this study and the slow growth of *in situ* polyps supports the view that infrequent or no colonoscopic follow-up is required after the first colonoscopy in individuals at average risk of CRC. The recent 13-year follow-up data does not substantially change this conclusion.[13] To some extent, this finding is in conflict with the finding of substantial numbers of polyps at follow-up colonoscopy in the Funen FOBT RCT[14] and the National Polyp Study[15]. Many of these polyps were thought to represent recurrences of previously identified but incompletely removed polyps and the new polyp rate was estimated at 3.2 percent over four years.

The National Polyp Study claimed a 76 to 90 percent reduction in CRC after colonoscopy and polypectomy.[15] However, the comparison was with historical controls and definitive proof that polypectomy leads to a reduction in incidence of CRC is lacking.

Efficacy of colonoscopy as a primary screening test

There have been no RCTs of primary colonoscopic screening for CRC detection and prevention. However, there is indirect evidence supporting the use of primary colonoscopic screening since trials of screening with FOBTs have mainly used colonoscopy to follow up positive results; therefore, any benefit gained may be indirectly attributable to the use of colonoscopy.

Efficacy of colonoscopy within other screening programmes

Colonoscopy is an integral component of the RCTs of FOBT screening discussed on pages 31-50. The three major trials have shown significant reductions in CRC-related mortality, and it has been suggested that the success of these programmes (particularly the Minnesota study) is largely related to the increased use of colonoscopy in participants, regardless of the FOBT.[16] Others have argued this is not the case and that only 25 percent of the effect can be attributed to colonoscopy *per se*.[17] If FOBT plus colonoscopy can reduce CRC mortality by 30 percent,[18] first-line colonoscopy could achieve the same outcome or better, as long as participation levels were adequate.

Among available screening modalities, colonoscopy has the highest sensitivity and specificity for detection of existing CRCs. In addition, through adenoma detection and removal, it has potential for cancer prevention. FOBTs fail to detect up to half of existing cancers and will detect only the minority of adenomas. FS, although cheaper than full colonoscopy, will miss approximately 30 percent of cancers and polyps which are proximal to the extent of examination. Moreover, patient tolerance of FS is no better then tolerance of standard colonoscopy.[19]

Three studies of screening colonoscopy in asymptomatic individuals have shown that between 29 and 51 percent of those with adenomatous polyps had no marker polyps within the distal 60 cm, within reach of the flexible sigmoidoscope.[20, 21, 22] Tandem FS and colonoscopy showed that the incidence of significant proximal neoplasia can be the same in those with and without distal marker polyps.[20, 23] In one study only 23 percent of patients with proximal CRC had distal adenomas within reach of FS.[24] Anything less than full examination of the bowel will result in a significant number of missed lesions, even with strategies such as combining FS and FOBT or undertaking full colonoscopy when distal neoplasms are found on FS.

What age group should be screened and at what intervals?

The timing of an initial screening colonoscopy and the intervals between colonoscopy screenings in asymptomatic individuals is still a matter of debate. Most agree that screening should begin five to 10 years before the incidence of CRC begins to rise. Because, in the average-risk population the incidence rises sharply in the sixth decade, screening should begin in the fifth decade, especially if the adenoma-carcinoma sequence is going to be interrupted at an early stage (see Chapter 4, pages 22-6). In the absence of lesions a 10-year interval is probably safe, based on pathological studies of adenoma formation and transformation.[25] This is supported by a low yield of only 0.75 percent for polyps greater than 10 mm in such patients undergoing repeat colonoscopy after five years.[26] The interval between colonoscopies in those with polyps at initial screen (now called surveillance rather than screening), depends on the number and size of adenomas and age of the patient.[27, 28]

The 'once-in-a-lifetime' option

The option of a once-only colonoscopy has been suggested; however, there is insufficient data on colonoscopy follow-up beyond five years in patients with an initially 'clear' colon. In terms of cost, the once-only option would compare favourably with other strategies, but its effectiveness is unknown.

Are the anticipated risks acceptable?

Safety

Analysis of reported complication rates for colonoscopy show perforation rates of 0.17 percent (0.06-0.57), haemorrhage rates of 0.03 percent (0-0.11) and mortality rates of 0.02 percent (0-0.15). These figures relate mainly to colonoscopy in symptomatic patients, rather than colonoscopy done in the context of a screening programme,[29] and were reported when colonoscopy was in its infancy. Colonoscopy complications are discussed in detail in Chapter 6.1 (pages 43-5).

Complications can reasonably be expected to be lower when interventions such as polypectomy are not performed. Conversely, the greatest risks would be incurred by those most likely to benefit - that is, those with polyps.[30] Polypectomy rates could be as high as 20 percent, depending on the average age of participants. Risks of colonoscopy with and without interventions such as polypectomy would need to be carefully evaluated to fully inform decision making.

An important aspect of safety is related to the skill and experience of the colonoscopist. Both bleeding and perforation are more common early in the colonoscopist's experience.[31] This is important in the New Zealand context, because currently there are insufficient experts available to undertake additional procedures arising from population screening. A potential advantage of sigmoidoscopy over colonoscopy is that FS can be learned more quickly and complication rates are lower. No direct evidence for mortality has been reported. As a single procedure, it is safer than colonoscopy;

however, if all patients with identified polyps or cancers were then subjected to colonoscopy the margin of safety may be diminished.

The safety of primary colonoscopic screening is a major consideration, even if the risk is relatively small, because healthy individuals are sought out and exposed to risks that they would otherwise not be exposed to.

Could New Zealand achieve the expected benefits?

Participation

Even though the efficacy of colonoscopic screening is likely to be high, it can only be effective if the participation rate is also adequate. In a model for comparing several colon screening programmes, Lieberman determined that to achieve a 25 percent reduction in mortality the compliance with one-time colonoscopy screening would need to be 30 percent.[32] Compliance with primary colonoscopic screening may be expected to be low, because it is an invasive procedure associated with some degrees of discomfort, embarrassment, and risk.

In a New Zealand study,[19] acceptance of an offer of either colonoscopy or FS in over 200 patients was about 65 percent; however, more than half those offered the screening had a family history of CRC. Acceptance in other reports has varied from 29 percent[33] to 75 percent[34]. The lowest, and most quoted, figure is 6 percent of physicians, dentists and their spouses in Indiana University Medical Centre;[35] however, these individuals knew they had negative FOBTs, which may have influenced their choice.

What is clear from studies of participation is that the method of approach to prospective participants is crucial to the level of participation achieved. Leard has recently reported that colonoscopy is the preferred screening procedure in 50- to 75-year-old average-risk patients presented with background information about all the available screening options.[36] Of those who had not had colonoscopy before 38 percent preferred this option, whereas of those who had had a previous colonoscopy 72 percent preferred this option.

There is very limited information on the acceptability of colonoscopic screening in the New Zealand context,[19] and this would need to be determined more fully before colonoscopic screening could be considered.

Resources

Simple calculations suggest that to offer colonoscopies to all 55-year-olds would generate a substantial workload. At a 50 percent participation rate, 37,500 invitations per year would generate 18,750 procedures per year. To this workload must be added the procedures necessary for surveillance colonoscopy in those found to have significant adenomatous polyps; assuming a 20 percent adenoma yield, this would add up to 3,750 new patients per year, who would probably require two surveillance colonoscopies during a 10-year period (an estimated additional 750 colonoscopies annually). Therefore, the total number of colonoscopies per year would be over 20,000.

Based on an informal survey of the four main urban centres, it is estimated that at present the total number of colonoscopies done in New Zealand per year is around 23,000 (page 46). A once-only colonoscopy screening programme would require double the present resources. Estimates from the USA and Britain suggest that each of the practising gastroenterologists would need to perform 300 to 1,000 extra colonoscopies per year in a once-only colonoscopy screening programme at age 60 years.[37] Currently, there are around 50 colonoscopists in New Zealand, so this would mean that on average each would need to do at least another 400 to 600 procedures per annum. Assuming that six colonoscopies in a single session is a maximum workload, then 70 to 100 new sessions per year would be necessary. This also equates to a doubling of the current colonoscopy workload. Some have argued this is relatively easily achieved;[37] others would not agree.[38]

The resource implications for Auckland of one-off colonoscopy at varying levels of compliance are outlined in Table 6.10 opposite. A 30 percent participation rate spread over five years would increase the total number of colonoscopies being performed in Auckland by as much as half again – if confined either to the public or private system the colonoscopy workload would, as predicted, double. This predicted workload increase is conservative because approximately 20 percent of those examined will have adenomas requiring a further colonoscopic follow-up within the next five-year period.

Table 6.10 One-off colonoscopy screening: resource implications for Auckland

Screening Participation rate* %	Additional procedures per year	Current number†	Annual total number
10	900	5,894	6,794
20	1,800	5,894	7,694
30	2,700	5,894	8,594
50	4,500	5,894	10,394

* *Auckland population aged 55-59 = 45,000 (Statistics New Zealand.1996* Census. *Wellington: Statistics New Zealand, 1996).*

† *In public and private sectors.*

Has primary colonoscopic screening been shown to be cost-effective in any population?

The short answer is no. However, the perceived advantages in sensitivity and specificity of colonoscopic screening over other methods has led some to propose that on cost-efficacy grounds it might be a first-choice procedure for CRC screening. To date, there is no published evidence from RCTs on the effectiveness of screening by colonoscopy. Therefore there is no firm information on cost-effectiveness. In a model of CRC screening, 'once-in-a-lifetime' colonoscopy had the greatest impact on mortality from CRC.[7] Theoretical cost-benefit analysis also shows that primary colonoscopic screening, because of its high sensitivity and specificity, could under certain conditions be competitive with other cancer and CRC screening programmes in the United States.[32,39] These models have limitations and these are discussed in Chapter 11 (pages 82-93).

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6.4 Double-contrast barium enema as first-line screening

- In the absence of RCT evidence for reduction in mortality through CRC screening, a national programme based on double-contrast barium enema screening would not be justified.
- There is indirect evidence to suggest that double-contrast barium enema may be effective as a primary screening test, and that it may have some potential advantages over other methods.
- Potential advantages include examination of the entire large bowel (cf FS), safety (cf colonoscopy), cost (cf colonoscopy), and ability to detect polyps as well as cancers (cf FOBT).
- These potential advantages may be offset by a number of disadvantages, including lower sensitivity (cf colonoscopy), requirement for follow-up colonoscopy to investigate or treat abnormalities on DCBE, and limited acceptability.

Is double-contrast barium enema a suitable screening test?

Sensitivity

Double-contrast barium enema (DCBE) has become the standard technique for investigating the bowel in most centres because of higher detection rates for small lesions, better visualisation of the rectum, and less dependence on fluoroscopic expertise for lesion detection than with the single-contrast technique.[1] There are no data available on the sensitivity or specificity of DCBE for polyp and cancer detection in the setting of average-risk population screening. One of the RCTs of FOBT used DCBE combined with FS to follow up positive FOBTs.[2] Two percent of carcinomas were overlooked in subjects with a positive FOBT.[3]

Nearly all studies in which the sensitivity of DCBE has been measured have involved symptomatic patients. The American Office of Technology Assessment (OTA) critically analysed 22 such studies.[4] The overall sensitivity for polyp and cancer detection was calculated to be in the range of 85 to 95 percent; however, most studies suffered serious biases, and a more conservative estimate of 70 percent (range 60-80%) sensitivity was estimated on the basis of a small number of prospective studies.[5, 6, 7] Since that report, Rex retrospectively compared the sensitivity of DCBE and colonoscopy in 2,193 patients with CRC.[8] Colonoscopy performed by a gastroenterologist had the highest sensitivity (97.3%) followed by non-gastroenterologist colonoscopy (87%) and DCBE (85.2%). However, there are fundamental difficulties in interpreting such studies.[9] DCBE does have some advantages over colonoscopy in being able to detect more right-sided lesions if the caecum cannot be reached by the endoscopist,[10] and may occasionally detect other lesions missed on colonoscopy.[11]

As with colonoscopy, the sensitivity of DCBE for polyp detection varies in accordance with polyp size.[12] Although the vast majority of missed polyps are under 10 mm, and therefore not associated with an appreciable cancer risk, 30 percent or more of polyps over 10 mm may also be missed on DCBE.[5, 6, 7] The sensitivity of DCBE for detection of significant polyps is therefore better than FOBT but not as good as colonoscopy.

Can the sensitivity of DCBE be improved?

The sigmoid colon presents the greatest difficulty in polyp detection,[13, 14] which has led to the suggestion that DCBE should be combined with FS to improve sensitivity. In a randomised study, the sensitivity of combined DCBE and FS was found to be similar to colonoscopy alone.[15] There is evidence that the sensitivity of DCBE can be improved by double reading of films. A study by English radiologists looked at DCBEs performed on 557 patients with CRC in a range of teaching and non-teaching hospitals.[16] Eighty-five percent of carcinomas were reported, which is consistent with the sensitivity reported elsewhere.[7] However, on reviewing the films, 97 percent of the lesions were visible. A Canadian study also showed that the most frequent cause of error was failure to observe the abnormality.[17] A study in New Zealand showed that 76 percent of unreported lesions subsequently detected by colonoscopy were visible on DCBE with the benefit of hindsight.[18] The missed lesions ranged in size from 20 to 100 mm and errors were made by experienced as well as more junior staff. Double reading of films would probably reduce (but not eliminate) this source of error, but would also have significant resource implications.

Cost-effectiveness

Despite an estimate of 70 percent sensitivity for detection of neoplasms on DCBE, the American OTA study concluded that both DCBE and FS were each likely to be more cost-effective than other strategies for CRC screening.[4] This conclusion has also been reached by others using mathematical modelling.[19] From 1 January 1998, the US Medicare programme approved reimbursement for annual FOBT and a DCBE every four years for 'not-at-high-risk patients', with colonoscopy being reserved for the high-risk group only.[20] The American Cancer Society's most recent recommendation was for either FOBT and FS, or total colon examination by colonoscopy or DCBE, for average- and some moderate-risk patients.[21]

Nevertheless, there are no direct data to measure the cost-effectiveness of population screening by DCBE. Indirect evidence of effectiveness comes from the Göteborg trial, in which positive FOBTs were followed up with DCBE and FS. Final results are not due to be reported until 1999, but are expected to show around a 10 percent reduction in CRC mortality in the screened group. It is therefore reasonable to surmise that primary screening with DCBE and FS could achieve as good or better mortality reduction from CRC, depending on the participation rate achieved.

Although DCBE is a cheaper primary investigation than colonoscopy, the need for follow-up colonoscopy to investigate and treat abnormalities detected on DCBE is a major drawback. Post-mortem studies have revealed a prevalence of colorectal adenomas of 30 to 40 percent over the age of 60. In a DCBE screening programme, allowing for incomplete detection (70% sensitivity), about 20 percent of participants over age 60 would therefore be expected to have a lesion identified on DCBE. Even though the majority of these would be polyps under 10 mm, a significant number would require colonoscopy to confirm or remove detected abnormalities. Colonoscopy rates are a major determinant of the cost of screening (see Chapter 11, pages 82-93). In the Funen and Nottingham FOBT trials, colonoscopy rates were 4.3 and 4.0 percent respectively.[22, 23] These rates would be matched or exceeded by a DCBE-based screening programme if 25 percent or more of participants with abnormal findings on DCBE required colonoscopic follow-up.

What age group should be screened and at what intervals?

DCBE and colonoscopy are similar in this regard; they should be instituted to coincide with the age-dependent rise in incidence of polyps and cancers (see Chapter 3, pages 17-21). Screening should therefore begin in the fifth decade.

If no abnormality is detected on the initial screen, an interval of five to 10 years is recommended, based on yields reported for follow-up colonoscopy.[24] The reduced sensitivity of DCBE may be an argument in favour of a shorter screening interval of three to five years.[19]

Individuals with single small polyps under 10 mm would need repeat DCBE sooner, probably within three years. Those with large polyps greater than 10 mm, or multiple polyps of any size, would undergo colonoscopy and by definition no longer fit into the 'average-risk' category (see Chapter 12, pages 94-100).

Are the anticipated risks acceptable?

There are no data available on the safety of DCBE for screening asymptomatic individuals. A review of 283,500 patients undergoing DCBE revealed a perforation rate of one per 10,000 and a mortality rate of one per 50,000.[25] The risks associated with follow-up colonoscopy for abnormalities detected on DCBE need to be added to this (see chapter 6.1, pages 43-5).

Patients are exposed to about 300 mrem of radiation during a mammography compared with 300 to 500 mrem during a DCBE examination. A screening programme using DCBE at the age and frequency usually recommended would deliver a lifetime dose of radiation lower than that from mammography screening.[21]

Could New Zealand achieve the expected benefits?

Participation

There are no data available on the acceptability of DCBE as a screening test in New Zealand and limited data from elsewhere. It has been claimed that DCBE is less acceptable than colonoscopy, although this view is not universally supported.[6] Although the procedures have many similarities (both require bowel preparation, may be embarrassing, and can cause considerable discomfort), colonoscopy is usually done under sedation whereas DCBE is not.

Resources

There is evidently under-utilisation of equipment required for DCBE, perhaps created by the increasing use of endoscopy in recent years. However, population screening would require a requisite increase in radiologist and radiographer time, especially if double reading of films were adopted to improve sensitivity.

In addition, there would be a substantial increase in demand for colonoscopy to follow-up abnormalities on DCBE. The number of extra colonoscopies would depend on the level of participation and polyp detection rate, both of which are unknown.

Future prospects

Computed tomography (CT) and magnetic resonance imaging (MRI) have both been used to produce a computer-generated 3D view of the lining of the colon (termed 'virtual colonoscopy'). The results to date have been extremely promising and development work is proceeding rapidly in the United States. The cost is likely to be greater than DCBE but less than colonoscopy. It is anticipated that if the projected diagnostic goals are achieved, the underlying computer technology will be available to allow clinical utilisation in three to five years. The technique would be rapid, low risk and possibly better accepted by patients than the current diagnostic methods.[26, 27]

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7. PARTICIPATION IN CRC SCREENING

- The level of participation in CRC screening is a critical factor determining the effectiveness of population screening in reducing mortality from CRC.
- The acceptability of CRC screening tests to New Zealanders is largely unknown and would be a major determinant of participation.
- The levels of participation demonstrated in the RCTs of screening with FOBT may not be achievable in the general population of New Zealand in the absence of population listings or accurate general practitioner registers.
- To achieve similar levels of participation in New Zealand, a significant amount of programme resources would be required for recruitment strategies.

The extent to which screening impacts on mortality from CRC depends not only upon the sensitivity and specificity of the test but also on the number of individuals who participate in screening. A recent literature review on CRC screening participation cites the work of several authors who stress that high participation in CRC screening is needed to ensure effectiveness, both in health outcomes as well as in economic terms.[1]

Another factor impacting on the success of screening is how many individuals participate in future as well as initial screening rounds. Often the terms 'participation' and 'compliance' are used interchangeably, and this is the case at times in this report and in the literature. Strictly speaking, however, 'participation' means the number of individuals who take part in one or more screening rounds, and 'compliance' refers to those who, once having agreed to be screened, complete the screening protocol.

According to modelling by Lieberman,[2] for FOBT alone to be the most cost-effective CRC screening method, the proportion who complete (or 'comply' with) the screening protocol must be 80 percent to equal the mortality reduction achieved with one-time colonoscopy at 50 percent, or with annual FOBT plus periodic sigmoidoscopy at 60 percent.

Patterns of participation

Information regarding initial and subsequent screening rounds in the four RCTs for FOBT is shown in Table 7.1. As indicated, these trials vary in their methods of recruitment, follow-up procedures, participant characteristics, and range of participants. It is important to distinguish between the percentage of participants who completed at least one screen and those who completed all rounds of screening. In the Nottingham study, for example, 53 percent attended the first screening round and 38.2 percent completed all tests offered.[3] In the Funen study, these figures are 67 percent and 45.9 percent respectively.[4] In the Minnesota trial, all the screenings were completed by 46.2 percent and 59.7 percent of the groups screened annually and biennially respectively.[5]

The question arises as to the extent to which these participation and completion rates can be achieved in the general population, and sustained over time. Data from a range of studies on FOBT rescreening indicate that it will be difficult to achieve compliance in annual FOBT screening of more than 50 percent in the general population.[1]

Among the three FOBT trials fully reported, a volunteer population (Minnesota) yielded a higher participation rate than one derived from a general-practice register (Nottingham) or population register (Funen). Widely differing rates among Nottingham general practices could reflect differences in practice populations or differences in the practice characteristics (eg, GP and staff attitudes to screening). These results are likely to have implications for screening in New Zealand, if screening were to be general-practice based. It should also be noted that New Zealand has neither a population listing nor complete general-practice registers as used in the two population trials (Nottingham and Funen).

The rates by which participants with positive FOBTs undergo follow-up procedures are also an important factor, as an absence of follow-up can result in lack of treatment for cancer and therefore no benefit from screening. In the Minnesota and Funen studies, over 90 percent of those with abnormal results completed follow-up procedures (the

Table 7.1 Participation in four randomised controlled trials of CRC screening

Study	Study population	Recruitment techniques	Application of test	Follow-up method	Screening offered	Participation
Funen (Kronborg *et al*, 1987[4]).	Recruitment of inhabitants of the island of Funen, Denmark, from population register, aged 45-75.	Mailed invitations and FOBT kit.	Self administered with dietary restrictions.	Two reminder letters in round 1; one reminder in rounds 2-5. Only those completing round 1 invited for further screening.	Biennial screening in 5 rounds over 10 years.	67% completed round 1; 45.9% completed all 5 rounds.
Minnesota (Mandel *et al*, 1993[5]).	Volunteers from American Cancer Society and fraternal, veterans & employee groups in Minnesota state, USA, aged 50-80.	Mailed FOBT kit.	Self administered with dietary restrictions.	Reminder letter at 4 weeks and telephone call at 10 weeks. All eligible participants reinvited for further rounds regardless of whether screened.	Two groups: 1) annual, and 2) biennial screening in two phases for a total of 11 years.	*Annual screening group*: 90.2% completed round 1 ; 46.2% completed all rounds. *Biennial screening group:* 89.9% completed round 1; 59.7% completed all rounds.
Nottingham (Hardcastle *et al*, 1996[3]).	Recruitment of 50-74 year-olds from general practice registers in Nottingham area.	Mailed invitations and FOBT kit and explanatory letter from GP.	Self administered (no dietary restrictions).	Reminder letter at 4-6 weeks. Initially only those completing screening were reinvited; later, all eligible participants reinvited every two years.	Biennial screening; participants offered tests between 3 and 6 times over 14 years.	53% completed round 1; 38.2% completed all rounds. (Participation ranged from 29-74%, according to general practice screened.)
Göteborg (Lindholm *et al*, 1988[13]).	Recruitment of inhabitants of Göteborg from population registers, aged 60-64 in 1992.	Mailed invitation, questionnaire and FOBT kit.	Self administered; 50% with dietary restrictions, 50% with no restrictions.	Two reminder letters, the second containing another FOBT kit All eligible participants reinvited for further rounds.	Two screening rounds over 18-24 months.	42% completed round 1; 68% completed 1 or both rounds.

Nottingham study did not report levels of response to follow-up investigations). US research, cited by the AHTAC report,[6] found that having an abnormal FOBT result and exposure to first-round follow-up tests are significantly and negatively associated with repeat participation.[7] As the positive predictive value of FOBT is low, the implications of these findings are that the majority of those requiring follow-up procedures are unlikely to benefit and will be less inclined to participate in future.

At present, little is known in New Zealand about the current extent of CRC screening among asymptomatic individuals. A recent survey of a random sample of 252 GPs found wide variation in screening practices, which is not surprising in the absence of any guidelines for CRC screening in New Zealand. With regard to their advice for screening asymptomatic patients over 50, 24 percent of respondents recommended FOBT, 7 percent sigmoidoscopy and 5 percent colonoscopy.[8]

International research indicates that the response to recommendations for CRC screening is low, even with doctor recommendations and active recruitment procedures. Response to screening recommendations is higher for FOBT than for sigmoidoscopy. Low use of colorectal screening tests is partly due to low rates of doctor recommendations,[9] even in RCTs of intervention programmes in which doctors are instructed to recommend screening.[10] An analysis of a sample of trials from around the world in which more than 10,000 people were offered FOBT showed that the average participation was about 63 percent, ranging from 35 to 95 percent.[11] In general, utilisation rates are higher for first-degree relatives of CRC patients than for individuals with no family history of CRC (see Vernon[1] for a systematic review).

Factors affecting participation

A number of factors have been shown to influence participation in CRC screening.[1, 11] These are reviewed below.

Acceptability of the screening test

One of the main determinants of participation is the acceptability of the screening test.

FOBT

Of all the tests being considered at present, the FOBT is the least invasive and most acceptable. Nevertheless, it is not ideal, and simpler tests remain desirable. Some of the obvious barriers are: having to handle faecal material, distaste for the procedure and logistical difficulties (eg, obtaining and returning tests). In one British general-practice study, the unpleasantness of the procedure was often given as a reason for not returning mailed-out FOBTs.[12] It was also a reason for not participating in screening in the Göteborg trial.[13] Several other studies have found perceptions that the test is messy or inconvenient to be significantly associated with lower use of the FOBT.[9, 14] The number of days of stool testing is also likely to be a factor – for example, whether testing is done for one, three or six days.[15, 16]

Dietary restrictions, if called for, are also a factor likely to reduce participation.[17] These include avoiding red meat, certain vegetables and Vitamin C. One option, as in the Nottingham study, is to limit dietary restrictions to participants who have had a positive result and who then repeat the test.

One of the key problems with FOBTs is the inaccuracy of the test. Because FOBT screening has a low positive predictive value, the majority of individuals with a positive result will not have cancer, yet will require follow-up procedures. Research from the United States has found that having abnormal FOBT results and diagnostic tests during the first round of screening negatively impacts on future participation in screening.[7]

Flexible sigmoidoscopy

The participation rate with FS screening has been reported to vary from 12 to 75 percent (see Chapter 6.2, page 53). Issues likely to affect acceptability are embarrassment, discomfort and pain. One study found reactions of participants to these factors to be 27 percent, 42 percent and 31 percent.[18] Other studies have also identified pain perceptions and embarrassment to be associated with lower screening rates.[9, 10] In a New Zealand study the majority of subjects found colonoscopy more acceptable than FS, mainly because the former was done under sedation.[19] Authors of one Australian study, in which 12 percent agreed to participate, identified acceptability as a major issue if screening with FS were to be introduced.[20]

Colonoscopy

There is little literature on the acceptability of colonoscopy as a primary screening test. In a New Zealand study,[19] compliance with an offer of either colonoscopy or FS in over 200 patients was about 65 percent; however, more than

half those offered the screening had a family history of CRC. Participation in other reports has varied from 29 percent[21] to 75 percent[22]. The lowest, and most quoted, figure is 6 percent of physicians, dentists and their spouses in Indiana University Medical Centre;[23] however, these individuals knew they had negative FOBTs, which may have influenced their choice. Because of the high sensitivity of colonoscopy, ways to improve its acceptability should be investigated. However, it is unlikely that colonoscopy would be acceptable for use in screening the whole population.

Double-contrast barium enema

Little is known about the acceptability of DCBE as a screening test. Some evidence from an occupational study of those at increased risk (and thus more likely to participate) who were offered DCBE and FS found that participation rates were extremely low for both tests.[24] The report concludes that the high probability of a low participation rate with DCBE makes it unsuitable for screening.

Demographic, social and psychological factors

Age

Most research on FOBT screening suggests increasing participation with increasing age. In the Minnesota trial of FOBT screening, peak participation was in individuals about 70 years old.[25] Vernon reports that although in some FOBT programmes participation was lowest among those 70 years of age and older, in others this pattern was not apparent.[1] Higher rates of sigmoidoscopy use have been reported among first-degree relatives 30 to 49 years old, relative to younger and older cohorts.[26] Although the age ranges are not comparable, the differences in samples and screening procedures may account for these discrepancies.

It should be noted that in the New Zealand context, rates of cervical screening have been highest among young women, with special efforts needed to persuade older women to be screened.

Gender

Evidence suggests that women are more likely than men to use CRC screening procedures. For example, higher rates of FOBTs have been found among women than among men,[27, 28] as well as higher FOBT rates for women in the control situation.[14] However, Colombo *et al* did not observe gender differences in sigmoidoscopy use among first-degree relatives of CRC patients.[26] Gender differences may therefore vary by family history of CRC or across screening procedures.

Socio-demographic factors

Information on the influence of such factors as education, income and occupation on CRC screening is more limited than that about age and gender.[1, 6] However, an association between higher education and screening participation has been observed, with higher levels of education being associated with awareness and use of FOBTs.[29, 30] The Vernon review also concludes that FOBT and sigmoidoscopy rates are positively associated with higher education levels.[1] A South Australian programme (using self-recruitment) documented higher participation among those living in areas of higher socio-demographic status.[31]

The results of these studies are consistent with the experience of both cervical and breast screening where higher socio-economic status is associated with higher screening rates.

Family history

Studies have shown that personal experience with cancer and having a relative or friend with the disease is linked with participation in screening. With regard to CRC screening, family history has been associated with higher participation in sigmoidoscopy screening.[10, 32] A screening programme in South Australia found that 20 percent of those participating reported a family history of CRC.[31] Having more than one relative with colon cancer has also been found to promote the use of FOBT, sigmoidoscopy and colonoscopy.[1, 9]

Knowledge, attitudes and beliefs about CRC and CRC screening

In order to appreciate the benefits of screening for CRC, people need to know of its existence and its purpose. As there are no guidelines for CRC screening in New Zealand, knowledge is likely to be limited. Those most likely to be aware of screening are those with relatives who have been treated for CRC. This is quite a different scenario from that in Australia and the USA where there appear to be greater levels of awareness. A survey in South Australia, for example, found that two-thirds of individuals surveyed were aware of screening tests for CRC and 15 percent had had a screening test.[33] In the USA, the level of awareness and use of screening tests have been shown to be even greater: over

80 percent of people over 40 who had participated in a large survey of 9,000 people had heard of FOBT and over 36 percent had had the test.[29]

In addition, worry about cancer and perceptions of cancer risk are associated with screening participation. Several studies assessing either cancer worry or perceptions of cancer risk reveal a common pattern: the greater the concern about personal risk, the greater the use of CRC screening procedures.[1] Risk perceptions are positively associated with use of sigmoidoscopy,[10] and the use of CRC screening practices in general.[9] It is likely that family history promotes screening use because of increased concern about personal cancer risk.[34]

Medical care variables

In recent years, research on factors affecting screening participation has shifted from a focus on socio-demographic and psychological factors that affect individual behaviour to the characteristics of the screening services and the behaviour of health professionals offering such services. In the area of cervical screening, for example, researchers have emphasised the importance of the screening service being oriented to the needs of women.[35, 36] For women to take part, they must understand not only that screening will be of benefit to them, and feel comfortable about the procedure, but also be personally invited to take part. In a New Zealand study, women not previously screened said they would take part if screening were offered on a regular basis with a full explanation of the procedure and its purpose, in language they understood.[37]

Overseas research into factors affecting CRC screening participation confirms that recommendations from an individual's doctor appear to be a powerful motivator for participating in screening.[9, 10, 38] In addition to recommending screening, explaining its importance to the individual may significantly promote participation; for example, increased use of sigmoidoscopy was observed among those whose doctors explained its importance.[10] Empirical evidence that those who have a regular source of care are more likely to receive preventive health services, including screening, has also been cited.[1]

The setting in which screening is offered may also be a factor; for example, having to go to a more clinical environment for a colonoscopy may be a disincentive for some.

Reasons for non-participation in CRC screening

Among the reasons for people not participating in FOBT screening, those which ranked first in most of the studies reviewed by Vernon are practical reasons, such as conflicts with work or family, inconvenience, being too busy, being out of town, lack of interest and cost.[1] Other key reasons included not having any current health problems or symptoms of CRC, perception of the test as embarrassing or unpleasant, not wanting to know about health problems, or being anxious about test results. Similar results were found in studies of those who did not participate in sigmoidoscopy.[1]

Strategies to increase participation in CRC screening

The AHTAC report[6] and 1997 Vernon review[1] provide comprehensive summaries of strategies to enhance participation in CRC screening (see Table 7.1, page 65, for those undertaken by the main trials). These include sending reminder letters and telephoning non-respondents at varying intervals after the tests have been sent. Efforts to increase participation resulted in an increase of about 15 percent in the Göteborg and Funen trials. In the Minnesota study, such efforts increased the response rate to both screening and follow-up procedures during the second phase by almost 25 percent; it should be noted that these efforts also included staff making hotel and travel arrangements for those coming to hospital for follow-up colonoscopy and evaluation.

A number of strategies, or combination of strategies, have also been undertaken in a variety of settings outside the main trials. These have used both a public health model that targets entire communities (eg, mass-media campaigns) and a model that targets individuals (eg, general-practice patients).[1] The latter model has included personal communication by doctors, various types of mail-out strategies (including educational materials and FOBT kits), letters inviting participants to collect kits, and reminder telephone calls and letters. Study populations have varied (eg, those within particular medical care settings, those at average risk and others at increased risk), and most of these efforts to promote CRC screening have not included systematic evaluation of strategies. Furthermore, few studies have looked at the effects of an intervention on the likelihood of participants accepting an offer to be rescreened.[1]

Both the AHTAC[6] and Vernon[1] reviews stress that the method of approach used to initiate involvement in screening is important and that intensive efforts are warranted, especially if the procedure is invasive.[1] Furthermore, once screening has been initiated, intensive efforts are needed to maintain participation.

Importance of the screening context

In summarising the effects of interventions to increase participation in CRC screening, Vernon points out that the larger social context into which screening is introduced should not be underestimated.[1] Progress over the past decade in cardiovascular risk reduction and mammography screening, for example, in part is due to the advocacy of groups supporting these issues.

It should not be assumed, therefore, that what may be considered a 'good idea' by health professionals, or even an evidence-based strategy, will necessarily meet with community approval, even with well-designed interventions. Ideas that come from the community have often circulated for a considerable period of time amidst much discussion and debate, and these ideas frequently undergo a filtering process prior to being presented as a 'community demand'. This process often generates considerable interest, with a subsequent willingness within the community to support implementation of the idea. Ideas or plans that do not actively involve the community may be more difficult to generate community interest and obtain support.

In New Zealand, experience in establishing the National Cervical Screening Programme provides an example of the importance of social context, including wide community support. Introduction of the programme at a time when public awareness about cervical screening was high due to the Cartwright Inquiry resulted in a high level of enthusiasm and grassroots support existing for cervical screening. (However, although the political profile of the programme helped ensure support among women, it alienated some health professionals, particularly because of the initial lack of consultation with them.) At present, there is no such advocacy or support for CRC screening from either the wider community or health professionals; indeed, there remains wide variation of opinion on the value of FOBT among the latter group.[8]

Conclusion

The levels of participation in CRC screening is a critical factor in determining the effectiveness of screening in reducing mortality from CRC. Key issues are the extent to which people accept initial offers for screening, and how many participate in rescreening, and in follow-up procedures for abnormal results.

The AHTAC report concludes that a considerable amount of programme resources are required for recruitment strategies to achieve levels of participation in the general population that were reached in study populations.[6] In Australia, the development and implementation of strategies to achieve adequate levels of participation in national mammography screening has consumed a substantial proportion of the programme's resources. The New Zealand experience of cervical screening is similar, even though support for cervical screening has been widespread, both among health professionals and women.

The finding that those with higher risk of developing CRC are more likely to participate in screening may have implications in whether screening is offered to increased-risk groups rather than average-risk populations. However, the WHO notes that screening which concentrates solely on increased-risk groups is rarely justified, as identified risk groups usually represent only a small proportion of the cancer burden in a country.[39]

Because of the value of a doctor explaining the benefits of screening and actively offering it to patients, tests (such as FOBT) that can be provided in a general-practice setting may have greater potential for participation than other methods (eg, colonoscopy). The characteristics and method of recruitment via general practice in the Nottingham study suggest such levels of participation could be achieved in New Zealand. In general, New Zealand patients have an identifiable GP and recruitment by face-to-face invitation rather than letter has been shown to improve uptake of screening in general.[40] However, New Zealand general practice differs from that of Britain in respect of costs for consultations; furthermore, it is unlikely that all practices would have accurate practice registers. Without registers, and without a population listing as used in the Funen study, levels of participation demonstrated in these two trials may not be achievable in New Zealand.

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8. PUBLIC CONCERNS ABOUT SCREENING

- A screening programme may cause anxiety about cancer as well as worry while awaiting test results and/or having a positive result.
- The level of public support for screening programmes is likely to be affected by the accuracy of the tests and their possible adverse consequences.
- For the public to accept another screening programme, they would need to recognise that CRC is a major health problem (and important enough to overcome the unpleasant features of the screening tests).
- The public would need to be reassured that the recommended screening tests are effective and the processing of the results reliable.
- It would be necessary to demonstrate that spending limited health resources on a CRC screening programme is justified.
- The New Zealand public would need to be convinced that resources would be available to ensure quality and provide follow-up diagnostic and treatment facilities to those who needed them throughout the country.

It is reasonable to assume that New Zealanders will be concerned by the significant numbers of people who die from CRC and interested in strategies that could be effective in reducing the number of deaths. However, the level of public support and interest in tests that detect disease in asymptomatic people is likely to be affected by how good the tests are at detecting cancer and by the possible adverse consequences of the tests.

The quality of the programme

Consumer expectations of a screening programme are very high in relation to quality. These expectations encompass the skills, training and expertise of the people involved in carrying out the screening and interpreting the tests. Consumers expect a high level of accuracy of test results, a good follow-up system and a seamless follow-through to treatment services where this is required. The quality of a screening programme should be ensured through compulsory accreditation requirements.

Internationally, it is well recognised that national coordination is an essential component of successful screening programmes.[1] There is general concern among health consumer groups in New Zealand that any deviation from strong central coordination of screening programmes could result in inequitable regional differences and a fragmented ad hoc approach to screening.

Screening harms

There is very little research that specifically addresses the potential for harm if a national CRC screening programme is established. However, the risks of medical procedures used for CRC screening, as well as information from other screening programmes, suggest potentially adverse effects that could arise in a New Zealand programme.

It is important to make the distinction between a screening and a diagnostic approach when considering potential harm, since screening is carried out on well people who have no symptoms. With cervical screening and the proposed breast screening programme, steps have been taken to clearly spell out the differences. With CRC screening, there are difficulties in defining who is symptomatic and who is asymptomatic. Because symptoms that are present in the early stages of CRC are often vague and non-specific, the distinction between those who need a diagnostic test for CRC and those who are suitable for screening may be more difficult than usual, and harder to explain.

Complications of screening and follow-up procedures

If a screening programme used the FOBT, the screening test with the least intervention, in each screening round 1 to 2.4 percent of participants will have a positive test requiring a follow-up colonoscopy, sigmoidoscopy or DCBE.[2, 3] These people then risk the complications associated with the more invasive procedures, particularly colonoscopy and sigmoidoscopy. Although rare, these complications include death, cardiopulmonary complications, bowel perforation, bleeding and infection (see Chapter 6.1, pages 43-5). Severe complications may result in the need for major surgery.

The importance of CRC screening needs to be demonstrated in order to overcome the unpleasant features and risk of complications of existing screening tests and follow-up procedures, otherwise levels of participation will be affected by concerns about screening harms. There is a need to consider exploring the value of new tests currently being developed, which could offer effective results with less risks of potential harm.

False positives and negatives

Studies have shown that the more sensitive the test, the greater the detection rate – and the greater the number of false results. This means that some people with cancer or a pre-malignant condition will be wrongly reassured and others will be subject to unnecessary procedures and stress. When adenomas and carcinomas have been missed, a negative result will give false reassurance, with the increased possibility that there will be delay in diagnosis and treatment.

The advantages of increased sensitivity have to be weighed against the significant increase in false positives, the consequential number of colonoscopies carried out, and the possible reduction in the specificity of the FOBT. False-positive results expose healthy people to unnecessary interventions and alarm, as well as generating considerable additional costs. Mammographic screening research has also reported significant anxiety and distress among women who test false positive, which may affect women's perceptions about mammography, and thus make them anxious about future examinations, resulting in them putting off having further screening mammograms.[4, 5,]

The credibility of a screening programme can easily be undermined if the screening tests are considered unreliable. False-positive rates for FOBT range from 2.1 percent[6] to 5 percent[7]. Two studies raised the possibility of loss of confidence in the test results.[8, 9] They found that FOBT use was lower among those who had previously had a positive FOBT result that was found to be a false-positive after follow-up procedures. However, another study found that most participants who received a false-positive result reported that they had appreciated the screening experience.[7]

Anxiety and other psychological factors

The anxiety that can be associated with screening has resulted in a view that a screening programme may generate fear and apprehension well beyond the real risk of the disease. Harmful effects that have been noted included adverse psychological sequelae following an abnormal cervical smear.[10]

As well as the stress and anxiety caused by false-negative and false-positive results, people tend to worry while awaiting test results and be anxious about ongoing investigations.[11, 12, 13] Even the invitation to participate in screening can be alarming for some people, leading to anxiety about the possibility of having cancer.

General hygiene matters associated with handling faecal material required for FOBT could also be a source of anxiety. Two studies have reported associated concerns about the test being messy, unpleasant and inconvenient, resulting in lower use of FOBTs.[8, 14] Among the reasons most often given for not completing FOBT screening are the embarrassing or unpleasant nature of the test and not wanting to know about health problems.[15]

Preoccupation with cancer

A number of studies have reported a high correlation between anxiety about cancer and a person's perception of his or her own level of risk.[14, 15, 16, 17] These studies have noted that the greater the level of concern about personal risk, the greater the use of CRC screening procedures (see also pages 67-8).

Additional issues surround the screening of well people with no symptoms. Consumer groups in New Zealand have expressed concern about the effects of generating a preoccupation with various parts of the body developing cancer. Some groups have posed the question of whether it is reasonable or healthy to suggest people need a 'certificate of fitness' when they have no symptoms to suggest anything is wrong. Discussions continue about the need to get the balance right, so that public health measures are effective without being unreasonably intrusive.

Service settings

Overseas studies have concluded that contact with medical services appears to strongly influence participation in screening programmes.[18, 19] It has been found that people are more likely to have a CRC screening test if it is recommended by their doctor, and that involving a practice nurse could also be of value. At least one study suggests that nurses, given appropriate training, can accurately and safely carry out flexible sigmoidoscopy for screening.[20] Similar patterns are quite likely in New Zealand.

Differing levels of acceptability

There are generally different levels of acceptability about screening interventions and possible adverse effects. Those who identify themselves as being at risk and those who have no recognised risk factors are likely to have different tolerance levels of potential harm. For example, the participation in screening sigmoidoscopy rates varied considerably in US studies.[15, 21] Rates as high as 100 percent have been achieved in people over 50 with a family history.[22] In another study of people over 50 with no family history, the response to a recruitment letter was as low as 1.3 percent.[23] A personal experience with cancer can significantly influence the decision of whether to participate in screening.[24, 25] Having a relative with cancer also appears to be an important mitigating factor; for example, US research found participation in FOBT and endoscopic screening to be significantly higher in individuals with a family history of CRC.[22]

Participation levels of older people

Although overseas research on FOBT screening suggests increasing participation with age,[26, 27, 28] in New Zealand special efforts have had to be made to encourage older women to participate in the cervical screening programme.[29] If older people, the age group most at risk of CRC, are unlikely to participate at significant levels, the effectiveness of a screening programme would be greatly reduced. It is also important to establish whether a screening programme will be helpful for older people. Will it subject them to a host of intrusive tests and worry that may undermine their quality of life, in order to prolong their life for a relatively short period of time? Does early detection really extend older people's lives or does it mean that they are living with the knowledge of cancer or of their increased risk of getting pre-cancerous polyps for a longer period of time? There is no research that looks at whether this knowledge actually compromises quality of life.

Risks of multiple programmes

There are consumer concerns in New Zealand that people are being over-screened – for one condition too often, and for too many conditions – and that having a number of screening programmes may compromise the potential to do any programmes well. Women's groups still have some outstanding concerns about the National Cervical Screening Programme, although these are not uniform throughout the country. Examples include the waiting times for follow-up and treatment; recruitment and support for those who have difficulties accessing the programme, and economic barriers (such as costs of consultations, loss of earnings when time has to be taken off work for appointments and follow-ups). Of serious concern are the past resourcing difficulties in one major centre which led to the inadequacies of the computer-based register, resulting in communication problems which follow on from this. In addition, the quality control aspects of the cervical screening programme – for example, the monitoring and evaluation of smear-taking techniques, transportation of samples, and laboratory testing standards – have still not been satisfactorily addressed in some regions.

These factors have resulted in some expressions of ambivalence and lack of confidence about screening. Media coverage of people 'slipping through the safety nets' and not being correctly diagnosed has also affected the levels of confidence people have in screening tests and techniques. Historically, the promotion of screening has tended to raise people's expectations of its capabilities, and results often may appear to fall short of these expectations.

The need for public support

The National Cervical Screening Programme is the first national cancer screening programme to be established in New Zealand. It is worth noting that one of the initial strengths of the programme was the high level of enthusiasm and grassroots' support for cervical screening among women and women's groups. It appears very unlikely that a CRC screening programme would receive the collective support and enthusiasm that was seen with cervical screening.

Diversion of health resources

Of likely concern to the general public is that the high cost of a screening programme could be at the expense of public health initiatives and health promotion strategies that support self-help and low-tech approaches. For example, the benefits achieved from a health education programme in which people are encouraged to make lifestyle and dietary changes, exercise more, give up smoking and reduce alcohol and drug taking have the potential to improve a range of health outcomes.[30, 31]

Additional adverse consequences could include the lack of financial resources to deal with the increased reporting of cancers generated by a screening programme. Associated problems could include a lack of appropriately trained people to deal with the screening programme, the diagnostic follow-up, and the inevitable increases in demand for treatment.

Screening and insurance

Now that studies have clarified the incidence of CRC and strategies that may be effective in detecting and treating it, there is concern about the potential response of insurance companies and employers. Some insurers already require women to state the date and result of their last cervical smear. If a CRC screening programme were introduced, applicants may also be required to supply the date and result of their last FOBT or colonoscopy – and be charged higher premiums if they have not been screened or have had a positive result. Other issues include whether a person could be refused cover on the basis of a screening test result or a refusal to have a test, and whether insurance companies would pay the cost of screening tests.

Conclusion

Consumers would want to be assured that any programme that is set up is properly coordinated, professionally run with a multi-disciplinary approach, that people are not discriminated against because of where they live or because of cost barriers, that the programme's objectives can be achieved, and that New Zealand can sustain the demands of yet another screening programme.

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9. CULTURAL IMPLICATIONS OF SCREENING FOR MĀORI

- Māori should be considered at similar risk of CRC as non-Māori - there are inaccuracies in reported data due to collection and reporting difficulties.
- Screening programmes should target Māori as a distinct group with particular needs.
- Any screening programme for Māori should follow the 'Framework for effective screening' suggested in this chapter.

Prevalence of CRC for Māori

Rates of CRC for Māori are reported to be lower than for non-Māori. Recent registrations for CRC in New Zealand, reported more completely in Chapter 3 (pages 17-21), are as follows:

Table 9.1 CRC registrations in New Zealand by ethnicity, 1991-93

Site (ICD)	Māori*	Non-Māori*
Colon (153)	14.9	29.8
Rectum (154)	11.0	15.0
Large bowel (153-154)	25.9	44.7

**Average annual age-standardised rate 1991-93 per 100,000 standardised to Segi's world population.*

Source: New Zealand Health Information Service. Cancer New Registrations and Deaths 1993. *Wellington: Ministry of Health, 1997.*

These data lead to the conclusion that non-Māori New Zealanders are at high risk of developing CRC, with Māori being a relatively low-risk population. On the face of it, this apparent and atypical health advantage should be applauded as one of the few disparities in health status in favour of Māori. However, it is necessary to question whether this is an accurate picture.

Problems with recording ethnicity for Māori are well documented.[1] In general, the collection, quality and dissemination of information on Māori health is inadequate. The situation is complicated because data on which analysis is based have been collected by different agencies using different definitions of Māori. Self-identity is now the preferred norm, but subtleties in the way questions are asked and answered result in significant variations over time, confounding the accuracy of reported health status and trends. Problems with the statistical baselines also result in possible anomalies. Statistics New Zealand has, over recent censuses, collected Māori demographic data in such a way that three groups of Māori can be identified and, more importantly, consistently enumerated. The three groups are:

- those of Māori ancestry
- those who identify themselves as Māori and any other ethnic group(s) (mixed Māori identity)
- those who identify solely as Māori (sole Māori identity).

In acknowledging the difficulties of reporting and collecting Māori data, Statistics New Zealand has made recommendations concerning the appropriate denominators for calculating Māori specific rates: when calculating morbidity rates the appropriate denominator is the 'mixed Māori identity', and when calculating mortality rates, the appropriate denominator is the (smaller) 'sole Māori identity'.[2] At the 1991 census these denominators were approximately 400,000 and 300,000 respectively. The use of the smaller denominator for death rates is justified by the acknowledged poorer reporting of ethnicity in mortality statistics together with changes in definitions used for reporting Māori deaths.

Three issues arise, in considering the apparently lower Māori rates of CRC:

- The rates calculated may be incorrect: there is probably considerable under-reporting of Māori deaths and hospitalisations because ethnicity is often not documented correctly.
- CRC morbidity and mortality rates could be masked by other causes for which the Māori disparity in health status is currently greater.
- The shorter Māori life expectancy compared with non-Māori (4 years for males; 5 years for females) may mean Māori do not live long enough to develop symptomatic CRC.

If any, or all, of these assumptions are correct, then rates of CRC for Māori can only be expected to increase.

The safest course is to assume that Māori rates of CRC are similar to that of non-Māori (or will be), and that any population screening programme must view Māori as (at least) at equivalent risk. Therefore, the particular cultural implications for Māori of such a programme must be taken into account.

Māori and screening

Discussion of any screening programme brings into focus the debate centering on ethnicity - that is, on whether 'biology' or 'identity' should be the standard for ethnicity reporting. From a health gains perspective, the implications for Māori of a CRC screening programme need to take into account:

- possible Māori genetic predisposition to CRC (including familial risk)
- possible Māori lifestyle risk of developing CRC (eg, diet)
- Māori cultural issues affecting participation in screening programmes.

Possible genetic disposition

The first point centres on some notion of genetic risk. Similar arguments have held true internationally (eg, the high familial risk of sickle-cell anaemia within some black populations). Although statistics can record the number of people claiming Māori descent, data specifying such information as 'amount of blood' (ie, the ethnicity of both parents and all grandparents) are no longer kept; however, knowledge of whakapapa can assist in determining familial risk. Nevertheless, without marked evidence for disproportionately greater rates of CRC among Māori, it can be assumed that Māori biology is not primarily a risk factor. Yet neither can apparently low rates validate possible biological protection. In any case, the high level of integration of Māori and non-Māori over several generations may have moderated any genetic disposition one way or another.

Possible lifestyle risk

Although the most significant risk factor that influences a person developing CRC is family history of the disease, there is some evidence that diet and alcohol intake may also play a role. See Chapter 5 (pages 27-30) for a discussion of these and other possible, modifiable, risks.

Participation in screening

The third point centres on specific cultural issues, unique to Māori as a population, which screening programmes must respond to in order to produce greater participation. Failure to recruit Māori participants may result in the development of symptomatic CRC, with corresponding morbidity and mortality.

Generally, population screening programmes have been less effective for Māori than for non-Māori. This can be viewed in two ways: as a lost opportunity by a population at fault for not participating, or as a lost opportunity by the screening programme providers in failing to meet the needs and expectations of a significant population. Both views are unnecessarily pejorative – yet the reality is that the programmes and the Māori population are not achieving optimum outcomes.

A consensus hui about screening for Māori, Hui Whakamārama, was held in Wellington in 1992. The hui endorsed 'Māori requirements' for effective screening programmes:[3]

- The condition screened for should be a significant problem within the community.
- The natural history of the disorder is known, and there is a recognisable pre-symptomatic or latent stage.
- Effective and acceptable treatments are available once the disorder is diagnosed.
- The screening test needs to be safe, simple and reliable with no important side effects.
- The screening programme needs to reach those who need it most.
- The screening programme will be adequately resourced and managed.

- Downstream services are in place to deal with those screened.
- Screening should do more good than harm.

Screening and information bases were also widely discussed at Hui Whakamārama. Because information is a taonga, 'as such, the safety, management, guardianship and the use of this information, both personal and aggregate,' is critical. For a full discussion of the management of Māori health information, see the discussion document *He Taonga Te Matauranga*.[4]

Lessons from the cervical and mammography screening programmes

Both the National Cervical Screening Programme and the breast cancer screening pilot programmes have identified lower than optimal coverage of at-risk Māori populations.[5, 6, 7] A 1989 National Research Bureau survey found that Māori women were twice as likely not to have had a cervical smear in the last three years as Pākehā women.[8] At the Hui Whakamārama, the following recommendations were included in a background paper on cervical screening,[9] and are relevant to any discussion of increasing Māori participation in screening programmes:

Where would you concentrate your efforts?
- Increasing the uptake of cervical screening by Māori women by finding ways to encourage unscreened women to have a smear.
- Improving cervical cytology registers for recall, follow-up of women with abnormalities, and quality control.
- Improving access for Māori women to acceptable primary care for cervical screening and for the investigation of gynaecological problems.

What advice would you give to the purchasers of health services?
- Screening services which are culturally appropriate for Māori should be purchased.
- Regional managers should continue to be employed to work with local communities to find ways to encourage unscreened women to be screened.
- Regional managers should also be employed to maintain the regional component of cytology registers, to recall women, to ensure women with abnormalities are followed up, and to co-ordinate quality control.
- National coordination and evaluation of screening is required.

The mammography pilot programmes were set up in Otago-Southland and in Waikato in 1991.[6, 7] In Waikato, Māori health educators went to marae and explained about the pilot programme and invited eligible women to participate. In Otago-Southland all women were invited by mailed invitations (with the help of GPs where possible). Māori women from Owaka organised the official opening ceremony and powhiri for the Otago-Southland mobile unit, which has travelled to marae throughout the region.

Specific CRC screening issues

The tests identified for CRC screening present significant cultural problems for Māori. (Many of these problems are also likely to be of concern to many non-Māori.)

FOBTs require participants to collect and store a series of faecal samples before sending them for analysis. Sigmoidoscopy and colonoscopy require participants to undergo a clinical investigation by the insertion of an endoscope into the lower colon. With radiography, the colon is examined after insertion of barium, an X-ray contrast material.

The problem of dealing with faecal material in a method consistent with effective testing means that the least invasive screening test, FOBT, presents the most obvious cultural difficulties: for example, the recommendation of storing samples in the refrigerator, where food is kept, would be problematic, as would posting samples through the mail. Even with culturally appropriate information, many older, more traditional Māori (ie, those most likely to be screened) will have fundamental difficulty with handling faecal material. It is likely, of course, that such negative views of FOBTs are shared by non-Māori.

The more invasive methods, sigmoidoscopy and colonoscopy, are possibly more acceptable once candidates are positively recruited. The primary difficulty remains in recruiting participants – particularly those who are asymptomatic.

An effective CRC screening programme for Māori

Overall, there is an improving record by service providers in meeting Māori needs and expectations, and some specific research has been undertaken in areas of service effectiveness for Māori. Several authors have produced frameworks to assist service providers in designing, delivering and monitoring health services directed at Māori consumers.[10, 11, 12, 13, 14]

Figure 9.1 A framework for screening

An effective screening programme for Māori is likely to have the following attributes.[3] It will:

- have clinical inputs which are consistent with the best possible outcomes
- utilise clinical delivery which is technically competent
- operate from a cultural context that makes sense to participants and their whānau
- have outcome measures which are patient-focused
- be delivered within a responsive framework (attending to Treaty of Waitangi issues, workforce issues, ownership of information issues)
- enable participation of Māori in the delivery and promotion of the programme
- be integrated with other aspects of positive Māori development
- be integrated with other health services.

Conclusion

It appears that Māori are not characterised as a high-risk group for developing CRC. However, it would be unwise to rely on the accuracy of apparently lower Māori rates currently reported, and the most sensible approach would be to view Māori as equivalent (rather than lower priority) candidates for screening. This conclusion then requires that any recommendations for a New Zealand screening programme address specific sub-population issues, especially including those for Māori.

It is also apparent that CRC is not one of the major health concerns for Māori. The disparity in Māori poor health is attributable to a number of other conditions, and it is these which must remain clear priorities for attention by the health sector. Nevertheless, this does not remove the need to focus possible screening on the needs and expectations of Māori as a distinct population who also holds the status of a 'health gain priority area' for the health sector.

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10. ETHICAL AND LEGAL CONSIDERATIONS

- Because individuals taking part in population screening are invited on the basis that screening could benefit them, there is an ethical obligation on those funding and providing the programme to ensure that it is effective.
- Those invited to take part in population screening must be provided with appropriate information, which includes an estimate of likely risks, benefits, and side effects.
- The information provided should be appropriate to enable a potential participant to make an informed choice and give informed consent to take part in a screening programme.

Ethical issues

If an individual requests or obtains a screening test for CRC, this is a personal decision, hopefully made after consideration of the likely risks and benefits for that individual. But if an individual is invited to be screened for CRC (either by FOBT, colonoscopy, or other screening test), and given the expectation that he or she will benefit by taking part, there is an ethical obligation placed on whoever issued the invitation:[1]

> We believe that there is an ethical difference between everyday medical practice and screening. If a patient asks a medical practitioner for help, the doctor does the best he [or she] can. He [or she] is not responsible for defects in medical knowledge. If, however, the practitioner initiates screening procedures he [or she] is in a very different situation. He [or she] should, in our view, have conclusive evidence that screening can alter the natural history of the disease in a significant proportion of those screened.

This ethical obligation on the instigator of screening exists for health professionals who send out invitations to their patients, but also for health providers who instigate population screening programmes.

The risks and benefits of screening are summarised in Table 10:1. For a New Zealander aged 40 to 54 at average risk, the risk of developing CRC in a year is less than one in 1,000. For an average-risk individual aged 55 to 74 the risk is less than four in 1,000 per year.[2]

Table 10.1 Benefits and risks of screening

Benefits	Risks
Improved prognosis for some cases detected by screening	Longer morbidity for those whose prognosis is altered
Less radical treatment which cures some early cases	Over-treatment of questionable abnormalities
Resource savings	Resource costs
Reassurance for those with negative test results	False reassurance for those with false negative results Anxiety and sometimes morbidity for those with false positive results Hazards of screening test

Source: Based on Chamberlain JM. Which prescriptive screening programmes are worthwhile? J Epidem Comm Hlth *1984; 38: 270-7.*

In the Nottingham RCT, FOBTs had 53.6 percent sensitivity and 96 to 98 percent specificity,[3] so for every person with a true positive test (who may benefit from the early detection of CRC), there would be someone with a false-negative test (in whom CRC is missed); see Table 1, page 10. For every 100 people with true negative tests, there would be four people with false-positive tests who would undergo unnecessary investigations.

Assuming 98 percent specificity, if 1,000 individuals aged between 50 and 74 are screened in a year, up to four would have CRC (in the Nottingham trial the prevalence of CRC in the first screening round was 2.1 per 1,000). Of the 1,000 FOBTs performed, two would be true positives, two would be false negatives, 978 would be true negatives, and 18 would be false positives. Thus, of the 20 people undergoing colonoscopy, two would be diagnosed with CRC (one in 10). Six would have been identified as having an adenoma greater than 10 mm; adenomas of this size are associated with an increased risk of CRC, but cancer would not necessarily develop in all such adenomas.

Some of those with true positive tests will have their lives extended, but some will not have their prognosis changed. Those with false-positive tests will undergo the anxiety and morbidity associated with investigations such as colonoscopy. The risk of serious health effects of colonoscopy is small, but important: for every 5,000 colonoscopies performed it is likely that there would be two to nine perforations and possibly one death[4, 5]; see pages 43-5. Those with true negative tests may be reassured, but those with false-negative tests may be falsely reassured and delay seeking help for symptoms of CRC.

Another way to assess the likelihood of benefit from a population screening programme in New Zealand is that for those aged between 50 and 74 with CRC (who comprise fewer than 1% of those screened), there is about a 32 percent chance that the cancer would be detected by a FOBT screening programme (given that the test has 53.6 percent sensitivity, and assuming 60 percent of eligible New Zealanders would participate in screening). For individuals without CRC (who comprise over 99% of those screened), the chance of undergoing unnecessary colonoscopy is about 2 percent (assuming 98% specificity).

Clearly there are some individuals who are at higher than average risk of CRC. In weighing up the risks and benefits of screening, these people may be prepared to accept a different level of risk associated with screening than individuals who are at average risk.

Legal issues

There is a duty to inform those invited to take part in a screening programme of the likely risks and benefits, as would be expected by a 'reasonable consumer'. This is clearly outlined in the Code of Consumers Rights which was produced by the Office of the Health and Disability Commissioner under the Health and Disability Commissioner Act 1994.[6]

> The Code of Rights, along with the right to be treated with respect and dignity, and to receive proper standards of treatment, includes the right of all consumers to receive appropriate information, which includes an estimate of 'likely risks, benefits, and side effects'. The information should be information that a 'reasonable consumer, in that consumer's circumstances, needs to make an informed choice or give informed consent'.

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11. THE COSTS OF A SCREENING PROGRAMME

- Mathematical models based on the results of the Nottingham and Funen RCTs show that, in terms of cost per year of life saved, screening for CRC by FOBT is comparable with breast cancer screening.
- Estimates of health services costs per quality-adjusted year of life (QALY) gained from the Nottingham RCT are NZ$16,900 for men and $14,700 for women for a British biennial screening programme age range 50 to 74 years, compared with $17,800 for mammography.
- In comparing the cost-effectiveness of CRC screening with other screening programmes, the total cost, the total benefits and the adverse effects of screening (including false positives) for the population screened need to be taken into account, in addition to the cost per year of life saved. The models do not take into account intangible costs of the adverse effects of screening.
- No published cost-effectiveness analyses include the full health services costs of a screening programme, in particular health promotion, recall systems, administrative overheads, set-up costs and staff training.
- Results on the most cost-effective age range for FOBT screening are conflicting. Further information is required from meta-analysis, and from longer follow-up of the trials on the life years gained by age, to determine the best age group for screening.
- Cost-effectiveness of FOBT screening is highly sensitive to the mortality reduction and to the specificity of the FOBT. The cost per year of life saved is less sensitive to the unit costs of the FOBT, colonoscopy and cancer treatment.
- Total costs and total benefits depend on the participation rate but, as estimated by the models, the cost per year of life gained is not strongly affected, within the range 60 to 70 percent for initial participation.
- The cost-effectiveness of other screening modalities (flexible sigmoidoscopy, colonoscopy, DCBE) cannot be properly ascertained because of the lack of RCT-based evidence on effectiveness. The level of participation is likely to be low.
- The cost of a national screening programme in New Zealand with biennial FOBT and 54 percent participation of people aged 50 to 74 years is estimated at approximately $24 million (GST exclusive) for the first screening round, reducing to $22 million for subsequent rounds.
- In the first screening round $5 million would be expended on colonoscopies for people who did not have cancer.
- Overall, the level of resources, and therefore costs, required to achieve the benefits obtained in the Nottingham or Funen RCTs is likely to be higher in New Zealand.
- Increased resources would be needed to identify the eligible population, achieve participation (especially for Māori and other non-European ethnic groups), provide follow-up and treatment services to people in rural areas, and train medical personnel to undertake colonoscopy.

Resources required for a screening programme

The resources required to support a screening programme span the activities on the screening 'pathway': recruitment, the screening test, follow-up diagnostic investigations, appropriate treatment and surveillance, and recall. There is also a considerable administrative component – particularly for recruitment and recall, for quality assurance, and for monitoring and evaluation. The costs of a programme depend on the level of resources dedicated to these activities. They also depend on the type of resources used, including ownership of facilities (public or private) and the skill mix of personnel.

Public sector costs

Recruitment Recruitment involves three main activities: identification of the eligible population, invitation, and health promotion. People in the required age group need to be identified using GP age-sex registers, electoral rolls or other means; and those with bowel disease and deceased people excluded. Eligible people are invited by letter, or in person at a GP consultation. Underpinning this is a health promotion campaign aimed at consumers and GPs to encourage participation. The cost of recruitment depends on the methods used for each activity and the effort put into increasing the population coverage (eg, using several reminder letters or increasing health promotional activities).

Screening test Resources deployed on the screening test, and therefore its cost, depend on the choice of test and within this the operational specifics (eg, whether FOBT kits are mailed out or collected by patients, whether they are returned by mail or in person, and who conducts and interprets the tests).

Follow-up diagnostic investigations The cost of follow-up diagnostic investigations depends on the choice of procedure, and on the existing level of facilities available. A training component may be included, if there is a shortage of skilled personnel.

Treatment and surveillance This includes the costs of polypectomy, surgical resection, adjuvant chemotherapy and palliative care. A training component may be included, if there is a shortage of skilled personnel.

Recall The costs of recall depend on the screening interval and on the recall coverage target set by the programme. Additional costs will be incurred in tracking people who move.

Monitoring and evaluation Screening programmes are a composite of many different activities. Monitoring is required to determine whether all activities on the screening pathway are occurring, and at the appropriate standard.

Information system An information system is required to reliably identify, invite and recall people for screening, and to monitor their progress.

Personal costs

The personal costs of a screening programme include patient fees for medical services, time off work, transport and other costs of accessing services. There may be anxiety from positive test results, and discomfort, pain and rarely death from the follow-up diagnostic investigations.

Costs averted by screening

Screening for CRC is a detection rather than a prevention programme. Cost savings may emanate from earlier detection, which allows treatment of the disease at an earlier rather than a later stage. Such cost savings partially offset the cost of a screening programme. The actual costs averted depend on the stage shift at treatment, the numbers of people with cancer who experience this shift, and the relative cost of treating at different stages. The numbers of people treated earlier depend on the stage at presentation without screening, the screening participation rate, and the sensitivity of the screening test.

Unproductive use of resources

Screening programmes involve tests and procedures on people who are disease free. From an economic point of view, this represents unproductive use of resources. For the individual, this represents unnecessary inconvenience and, where there are adverse effects of procedures, personal suffering. The amount of resources expended in this way depends on the specificity of the screening test and on the participation rate.

Cost-effectiveness of screening

There are several cost-effectiveness analyses based on the results of overseas trials, but none of them includes the full range of costs for a screening programme, which have been outlined above. All studies use some modelling technique, and the underlying assumptions need to be carefully examined. Parameters for these models are taken from RCTs and other clinical data. Many studies undertake sensitivity analysis to explore the effects of varying parameters that are uncertain (eg, screening participation rates, mortality reduction rates and unit costs), or which may be set by the programme (eg, the number and type of tests and the treatment regimes). Most studies vary only one parameter at a time. Therefore, knowledge of the robustness of the conclusions about cost-effectiveness is limited.

Three measures of cost-effectiveness have been used:

- cost per cancer detected
- cost per life saved
- cost per life year saved.

The first two are limited as measures of the value of a programme. The cost per cancer detected provides no information on resultant health outcomes or benefits, although it is useful as a process measure, indicating the level of resource

utilisation. The cost per life saved does not discriminate between programmes or procedures that save lives 'earlier' rather than 'later'. The third measure, cost per year of life saved (CYLS), provides information on the quantity of benefit achieved for the cost incurred and permits comparison with other programmes for the same disease and with treatments for other diseases. In comparing different screening strategies, or different health programmes, it is important to include other measures, such as the total cost and total health benefits, as well as the cost per year of life saved.

In the case of screening, which is a population strategy, it is also important to consider the number of people with the disease who, due to the limitations of the screening test, will not benefit from the programme, and conversely the number of people without the disease who undergo unnecessary procedures. The first group represents lost opportunity to benefit; the second represents unproductive resource use.

Cost-effectiveness of screening using FOBT

Cost per cancer detected

Wynes *et al* modelled screening for CRC using early results from the Nottingham trial, supplemented by data from Scandinavian trials.[1] Costs and cancers detected were estimated for the first screening round only, for 12 scenarios that varied the number of FOBTs and the level of participation.

Both the total cost of screening and the number of cancers detected increased with greater participation. The cost per cancer detected decreased, but only slightly. For three FOBTs and 75 percent participation, the cost per cancer detected was estimated at £2,422 (£1 = NZ$2.97), and the cost per person screened was £5.32. For 91 percent participation, the cost per cancer detected fell to £2,236, and the cost per person screened fell to £4.92.

The authors estimated the cost per cancer detected would increase for subsequent screening rounds, because the prevalence of cancers would fall. Halving the prevalence doubled the cost per cancer detected.

This study does not include the costs of identification of eligible patients, health promotion costs, or maintaining an information system to support future recall. Inclusion of these expenses would increase the cost per cancer detected and increase the sensitivity of the cost to changing compliance. Costs of treatment are also not included.

Cost per life saved

Lieberman developed a cost model to identify key variables impacting on programme effectiveness.[2] Analysis of annual FOBT screening of people aged 55 to 65 years, based on the results of the Minnesota trial, yielded an estimate of the cost per death prevented from CRC at US$260,000 (US$1 = NZ$1.82) for 75 percent participation. This cost includes the cost of treatment for those with cancer, but does not include the cost of health promotion, information system or screening programme administration costs.

The cost estimate was found to be sensitive to the participation rate, increasing to US$331,000 per death prevented if population participation fell to 50 percent.

Cost per life year saved

- **Australia**

The costs and benefits of annual FOBT screening have been modelled by Salkeld using Australian costs applied to the results from the Minnesota trial.[3] The costs were those incurred in the health sector and did not include costs borne by private individuals.

The health sector costs included were the costs of the FOBT (test kit, pathology and a nominal mail cost), colonoscopy, sigmoidoscopy, clinical examination, perforation and treatment (by stage). The analysis did not include the costs of health promotion, or any infrastructural costs of a screening programme, such as identification of the eligible population, inviting and recalling patients for screening, maintaining records to invite and recall patients. Their inclusion would increase total costs.

The estimate of years of life saved was based on the assumption that the survival benefits would persist for 13 years after the end of follow-up. The cost per year of life saved (discounted at 5%) was estimated at A$24,660 (A$1 = NZ$1.15).

Sensitivity analysis was undertaken, changing one variable at a time (see Table 11.1). The wide confidence interval of the estimate of mortality reduction (11%-56%) translated into a wide range for the estimate of cost per year of life saved ($12,695 to $67,848). The cost per year of life saved was also sensitive to the life expectancy gains beyond the trial, the cost of colonoscopy and the positivity rate. The cost per year of life saved was not sensitive to the cost of the FOB test, the cost of cancer treatment, or the stage distribution.

Table 11.1 Sensitivity analysis of cost per year of life saved (CYLS) for CRC screening in Australia, based on the Minnesota trial

Parameter	Model value	New value(s)	Cost per year of life saved
Mortality reduction	33%	56% 11% (95% CI)	$12,695 $67,848
Life expectancy gains beyond follow-up	13 years	None 2 years	$47,960 $40,900
Cost of colonoscopy	$800	$400 $1,000	$12,319 $30,830
Positivity rate (specificity unchanged)	7.4%	1%	$3,000

Note: Costs are expressed in Australian dollars.

Source: Based on Salkeld et al*, 1996.*[3]

The estimated cost-effectiveness was regarded as comparable to other screening programmes (A$16,533 per YLS for screening for breast cancer and A$34,168 per YLS for cervical screening). The authors noted that the high colonoscopy rate (resulting from the low specificity of the FOBT) may have been responsible for the high mortality reduction in the Minnesota trial and recommended that further evidence of efficacy of FOBT screening was required before resources were committed to national screening. They concluded that in the event that efficacy was confirmed by later trials, Australian data would be required on participation, the FOBT false-positive rate, and the potential for harm (including complications of follow-up investigations and adverse psychological effects) in order to support national health policy decisions about screening.

In retrospect, the estimate of A$24,660 per year of life gained could be optimistic in view of the larger mortality reduction found in the Minnesota trial (33%), compared with later RCTs (15% for Nottingham and 18% for Funen). On the other hand, this could be partially offset by the cost of the large number of colonoscopies (based on the Minnesota trial).

- **United States**

Wagner *et al* simulated FOBT screening of a cohort of 100,000 persons aged 50 years over a period of 25 years, varying the polyp dwell time.[4] The model assumed specificity of 90 percent and sensitivity of 60 percent. Costs of complications arising from follow-up investigations and costs averted by treating patients at an earlier stage were included. Costs of recruitment and maintaining quality were not included. Full participation was assumed.

The estimated cost per year of life gained for annual FOBT screening assuming 10-year polyp dwell time was US$9,606. The cost per year of life gained depended on assumptions made in the model, particularly with regard to the polyp dwell time. The CYLS for a five-year polyp dwell time was US$13,581. Using non-rehydrated tests was predicted to save fewer lives, but the cost per year of life saved was less.

The authors stated that: 'Estimated costs and effects depend on assumptions about the natural history of the disease, test accuracy . . . medical risks and costs. All models are to some extent abstractions of reality. At best they are rough maps of what can be expected from the implementation of the program.'

The validity of the model was explored by comparing some intermediate model results under a FOBT strategy similar to the Minnesota trial with the results of the Minnesota trial. There was a reasonable level of agreement, although the model predicted a mortality reduction of 25 percent compared with 33 percent for the trial.

- **Denmark**

A comprehensive cost-effectiveness analysis of CRC screening for different age groups and screening intervals has been undertaken using a model based on data from the Funen RCT.[5] Screening was simulated over 36 years on a fixed age and sex population, for 15 different age ranges with four screening intervals: a total of 60 screening options. Screening participation rates by age and sex were taken from the Funen trial. (The overall rates were 67.3% for the initial screen and 93.5 % for subsequent screens.)

The CRC sojourn time and the sensitivity of the FOBT were estimated by the model. Then the number of cancers occurring each year of the simulation was estimated, taking into account prevalence by age. FOBT sensitivity was estimated at 62.1 percent (higher than the value from the Funen RCT) and the CRC sojourn time was estimated at 2.1 years. An excess survival of 30 percent for people screened was assumed (slightly lower than achieved in the RCT) and this was converted into years of life saved by applying the age-specific life expectancy. Costs of screening were calculated and included administration, an information system, reporting of results to all participants, and medical consultations for patients screening positive, in addition to the direct costs of tests and follow-up diagnostic procedures. No allowance was made for any savings due to earlier or avoided cancer treatment.

Six efficient strategies were identified. The estimated cost per life year gained (1DKK = NZ$0.27) ranged from 17,000DKK (for biennial screening for ages 65-74) to 26,000DKK (for annual screening ages 50-74). The cost per life year saved for biennial screening was higher for earlier starting ages, although not markedly so (eg, 18,800DKK for screening ages 55-74). Interestingly, the strategy closest to that adopted in the RCT (biennial screening for ages 50-74) was not on the efficient frontier, and its cost was not reported.

Sensitivity analysis showed the results were most sensitive to the excess survival rate, with costs increasing by 40 percent if excess survival was only 20 percent. Costs were less sensitive to the cost of the FOBT kit or to the cost of colonoscopy.

The analysis does not address the issue of achieving or maintaining participation. The costs of health promotion were not included in the total cost. There was no sensitivity analysis of participation rates, even though the simulation continued beyond the life of the clinical trial.

The costs of the six efficient options were compared with mammography screening. They were comparable to Danish estimates for biennial mammography screening for women aged 60 to 69 (29,500DKK per discounted YLS) and were considerably less than for mammography for women aged 50 to 59 (40,000DKK per discounted life year gained).

The cost estimates for CRC screening were also compared with various options for cervical screening in Denmark.[6] Biennial screening for CRC every two years for people aged between 60 and 74 was found to be more cost-effective than any cervical screening strategy. The author concludes that CRC screening is cost-effective compared with screening for cervical cancer and that resource allocation would be improved by moving funds from cervical screening to CRC screening.

The cost per year of life saved is only one factor in making decisions about screening programmes. Intangible costs of unnecessary diagnostic procedures and treatments are also important. These were acknowledged by the author but not included in the analysis.

- **England**

The Nottingham RCT has been accompanied by a series of economic studies, beginning with studies to provide estimates of the costs of tests and procedures associated with CRC screening, continuing audits of resource use throughout the trial and culminating in cost-effectiveness analysis. The most recently published study is a cost-effectiveness analysis, which estimates the cost per quality-adjusted year of life (QALY) saved for the Nottingham RCT and compares this with other screening strategies.[7]

Using a mathematical model, FOBT biennial screening of a cohort of 100,000 subjects is simulated. The life years gained from screening are modelled from the trial data. The cost per QALY for the simulation is £5,685 for men and £4,951 for women. This is based on the population structure as in the RCT (ages 50-74 at entry to screening), using participation rates from the trial and screens for 10 years. A simulation extending over the full lifetime of all participants yielded much lower costs per QALY (£2,047 for men and £1,371 for women). This assumed that participation in rescreening would continue to decline at the rate observed in previous years.

The initial participation rate over all age groups in the RCT averaged 53 percent. Analysis of the model showed that increasing this to 70 percent did not largely affect the cost per QALY, the authors interpreting this as the compensating effect of the increased life years gained (from the greater cancer yield) and the resultant higher costs of diagnosis. However, the model did not incorporate any costs of achieving this increased level of participation.

Changing the starting age for screening down to 40 years (or up to 60 years) resulted in similar costs per QALY as for starting at age 50, although the cost per QALY was higher for men over 65. Similarly, the model showed annual screening had little effect on cost per QALY, both cost and cancer yield increasing in 'roughly equal measure'. Some of these analyses (increased compliance and annual screening) are beyond the trial's experiences, and the authors noted that there was little primary information for this analysis.

The results were not highly sensitive to increases in the prices of the FOBT or colonoscopy, but the cost per QALY doubled if FOBT specificity fell by 10 percent.

The authors found the costs estimated from the model to be lower than those for the British breast cancer screening programme, but caution that they do not represent the full costs of a national CRC screening programme. Additional costs would include capital investment in endoscopy facilities, staff training, and a computerised call-recall system. The Nottingham RCT did not involve health promotional activities, and these costs were also not included in the cost-effectiveness analysis. The authors recommend that in comparing CRC with breast cancer screening, account should be taken of indirect costs, including anxiety.

Cost-effectiveness of other screening modalities

Screening by other modalities, including flexible sigmoidoscopy and one-off colonoscopy, has been suggested. There is no evidence from RCTs of the effectiveness of these screening options, therefore their cost-effectiveness cannot be properly determined. A few studies have compared different screening strategies with FOBT screening, by constructing models using the available clinical information. Two studies, both undertaken in the United States, are reported here. Lieberman modelled five screening programmes for people aged 55 to 65 years and identified key variables impacting on the effectiveness of the programmes.[2] Cost-effectiveness was measured by cost per death averted.

To achieve a 35 percent mortality reduction from CRC (similar to the Minnesota trial), the cost per death averted and required participation levels were calculated for each screening programme. The model shows that annual FOBT is the most cost-effective strategy, achieving 35 percent mortality reduction with 75 percent participation at a cost of US$260,000 per death averted. One-off colonoscopy cost US$354,000 with 44 percent participation; DCBE cost US$335,000 with 61 percent participation and flexible sigmoidoscopy cost US$305,000 with 67 percent participation. Participation was an important determinant in cost per death averted for all programmes.

The model included the cost of cancer treatment. Since FOBT prevents fewer cancers than other programmes (for a given level of participation), the cost of cancer treatment formed a larger share of the cost and the cost per death averted by FOBT screening was sensitive to the cost of cancer treatment.

For those screened, one-off colonoscopy has the greatest impact on mortality. One result of the model was that one-off colonoscopy could be cost-effective, compared with the other programmes, if the cost of colonoscopy could be reduced to below US$750. The study acknowledged the likely low participation in colonoscopy screening, but does not include the costs of recruitment in the model.

The conclusions are based on cost-effectiveness measured by cost per death averted and, as discussed earlier, this is a less adequate measure than cost per year of life gained because it does not take into account the age at which death is averted. This is a particular difficulty when comparing different programmes for which participation may vary by age. Wagner *et al* modelled screening in the United States under 32 screening strategies, incorporating FOBT, flexible

sigmoidoscopy, DCBE and colonoscopy, and varying the screening interval and polyp dwell time.[4] Screening of a single-age (50 years) cohort was simulated for 25 years. The model was based on assumptions about the specificity and sensitivity of the tests, complication rates, and unit costs of treatments and tests. Costs averted by treating patients at an earlier stage were included. Costs of recruitment and maintaining quality were not included. Full participation was assumed.

The cost-effectiveness of other screening modalities was comparable with FOBT only for infrequent screening intervals. The estimated cost per year of life gained, assuming 10-year polyp dwell time, was (in US$):

- $7,966 for flexible sigmoidoscopy every 10 years
- $9,287 for colonoscopy every 10 years
- $9,224 for DCBE every 10 years

compared with $9,606 for annual FOBT. Costs for more frequent screening were higher (eg, $17,424 for colonoscopy every three years, $13,001 for FS every three years, $11,115 for DCBE every three years). The cost per year of life gained depended on assumptions made in the model, particularly with regard to the polyp dwell time, and this caused a reordering with respect to cost-effectiveness. For a five-year polyp dwell time, the CYLS even for 10-yearly screening was high ($22,171 for colonoscopy, $20,122 for FS and $21,887 for DCBE) compared with annual FOBT ($13,581).

The study concluded that screening was a 'relatively good investment' for the US population compared with other health interventions, but that the choice of the best screening method could not be determined with certainty.

This conclusion is not particularly helpful for developing a national screening strategy and is, of course, predicated on the high cost of hospital interventions in the US generally, which it may be cost-effective to avoid. The lack of RCT-based evidence seriously challenges the claims of cost-effectiveness of these 'non-FOBT' screening strategies. A further problem is the difficulty of achieving high levels of participation, an issue that was not fully addressed in either of these analyses.

Major determinants of cost for FOBT screening

The cost-effectiveness analyses have identified a number of factors that have a large influence on overall cost. The single most important determinant of cost-effectiveness is efficacy. The confidence interval on mortality reduction reported from the RCTs is wide, and this translates into large variations in cost per year of life saved. Also important is survival beyond the follow-up reported in the trials. Further information from the trials is required on this.

The costs of diagnostic procedures following positive FOBT results are high and have a major effect on total cost. This could be reduced if the number of false-positive results (for which the follow-up diagnostic investigations yield no benefit) could be lowered, but there is no evidence of this being achieved at present. It has been suggested that the price paid for follow-up investigations – for example, for colonoscopy – might be reduced, but there is insufficient information on the viability of this for a screening programme. Colonoscopy is a labour-intensive technique and economies of scale would be limited to equipment. The price paid must be sufficient to assure quality, in terms of diagnostic and therapeutic competence and minimisation of complications, in order to achieve the mortality reductions from a screening programme.

The cost-effectiveness, in terms of cost per year of life saved, seems not to be very sensitive to the level of participation, although total costs and total benefits clearly are.

Estimates of the costs for a national screening programme should include the costs of health promotion; the costs of identification, invitation and recall of the screening population, and other infrastructural costs such as information systems. These are not always included in cost analyses reported in the literature. Including these will increase the cost per cancer detected, cost per life saved, and cost per year of life saved.

In comparing the costs of CRC screening with other screening programmes, the total cost, the total benefits and the adverse effects of screening (including false positives) for the population screened need to be taken into account, in addition to the cost per year of life saved.

Age for screening

There is very little cost-effectiveness analysis comparing the age range for screening. The three FOBT trials present the average mortality reductions calculated for all those screened. Yet the age range for screening is wide. The benefits may differ by age group and it is unclear what proportion of the benefits, in terms of years of life saved, fall to each age

group. In addition, it is not certain what the age range for screening should be. The incidence of cancer is higher for older people, but the years of life saved per older person with detected cancer would be less than for a younger person, because the older person's mortality from other causes is higher.

Little information on benefits by age at first screen is available. A mortality benefit of 19 percent for those aged under 65 years and 10 percent for those aged over 65 years or more was reported from the Nottingham trial.[8] The Funen RCT reported mortality reductions of 23 percent for people under 60 years and 16 percent for those aged 60 years or more.[9] These results seem not to be statistically significant. The numbers in age subgroups are probably too small and the follow-up period too short.

The results from the trials have been incorporated into cost-effectiveness analyses, with conflicting results. Whynes shows the cost per QALY is largely invariant by age at first screen for women, but starts to increase for men over 60 and is higher still for men over 65 years.[7] Gyrd-Hansen reports that the most cost-effective age range for screening is 65 to 74 years.[5] This may be partly due to assumptions of the models used, Gyrd-Hansen using a constant excess survival rate for all ages.

More information on years of life saved by age at first screen is required to determine the age to begin screening. This would include studies of polyp surveillance. Screening earlier may not contribute significantly to increased benefits, yet it increases the costs. The same applies to the upper age for screening. More detailed information is required from the RCTs. Longer trials and meta-analyses of many trials are required to provide the required information for a reliable cost-effectiveness analysis.

Applicability to New Zealand

Adapting the results of economic evaluations from one country to another is problematic, due to differences in demography, the epidemiology of the disease, availability of health care resources, variations in clinical practice, incentives to health care professionals and institutions, and relative prices or costs.[10]

When translating results for a screening programme from one country to another, the key factors are the incidence of the disease, and whether the programme can be mounted to achieve the same test characteristics and reach a similar proportion of the population. Some of this information, including acceptability and participation in the programme, can only be determined by pilot programmes in the country of interest. A further consideration is that, to date, there have been no national CRC screening programmes. Information on CRC screening is based on clinical trials, where standards may be higher than could be achieved countrywide. Therefore the performance of CRC screening nationally for any country is unknown.

Demography and epidemiology

In New Zealand, the incidence of CRC is higher than in Britain and the Scandinavian countries, the stage at presentation is similar, but the age and ethnic structure of the population differs in that there is a lower percentage of older people in this country. Therefore, results of RCTs need to be adjusted for these differences. The Nottingham study found numerically greater, but not statistically significant, benefits for younger people, with reduction in CRC mortality of 19 percent for those aged under 65, and 10 percent for people aged over 65 years. This suggests that a CRC screening programme could bring more health benefits in New Zealand, but the confidence intervals on these estimates are so wide (1% to 34% for people aged under 65 years, and -9% to 26% for people aged over 65 years) that this implication is only tentative. Also, participation is likely to vary by age and ethnicity.

Identification and participation of the eligible population

The screening coverage reached by the RCTs may not be achievable in New Zealand, or it may be more expensive to achieve, mainly due to problems of identifying the eligible population. The Minnesota trial was on volunteers and it is most unlikely that the high participation in that trial would be achieved in a general population. The Funen and Nottingham trials were population based, but there was access to population registers, whereas coverage of the New Zealand population by GP age-sex registers is incomplete and electoral rolls are unavailable for screening purposes.

Reduced coverage saves on the costs of tests and follow-up procedures and treatment, but the overall benefits of the programme are reduced. Achieving higher coverage through health promotion would involve additional expense.

None of the trials included health education campaigns, therefore the effects these might have on participation are

unknown. The suggestion that the level of participation for the Nottingham trial could be increased by introducing an education campaign trial may prove unfounded – for example, because information on the low sensitivity of the test could have a negative effect. Participation in the Nottingham trial varied by GP, but this could be partly explained by socio-economic status. The level of participation in the two population RCTs may have been increased by including married couples (Funen) and all eligible household members (Nottingham). This would need to be taken into account in the New Zealand situation.

There are significant issues for Māori, which may adversely affect participation (see Chapter 9, pages 76-9). Expenditure on appropriate health promotion may be required to address this.

Returning the FOBT
The acceptability by the New Zealand postal service of mailing samples is unknown. Requiring the test to be taken to a clinic or laboratory would increase costs to the patient and may reduce participation. This could be a particular problem in rural areas.

Colonoscopy
Access to colonoscopy could be a problem in New Zealand, especially in rural areas. This could reduce attendance for follow-up procedures, increase anxiety, and reduce the potential benefits of the programme. Improving access to colonoscopy could increase costs.

Currently, there is insufficient capacity within the public sector to provide colonoscopy to support a national screening programme, thus recruitment and training costs would be incurred.

Treatment
Treatment for cancer would be offered in urban centres in New Zealand. This would involve travel costs, some of which may be borne by the public health sector, dependent on the distance from treatment. Resources used for treatment may differ from those in the trials due to clinical management.

Relative costs
Screening for CRC incurs cost for ambulatory services (primary and outpatient) and saves in-hospital costs. The ratio of in-hospital costs to ambulatory costs is probably lower in New Zealand compared with some other countries, particularly the United States. Thus, the results of the cost-effectiveness analysis by Wagner, which includes averted hospital costs, may not be applicable.[4]

Implications for New Zealand

Overall, the level of resources, and therefore costs, required to achieve the benefits obtained in the Nottingham or Funen trials are likely to be higher for New Zealand. Increased resources would be needed to identify the eligible population, achieve good participation (especially for Māori), provide follow-up and treatment services to people in rural areas, and train medical personnel to undertake colonoscopy.

Costs of a CRC screening programme in New Zealand

Only a very crude estimate of the cost of a national screening programme for CRC can be compiled at present, due to the lack of reliable information on the unit costs of the various procedures associated with screening (outlined above) and the unknown level of participation of the eligible population. Programme parameters – including the age range for screening, the screening interval, the target coverage to be achieved, choice of test and follow-up investigations – also influence the resource use and the eventual cost.

A costing exercise was undertaken to identify the main cost components of a national screening programme with biennial FOBT (and follow-up colonoscopy). Unlike Australia, where there have been a number of cost studies on CRC screening, there are no New Zealand studies; therefore, the estimation relied on prices for tests and activities that would be undertaken for CRC screening, supplemented by published data on the costs of the cervical screening programme.

Table 11.2 provides an illustration of the main health services costs for the first screening round of a national programme based on the Nottingham trial, with FOBT screening every two years for people aged between 50 and 74, and with

54 percent participation. It is based on a New Zealand population of 968,413 in the eligible age group.[11] Invitation is by letter from the GP. It is assumed that 90 percent of the eligible population can be identified using GP age-sex registers, and that 60 percent of those invited would participate (resulting in 54 percent population participation).

The costing exercise was restricted in three ways. Firstly, although a screening programme incurs costs at both the national and regional levels, the cost estimation was limited to regional-level costs. National-level activities, such as policy development, quality assurance, national health promotion and monitoring and evaluation, are identified but have not been estimated. Secondly, the analysis included only public sector costs. Personal expenditure (eg, GP fees or travel costs to obtain colonoscopy) was not included. Thirdly, set-up costs, including extensive health promotion to launch a new screening programme, have not been estimated.

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Table 11.2 Estimates of regional-level costs (ex GST) of a CRC screening programme, first screening round

Activity	Volumes	Unit cost $	Cost $	Notes
Regional programme promotion	713,474	4.83	3,446,079	1, 2, 3
Identification/invitation (90%)	642,127	5.80	3,724,334	4
FOBT kit & lab analysis	385,276	6.04	2,327,067	5
FOBT kit only (40% not returned)	256,851	1.40	359,591	
Refer colonoscopy	8,091	9.00	72,819	6
Colonoscopy	8,091	768.00	6,213,731	7
Lab analysis biopsy (47.1%)	3,811	61.63	234,857	8
Administration	713,474	3.26	2,324,955	3
Operation of information system	385,276	5.56	2,143,737	3, 9
Set-up costs: information system	— — — — —	*not estimated*	— — — — —	10
Set-up costs: staff training	— — — — —	*not estimated*	— — — — —	11
Quality assurance	— — — — —	*not estimated*	— — — — —	
National-level activities	— — — — —	*not estimated*	— — — — —	12
First screening round			20,847,170	13

1 *Age eligible population (adults 50-74) = 727,224; existing CRC (1.89%) = 13,750; resultant eligible population = 713,474.*
2 *Health promotion for doctors and patients; does not include the cost of GP consultations; excludes national campaigns.*
3 *Based pro rata on the regional costs of the third year of the cervical screening programme,* adjusted for CPI movements in health care costs.†*
4 *Identification of people in the eligible population from GP age-sex register; excludes those with existing CRC; assumes 10 percent not on GP registers. Invitation by GP letter; includes return postage; excludes cost of FOBT kit.*
5 *Initial participation 54 percent (60% of 90%) based on Nottingham (53%) and Funen (67%) RCTs; cost includes test kit, collection, delivery and reporting to GP.*
6 *Assumes 2.1 percent positivity at the first screen, based on the Nottingham RCT; includes consultation subsidy for 60 percent with CRC; excludes patient fees.*
7 *Unit cost based on the 1996/97 average prices paid to hospitals by the Health Funding Authority: $682 without complications, $1,144 therapeutic.‡*
8 *Positive predictive value of a positive FOBT for neoplasia was 47.1 percent in first screening round of Nottingham RCT.*
9 *Exclusive of set-up costs for computer hardware and software.*
10 *An information system would be required to recall patients after two years, and to monitor their progress.*
11 *Staff training includes colonoscopists.*
12 *Policy development, monitoring and evaluation, national health promotion and coordination.*
13 *Excludes set-up costs (information system, staff training), national activities, quality assurance, treatment and surveillance costs.*

References

* *Green T.* Expenditure of the National Cervical Screening Programme at the Area Health Board Level 1992-93. *Wellington: Ministry of Health, 1994.*
† *Department of Statistics.* Consumer Expenditure Statistics 1997. *Wellington: Department of Statistics, 1998.*
‡ *Ministry of Health.* Purchasing for Your Health 1996-97. *Wellington: Ministry of Health, 1998.*

The total estimated cost of regional-level activities is $20.8 million (GST exclusive) incurred over the first two years of a national programme. National-level activities could add another $2 million. The costs of setting up the programme, including training of personnel and purchase of hardware and software for information systems, would be in addition to this; so would a national health promotion campaign prior to the commencement of the programme designed to encourage participation. These set-up costs could bring the total costs for the first two years to $24 million – that is, $12 million per year.

Unit costs are not well known in New Zealand, particularly for outpatient procedures (eg, colonoscopy). Costs have been based on prices paid to providers, and the relationship between cost and price is uncertain. There is likely to be considerable cross-subsidisation between different procedures. Moreover, these costs relate to the current 'no-screen' situation; costs may differ for the screening situation. No account has been taken of the capabilities of existing service facilities to manage the additional workload involved.

Some parameters have been based on the Nottingham trial, including participation and test positivity, with no information on their applicability to New Zealand. Other features are ignored completely, including failure to present for colonoscopy follow-up and the cost of complications arising from colonoscopy. Several costs have been based on the costs of the third year (1992/93) of the cervical screening programme: screening coverage in that year was 60 percent, which is comparable with the figure for the Nottingham trial. Yet some costs (eg, ongoing health promotion) could be higher for screening for CRC, a disease that does not have the same public profile as cervical cancer.

Actual costs of a screening programme depend on decisions made about procedures and protocols. Follow-up after a positive FOBT is assumed to be by colonoscopy and the resultant cost ($6 million for the first screening round) is a large component of the total. Deviations from this protocol would affect cost. The model assumes only one GP letter of invitation is sent to patients. Additional expenditure would be incurred for reminder letters or telephone calls.

It is assumed that patients are not routinely informed of negative test results, based on present practice in primary care. Allowance is made for one GP visit after a positive test result, at a cost equal to the government consultation subsidy, assuming 60 percent of those who test positive hold community services cards. If provision were made for more contact with patients, or indeed included support for patients who test positive, then costs would increase.

Sensitivity analysis

A very simple sensitivity analysis was undertaken to explore the effect of varying key parameters identified as important cost determinants in other studies. Increasing the level of participation to 60 percent of the eligible population increased the estimated cost for the first screening round by $1.7 million. Increasing the unit cost of a standard colonoscopy (without polypectomy) from $682 to $800 (in line with Australian prices) increased the cost by $1.4 million.

Ongoing costs

The costs of a screening programme beyond the first screening round can be expected to decrease, as the test positivity decreases and with it the number of follow-up investigations. On the other hand, there will be surveillance costs for those who tested positive in earlier rounds. A simple model was constructed to estimate the total number of colonoscopies each year, for the first eight years of a programme (see page 47). The number of colonoscopies after the first screening round averaged approximately 3,300 per year, compared to 4,045 for years one and two. This assumes no surveillance for adenomas under 10 mm. Provided this protocol were adhered to, there would be an associated reduction in cost of approximately $600,000 per year. Other costs in Table 11.2 (page 91) would be unlikely to change substantially. Efficiencies gained from an established programme could well be offset by activities involved in updating patient lists and retaining people previously screened. Annual costs for years three to eight could be in the region of $11 million. It should also be noted that costs beyond this could increase due to the ageing of the population.

Costs averted by screening

Costs averted by screening relate to treating the disease at an earlier rather than a later stage. Due to the low sensitivity of FOBT (53.6% in the Nottingham RCT), even if screening coverage reached 60 percent, at most one-third of people with CRC would have their cancers detected by screening (approximately 650 people per year). Thus, a screening programme may be able to save some part of the amount currently spent on surgery for this group. The actual amount saved would depend on treatment prices and the stage of cancer at detection, particularly if surgery could be avoided. Savings accruing to the public purse depend on the current and future mix of treatment in the public and private sectors.

In estimating the cost consequences of a screening programme, account needs to be taken of colonoscopies already undertaken in the public and private sectors, since a screening programme would substitute for some of this activity. The level of substitution depends on the current number of colonoscopies performed in the eligible screening age group. Again the effect on the public purse depends on the current levels of public sector activity. Accurate estimates are difficult to obtain, since the number of colonoscopies reported to be purchased underestimates those actually performed (see page 46). A total of 3,460 were purchased in 1995/96 and 3,053 in 1996/97.[12]

Failure to benefit

Due to the low sensitivity of the FOBT and the likely participation rate in screening, at least two-thirds of people with cancer would not have their cancer detected by the programme. Half of those whose cancer was detected by screening would also not experience any mortality reduction. Thus, even with expenditure of $11 to $12 million per year, five out of six deaths from CRC would not be prevented by the screening programme. These estimates are calculated from RCT-based evidence of mortality reduction of 16 percent. If this mortality reduction were not achieved in New Zealand, cost-effectiveness of CRC would be severely affected.

Unproductive use of resources

Within a FOBT-based population screening programme, the positive predictive value of a guaiac FOBT for CRC is around 10 percent. Thus, 90 percent of colonoscopies (approximately 7,300 in the first screening round) would be conducted on people who do not have cancer. A number of these people (approximately 2,600) would have large adenomas, and although the primary objective of a CRC screening programme is to detect cancer, some benefit may be achieved by adenoma removal. The remaining 4,600 cases would have neither cancer nor large adenomas. Colonoscopy for this group would involve considerable resources and would account for over $3 million expenditure, even if all cases were free of complications. Additional expenditure and personal suffering would be incurred were there any adverse effects of colonoscopy for this group of people.

Alternatives to screening

A population screening programme involves the commitment of considerable health sector resources. Unlike other diseases – for example, breast cancer where there are no known preventive strategies – there is some evidence of a relationship between diet and CRC. Hence, there may be dietary strategies as alternatives to CRC screening. Dietary strategies have the advantage that, unlike screening, there are no known associated adverse effects. Moreover, dietary strategies align with those to reduce heart disease and, therefore, would bring other health benefits.

In assessing the cost-effectiveness of CRC screening, consideration needs to be given to the gains that might be achieved from these other strategies for a similar or lower resource outlay. It may be that these other strategies need to be embarked on first.

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12. INCREASED-RISK GROUPS FOR CRC

- Individuals at increased risk of CRC – namely those with a family history of the hereditary CRC syndromes, a family history of sporadic CRC (particularly if the relative developed CRC under the age of 55, or if there are two first-degree relatives with CRC), or a personal history of CRC, colorectal adenoma or long-standing extensive inflammatory bowel disease – are excluded from recommendations for population screening of average-risk subjects.
- The Working Party recommends wider consultation and further consideration be undertaken to develop appropriate advice on surveillance recommendations for groups identified to be at increased risk.

Recommendations pertaining to population screening for CRC apply to asymptomatic individuals considered to be at average risk of developing CRC. However, an increased risk for developing CRC has been recognised in certain individuals, namely those with hereditary syndromes, a family history of sporadic CRC, and those with a personal history of colorectal adenoma, CRC or inflammatory bowel disease. It is important to identify these individuals who are potentially at increased risk as the surveillance strategies advised will be different from those advised for the normal population. This chapter reviews these increased-risk groups.

Hereditary syndromes

A number of well-defined hereditary syndromes are associated with an increased risk of developing CRC.

Familial adenomatous polyposis (FAP)

This is an autosomal dominant disease with almost complete penetrance. The reported incidence is approximately one in 10,000 births, with new mutations considered to be responsible for the 25 percent of cases where there is no discernible genetic predisposition.[1] FAP has been estimated to account for 1 percent or less of CRC, but recent figures indicate that this is now around 0.2 percent.[2] This decrease is considered to reflect the improved management of FAP families, with sigmoidoscopic screening and colectomy for affected individuals becoming standard practice. The disease is characterised by the presence of multiple small polyps (>100) throughout the colon and rectum. These polyps develop in the early- to mid-teens, and in over 95 percent of gene carriers multiple adenomas are present by the age of 20 years.[3] The median age at diagnosis for CRC in untreated affected individuals is 40 years. An attenuated form of FAP has been described, with fewer colonic polyps and the development of CRC at a later age.[4]

In individuals affected with FAP, polyps can be found in other parts of the gastrointestinal tract, particularly the duodenum where adenomas are identified in approximately 90 percent,[5] and duodenal or periampullary cancer develops in approximately 5 to 8 percent.[6, 7, 8] Other extracolonic manifestations of the disease include osteomas, congenital hypertropy of the retinal pigment epithelium, epidermoid cysts, dental anomalies and desmoid tumours. FAP and Gardner's Syndrome are now known to be synonymous.

Prophylactic colectomy reduces the incidence and mortality of CRC in individuals with FAP,[2] but the relative risk of dying after prophylactic colectomy is still 3.35 times higher than a matched group of the general population. The three main causes of death post-colectomy are upper gastrointestinal malignancy, desmoid disease and perioperative complications.[6]

The majority of cases of FAP are associated with mutations in the APC gene on the long arm of chromosome 5.[9, 10] The APC gene is subdivided into 15 coding exons, with the last exon accounting for most of the coding sequence of the gene. Most known mutations in FAP occur in exon 15. The location of the germ-line APC mutation influences disease expression, with profuse polyposis being associated with mutations between codons 1250 and 1464.[11]

A number of genetic tests for the diagnosis of FAP are available. The protein truncation test takes advantage of the fact that the majority of disease-causing mutations in the APC gene result in truncation of the APC protein, and thus individuals can be identified as having the disease in the absence of other family information. Protein truncation testing can identify at least 90 percent of affected individuals.[12] Linkage testing requires a firm clinical diagnosis in at

least two family members before the DNA markers can be used to make genetic diagnoses in the other family members. Mutation testing in FAP families requires that the specific mutation for each family be identified; currently, this remains the domain of research laboratories.

Hereditary non-polyposis colorectal cancer (HNPCC)

HNPCC is an autosomal dominant inherited condition estimated to account for 1 to 4 percent of all CRC. It is characterised by the development of CRC at a mean age of 45 years,[13] and was previously known as the Lynch Syndrome. The colonic tumours tend to be right-sided and may be multiple. Extra colonic cancers also occur, particularly endometrial, but the stomach, ovary, small bowel, pancreas, urinary tract and biliary system can also be involved.[14] The lifetime risk of developing bowel cancer is 80 to 90 percent in males, but for women is variably reported to be 30 to 80 percent.[8, 15, 16] The lifetime risk of endometrial cancer is 40 to 50 percent.[8]

The term 'non-polyposis' is used to distinguish this form of inherited predisposition to CRC from FAP. However, the development of most CRC in HNPCC is considered to be through the adenoma-carcinoma sequence, albeit with an accelerated time sequence.[17] The number and distribution of polyps throughout the colon is the same as that of the general population, but the polyps tend to show more severe histological features and occur at a younger age.

The Amsterdam criteria were developed to identify HNPCC families and provide uniformity in the genetic diagnosis.[18] Three or more relatives with verified CRC are required, one of whom is a first-degree relative of the other two. CRC should involve two generations, and one or more cancer cases must be diagnosed before the age of 50 years. The limitations of these criteria, particularly the lack of reference to extra colonic tumours or family size, need to be recognised.

HNPCC has recently been demonstrated to be caused by mutations in one of four mismatch repair genes,[19, 20, 21, 22] although the majority occur in two of the four genes (hMSH2 and hMLH1). These genes normally repair errors that occur in DNA as a result of normal cell replication. Mutations in these genes result in the accumulation of mutations in other genes. Tumours resulting from defective mismatch repair can be detected by particular genetic techniques and are said to show replication error phenotype RER+, or microsatellite instability. This phenotype is seen in 70 to 90 percent of colon cancers from HNPCC patients,[23] but in only about 15 percent of sporadic CRC.[23, 24]

Genetic testing for HNPCC is more complex than in FAP because disease-causing mutations can occur in one of four genes. Such testing is not routinely available in New Zealand except in the research setting and is generally confined to members of well-defined HNPCC families. Determination of tumour RER status helps define such families where suspicion is high but the strict Amsterdam criteria are not met.

Colonoscopic screening of at-risk relatives or carriers of mismatch repair gene mutations has been shown to decrease the incidence of CRCs in those screened.[25] This is usually advised from the age of 25 years. There is some controversy as to the screening interval with one- to three-yearly being recommended in a consensus statement from the Cancer Genetics Consortium in the United States.[26] The shorter intervals of one to two years are generally advised in confirmed mutation carriers because of the development of interval cancers.[27] The risk of a metachronous CRC (ie, another new cancer) after limited bowel resection for CRC in HNPCC is 30 percent at 10 years and 50 percent at 15 years.[28, 29] Colectomy with ileorectal anastomosis is therefore usually advised once cancer develops in at-risk or gene-positive individuals. Screening for endometrial cancer is also advised, particularly where there is a family history of this malignancy.[30]

Hamartomatous polyposis syndromes

These are rare syndromes with autosomal dominant inheritance associated with hamartomas in the small and large bowel. The risk of CRC is increased but the magnitude of this risk is not clearly established. The Peutz-Jeghers Syndrome is characterised by predominantly small bowel hamartomas and cutaneous pigmentation, particularly involving the lips and perioral area. In juvenile polyposis the hamartomatous polyps are predominantly colonic. The risk for colonic cancer in this condition has been estimated to be at least 9 percent.[31] Gastric and duodenal carcinomas have also been reported.

Hereditary CRC registries

These registries have been established in a number of medical centres to facilitate the diagnosis and treatment of patients suspected to have hereditary CRC. The registries are usually staffed by a multi-disciplinary team comprising

specialists in genetics, gastroenterology, surgery, counselling, oncology and pathology. One of the most important roles of a registry is to obtain an accurate family history with confirmatory data from hospital records, pathology departments and death certificates. This clinical, demographical and genealogical information provides the basis for a diagnosis of hereditary CRC and subsequent assessment of cancer risk for family members. Genetic testing and cancer screening, within the context of appropriate counselling, can be coordinated through the registry.

In Auckland, as elsewhere internationally, the establishment of registries has been crucial in facilitating research into the genetic basis and management of these conditions.[32, 33] A Familial Cancer Registry, incorporating the FAP and HNPCC registries, has been established by the Clinical Genetic Services of Auckland Healthcare Ltd to provide services to a defined geographical region. However, because family members involved are spread throughout New Zealand, a national network to facilitate diagnosis and coordinate cancer screening, genetic screening and counselling is necessary.[34]

Sporadic CRC and familial risk

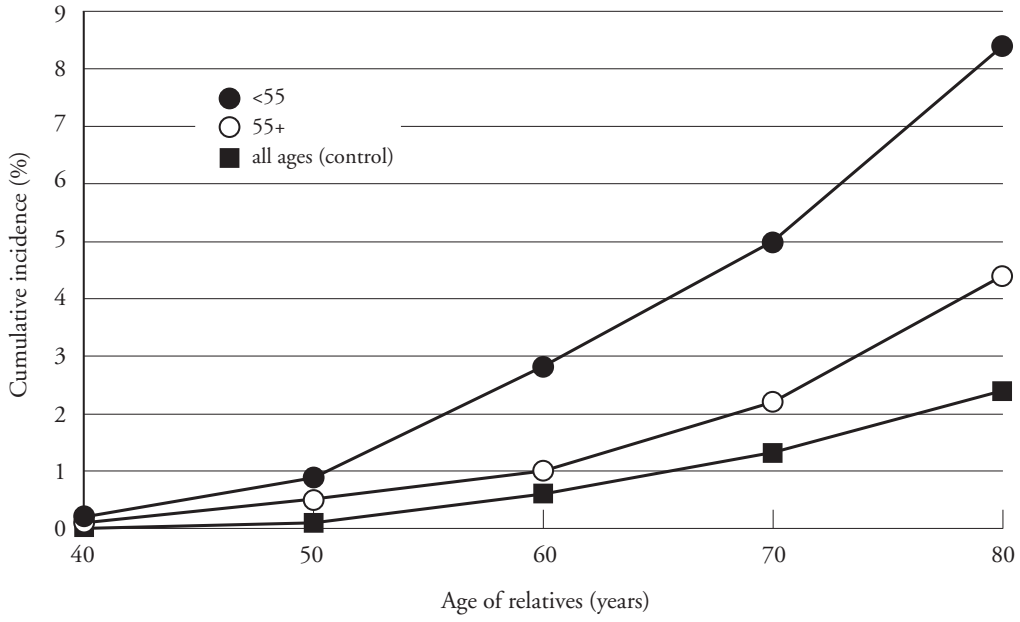
Approximately 20 percent of all patients with CRC will have a family history of the disease (with a minority being accounted for by the well-established genetic syndromes). An inherited susceptibility is considered to account for much of this increased risk,[35] but no specific gene has been identified to date. A low penetrance dominant inheritance has been postulated in those families with clustering of CRC.[36]

The level of increased risk of CRC for relatives (excluding those relatives of families with the well-defined hereditary CRC syndromes, FAP and HNPCC) depends on the number of first-degree relatives affected and the age at which such relatives were diagnosed to have CRC.[37, 38, 39, 40]

- For those with one affected first-degree relative diagnosed at an age of 55 years or older, the relative risk is approximately 2.0.
- For those with one first-degree relative diagnosed between the ages of 45 and 55 years, the relative risk is approximately 3.0.
- For those with one first-degree relative diagnosed at less than 45 years, the relative risk is approximately 4.0.
- For those with two or more first-degree relatives affected, the relative risk is between 3.0 to 6.0.

Figure 12.1 below shows the cumulative incidence of CRC in relatives, as related to the age at diagnosis of CRC for case subjects.

Figure 12.1 Cumulative incidence of CRC in relatives



Source: Based on data from St John et al*, 1993.*[37]

The graph documents continuation of increased risk at older ages. However, in the prospective study by Fuchs the risk to relatives decreased with age, and for relatives 65 years or older the relative risk associated with a family history approached 1.[38] Conversely, the relative risk of CRC risk in relatives aged under 45 was 5.37. The issue of whether the increased risk for CRC applies to older yet unaffected relatives is still unresolved.

A number of studies on screening relatives of patients with CRC have been published, many uncontrolled. Brewer reviewed the relevant literature and concluded that:[41]

- first-degree relatives of patients with CRC have a higher incidence of neoplasms (ie, adenomas and carcinomas)
- incidence is higher in those individuals with more than one affected first-degree relative
- risk increases with advancing age
- colonoscopy appears to have a detection advantage as a screening tool.

The distribution of neoplasms in screened relatives does not appear to be different from the distribution of neoplasms in the normal population. Up to 48 percent of lesions were considered beyond the reach of the flexible sigmoidoscope and 5 to 22 percent had no sentinel neoplasms distal to the splenic flexure. Colonoscopy has been recommended as the first-line investigation rather than flexible sigmoidoscopy.[42] The cost advantage of flexible sigmoidoscopy was largely offset by the cost of follow-up colonoscopies for all subjects with polyps, and there was no difference in participation levels for the two procedures.

All RCTs of screening for CRC have been done in the average-risk population, and the evidence that screening relatives at increased risk of developing CRC (excluding families where an hereditary syndrome is apparent) will reduce mortality from CRC is indirect. It is difficult to foresee that randomised trials of screening can or will be done in these increased-risk groups.

In assessing CRC risk, Lang and Ransohoff make the point that it is important to consider absolute as well as relative risk.[43] Although a family history of CRC is associated with substantially increased relative risk of CRC at younger ages, the absolute risk at younger ages remains low. However, loss of life from potentially preventable CRC at younger ages is significant, and, at the same time, the effort and risks involved in intensive colonoscopic surveillance are relatively large. Future decisions about government-funded screening protocols for relatives of patients affected with CRC may be grounded in careful estimates of absolute CRC risk compared with estimates of potential screening benefit/risk.

In its recently published guidelines on familial aspects of cancer, the Australian Cancer Network considers that the use of colonoscopic surveillance in first-degree relatives of individuals with CRC 'appears prudent in those at a three- to six-fold increased risk despite the absence of published mortality data, but the optimal frequency and age of commencement is not known.'[44]

Sporadic colorectal adenoma and familial risk

The National Polyp Study reported a relative risk for CRC of 1.78 for the parents and siblings of patients with adenomas (95% CI 1.18-2.67). The risk of siblings developing CRC was also influenced by the age at which adenomas were diagnosed in the index relative – a relative risk for CRC of 2.59 being reported for siblings of those diagnosed with adenoma before the age of 60 years compared with siblings of those diagnosed with adenoma at age 60 years or greater. The younger the age at adenoma diagnosis, the higher the risk of CRC for siblings.[45] A recent study confirms this, reporting the risk among first-degree relatives of patients who were 50 years of age or younger when the adenoma was diagnosed to be more than four times greater (RR 4.36 CI 2.24-8.51) than among first-degree relatives of patients who were older than 60 years when the adenoma was first diagnosed.[46]

Personal history of colorectal adenoma

If the adenoma-carcinoma theory is correct, removal of adenomas should reduce the incidence of CRC. However, a RCT to prove this would involve a no-intervention control arm, which is not ethically feasible. A number of observational studies, particularly the National Polyp Study,[47] have demonstrated a reduction in CRC incidence following colonoscopic surveillance with removal of all polyps.

However, autopsy studies have revealed that 30 to 40 percent of people aged 60 years and over will have adenomas, yet the lifetime risk for CRC in western countries is around 5 percent. The potential colonoscopic burden of polyp

surveillance is enormous unless it is targeted to those with high-risk adenomas. A Norwegian study estimated that the annual conversion rate to cancer for all adenomas was 0.25 percent. An increased annual conversion rate was identified in adenomas greater than 10 mm in size (3%), adenomas that were villous in nature (17%) and adenomas with severe dysplasia (37%).[48] Adenoma size and villous histology were associated with an increased risk of high-grade dysplasia in the National Polyp Study.[47]

The National Polyp Study also addressed the question of frequency of follow-up colonoscopy after polypectomy. Multiplicity of adenomas, large size of adenomas and age greater than 60 years were independent risk factors for adenomas at follow-up. Multiplicity was the most important risk factor for polyps with high-risk histological features. A positive family history (one or more first-degree relatives with CRC) was an independent risk factor for adenomas greater than 5 mm in size detected at follow-up colonoscopy. When colonoscopic surveillance was performed one or three years after initial polypectomy, there was little difference in the yield of polyps or in the number of polyps with advanced histological features.[47]

Findings at the first follow-up colonoscopy were predictive of findings at subsequent examinations, suggesting that a longer interval between repeat examinations would be reasonable if no adenomas were identified at follow-up. There is some evidence to suggest that single rectosigmoid tubular adenomas less than 10 mm in size are not associated with an increased risk of developing CRC,[49, 50, 51] and therefore, by implication, further colonoscopic surveillance in such patients would not be indicated.

Personal history of CRC

In patients with known CRC, synchronous adenomas and cancer will be present in 25 to 40 percent and 2 to 6 percent respectively.[52, 53] Metachronous colorectal adenomas occur in 25 to 40 percent and metachronous cancer in 3 to 8 percent of patients with a history of CRC.[54, 55] A recent study by Schoemaker reported that, providing a complete perioperative colonoscopy had been performed, yearly colonoscopy, liver CT and chest radiography did not influence five-year survival of CRC patients.[56]

Chronic inflammatory bowel disease

An increased risk of CRC is associated with extensive and long-standing chronic inflammatory bowel disease (IBD). The magnitude of this risk has been difficult to assess because of the sources of population studied (specialist centres versus community), the change in diagnostic methods with the introduction of colonoscopy, and the variation in definition of disease extent.[57] However, the majority of studies show that the incidence of carcinoma increases with more extensive involvement of the colon and the duration of disease. In patients with extensive disease, the incidence of CRC begins to increase after eight to 10 years, with a cumulative incidence of 3 percent at 15 years, 7 percent after 20 years, and 12 percent after 25 years.[58]

There is little or no risk associated with proctitis or proctosigmoiditis.[59, 60] The risk of CRC increases somewhat with left-sided colitis; the magnitude of risk increase being 2.18[58] and 2.8[59] times higher than average. The risk does not appear to increase until 16 to 20 years after onset of symptoms.[61]

Community-based studies suggest there is probably a small increased risk of CRC associated with Crohn's colitis. If the colonic involvement is extensive, the risk may approach that of ulcerative colitis, although the higher resection rate in Crohn's makes determination of true risk difficult.

There is controversy about the value of colonoscopic surveillance in extensive colitis. No surveillance programme has been proven to prevent CRC or to have reduced cancer mortality. There is some evidence that surgery for dysplasia may prevent some cancers and that asymptomatic cancers tend to be diagnosed at an earlier stage than when they present with symptoms.[57]

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13. CONCLUSIONS AND RECOMMENDATIONS

The Working Party was asked to review the evidence for the benefits and risks of introducing population screening for colorectal cancer, to identify the implications of introducing a CRC screening programme, and to make recommendations to the National Health Committee about the introduction of a screening programme in New Zealand. This chapter summarises information already presented in more detail in the body of the report and presents the recommendations of the Working Party.

The Working Party made an early decision not to recommend screening methods (such as colonoscopy, flexible sigmoidoscopy and DCBE) which were not supported by evidence from randomised controlled trials (grade 1 evidence). FOBT screening is the only CRC screening modality for which there is grade 1 evidence of efficacy. The Working Party acknowledged the potential of screening tests other than FOBT, but, because of the lack of grade 1 evidence, did not consider any of these a possibility for population screening at the present time.

After considering the evidence for population FOBT screening for CRC, and the implications of population FOBT screening in New Zealand, the Working Party concluded that:

> Given the modest potential benefit, the considerable commitment of health sector resources and the small but real potential for harm, population-based screening for colorectal cancer with faecal occult blood tests is not recommended in New Zealand.

The major determinants of this decision are summarised below. The final recommendations were based on consideration of three key issues (benefits, resources and risks). Understandably, members of the Working Party brought different perspectives to each of these issues. However, after joint consideration of all the evidence, agreement was unanimous about the major recommendations of the report.

There is a modest mortality benefit from population screening for CRC with FOBT but the variance around this benefit, as measured by the 95 percent confidence interval, is large.

Three RCTs (Funen, Nottingham and Minnesota) have provided evidence that screening for CRC with guaiac-based FOBT can reduce mortality from CRC. Two of these, Funen and Nottingham, are population based and therefore are the most relevant to the terms of reference of the Working Party. Screening with FOBT was offered to men and women aged 50 to 74 in Nottingham and 45 to 75 in Funen.

A meta-analysis of these two population-based trials reveals a 16 percent reduction in CRC mortality in the population offered screening over an eight- to 10-year period. This means that one out of six CRC deaths could be prevented in people offered screening; the other five deaths would not be prevented. However, the 95 percent confidence interval around this estimated mortality reduction is wide (6%-25%).

Based on the Nottingham study, in the target population of about 727,000 New Zealanders presently aged 50 to 74, a population screening programme could result in about 512 (95% CI 68-887) fewer deaths from CRC after eight years (see Table 13.1, over).

Because CRC incidence is higher in New Zealand than in Britain, a screening programme here might be expected to avert slightly more than 512 deaths, provided that the results of the RCTs were able to be reproduced in a population-based programme in New Zealand, and subject to the variation reflected in the 95 percent confidence interval. On the other hand, mortality reductions found in Nottingham may overestimate the benefits of such a population screening programme because of differences in study design. A New Zealand population screening programme would screen people in a specified age range (50-74) with people ageing in and ageing out each year, unlike the RCT studies which screened a closed cohort for a fixed period and this cohort aged over the course of the trials. Consequently, the

benefits found from the trials are based on results that include some screening of people over the age of 75 years, ages at which CRC incidence is higher.

Table 13.1 Estimates based on Nottingham RCT for a cohort of New Zealanders aged 50-74 undergoing FOBT screening over eight years

New Zealand eligible population (adults aged 50-74)	727,224
Exclude those with existing CRC (13,750 people, approx 2%)	713,474
Identification of eligible people using GP age-sex registers (90%) and invitation to FOBT screening	642,127
Participation in screening at first round (60%)	385,276
Number of FOBTs (adjusted for declining participation after first screening round)	1,100,000
Number of colonoscopies for positive FOBTs in 8 years (4.6% of those screened); excludes surveillance colonoscopies for those diagnosed with CRC or polyps	17,723
People diagnosed with CRC*	7,619
Deaths from all causes	107,719
Deaths from CRC	3,072
Expected number of deaths from CRC averted by screening	512 (95% CI 68-887)

** Includes diagnoses made outside the screening programme.*

Sources: Based on data from Hardcastle et al, *1996;[2] New Zealand Health Information Service,* Cancer: New Registrations and Deaths 1993, *Wellington: Ministry of Health, 1997; and Statistics New Zealand,* 1996 Census, *Wellington: Statistics New Zealand, 1996.*

Resource commitment

A population screening programme involves the commitment of considerable health sector resources. Based on the Nottingham RCT and assuming similar levels of participation, a national FOBT screening programme in New Zealand would require about 1.1 million FOBTs and 17,700 colonoscopies over the first eight years.

The resource implications, for colonoscopy in particular, are significant: approximately 4,045 people undergoing colonoscopy each year in the first two years of screening if the Nottingham protocol were followed in New Zealand. A constant subsequent colonoscopy demand, allowing for polyp surveillance, of 3,300 procedures per year has been estimated. This represents a substantial increase over the estimated 10,000 colonoscopies currently performed each year in the public sector, and could not be met within the public health system at the present time. Additional colonoscopy capacity would have to be provided so that resources were not diverted from services for symptomatic patients.

There is insufficient information to estimate precisely the costs of a national screening programme. A model based on the Nottingham protocol (biennial FOBT screening for those aged 50-74 and assuming 54% population participation), and taking information from existing screening programmes in New Zealand, yields estimates of approximately $24 million for the first screening round, reducing to $22 million for subsequent rounds.

FOBT screening for CRC exposes a well population to potentially serious adverse effects

Within a population screening programme, the follow-up bowel investigation for a positive FOBT would be colonoscopy. About 2 percent of people screened in the first screening round require colonoscopy. Overall, in the Nottingham trial, 4 percent of those who accepted at least one FOBT underwent full colonoscopy on one or more occasion; the majority of these colonoscopies were performed in individuals who did not have CRC or significant polyp pathology.

For every 10 people proceeding to colonoscopy on the basis of a positive FOBT: one will have CRC and three will have an adenoma greater than 10 mm. Six will have no significant abnormality, yet will be exposed to the rare but

significant risks of colonoscopy including: bleeding, perforation to the bowel wall and occasionally death. The level of risk for colonoscopy used in a screening programme is uncertain. The limitations of the literature concerning colonoscopy complications have been outlined in Chapter 6.1 (pages 43-5). Estimates for the risk of perforation for diagnostic procedures range from 0.045 to 0.17 percent. The mortality rate for diagnostic colonoscopy was reported as 0.02 percent in 1989 but in later studies the same, or a lower, figure has been reported for combined diagnostic and therapeutic procedures.

Barium enema is a safer procedure than colonoscopy. However, many of the abnormalities identified with this examination will require follow-up colonoscopic investigation and there is no published evidence from RCTs of the effectiveness of screening by FOBT followed by DCBE. Interim data from the Göteborg RCT of population screening with the faecal occult blood test (using rehydrated Hemoccult II slides) in which positive FOBTs were investigated with proctoscopy, rectosigmoidoscopy (60 cm) and DCBE, suggest a 10 percent relative reduction in mortality in the screened group.[1]

The risk of adverse events resulting from colonoscopy in a screening programme has to be weighed against the benefits of the programme.

The level of public support for screening programmes is likely to be affected by the accuracy of the tests and by their possible adverse consequences.

Comparison of FOBT screening for CRC with mammographic screening for breast cancer

It is helpful to compare the benefits of screening for CRC with FOBT (according to the Nottingham protocol) with the benefits and risks of other screening programmes. The comparison in Table 13.2 (page 104) is based on data from the Swedish two-county trial of screening for breast cancer, restricted to results for an eligible population of 100,000 women aged 50 to 69, and the Nottingham trial of screening for CRC for an eligible population of 100,000 aged 50 to 74, over approximately eight years for each screening programme.

FOBT screening is less likely to detect CRC than mammography screening is to detect breast cancer (32% of cancers detected compared with 64%). This is because of the lower sensitivity of the FOBT (53.6% compared with 86%) and the lower participation in CRC screening (60% for FOBT in the Nottingham RCT compared with 90% for mammography in the Swedish RCT). In New Zealand, participation was 74 percent in the Otago and Southland breast cancer screening pilot programme.

In an FOBT screening programme only one in 10 people undergoing colonoscopy has CRC.[2] In a breast cancer screening programme over half of the women who undergo breast biopsy have breast cancer.[3]

Reproducibility in New Zealand

The mortality reductions demonstrated in RCTs are unlikely to be reproduced in screening programmes conducted in the 'real world'. This is of particular concern for CRC screening given that the benefit found in the research setting of the Nottingham and Funen trials was modest.

This uncertainty relates largely to the level of participation, service quality and provision of adequate resources, particularly to meet the increased demand for colonoscopy.

These issues could conceivably be addressed by pilot programmes designed to test that the benefits reported in RCTs are achievable in a local setting. For example, pilot programmes were established for breast cancer screening in New Zealand. In 1988 a working party which assessed the RCT-based evidence of benefit and risk for screening by mammography reported a 30 percent reduction in breast cancer mortality. Acknowledging that the efficacy of breast screening had been established in overseas studies, the working group recommended that pilot programmes be undertaken to determine whether the benefits reported from these studies could be reproduced in New Zealand at reasonable cost.[4] FOBT screening differs in that pilot programmes cannot address the major issues of concern: the modest potential benefit and the small but real potential for harm. Therefore, the Working Party does not recommend pilot programmes.

Table 13.2 Comparison of faecal occult blood screening with mammographic screening

	Screening programme	
	Colorectal cancer	*Breast cancer*
Population	100,000 men & women aged 45-74	100,000 women aged 50-69
Number of person-years	800,000	800,000
Screening test	faecal occult blood test	mammography
Screening frequency	two-yearly	two-yearly*
Participation rate	53% at first screen (but 60% screened at least once)	90% at first screen
Number screened	60,000	90,000
Sensitivity of test	53.6%	86%
Number of colonoscopies/ breast biopsies	2,400 people have at least one colonoscopy	2,390 women have breast biopsies
Complications arising from investigations	4 perforations (0.17%)† 0-4 deaths (1 death per 5,000 colonoscopies; range 0-0.15%)†	0 deaths (<1 in 100,000 anaesthetic-related deaths in ASA I and II patients)
Number of deaths prevented in population of 100,000 over 8 years	11 to 146 (range based on 95% CI around relative risk)	64 to 180 (range based on 95% CI around relative risk)
NNT (Number of person-years required in the eligible population to prevent 1 death)	5,500-72,700	4,400-12,500‡
NINT (Number of people required to be offered screening)	690-9,090	550-1,560
Number of screens performed for each death prevented §	1,200-16,200	1,400-4,000‡
Number of colonoscopies/ breast biopsies per death prevented	16-218	13-37

* *The mean screening interval for women aged 50-69 in the Swedish two-county trial was actually 33 months.*
† *See Chapter 6.1, pages 43-5.*
‡ *Calculated over 8 years (rather than 5 years, as in Tabar* et al, *1989*[3]*).*
§ *Adjusted for declining participation after first screening round.*

Sources: Based on data from Hardcastle et al, *1996,*[2] *Tabar* et al, *1989;*[3] *and Tabar L, Fagerberg G, Duffy SW,* et al, *Update of the Swedish two-county program of mammographic screening for breast cancer,* Radiol Clin Nth Am *1992; 30: 187-210.*

Future prospects

The Working Party recognises that CRC is an important cause of morbidity and mortality in New Zealand and, as evidence of benefit from new FOBTs and other screening modalities becomes available, the decision not to screen should be reviewed.

Recommendations

1 Given the modest potential benefit, the considerable commitment of health sector resources and the small but real potential for harm, population-based screening for colorectal cancer with faecal occult blood tests is not recommended in New Zealand.
2 Population-based screening for colorectal cancer with other modalities, such as flexible sigmoidoscopy, colonoscopy or double-contrast barium enema, is also not recommended as there is not yet evidence from randomised controlled trials that screening with any of these modalities produces a reduction in colorectal cancer mortality.
3 These decisions should be reviewed as evidence of benefit from new faecal occult blood tests and other screening modalities becomes available.
4 Colorectal cancer is recognised as an important cause of morbidity and mortality and it is recommended that New Zealand participate in international research in this area.
5 Wider consultation and further consideration should be undertaken to develop appropriate advice on surveillance recommendations for groups identified to be at increased risk of colorectal cancer.

References

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APPENDIX 1: MEMBERS OF THE WORKING PARTY

Susan Parry (Chair)	Gastroenterologist, Middlemore Hospital, Auckland
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Judi Strid	Consumer Representative, Women's Health Action, Auckland
Clint Teague	Pathologist, Medical Laboratory, Wellington

APPENDIX 2: INTERNATIONAL RECOMMENDATIONS ON CRC SCREENING

A number of overseas organisations have published positions or policies on screening for CRC, summarised below. The first five reports were published after the December 1996 publication of results from the Nottingham and Funen RCTs.

Reports published 1997 and later

The Cochrane Collaboration

A systematic review of the effects of screening for CRC using FOBTs. The findings were that: 'Although benefits of screening are likely to outweigh harms for populations at high risk of colorectal cancer, more information is needed about the harmful effects of screening, the community's responses to screening, and costs of screening for different healthcare systems before widespread screening can be recommended.'[1]

National Cancer Institute

The Institute found evidence to support the following:

- Screening with guaiac-based FOBTs, either annually or biennially, in people aged 50 to 80 decreases mortality from CRC.
- Regular screening by sigmoidoscopy in people over 50 years may decrease mortality from CRC; however, there is insufficient evidence to determine the optimal interval for such screening.[2]

American Gastroenterological Association

Endorsed by American Cancer Society, American College of Gastroenterology, American Gastroenterological Association, American Society of Colon and Rectal Surgeons, American Society of Gastrointestinal Endoscopy, Crohn's and Colitis Foundation of America, Oncology Nursing Society and the Society of American Gastrointestinal Endoscopic Surgeons. Recommendations for people at average risk for CRC (asymptomatic, age 50 years, no other risk factors):

- Screening: offer FOBT screening each year.
- Diagnostic work-up of positive FOBT: average-risk people with a positive test with any sample should have an examination of the entire colon and rectum by colonoscopy. An alternative is DCBE, preferably with flexible sigmoidoscopy.

Recommendations were also made about screening average-risk people with flexible sigmoidoscopy, DCBE and colonoscopy.[3]

Agency for Health Care Policy and Research

An evidence-based review of approximately 3,500 citations, published between 1966 and 1994, on screening for CRC and adenomatous polyps in asymptomatic persons at average risk for CRC, subsequent follow-up procedures in those with positive screening tests, and surveillance of those with CRC. The review identified a number of areas that require further research, including:

- the optimal screening intervals for the currently available screening tools
- the effect of CRC screening and subsequent diagnostic evaluation on patient quality of life
- the effectiveness of screening flexible sigmoidoscopy, colonoscopy and barium enema, ideally with RCTs.[4]

Australian Health Technology Advisory Committee

- On the basis of published evidence, and subject to favourable preliminary testing, it was recommended that Australia develop a programme for the introduction of population screening for CRC by FOBT for the average-risk population (well population aged over 50).
- Given the uncertainties relating to the most effective means of implementing such a programme and to the feasibility, acceptability and cost-effectiveness of such a programme in the Australian setting, the screening programme should commence with preliminary testing involving a number of pilot and feasibility studies.[5]

Reports published up until the end of 1996

World Health Organization

Guidelines from the WHO Collaborating Centre for the Prevention of Colorectal Cancer on the primary prevention of CRC, the screening of average-risk individuals, the screening of relatives of patients with CRC, and the surveillance of patients with colorectal polyps and ulcerative colitis. WHO found that there were strong data to support the effectiveness of screening of average-risk individuals with FOBT and sigmoidoscopy, and colonoscopic polypectomy for patients with polyps.[6]

US Preventive Services Task Force

Screening was recommended for those 50 years and older with either annual FOBT or sigmoidoscopy, or both; however, insufficient evidence was found to determine which screening modality is preferable or whether the combination of FOBT and sigmoidoscopy produces greater benefits than does either test alone.[7]

American College of Physicians

The ACP recommended offering a variety of screening options to people aged 50 to 70, depending on local resources or patient preferences:

- Screening was recommended with flexible sigmoidoscopy, colonoscopy and air-contrast barium enemas, repeated at 10-year intervals.
- Annual FOBT should be offered to persons who decline the screening tests mentioned above.
- Screening should start at age 50 and conclude at 70 years.[8]

US Office of Technology Assessment
A cost-effectiveness study of screening for CRC. Screening in average-risk individuals beginning at the age of 50 was found to be a 'relatively good investment for society'. The choice of screening strategies was not clear, however: strategies that involved either flexible sigmoidoscopy or DCBE (but not both) appeared to be comparable and were also more cost-effective than other screening modalities.[9]

Canadian Task Force on Periodic Health Examination
The CTF found 'insufficient evidence to support the inclusion or exclusion of faecal occult blood, sigmoidoscopic or colonoscopic screening of asymptomatic individuals over the age of 40.' It recommended that 'efforts directed at identification of different risk groups and development of different strategies for these groups may be appropriate.'[10]

European Group for Colorectal Cancer Screening
It was found that mortality from CRC could be reduced in people screened using guaiac-based FOBT or sigmoidoscopy. Ongoing trials in Britain, Denmark, Sweden and France would indicate the extent of mortality reduction that can be achieved with FOBT population screening.[11]

Italian National Committee for Colorectal Cancer Prevention
The NCCCP concluded that there was no convincing evidence to support population screening; instead, it recommended a centrally coordinated intervention programme to evaluate the clinical effectiveness of various screening modalities, whether screening was cost-effective, and the impact of screening upon the Italian health system.[12]

Royal Australian College of General Practitioners
For average-risk people, the best option was uncertain. FOBT should not be used for investigation of rectal bleeding, and was not currently recommended for screening in Australia.[13]

Gastroenterology Society of Australia, Australian Gastroenterology Institute & Australian Cancer Society
Endorsed by the Australian Cancer Network. Recommendations included the following:
- Funding should be made available for high-quality exploration of the implications and mechanisms of introduction of screening for CRC in Australia.
- Routine screening for people aged 50 years or over who have no symptoms and no special risk factors is not recommended.[14]

Colorectal Surgical Society of Australia & The Gut Foundation
A guide for medical practitioners on the prevention, diagnosis and treatment of CRC. Findings included:
- Although selective screening of high-risk groups of patients was feasible and should reduce mortality and morbidity from CRC, screening the entire population by colonoscopy was not practical.
- Colonoscopy was seen as the procedure of choice for detecting adenomatous polyps proximal to the splenic flexure.
- As up to 50 percent of adenomatous polyps occur beyond the reach of the flexible sigmoidoscope, it was recommended that the discovery of any polyps in the left colon should be followed by complete colonoscopy.
- Average-risk individuals should be screened by FOBT annually from 40 years of age.
- All positive tests need investigation, preferably with colonoscopy.
- GPs should consider screening with flexible sigmoidoscopy beginning at 50 years of age, repeating every three to five years in conjunction with annual FOBT.[15]

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GLOSSARY

Absolute risk reduction	The absolute difference in the rate of events between the experimental group in a study and the control group. If the risk reduction is 0 there is no difference between the groups. For undesirable outcomes such as cancer, a relative risk that is less than 1 means that the intervention has been effective in reducing the risk of that particular outcome.
Adenoma	A non-cancerous growth in the lining of the bowel which can progress to cancer. Same as adenomatous polyp.
Adenomatous polyp	See adenoma. It is thought that a majority of CRCs develop from pre-existing adenomatous polyps; however, only a minority of adenomatous polyps are thought to progress to cancer.
Adjuvant therapy	The addition of one or more therapies to aid the original treatment.
Assessment	All follow-up investigative procedures arising from a positive test result.
Autosomal dominant	An autosome is any chromosome that is not a sex chromosome; autosomal dominant is a dominant gene carried on an autosome.
Barium enema	X-ray examination using barium sulphate to outline the contour of the large bowel.
Colon	The large bowel (extending from the end of the small intestine to the rectum), excluding the rectum and anus.
Colonic mucosa	The lining or surface of the intestines.
Colonoscopy	Visual examination of the colon via a flexible tube (colonoscope) performed under sedation by a specialist.
Colorectal neoplasm	See neoplasm.
Confidence interval (CI)	The range within which the true size of effect of a treatment or intervention (never exactly known) lies with a given degree of assurance. A 95 percent confidence interval is the interval which includes the true value in 95 percent of cases.
Confounding factor	A factor to consider when looking at the association between exposure to a cause (or risk factor) and the occurrence of disease. Age groups and sex are common confounding factors as they may be associated with some exposures and also the older a person gets the more likely he or she is to develop some diseases.
Cost-benefit analysis	A cost-benefit analysis is an evaluation which places a monetary value on benefits or outcomes. The costs and benefits are expressed in dollar terms and examined to find out whether the benefits outweigh the costs.
Cost-effectiveness	Cost-effectiveness analysis is a comparative technique. Two or more health programmes, or programme options, are compared in terms of the cost per unit of output (eg, cost per cancer detected) or cost per unit of outcome (eg, cost per life saved, cost per year of life saved, cost per quality-adjusted year of life saved).
Coverage	The proportion of all eligible people screened by the programme, calculated as the total number screened divided by the number of those who are eligible by age and domicile, according to the census.
De novo	New; not pre-existing.
Detection rate	The number of people with cancers detected within the screening population, calculated by the number with cancer diagnosed by screening divided by the number of people screened in a specified time period.
Distal colon	A section of the bowel, from the splenic flexure to the anus.
Dukes' Classification	A system of classifying colorectal tumours, based on the depth of invasion and degree of metastasis.
Dysplasia	Alteration in size, shape and organisation of adult cells, often seen in colonic adenomas.
Effectiveness	The extent to which a specific intervention, procedure, regimen or service, when deployed in the field, does what it is intended to do for a defined population.
Efficacy	The extent to which a specific intervention, procedure, regimen or service produces a beneficial result under ideal conditions. Ideally, the determination of efficacy of CRC screening is based on the results of a randomised controlled trial (with CRC mortality as the outcome measure).
Endoscopy	A visual examination of internal structures of the body with a lighted instrument. Colonoscopy and flexible sigmoidoscopy are endoscopic examinations of the bowel.
Epithelium	The layer of cells which covers all the body surface and lines all the cavities and hollow tracts (eg, the gastrointestinal tract).
Exudation	Leakage of fluid and cells from a blood vessel.
False negative	A negative screening test in a person who has cancer at the time the screening test is conducted. This is estimated in terms of interval cancers.

False positive	A positive screening test result in a person who does not have the disease being screened for.
Flexible sigmoidoscopy	See sigmoidoscopy.
Fluoroscopic examination	Examination with a fluoroscope, which is an instrument for visual observation of the body using X-ray. Radio opaque agents are often used during this procedure.
Germ-line mutation	A permanent change in a gene which is then able to be inherited. Mutations can occur naturally and spontaneously or they may be due to exposure to mutagens.
Histology	The study and reporting of diseased tissue.
Ileorectal anastomosis	A connection between the ileum (small bowel) and the rectum; it is not normal for these to be connected.
Index relative	The first family member to be identified with an hereditary condition or disease.
Lead-time bias	Screening advances the date of diagnosis, thereby extending the interval between diagnosis and death, even if the time of death is unchanged. In screened individuals, diagnosis is made earlier than it would have been in the absence of screening; this is known as the 'lead time' obtained by screening. The survival time is measured from time of diagnosis until death; individuals diagnosed on screening will have longer survival times, even if screening had no effect on their time of death.
Length bias	Tumours grow at different rates and therefore remain for differing periods in the presymptomatic screen-detectable phase. With each screening round, the probability of detecting slow-growing tumours is greater than that of detecting fast-growing tumours, because slower growing tumours remain in the presymptomatic screen-detectable phase for longer. Thus, there will be fewer fast-growing tumours in a screened group compared with an unscreened group. Slow-growing tumours tend to have a better prognosis, which may account for differences in outcome between the groups.
Lumen	The cavity or channel within the intestine.
Lymphatics	Capillaries or vessels that collect lymph from the tissues and carry it to the blood stream,
Mesentery	A fold of membrane that attaches various organs to the body wall, especially the intestine.
Metachronous	Cancers arising at a later time than the index lesion.
Metastastic disease	The spread of cancer to other parts of the body.
Morphology	The form and structure of a particular organ, tissue or cell.
Mucosa	The mucous membrane which lines certain organs (eg, the colon or rectum).
Negative predictive value	The probability that a person with a negative test truly does not have the disease.
Neoplasia	See neoplasm.
Neoplasm	A new, abnormal growth.
Odds Ratio (OR)	An estimate of the relative risk.
Opportunity cost	The opportunity forgone by allocating resources to a particular option.
Overdiagnosis bias	Screening detects very early lesions. It is possible that some detected cancers would not affect a person in his or her lifetime (the person remaining asymptomatic and dying from some other cause). Because these cancers are more likely to be found in a screened rather than an unscreened group, comparisons of outcome could favour the screened group irrespective of any real effect of screening.
Participation rate	The total participation rate, calculated as the total number of people screened divided by the number invited.
Phenotypic changes	The expected changes or features expressed in a disease process that aids recognition of the disease.
Polyp	A growth in the lining of the bowel. A polyp can be sessile (no stalk) or on a stalk or stem. There are several kinds of polyps: adenomatous polyps can develop into cancer; hyperplastic polyps are not thought to progress to cancer. A minority of CRCs can arise from small flat polyps called flat adenomas.
Polyp dwell time	The average period of time an adenomatous polyp takes to evolve from a small adenoma into cancer.
Polyposis	The condition of having many polyps in the large bowel.
Population screening	The organised application of screening to large groups of people – also described as 'mass screening'. Population screening differs from opportunistic screening, where tests are offered on an ad-hoc basis to individuals in the population.
Porphyrin	An iron or magnesium-free cyclic tetrapyrrole derivative which forms respiratory pigments in animals and plants.
Positive predictive value	The probability that a person with a positive test truly has the disease.
Proctitis	Inflammation of the rectum.
Proctoscopy	Examination of the rectum with a proctoscope (a speculum or tubular instrument with a light).
Proctosigmoidoscopy	Examination of the rectum and sigmoid colon with a sigmoidoscope.
Proctosigmoiditis	Inflammation of the rectum and sigmoid colon.
Prophylactic colectomy	Excision of the colon in a person at increased risk of developing a colon cancer.
Proximal colon	The caecum, ascending and transverse colons. In this report often refers to the portion of the bowel not examined by a flexible sigmoidoscope.

Quality-adjusted life year (QALY)	Each year of life gained by a health programme is weighed by the value of that year. The weight for a year of good health is 1; the weight for a year of poorer health or disability is less than 1. QALYs are used in comparisons of programmes which yield different levels of improvement in health status.
Randomised controlled trials (RCTs)	Trials in which people in a population are randomly allocated into two groups, usually called study and control groups, to receive or not to receive an intervention. For trials to assess screening procedures, the study group is offered screening and the control group is not. The results are assessed by comparing rates of death (or other end points) from the disease in the two groups. RCTs are generally regarded as the most scientifically rigorous method of assessing the efficacy of screening.
Rectosigmoidoscopy	Examination of the rectum and sigmoid colon.
Rectum	The lower section of the bowel ending with the anus.
Risk factor	An aspect of a person's condition, lifestyle or environment which increases the probability of occurrence of a disease.
Screening	The examination of asymptomatic or well people in order to classify them as likely or unlikely to have a disease.
Screening pathway	The stages of an organised approach to screening. These include: identifying and inviting the eligible population to be screened on a regular basis; providing tests which are acceptable and accessible; high-quality laboratory services for the examination of the tests; high-quality services for the assessment and diagnosis of those with positive tests; adequate treatment of those with abnormalities. The pathway also includes monitoring and evaluation of all of these stages.
Selection bias	Screening is offered to a particular group of people, not all of whom decide to accept. People who choose to take part may have different underlying risks of developing or dying from the disease being screened for (eg, those with a family history of the disease may participate because they perceive themselves to be at higher risk); therefore, their prognosis would differ from non-participants even in the absence of screening. Selection bias can operate in two directions: if low-risk people are more likely to be screened, then mortality is likely to be lower anyway and the effect of screening will be overestimated; if high-risk people are more likely to be screened the screening effect could be underestimated.
Sensitivity	The probability of screening positive if the disease is truly present.
Sigmoid colon	Lower part of the descending colon.
Sigmoidoscopy	The examination of the rectum and sigmoid colon using a lighted tube (sigmoidoscope). The sigmoidoscope may be flexible or rigid.
Snare polypectomy	A procedure for removing polyps, usually during a colonoscopy, where a thin wire is slipped on the polyp like a snare.
Somatic mutations	Any mutation of a cell in the body that is not in a reproductive cell (sex cell).
Specificity	The probability of screening negative if the disease is truly absent.
Splenic flexure	The bend in the colon between the transverse and descending colons.
Sporadic cancer	A cancer which has no genetic or familial link.
Stage	A description of how widely a cancer has spread to adjacent lymph nodes and distant spread.
Stoma	An incised opening which is kept open for drainage. After removal of the colon, a colostomy bag is attached to a stoma in the abdominal wall to collect faecal matter which would normally have passed through the colon and from there to the rectum.
Surveillance	Monitoring people known to have a disease or to be at increased risk of a disease.
Tumour marker	A substance in the body associated with the presence of a cancer.
Villous architecture	Adenomatous polyps of the colorectum are divided into three main microscopic types: tubular, villous and mixed tubulovillous. Tubular architecture is present when the glands of the tumour form hollow tube-like structures; villous architecture is present when the glands form delicate frond-like (finger-like) structures; tubulovillous architecture is present when tubular or villous architecture forms less than 80 percent of the total. Villous architecture is associated with the greatest potential to undergo malignant change and tubular architecture with the least potential to undergo malignant change.

THE NATIONAL HEALTH COMMITTEE WELCOMES YOUR COMMENTS

Do you agree with the three main reasons the Working Party decided not to recommend population screening with FOBT at this time?

- the potential modest benefit
- the considerable commitment of health sector resources
- the small but real potential for harm.

Do you agree with the decision regarding other screening modalities?

Please send your comments by 31 December 1998 to:

Population Screening for Colorectal Cancer
National Health Committee
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Wellington