Recommendations for Population-based Colorectal Cancer Screening

Reducing Canadian Colorectal Cancer Mortality Through Screening

In 1998, following discussion with experts and stakeholders in Canada, Health Canada established a National Committee on Colorectal Cancer Screening comprised of members from provinces and key organizations from across the country. The Committee's mandate was to explore the scope and issues surrounding population-based colorectal cancer (CRC) screening, and to develop a set of final recommendations. During its 2 years, the Committee examined evidence from randomized controlled trials (RCTs) and statistical modeling. The Committee also reviewed recommendations/reports from other countries which had undertaken similar evaluations, and information from expert opinion. Throughout the process, the Committee members were encouraged to identify issues or gaps in data/knowledge for which they required more information to formulate the final set of recommendations. (A companion document, *Technical Report for the National Committee on CRC Screening*, presents the technical information that was considered over the 2 years). The National Committee came to a consensus and developed its recommendations for population-based CRC screening in Canada.

Evidence, Information and Issues Considered for Recommendations

Based on evidence from available randomized controlled trials[1-4], the National Committee agreed that there was strong evidence to support that fecal occult blood screening could reduce CRC mortality by 15% to 33% in a targeted population of 50 to 74 year olds. Since an estimated 6,400 CRC deaths were expected to occur in Canada in 2001, and since the majority of these would be among Canadians aged 50 or older, the National Committee believed there could be a substantial potential for population benefit with CRC screening. However the National Committee also recognized that CRC screening carries some risks and opportunity costs.

Among the various tests which have been used for screening, only the Fecal Occult Blood Test (FOBT), to date, has been shown to be effective and evaluated in randomized trials as the initial screening test. By itself, and used alone, it carries negligible risk; nonetheless, follow-up with colonoscopy (as has been the practice in most RCT's), presents low but measurable risks of serious complications. The issue of follow-up with another test is important because FOBTs are associated with false positive results.[5] The Population Health Model (POHEM) developed by Statistics Canada estimated that 75 deaths and 611 perforations could result from diagnostic colonoscopy with a biennial screening program that starts in Canada in 2000 and ends in 2009. This is in contrast to an estimated reduction in CRC mortality of 16.7% (or 7,740 deaths) with biennial screening over the same 10 year

period. At the individual level, the lifetime probability of death from CRC would fall from 0.29% to 0.19% for an individual who participates in all screening events, of a biennial program, from the age of 50 to 74; the lifetime risk of colonoscopy-induced death would be 0.005% for that same individual.

Clearly, these estimates are difficult to verify/quantify at the population-level, as most studies reporting colonoscopy complications are carried out in patient groups that include symptomatic individuals. The risks among a healthy screening population are so low that they are difficult to estimate from the RCT's presented to date. Nevertheless, the National Committee concluded that while the benefits clearly outweigh the risks, any individual contemplating screening with the FOBT should be made aware of both the risks and benefits prior to the initial screen, and should give an informed consent to be screened.

For a screening test to have a population-based impact, there must be adequate uptake (i.e. participation) in the target population. Thus, the National Committee evaluated the potential acceptability of the test and concluded that there was little or no information available on the likely participation rate that could be expected with a biennial screening program. In the RCTs to date[1-4], adherence to the initial screening test (the FOBT) ranged from 53% to 67% in non-volunteer populations, with 38% to 46% of those invited completing all of the recommended screening and diagnostic tests. However, participation rates in RCTs, where the test efficacy is questionable by definition, may be different than when the test is proven to have a mortality benefit.

Finally, the National Committee recognized that any recommendations about population-based CRC screening will have resource implications. Resources may differ among provinces so provincial strategies may need to take this into account. Prime resource impacts include the costs of the initial medical consultation prior to taking the FOBT, and the availability of resources for colonoscopy or other follow-up diagnostic tests, such as double contrast barium enema or flexible sigmoidscopy for some geographic areas. Based on participation and re-screen rates of 67% and 93% respectively among Canadians aged 50 to 74, the POHEM estimated the cost-effectiveness of a biennial FOBT screening program to be $11,907 per life year gained. The literature has reported that screening average risk individuals for CRC is as cost-effective as screening for other cancers.[6] The cost per life year gained has been quoted at $20,000 (US), which falls well within the range of commonly accepted, cost-effective screening programs.[7]

The National Committee strongly urges the need for regular, periodic review of new technologies for CRC screening. Furthermore, the National Committee also stresses the importance of on-going research into CRC and evaluation of CRC prevention interventions.

Final Recommendations

As a result of the aforementioned, the National Committee therefore recommends that:

1. Colorectal cancer screening should be made available to Canadians. In order to ensure quality screening which maximizes benefits and minimizes potential risks, ideally screening should be within an organized and structured environment, with the following elements in place:

    a. clear, concise and understandable information for patients and physicians on the risks and benefits of screening and on the administration of the test.

    b. informed consent following personal consultation with family practitioner or equivalent

    c. standardized protocols and procedures with a single entry test and options for follow-up

    d. systematic tracking and evaluation of all screening invitations (if used), testing frequency, results (including false positive and false negative rates), follow-up, and outcomes

2. Resources for screening be built up as appropriate. Recognizing disparity in human and financial resources, provinces may choose to phase in organized screening as resources permit.

3. The National Committee further recommends that, based on current evidence:

    a. Screening be offered to a target population of adults aged 50 to 74 years of age, using unrehydrated Hemoccult II or equivalent as the entry test.

    b. Individuals be screened at least every two years, recognizing that annual screening would have slight improvement in mortality reduction over biennial, but require increased resources.

    c. Positive tests be followed up by colonoscopy, with options of barium enema and flexible sigmoidoscopy where appropriate (e.g. patient preference/availability of services)

4. The National Committee believes that the benefits of screening outweigh the risks and that high quality population-based screening programs can reduce CRC mortality. Recognizing, however, that there are associated risks including death, the following elements need to be in place to protect the rights of Canadians and to maximize the benefits of screening:

    a. informed consent at the outset, including awareness of the risks and benefits of the entire screening cascade and not limited to the initial test;

    b. public awareness campaigns and promotional material including information on primary prevention and awareness of symptoms to inform the public of the availability of screening. These should supplement and not replace consultation with primary care practitioners;

    c. a high priority on quality assurance and monitoring, including criteria for endoscopy, to minimize potential risks;

    d. active education of patients and physicians while resources are being built, but that active organized recruitment be delayed pending evaluation of initial screening, i.e. compliance, complication rates, etc., in the Canadian context;

    e. ongoing evaluation procedures to ensure that organized screening be continued only if appropriate participation rate and level of safety can be maintained in the Canadian context. Targets for participation are important for population-based programs and evaluation; and

    f. research and evaluation of new tests for CRC screening be an on-going process.

These recommendations represent the consensus opinion of the group, with the exception of one participant. This participant did not feel that population based screening should be promulgated if there was a possibility to do serious harm. The remainder of the participants acknowledged this risk, but felt that it was outweighed by the possibility of benefit. Consequently, the majority opinion was that this information should be provided to individuals for their own informed decision making.

The following individuals constituted the National Committee during the period of November 1998 to December 2001 (list both). The recommendations represent the overall consensus of the individual Committee members, and not necessarily the endorsement by the respective organizations.

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Technical Report
for the National Committee on Colorectal Cancer Screening

May 2002

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Generous contributions are acknowledged from:

Dr. Francoise Bouchard (previously with Health Canada) and Dr. Heather Bryant (chair of the National Committee) for their on-going scientific contribution, support, and encouragement.

The National Committee on Colorectal Cancer Screening and the component working groups for their guidance on the content, with special mentions to Dr. Ross Stimpson, Dr. Christopher Balram, Dr. Andrew Coldman and Dr. Tony Fields.

Dr. Brent Moloughney for his insight and input on CRC screening and health services resource issues.

Dr. Francois Pierre Dussault for his guidance, updates of the literature

Maret Swayze and Leslie Gaudette for initial editing.

Marielle Demers and Rene Gelinas for their review of the french translations of the report and POHEM repsectively.

Jennifer Beaulac for the assistance in referencing and coordination of translation.

Eleanor Paulson and her team for the final editing, layout, and printing of the report, including development of the website application.

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Introduction

In 1998, following discussions with experts and stakeholders in Canada, Health Canada established a National Committee to examine the implementation of population-based colorectal cancer (CRC) screening in Canada. The Committee's mandate was to determine the issues of national importance and explore their scope, and on the basis of this information to develop recommendations with respect to population-based colorectal cancer screening in Canada.

This document presents the information that was integral to the development of the Final Recommendations by the National Committee according to agreed upon criteria.

Colorectal Cancer Screening

CRC is the third most commonly diagnosed cancer in Canada after prostate and lung cancer in men, and breast and lung cancer in women. It was estimated that in 2001, there would be 17,200 new cases and 6,400 deaths from the disease in Canada.[1] Although CRC incidence and mortality rates among men and women are declining, control strategies for this cancer are nonetheless important given that CRC continues to be an important cause of morbidity and mortality.

Evidence is limited with respect to the effectiveness and practicality of some strategies for the primary prevention of cancer. Attention has been focused, as a result, on opportunities for secondary prevention (i.e., screening), which aims to detect the disease at an early, treatable stage and thus to reduce rates of morbidity and mortality.[2]

Several randomized controlled trials (RCTs) have examined the efficacy of CRC screening using fecal occult blood testing.[3-6] While these studies have differed somewhat in the populations recruited and in the testing protocols, all have shown a benefit from screening, with a reduction in CRC mortality of 15% to 33% depending on the screening interval.[3-6]

The evidence of efficacy for screening in individuals is generally taken to be necessary but not sufficient to recommend population-based screening. Other countries have reviewed this evidence as well as the other factors that need to be considered for such screening and have come to differing conclusions. To date, no country has decided to establish national organized screening programs for colorectal cancer; however, large-scale, population screening programs with funding from government health agencies, are in place in Germany, Japan, and the USA with the implementation of others scheduled for Australia and Israel.[7] Pilot or feasibility studies have been recommended in Australia[2] and France[8,9] and have been proposed and established in Great Britain[10,11] to assess the benefits of screening a large scale population. Some jurisdictions in Israel, Australia, Italy, France, and China and some Health Maintenance

Organizations in the US are conducting or have conducted local or regional programs/studies using various FOB screening tests [12-17].

New Zealand has decided not to recommend a population-based screening program for CRC using the fecal occult blood test, given the modest potential benefit, the small but nonetheless real potential for harm, and the substantial commitment of health care resources that would be required.[18]

In Canada, some provinces have been considering the impact of implementing CRC screening. It was felt that a national committee might be able to provide some guidance on assessing population-based CRC screening.

The National Committee on Colorectal Cancer Screening

The National Committee on Colorectal Cancer Screening was chaired by Dr. Heather Bryant, Director, Epidemiology, Prevention and Screening and Vice-President of the Alberta Cancer Board; it was supported by Health Canada. Membership included nominees from the provincial cancer agencies/foundations; the Canadian Cancer Society/National Cancer Institute of Canada; professional and non-professional organizations; consumer groups; and Health Canada. The list of members of the National Committee and terms of reference for the group are presented in Appendix A.

The National Committee met six times over the course of 2 years (1998 to 2000) to explore the impact, feasibility and associated issues surrounding population-based CRC screening in Canada.

The mandate of the National Committee was not to address screening at the individual (clinical) level but, rather, to assess the impact and feasibility of population-based screening for average-risk individuals. The distinction between screening at the individual versus the population level should be emphasized. Population-based screening openly acknowledges that, in order to achieve the desired reductions in mortality, a substantial proportion of the population will need to be screened. Cost-effectiveness is closely examined when population-based screening is being considered. Screening on an ad hoc basis, as could occur if the Preventive Services Task Force recommendations were accepted and put into practice, would incur similar unit costs for individuals but would not be subject to the same scrutiny with regard to false positive rates, appropriateness of the screened population, and other measures that are important in population-based screening. This report takes a population-based approach, on the assumption that Canadians would expect a population-based benefit and that, in a publicly funded health system, appropriate monitoring to ensure maximal cost-efficiencies would be preferable to a non-organized approach.

Other Cancer Screening in Canada

In Canada, programs for organized breast cancer screening began in British Columbia in 1988 and have expanded to include all provinces, the Yukon, and the Northwest Territories. Although programs have grown over the last decade, provincial/territorial participation rates in 1997 and 1998 ranged from 11.5% to 54.7% for women 50 to 69 years of age, well below the rate of 70% targeted by screening programs in other countries.[19] The primary reason for the apparently low uptake, however, is the presence of opportunistic screening in several provinces. There is little information on screening that occurs outside of organized programs, but results from the National Population Health Survey (self-reported data) have shown substantial increases in mammographic screening in the target population. Furthermore, the rate of increase in uptake has been faster in provinces where there are organized screening programs.[20]

The need for comprehensive programs for cervical cancer screening was explored by the Conference of Deputy Ministers in 1973 and the "Walton Report" was published on behalf of the Task Force on Cervical Cancer Screening in 1976. Recognizing that cervical cancer was potentially preventable with early detection and screening, the Task Force recommended that health authorities support the development of screening programs for cervical cancer and that the participation of all women should be encouraged.[21] In 1980, the Walton Task Force was reconvened in response to the lack of implementation of these recommendations and to concerns about changes in sociosexual patterns.[22] Currently, British Columbia and Nova Scotia have well established, organized programs for cervical cancer screening. Recently, Alberta, Manitoba, Ontario, and Prince Edward Island launched programs that encourage the participation of all eligible women. Provincial programs target all women of a specified age range (usually 18-69) in their population however at the present time, no province encompasses population-based recruitment.[23]

Relevant Criteria for Population-based CRC Screening in Canada

According to Gordis, early detection of disease means "detecting a disease at an earlier stage than would usually occur in standard medical practice".[24] This implies detection at a pre-symptomatic stage, at which point the patient has no clinical complaint (no symptoms or signs) and, therefore, no reason to seek medical care for a condition.

The National Committee reviewed and assessed the appropriateness of the World Health Organization (WHO) screening criteria, developed by Wilson and Jungner in 1968 [25] from a population-based perspective, and modified them in order to reflect the Canadian context and to help fulfil the Committee's mandate. These criteria are presented in Table 1. The information that would be necessary to support each of the criteria was identified: sources of Canadian data were located, information gaps were

noted, emerging questions and issues were identified. The impact of population-based screening on mortality, the potential risk/benefit of population-based screening, and cost/resource implications were estimated using statistical modelling, through a collaboration between Statistics Canada and Health Canada.

Although the mandate of the National Committee was not specifically to address primary prevention of CRC, the Committee acknowledged that primary prevention would be complementary to any efforts towards its early detection. A short summary of the extensive literature surrounding primary prevention of CRC, as of July 2001, can be found in Appendix B.

When seeking recommendations for clinical practice, Canadian physicians can refer to the recommendations of the Canadian Task Force on Preventive Health Care (formerly the Canadian Task Force on the Periodic Health Examination). The recommendations of this group are aimed at guiding the use of preventive clinical practices for clinicians. (These recommendations were published in July 2001[26], after the last meeting of the National Committee, which took place in November 2000.) The evidence from RCTs on screening for CRC using the fecal occult blood test (FOBT) led the Canadian Preventive Services Task Force to upgrade fecal occult testing to an "A" recommendation, indicating that there is strong evidence to support the use of the test to prevent CRC. Groups at high risk of CRC are also addressed by the Canadian Task Force on Preventive Health Care.

This document describes the criteria chosen by the National Committee and the supporting information/evidence. Canadian data were used as much as possible when available and deemed to be valid.

CRC is an area of research that is rapidly evolving and changing. This document presents information that was available up to November 2000, when the National Committee met for the last time. The authors acknowledge that since that time there have been more studies and information/evidence, which are not considered in this report.

Table 1. Canadian Adaptation of the WHO Principles of Early Disease Detection*

Criterion	Canadian Adaptation of the Principles of Early Disease Detection	Principles of Early Disease Detection*
1	**•The condition should be an important health problem**	•The condition sought should be an important health problem.
2	**• The natural history of the condition, including development from latent to declared disease, must be understood. There should be a recognizable latent (asymptomatic) period or early symptomatic stage.**	• The natural history of the condition, including development from latent to declared disease, should be adequately understood. • There should be a recognizable latent or early symptomatic stage.
3	**• There should be a suitable screening test or examination.**	• There should be a suitable test or examination**.**
4	**• The overall benefit of the screening program should outweigh the potential harms from its application.**	
5	**• The test (inclusive of screening and diagnosis) and the screening program should be acceptable to the population.**	• The test should be acceptable to the population.
6	**• Evidence-based recommendations should be available regarding who should be offered further diagnostic investigation and/or treatment and the choices available to them.**	• There should be an agreed policy on whom to treat as patients.
7	**• Treatment or intervention that improves survival or quality of life (compared with not screening) should be available for patients with recognized disease.**	• There should be an accepted treatment for patients with recognized disease
8	**• Adequate staffing and facilities for recruitment, testing, diagnosis and follow-up, treatment, and program management should be available.**	• Facilities for diagnosis and treatment should be available.
9	**• The resources allocated to the screening program (including testing, diagnosis and treatment of patients diagnosed) should be economically balanced in relation to other health care priorities.**	• 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. • Case-finding should be a continuing process and not a "once and for all" project.

*Wilson JMG, Jungner G. Principles and practice of screening for disease. World Health Organization, 1968.

Criterion 1

The condition should be an important health problem.

General Canadian Patterns and Trends

CRC is a malignant tumour, which, after a relatively long period of localization in the bowel wall, invades the wall and metastasizes to the lymph nodes and other parts of the body.[2] Despite declining incidence and mortality rates, colorectal cancer continues to be an important cause of morbidity and mortality in Canada today. Trends in this cancer* over the past 30 years are shown in Figure 1. As there are differences in trends between men and women, Figures 2 through 5 compare trends in the incidence and mortality of CRC with those for the other most commonly diagnosed cancers in men and women: prostate, breast, and lung cancers.

Incidence rates of CRC peaked in 1985 among both men and women. Since that time, rates have been declining by 8% among men (Figure 2) and, more rapidly, by 19% among women (Figure 3).[1] This is in contrast to prostate cancer, whose incidence rates increased, somewhat dramatically, after 1990 and are now declining. Breast cancer, in which there were small but steady annual increases in incidence over the last 30 years, stabilized in 1993. In sharp contrast are incidence rates of lung cancer, which, after increasing over the past three decades and levelling off in 1993, continue to increase rapidly among women. The rates among men stabilized in the mid-1980s and have since shown a consistent decline.

Mortality from CRC has declined among both men and women and somewhat more rapidly since 1985, particularly among women. Similarly, mortality from breast cancer has declined since 1986. After years of slowly rising rates, mortality from prostate cancer stabilized in the early 1990s and has shown some small declines. In contrast to the decline in mortality among men, rates of mortality from lung cancer among women continue to increase.

Incidence in particular tends to show a slight east-to-west increasing gradient when provincial rates are compared. Rates are slightly higher among both men and women in eastern provinces than in western Canada. This east-west gradient is not as apparent in rates of mortality.[1]

* ICD-9:153-154

Cancer of the colon and rectum accounts for 11% to 15% of all cases of cancer in the Western world.[27] According to the most recent (1988-1992) worldwide cancer registration data,[28] very high age-standardized (world population) incidence rates are found in North America, Australia, and New Zealand. Europe is reporting somewhat lower rates, and the lowest rates are found in India and Africa. The Japanese male population in Hawaii and the non-Maori female population in New Zealand have the highest age-standardized rates of CRC incidence in the world (53.5 per 100,000 population and 40.8 per 100,000 respectively). In addition to variations among countries, in Europe there is variation in incidence rates within countries.[27]

When incidence rates of CRC are compared among racial and ethnic groups in the U.S., the influence of cultural and socioeconomic differences (e.g., lifestyle practices such as dietary habits) or the potential interaction of genetic and environmental factors is revealed. Incidence, mortality and survival patterns in these populations may also be influenced by the availability of, access to, and utilization of preventive medical services and high-quality health care.[29]

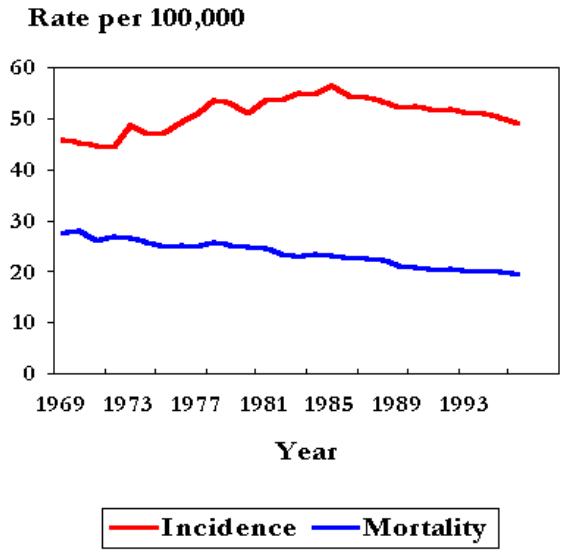
The risk of CRC increases with age (Figure 6) and occurs most frequently in the proximal colon, followed by the rectum, and distal colon. With increasing age, the percentage of cases with proximal colon tumours increases whereas the percentage with rectal tumours declines. Although the patterns in men and women are similar, the change with age in the relative contribution of proximal versus distal tumours is greater in women.[1] In Canada between 1979 and 1996, incidence rates among men were highest for rectal cancer, followed by proximal cancers and distal cancers. Among women, incidence rates of proximal colon cancers were highest, followed by rectal and distal cancers.[30]

Although incidence and mortality rates for CRC are falling, it is projected that the absolute numbers of new cases and deaths will probably continue to rise to the year 2010 because of the aging of the "babyboom" generation. Among males, the number of new cases and deaths will be approximately 1.34 and 1.36 times the 1998 values. Similarly, among females, these numbers will be approximately 1.16 and 1.21 times the 1998 values. Projected estimates of prevalence indicate that by 2010 the number of men and women in Canada who have CRC or have recovered from the disease will be approximately 1.7 and 1.5 times the number with colorectal cancer in 1998 (projected: 56,752 cases in males; 50,070 cases in females).[31]

In 2001, an estimated 17,200 new cases of CRC (approximately 13% of all new cases of cancer) were diagnosed. It was the second most commonly diagnosed cancer in women (7,900) after breast cancer, and the third most commonly diagnosed cancer in men (9,300) after prostate cancer and lung cancer. The estimated number of deaths from CRC in 2001 (6,400) ranked second only to lung cancer. Colorectal cancer is therefore

responsible for more deaths among Canadians that are not primarily due to the use of tobacco than any other cancer.[1]

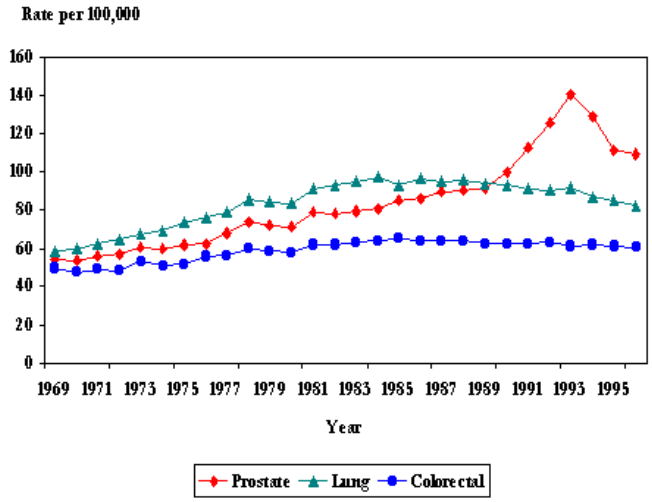
Figure 1. Age-Standardized Incidence and Mortality for Colorectal Cancer, Canada, 1969-1996



Note: Rates standardized to the age distribution of the 1991 Canadian population

Source: Statistics Canada data analyzed by Cancer Bureau, Centre for Chronic Disease Prevention and Control, Health Canada

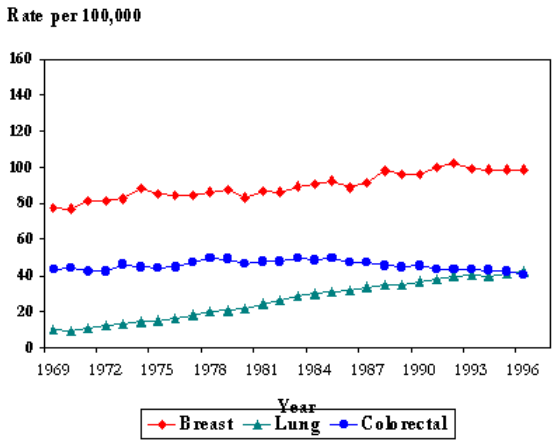
Figure 2. Age-Standardized Incidence for Prostate, Lung, and Colorectal Cancers, Males, 1969-1996, Canada



Note: Rates standardized to the age distribution of the 1991 Canadian population

Source: Statistics Canada data analyzed by Cancer Bureau, Centre for Chronic Disease Prevention and Control, Health Canada

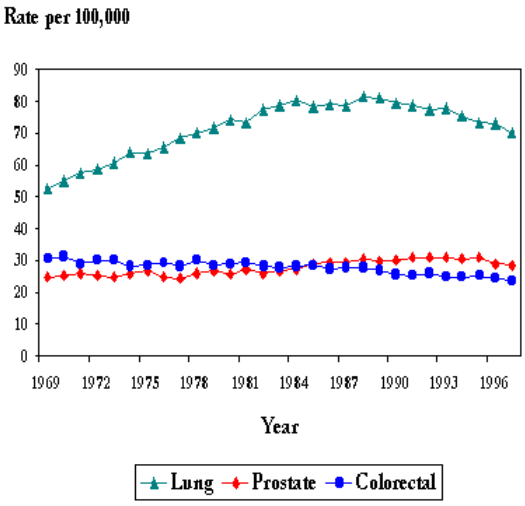
Figure 3. Age-Standardized Incidence for Breast, Lung and Colorectal Cancers, Females, 1969-1996, Canada



Note: Rates standardized to the age distribution of the 1991 Canadian population

Source: Statistics Canada data analyzed by Cancer Bureau, Centre for Chronic Disease Prevention and Control, Health Canada

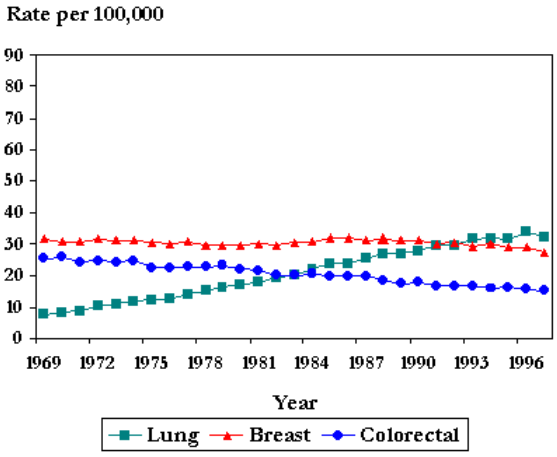
Figure 4. Age-Standardized Mortality for Lung, Prostate, and Colorectal Cancers, 1969-1997, Males, Canada



Note: Rates standardized to the age distribution of the 1991 Canadian population

Source: Statistics Canada data analyzed by Cancer Bureau, Centre for Chronic Disease Prevention and Control, Health Canada

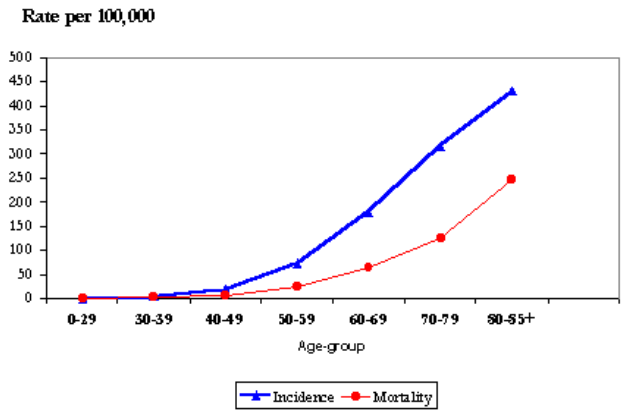
Figure 5. Age-standardized Mortality for Lung, Breast and Colorectal Cancers, Females, 1969-1997



Note: Rates standardized to the age distribution of the 1991 Canadian population

Source: Statistics Canada data analyzed by Cancer Bureau, Centre for Chronic Disease Prevention and Control, Health Canada

Figure 6. Age-Specific Incidence and Mortality Rates for Colorectal Cancer, 1987 - 1996, Canada



The probability (%) of Canadians developing colorectal, breast, prostate or lung cancer within a specific decade of age and the lifetime probability of developing or dying from these cancers are presented in Table 2.[1] The lifetime probability is presented both as the probability (%) and the inverse of the probability. For example, one in 18 women (lifetime probability of 5.5 %) and one in 16 men (lifetime probability of 6.3%) will develop colorectal cancer during their lifetimes. One in 39 women (lifetime probability of 2.5%) and one in 36 men (lifetime probability of 2.8%) will die from the disease. Women have a higher probability of dying from breast and men of prostate cancer than of colorectal cancer.

The short-term risk of cancer is described by the probability of developing cancer within the following decade. For example, although Canadian men have a lifetime risk of 6.3% of developing CRC, a 60 year old man has a 2% chance of developing CRC before age 70 (Table 2).

Table 2. Lifetime Probability of Developing or Dying from Colorectal, Lung, Breast and Prostate Cancer*

Probability (%) of Developing Cancer by Age Group (next 10 years)							Lifetime Probability (%)			
							Developing Cancer		Dying from Cancer	
	30-39	40-49	50-59	60-69	70-79	80-89	%	One in:	%	One in:
MALE										
Prostate	†	0.1	1	4.1	6.3	4.9	11.2	8.9	3.6	27.5
Lung	†	0.2	1.1	3.1	4.4	3.3	8.8	11.4	8.1	12.4
CRC	**0.1**	**0.2**	**0.8**	**2**	**3.1**	**2.7**	**6.3**	**15.9**	**2.8**	**36.2**
FEMALE										
Breast	0.4	1.3	2.3	3	3.2	2.2	10.6	9.4	3.9	25.8
CRC	**†**	**0.2**	**0.6**	**1.2**	**2.2**	**2.3**	**5.5**	**18.2**	**2.5**	**39.4**
Lung	†	0.2	0.8	1.7	2.1	1.2	5.3	19	4.5	22.4

*National Cancer Institute of Canada. Canadian Cancer Statistics 2001. Toronto, Canada, 2001: "The probability of developing cancer is calculated based on age- and gender-specific cancer incidence and mortality rates for Canada in 1996 and on the abridged life tables based on 1995-1997 all cause mortality rates. The probability of dying from cancer represents the proportion of persons dying from cancer in a cohort subjected to the mortality conditions prevailing in the population at large in 1997".
†Value less than 0.05

Cancer was the leading cause of potential years of life lost (PYLL) for men and women in 1997, at 894,000 years. In that year, the three leading cancers in terms of PYLL for men were lung, prostate, and colorectal cancer, accounting for 48% of the total PYLL. The three leading cancers for women were lung, breast, and colorectal cancer, accounting for 52% of the PYLL due to cancer.[1]

Table 3. Potential Years of Life Lost* Due to Colorectal, Lung, Breast, and Prostate Cancer, in Canada, 1997 †,

	Colorectal		Lung		Breast		Prostate	
	Male	Female	Male	Female	Male	Female	Male	Female
Potential Years of Life Lost (PYLL)due to Cancer	43000	42000	132000	100000	---	95000	33000	----

*Figures calculated on the basis of life expectancy. Childhood cancers also included within relevant sites.
†National Cancer Institute of Canada. Canadian Cancer Statistics 2001. Toronto, Canada, 2001

Survival

As age increases, the estimated crude 5-year survival from colorectal cancer decreases. Among those diagnosed with CRC at 40-49 years of age, 57% of men and 64% of women will survive 5 years. However, among those diagnosed at ages 80-89, survival drops to 24% for men and 30% for women. This is not unexpected as crude survival reflects mortality from cancer as well as all causes. Relative survival, however, which compares the rate of mortality of cancer patients to the overall rate of mortality of a population with the identical distribution of age, sex, and province of residence, will also decrease with increasing age. A Canadian man 60-69 years of age with a diagnosis of CRC has a 56% chance of surviving for 5 years compared with a man 60-69 not diagnosed with CRC in the same province. The relative survival among women in this age group is 62%. By age 80-99, however, relative survival drops to 50% and 51% for men and women respectively.[30]

Burden of Disease

The burden of CRC may be considered in terms of the impact on both the individual and society. For the individual, the burden is reflected in the potential years of life lost; the cost of treatment; the degree of disability, pain, and discomfort; and the impact on the family. For society, the burden may be described by mortality, morbidity, and the costs to society of treatment.[32]

In Canada, the total cost for all forms of cancer** in 1993 was estimated to be $13.1 billion, with direct costs of $3.2 billion and indirect costs of $9.8 billion. Hospital

**Defined as neoplasms: ICD-9:140-239

care accounted for 76.6% of the direct costs, and physician care expenditures, drugs, and research accounted for 13.9%, 7.3% and 2.3% respectively.[33]

A study of a population-based cohort of 593 residents of Nova Scotia with CRC estimated that the hospital costs for the cohort over the 3 year period after diagnosis in 1990 amounted to $9.8 million. Costs were significantly lower for patients with localized cancer, highest in the 6 months after diagnosis and throughout the 6 months before death, and highest in patients who were older and had significant comorbid conditions. Estimated costs incurred in the 3 years after diagnosis were less if the cancer was diagnosed early, suggesting that the costs of CRC care may be reduced by screening for the disease and diagnosing it at an earlier stage.[34]

A substantial increase in the burden of CRC is anticipated with the aging of the population. Examination of hospital discharge data for 1991-1994 from the Healthcare Cost and Utilization Project of the U.S. Agency for Health Care Policy and Research found that the mean total of hospital charges for colon cancer was $4.57 (US $) billion per year. Most of the charges were incurred by those 60 years of age or older (83.08%) and by those without known risk factors for the disease (93.96%).[35] The estimated annual expenditure for the treatment of CRC in the U.S. (1989) was approximately $6.5 billion (1990 US$), compared with expenditures of $6.6 billion for breast cancer, $5.1 billion for lung cancer, and $4.7 billion for prostate cancer treatment. An estimated $40 billion (US$) is spent annually on the treatment of all cancers in the U.S.[36]

In addition to morbidity, mortality and cost aspects, illness and disease create other facets of burden for the patient, family, friends, and society. The individual may experience poorer quality of life and financial hardship as well as pain, suffering, and the possibility of premature death from cancer. Similarly, family and friends may suffer financial losses and undergo emotional trauma and grief. Ultimately, there will be many social and economic implications of disease.[36]

It is expected that screening will detect cancer more frequently at a pre-invasive or earlier invasive stage, which will benefit the individual in that he or she will require less treatment and suffer less discomfort and disability.[37] Not only will the length of life be important, but the quality of that life will be equally important. Further, quality and length of life may be improved by screening. The extent or urgency of surgery, necessity of colostomy or need for chemotherapy may all be reduced, and the suffering of non-survivors may be lessened.[38]

With evidence that an intervention decreases the likelihood of invasive disease or long-term risk of advanced disease, concerns about screening may be lessened. Nonetheless, the earlier awareness of disease and the additional years of monitoring may invoke anxiety, of which the psychologic and behavioural effects are basically unknown.[37] If screening merely delays mortality rather than reducing it, a longer and more distressing disease process might follow.[38]

Criterion 2

The natural history of the condition, including development from latent to declared disease, must be understood. There should be a recognizable latent (asymptomatic) period or early symptomatic stage.

Precursor Adenomatous Polyps: General Evidence on Disease Progression

Knowledge of the natural history of a condition implies recognition of the stage at which the prevention of metastases and death is not possible. This information and knowledge of the stage of disease in the individual would be helpful in deciding when the application of a screening test would achieve maximum benefit and minimum overutilization of resources.[39]

Polyps are mucosal masses found in the colon and rectum that differ histologically and according to clinical importance. Approximately one-half to two-thirds of all polyps are adenomatous,[40,41] and it is generally accepted that the majority of cancers of the colon and rectum develop from them.[38] The probability that invasive cancer is contained within a colorectal adenomatous polyp increases with the size of the adenoma, the degree of dysplasia, and the degree of villous content.[42]

The progression from this precursor lesion to CRC has a natural history of approximately 10 years.[43,44] However, the duration of the pre-clinical phase, described by the mean sojourn time, has been estimated at between 4.5 and 5 years for all subsites combined and 3.5, 6.4, and 2.6 years for proximal colon, distal colon, and rectal cancer respectively.[45] The disease progression is a multi-step process accompanied by changes in a number of suppressor genes that result in abnormalities of cell regulation. Environmental factors and inherited susceptibility are also important in this progression,[46] since genetic alterations are hypothesized to lead to the development of adenomatous polyps, and further genetic changes are thought to be responsible for the progression of these polyps to cancer.[38]

The single most important prognostic indicator is the stage at which CRC is diagnosed. The overall 5-year survival rate is approximately 50% but rises to almost 90% for localized CRC.[3,47] Conversely, the 5-year survival rate falls below 50% once the disease has spread, which is typically the stage at which it is diagnosed. The most effective way of promoting survival from CRC is through earlier detection of asymptomatic disease.[48]

If the adenoma to carcinoma progression holds true, then one would expect to see a reduction in CRC incidence if this sequence is interfered with (i.e., by removing polyps). The National Polyp Study provides some evidence of the adenoma-carcinoma sequence[49,50] , while other studies have also shown reductions in the risk of cancer following colonoscopic polypectomy.[50] Less direct evidence supporting the adenoma to carcinoma sequence is derived from those populations at high risk for CRC who have more polyps than populations at average risk. [38] As well, the risk of carcinoma is at least doubled when there are findings of adenomas, and the risk for a subsequent adenoma or cancer is also increased.[50] Unremoved polyps can enlarge after an average period of 5.5 years, and invasive carcinoma has been reported at the site of the index polyp after 9 years of follow-up.[51]

Possible Contrary or Cautionary Evidence

Even though there may be gaps in fully understanding CRC's progression, gaps also exist in the understanding of the natural history of breast and cervical cancers, for which screening practices are in place.[52,53] For breast cancer, some authors have reported disease progression with respect to grade of malignancy whereas others have failed to report this progression. [52] With respect to cervical cancer, there is uncertainty surrounding the progression from normal to CIN1/2/3 with human papillomavirus infection and consequently why some women are able to clear such infections while other women develop persistent infections and go on to have more severe disease is unknown.[53]

Although the evidence does seem to support the adenoma to carcinoma sequence theory for CRC, there are indications that it may not hold true for all cases.[50] Carcinoma has been reported in patients who did not have adenomatous remnants. Furthermore, some researchers have found adenomas to be more evenly distributed than cancer. One study found the lowest proportion of adenomas in the rectum, despite the fact that cancer occurs there most frequently. This suggests that the adenoma to carcinoma sequence may not occur as often in the rectum, or that rectal adenomas may

become malignant more readily than colonic adenomas. Another finding has been an increase in adenomas in men compared with women, despite observations of similar cancer rates in the two sexes.[50]

Consequently, there is some debate as to the effectiveness of polypectomy in reducing the risk of developing CRC. Some studies have shown no reduction in cancer rates after benign polyp removal.[50] RCTs showing reductions in CRC incidence following polypectomy may be demonstrating the effect of detecting cancers at an earlier stage, and not the effect of removing polyps.[50,54]

Despite this, molecular biology strongly supports the adenoma to carcinoma sequence theory and offers little to refute it.[50]

Criterion 3

There should be a suitable screening test or examination.

A useful screening test should be demonstrably effective. It should have a high sensitivity and specificity, and lead to a reduction in mortality.

Evidence from Randomized Controlled Trials

The fecal occult blood test (FOBT) is the only test for which results from studies have demonstrated a reduction in mortality. Three clinical trials have published results on the efficacy of FOBT (the Hemoccult) as a screening tool (Table 4).[3-6] The remaining trials, in New York, Burgundy and Gothenburg, are either not complete or the analyses are in the process of being completed for publication.[55,56]

The Minnesota trial demonstrated a 33% reduction in CRC mortality,[3] using annual FOB testing primarily with rehydrated specimens, and a 21% reduction in mortality[4] through biennial screening (Table 4). Recently published results demonstrate that over an 18 year period of follow-up, the incidence of CRC was significantly reduced by screening annually or biennially with FOBT.[57] The trial conducted in Nottingham, United Kingdom,[5] using nonrehydrated FOBT and biennial screening, reported a 15% reduction in mortality, while the Danish trial in Funen, Denmark,[6] using nonrehydrated FOBT and biennial screening, reported an 18% reduction in mortality from CRC. In addition to reported reductions in mortality, other trials have consistently reported improvement in stage of disease detected in the screened group.[55]

Measures of performance of the FOBT include sensitivity, specificity and the positive predictive value. Sensitivity is related to the proportion of truly diseased individuals in the screened population who are identified as such by the screening test (true positives), and specificity is related to the proportion of truly nondiseased people in the screened population who are so identified by the screening test. The probability

Table 4. Relative Mortality Reduction (%) from CRC in the Minnesota, Funen and Nottingham trials*

RCT	Relative Mortality Reduction (%) from Colorectal Cancer	
	Annual	Biennial
Minnesota, USA	33% (13 years' screening and follow-up)	6% (Not Sig.) (13 years' follow-up)
	33% (18 years' screening and follow-up)	21% (18 years' follow-up)
Nottingham, UK	Not applicable	15% (median follow-up 7.8 years; range: 4.5-14.5 years)
Funen, Denmark	Not applicable	18% (10 years' follow-up)

*Adapted from Table 6.1. National Advisory Committee on Health and Disability (National Health Committee) New Zealand. Working Party on Screening for Colorectal Cancer. Population Screening for Colorectal Cancer, 1998.

that an individual with a positive test result truly has the disease defines the predictive value of a positive test.[58] The greater the sensitivity, the greater the number of early cancers and pre-cancerous polyps that will be found. The greater the specificity, the lower the number of needless evaluations of individuals with false positive results and the lower the cost of the program. The higher the positive predictive value, the greater the accuracy of the risk assessment for the individual who has tested positive.[59]

It is notable that the sensitivity of the FOBT appears to vary widely among the Minnesota, Nottingham, and Funen trials (Table 5). This is a result of the operative definition of sensitivity used in each trial. In Minnesota, sensitivity was defined as "the number of true positive results divided by the sum of true positive results and false negative results" under the assumption that cases of CRC were true positives if discovered within 1 year after positive screening (detected by screening) and were false negatives if discovered within 1 year after negative screening.[3] If, however, as has been suggested, the true sensitivity is calculated from the number of screen-detected cancers

divided by the total number of cancers, annual screening in Minnesota using FOB would equate to a sensitivity of approximately 50% after 13 years.[60-62]

The approximate 98% specificity for non-rehydrated FOBT still means that 2% of healthy people will have false positive tests and require further invasive, potentially dangerous, and costly colonic follow-up.[63] Further, because the positive predictive value of FOB is low, the majority of people who test positive will not have cancer.[64]

Table 5. Measures of FOBT Performance from RCTs: Sensitivity, Specificity, and Positive Predictive Value (as reported in the National Advisory Committee on Health and Disability *)

FOBT	**Minnesota (US)** Hemoccult		**Funen (Denmark)** Hemoccult II	**Nottingham (UK)** Hemoccult
	Rehydrated	**Non-rehydrated †**	**Non-rehydrated**	**Non-rehydrated**
Sensitivity (%)†	92.2	80.8	51	53.6
Specificity (%)	90.4	97.7	98 (estimated)	96-98 (estimated)
Positive Predictive Value (%)	2.2	5.6	37515	12

*National Advisory Committee on Health and Disability (National Health Committee) New Zealand. Working Party on Screening for Colorectal Cancer. Population Screening for Colorectal Cancer, 1998.
† Sensitivity (Minnesota) = true positives/(true positives [CRC discovered within 1 year of positive screen]+ false negatives [CRC discovered within 1 year of negative screen])

The Fecal Occult Blood Test (FOBT)

Detection of cancers of the colon and rectum by testing the stool for blood is based on the observation that there is more bleeding from a cancer than normal mucosa.[38] The test does not independently diagnose CRC but has been used in screening for the disease.[65] The FOBT is an inexpensive and painless chemical test used to detect

hidden blood in stools. A positive FOBT may indicate that there is blood in a stool sample, and possibly CRC, but it could also suggest other conditions, such as bleeding from hemorrhoids, ulcers, non-cancerous polyps or other non-cancerous disorders. Furthermore, non-steroidal anti-inflammatory drugs (NSAIDs) and vitamin C supplement use as well as recent consumption of red meat, high-peroxidase foods and alcohol can also lead to a false positive result. The FOBT is more likely to detect cancers that bleed and will not successfully detect polyps if they do not bleed. Therefore, different approaches are needed if the intent is to screen for polyps rather than for colorectal cancer.[66]

There are three types of FOBT: guaiac tests, immunologic assays, and heme-porphyrin assays (Table 6). Each type of test has its own limitations, and each brand has its own specificity and sensitivity.

Table 6. General Types of FOBT*

GUAIAC TESTS	IMMUNOLOGICAL ASSAYS	HEME-PORPHYRIN ASSAYS
• Detect pseudoperoxidase activity of heme or hemoglobin	**• Use reverse passive hemagglutination**	**• Based on the fluorescence of heme-derived porphyrins**
Hemoccult	**HemeSelect**	**HemoQuant**
Hemoccult Sensa	**Flexsure OBT**	
Hemoccult I & II		

*Allison JE. Review article: faecal occult bloodtesting for colorectal cancer. Aliment Pharmacol Ther 1998;12:1-10.
Simon JB. Fecal occult blood testing: clinical value and limitations. Gastroenterologist 1998;6:66-78.

Guaiac tests and immunologic assays are those that are suitable for CRC screening.[43] The guaiac tests have been the most widely used and evaluated in FOBT screening trials in the form of the Haemoccult, Hemoccult, Hemoccult II while Hemoccult II Sensa has only been evaluated in a few studies.[59] The guaiac-based tests are also the simplest and the least expensive, but delay in processing guaiac-based tests has

been shown to decrease sensitivity as a result of dehydration. Test interpretation has also been shown to be highly dependent on the experience of the interpreter.[66]

Improving the sensitivity of FOBTs, thereby increasing the number of true-positive results, can be achieved in several ways, although usually at the expense of specificity.[66] Rehydration of slides[66] has been reported to increase sensitivity but decrease specificity and positive predictivity.[3] Another approach to increasing sensitivity has been to use a combination of Hemoccult II Sensa and HemeSelect.[18]

Dietary restrictions may decrease the number of false positives but with an increase in the number of false negatives.[66] Dietary restrictions varied among the Minnesota, Nottingham and Funen RCTs (see Appendix F).

The success of FOBT as a screening tool is thus largely dependent on the conditions under which it is administered. For this reason, significant effort has been put into developing better fecal occult blood tests and into using diagnostic procedures — mainly colonoscopy — for screening purposes. Colonoscopy is often considered the gold standard for diagnosis.

Current knowledge on Sigmoidoscopy, Barium Enema, and Colonoscopy as Screening Tests

The performance of each of the available diagnostic procedures used for screening has not yet been evaluated in RCTs. These procedures are described in detail under Criterion 6 (pages 36-37).

Sigmoidoscopy

Although RCTs are under way in Britain[67] and the U.S.,[68] there are no RCTs to date demonstrating a reduction in mortality from CRC when flexible sigmoidoscopy has been used as a screening tool.[69] Three case-control studies suggest reductions in the mortality of screened patients.[70-72] Another case-control study by Muller and Sonnenberg[73] demonstrated that those without CRC were 50% more likely to have undergone endoscopic procedures than matched controls with CRC. A recent prospective cohort study provides further evidence that screening with sigmoidoscopy has a protective effect in terms of incidence and mortality. Among men aged 40 to 75 undergoing screening endoscopy (mainly sigmoidoscopies) in 1986-87, there was a 44% reduction in the diagnosis of CRC and a 50% reduction in deaths from CRC between 1986 and 1994. Controlling for family history of CRC, and dietary and lifestyle risk

factors did not appreciably alter the protective effect.[74] According to Simon, the mortality benefit could be 60% to 70% for up to a decade for cancers located within the reach of sigmoidoscopy.[75]

This procedure has disadvantages: flexible sigmoidscopy can accurately detect cancers and polyps in the high-risk left colon, but fails to diagnose right-sided cancers.[76] When used alone, the procedure detects only about half of all CRCs and polyps[75] while still causing discomfort, risk, and inconvenience to the patient. In two studies, approximately half of all patients screened with colonoscopy were found to have advanced proximal neoplasia but were free of distal adenomas. Had these asymptomatic patients undergone sigmoidoscopy, they would have been falsely reassured of having no adenomas.[77,78] Compliance is another problem. A study in western Australia noted that only 12% of subjects were prepared to participate in a program that used flexible sigmoidoscopy.[79]

Colonoscopy

Although there have been no studies that evaluate whether colonoscopy used solely as a screening test leads to a reduction in incidence and mortality from CRC in those at average risk of the disease, colonoscopy is considered superior to flexible sigmoidscopy because of its capability to examine the complete colon. As a result, colonoscopy results in fewer false positives and negatives. Colonoscopy can also detect proximal neoplasia in asymptomatic individuals, when it would not have been detected by sigmoidoscopy.[77,78] Furthermore, it can definitively treat polyps and some cancers.[38]

Opponents of colonoscopy for screening have criticized its direct and indirect costs as well as the possible lack of compliance with the procedure.[80] Both its cost-effectiveness and its general acceptance by the public as a screening tool have been challenged.[66,81] Colonoscopy is a more complex procedure than flexible sigmoidoscopy: it requires longer bowel preparation and demands greater technical skills on the part of the examiner.[75] Possible serious complications associated with colonoscopy include perforation, bleeding, and death.

Barium Enema

No studies have evaluated whether the use of double-contrast barium enema (DCBE) as a single screening test results in a reduction in incidence and mortality from CRC in individuals at average risk of the disease. Use of DCBE for screening can image the complete colon and detect cancers and large polyps better than the FOBT or

sigmoidoscopy, almost to the level of colonoscopy. However, small polyps may be missed, biopsies or the removal of polyps are not possible, and artifacts are more likely to be identified as polyps that would require a subsequent colonoscopy anyway.[38]

The overall sensitivity of DCBE for detecting adenomas is reported to be 39% and approaches 50% for adenomas larger than 1 cm. [44]

Future Technologies for Screening

Future screening strategies could be based on molecular markers for disease.[66] Genetic or biochemical alterations, such as ras mutations, which have been detected in the stool of patients who have large adenomatous polyps and cancers of the colon, could prove useful in augmenting the more conventional screening strategies.[82]

Virtual colonoscopy is "a new procedure that fuses computed tomography of the large bowel with advanced techniques to obtain three dimensional views of the colonic mucosa, similar to those obtained with the current form of colonoscopy". Preliminary results suggest that this procedure surpasses barium enema and approaches the sensitivity achieved by the current form of colonoscopy.[83]

A screening program can be improved through refinement of a screening test leading to a gain in both sensitivity and specificity.[84] In the future, it may be appropriate to substitute a newer test, such as virtual colonoscopy, for tests currently recommended. This would be acceptable if convincing evidence existed that the new test had comparable sensitivity and specificity in detecting cancers or adenomatous polyps at comparable stages, had the same patient acceptability, and was associated with complication rates and costs that were comparable or lower.[38]

Criterion 4

The overall benefit of the screening program should outweigh the potential harms from its application

Potential Benefits from Screening

Although RCTs have demonstrated the efficacy of the FOBT (see Criterion #3), it is essential to assess the effectiveness of this test at the population level. To accomplish this, two modelling exercises were carried out to evaluate the potential impact of a population-based screening program in Canada, in terms of the impact on both mortality and resources. The projected impact with respect to resources is reviewed in the discussion found under Criterion #8.

The two models are an Actuarial Model and Population Health Model (POHEM). The specifics of these models are discussed in greater detail in Appendices B and C. Canadian data were used when available and appropriate. Since the models differed in their methodology and their assumptions, it would be inappropriate to compare their results side by side. The Actuarial Model provided guidance for the National Committee to determine which parameters should ideally be included in further analyses. Since POHEM readily generated estimates on the effectiveness as well as the cost-effectiveness of implementing a population-based CRC screening program, only its results will be used when modelling is addressed in this report.

The results from POHEM estimate that a 10 year biennial CRC screening program could avert 7,740 deaths and thereby decrease CRC mortality by 16.7% (Table 8).

Table 7. Underlying Assumptions for Population Health Model (POHEM)

Assumption	POHEM
Eligible population	Canadians, aged 50-74 years, in the year 2000 n = 7,001,327
Test	Nonrehydrated Hemoccult II® (FOBT)
Sensitivity of FOBT	Biennial (Funen, Denmark): 51% Annual (Minnesota, USA): 80.8%
Specificity of FOBT	Biennial (Funen, Denmark): 98% Annual (Minnesota, USA): 97.7%
Participation rate	67% initial participation and 93% re screen participation
Follow-up period	10 years (2000 to 2009)
Complications Resulting from Colonoscopy[a]	Perforation: 0.17% Hemorrhage: 0.03% Death: 0.02%

[a] Habr, Gama, Waye, 1989

The gain in life expectancy from preventive interventions in populations at average risk has been estimated to range from less than 1 month to slightly more than 1 year for those receiving the intervention. An overall gain in life expectancy of 1 month can be considered large.[85] POHEM estimated that for a cohort of Canadians 50-74 years of age with 67% participation in a 25 year biennial screening program, the average life years gained , un-discounted, would be 0.040 years or approximately 15 days (or 0.016 years or 5.8 days respectively, if discounted at 5%). For annual screening, the average life years gained, un-discounted, would be 0.065 years or 24 days (0.025 years or 9.1 days, if discounted at 5%).

Table 8. Impact of a 10 Year Annual and Biennial FOBT Screening Program, in Canada, Projected from the POHEM

Parameter	POHEM
Projected # of incident cases of CRC in cohort (in Canadians aged 50-74 years)	111,381 cases (with biennial screening) 111,234 cases (with annual screening)
Projected # of deaths: . no screening . with annual screening . with biennial screening	 46,218 deaths 34,188 deaths 38,478 deaths
Decrease in mortality rate, with . annual screening . biennial screening	 26.0 % (CI = 25.0%-27.0%) 16.7 % (CI = 15.8%-17.7%)

Potential Harms from Screening

Although FOB testing alone does not in itself present physical danger, the possible follow-up diagnostic tests do have potential risks. The choice of follow-up diagnostic test, in the event of a positive FOBT, is the point at which there is the greatest opportunity for physical and/or psychological harm. This is especially true with the FOBT, since the reported specificity of nonrehydrated FOBTs ranges from 96% to 98%.[5,18] Two percent of asymptomatic individuals will have a positive test and then be subjected to further investigations that may be not only unnecessary but also unpleasant, worrisome and potentially dangerous, thus causing unnecessary grief.

Individuals with positive results, including those with false positive results, will be advised to undergo further diagnostic testing, which usually involves a colonoscopy. Some individuals may be offered a DCBE or flexible sigmoidoscopy because of resource issues or patient preference; however in the following discussion of potential harms, only the complications associated with colonoscopy will be addressed.

Complications from colonoscopy include bleeding, perforation and even death, the risks varying according to the reporting source and whether biopsies or polypectomies are performed.[54,86] One study found that 2% of all those who underwent polypectomy required hospitalization for complications. In a separate review of post-polypectomy studies, the number of deaths from colonoscopic perforation exceeded the number of deaths from colon cancer.[87] This is an important consideration, given that the prevalence of polyps increases with aging; 40% of 60 year olds and 50% of 70 years olds are quoted to have polyps.[88] Other reported complications include myocardial infarction, cerebrovascular accidents [77] and infection.[64,89] Less serious side effects include hypotension and abdominal pain or bloating, and general patient discomfort.[90]

The risks quoted in Table 9 are derived from reviews of prospective studies[38,89,91] and from studies that involved large numbers of colonoscopies.[90]

One of the major challenges in predicting complication rates for population-based programs is that reported rates from studies are generated within controlled environments. For example, in RCTs, endoscopies are likely to be performed by highly trained and experienced operators, which may not be the case once a program is deployed in the broader community. Some studies report higher complication rates with inexperienced operators than with experienced ones.[64,89] Complication rates could possibly be significantly higher in a population-based screening program than they are in controlled trials.

The POHEM projected the likely number of complications that could be expected (Table 10) with annual and biennial FOBT screening, using the assumptions presented in Table 7.

Table 9. Reported Major Complication Rates with Colonoscopy and Polypectomy (post-procedure)

Study/ test	Rate of Perforation	Rate of Hemorrhage	Death Rate	Other Complications
Cohort study of 3,121 mostly men, aged 50-75, who underwent screening colonoscopy[a]	0 perforations	19.22/10,000 gastrointestinal bleeding requiring hospitalization (or n = 6/3,121)	0 related deaths	3.2/10,000 (n = 1/3,121) myocardial infarction 3.2/10,000 (n = 1/3,121) cerebrovascular accident 3.2/10,000 (n = 1/3,121) Fornier's gangrene 3.2/10,000 (n = 1/3,121) thrombophlebitis
Review of 6 prospective studies on colonoscopy[b]	10/10,000 perforations*	30/10,000 major hemorrhage*	1-3/10,000 related deaths*	50/10,000 significant respiratory distress*

[a]Lieberman DA, Weiss DG, Bond JH, Ahnen DJ et al. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. N Engl J Med 2000; 343(3):162-8.

[b]Winawer SJ, Fletcher RH, Miller L, Godlee F et al. Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 1997;112:594-642.

*Rates indicated likely to be higher if polypectomy performed

Table 10. Projected Number of Complications Resulting from Colonoscopy During a 10-year Screening Program, in Canada (from the POHEM)

Complication	POHEM Projection*
# of **deaths** resulting from colonoscopy - . with annual screening . with biennial screening	 **159 deaths** **75 deaths**
# of **perforations** resulting from colonoscopy - . with annual screening . with biennial screening	 **1,296 perforations** **611 perforations**
# of **hemorrhages** resulting from colonoscopy - . with annual screening . with biennial screening	 **248 hemorrhages** **110 hemorrhages**

*Numbers have been rounded.

Table 11 summarizes individual risk estimates projected by POHEM for a 50-year old who participates in all screening events until the end of the designated screening program. Although the Committee's mandate was to assess population-based screening, it felt that in order to fully evaluate the risks versus benefits of CRC screening, it should consider individual estimates as well.

Table 11. Individual Potential Gains/Risks from Full Participation in a Biennial CRC Screening Program, Starting at Age 50 and Stopping at Age 74

Individual Risk Assessment	In 1st 10 Years (%)	In 1st 25 Years (%)	Lifetime (%)
Probability of developing CRC			
. If not participating in screening	0.68	3.17	5.88
. If fully participating in screening	0.68	3.30	5.91
Probability of dying from CRC			
. If not participating in screening	0.29	1.56	3.06
. If participating in screening	0.19	1.07	2.30
Probability of colonoscopy or resulting complication if participating in a screening program	10	25	
. colonoscopy			25
. death due to colonoscopy			0.005
. perforation due to colonoscopy			0.043
. hemorrhage due to colonoscopy			0.008
Gain in average life expectancy for 50 year old participating in all screening events of biennial program up to until/incl. age 74			0.10 yrs (37.8 days)
Gain in average life expectancy for individual diagnosed with CRC (cohort above)			1.75 yrs

Complication rates from performed colonoscopy in Canada do not exist to provide a baseline rate.

Balancing Potential Benefits and Risks

In any screening program, including FOB testing, the funding organization and those promoting screening need to evaluate whether the risk of causing greater distress and morbidity through unnecessary and unwanted intervention is offset by the potential advantage afforded by the screening program.[92,93] Since people are invited to participate in screening on the presumption of perceived benefits, the program must be proven to be effective,[18] and serious complications must be minimized.

Screening programs demand higher standards of informed consent and screening protocols than do straightforward consultations, because these investigations and treatments are unsolicited by healthy individuals and may even prove to be inappropriate. Adequate diagnostic services must be available and of a standard that permits correct diagnosis and informed decision-making.[92,93] The privacy and confidentiality of personal health records must also be protected.[94]

Ethical Considerations and Informed Consent

In Western society, biomedical ethics dictate that physicians should do good, do no harm, and respect their patients' wishes.[89,95] When any of these precepts is not observed, the physician's behaviour may be regarded as unethical.

In screening programs for CRC that use FOBT, the relationship between a health care provider and patient is substantially different from what is observed in clinical practice. For the purposes of this report, the health care provider will be referred to as a family physician, although other professionals could be involved in similar activities in the screening process. In clinical settings, the patient seeks out the services of the physician, usually because of illness.[63,89] The physician is then ethically bound to do his or her best in caring for the patient.[63,89,95] By contrast, in screening programs, the physician will recruit healthy, asymptomatic individuals. The physician may therefore be seen as someone who is promoting a health benefit by acting as an advocate of the screening program. There may even be the perception that he or she is soliciting business.[63,93,95]

There is an ethical and legal obligation on the part of the physician to obtain the informed consent of a patient before any test or treatment is carried out.[96] Furthermore, it is the patient's right to be informed about the possible advantages, adverse effects and

potential complications that may arise from a test (such as the FOBT) and from the diagnostic process that may ensue.[2,97] This applies also to the consequence of a negative test, which may in fact be falsely negative and may, in turn, mistakenly reassure an individual that he or she is free from cancer.[92,93] This is an important consideration, given that 50% of colon cancers may not be detected through FOBT,[64] and that individuals with negative tests may be less likely to seek medical help even if they are experiencing symptoms of CRC.[18] Furthermore, the patient should be informed of the way in which compliance with all screening events will affect the balance of risks and benefits.[2]

When screening is initially discussed with the individual, the evaluation of benefit and the potential complications or negative repercussions (including false positives and negatives) are often not addressed. Consent obtained from the individual may therefore not be completely informed.[63,98] True informed consent implies that the patient has played an active role in the decision-making process and has not simply complied with the recommendations of, for example, the physician. Information about all the steps of the screening process, along with their associated risks, must be presented at the outset. Without such accurate and comprehensible information, the patient may never be in a position to make an informed choice.[63,89] This is particularly significant given that the reported benefits of screening programs may only be enjoyed by a few.[63,89,95,98]

Even though some physicians may have difficulty finding the time to explain complex material directly to someone,[89] other factors could prevent individuals from having sufficient knowledge or confidence to make a fully informed decision. First, some people may be more likely to participate in a preventive program simply because it is recommended to them by their physician. There could be a perceived power differential between the patient and physician,[95] or the patient may place absolute trust in whatever the physician may recommend that will lead to improved health.[89] The common belief that preventive programs do no harm is frequently shared not only by the general public but by physicians as well.[89] Last, while the onus rests on the physician to inform and explain all aspects of an FOBT screening program, he or she may not be current with the research or able to synthesize all the information into relevant clinical practice.[89,95] Even up-to-date physicians are faced with the dilemma about how much information they need to share before a patient can make an informed decision.[89]

Another consideration is that the quality of life for people who have a pre-malignant condition and undergo regular screening may be impaired, because their anxiety is being reinforced at regular intervals.[93] Patients receiving negative test results may also be falsely reassured that they are free from CRC, when in fact they could have the disease.

A further ethical concern is the degree of consent required when forwarding data from a patient to a database being maintained for the screening program. Debates about what information should be derived for a database without informed consent have arisen through consideration of personal autonomy and privacy.[94]

Finally, from the overall health care perspective, an FOBT screening program is likely to be implemented at the expense of some other medical intervention or program that may have a better relative cost, mortality outcome or benefit, and potential for alleviating suffering.[63,93]

Public Education

It is obviously vital that information on CRC be readily available, accessible and in a format and language that is well understood. Information on various cancers is available from a number of organizations, including Health Canada, the Canadian Cancer Society and the Colorectal Cancer Association of Canada (CCAC), which is a non-profit organization dedicated to the provision of education and support to those living with colorectal cancer and their families and caregivers. The mission of the CCAC is "to support and improve the quality of life of Canadians with colorectal cancer, their families and caregivers. We are dedicated to public awareness, prevention, education and colorectal cancer advocacy." [99]

Criterion 5

The test (inclusive of screening and diagnosis) should be acceptable to the population.

Participation Rates

One of the major problems with CRC screening is the limited public acceptance of the FOBT, which has consistently resulted in low program participation and compliance rates.[100] Although compliance with all screening events is an essential component of any screening program, high compliance has been considered one of the most important factors in the success of FOB screening programs.[63,101,102]

Synthesizing the literature surrounding uptake of FOBT screening is difficult given that studies have been undertaken in different settings and have used different methodologies. Furthermore, the terms "participation" and "compliance" have been used interchangeably when in fact participation has recently been associated with the completion of a screening event, whereas compliance has been associated with the completion of all the screening events of a program. This section will discuss screening uptake in the broad context to mean participation and compliance, except when compliance is singled out.

Even though a 70% compliance rate has been proposed to achieve health and economic benefits for any type of screening program,[103,104] this rate has rarely been achieved in any FOB screening program.[100] Compliance rates generally average between 40% and 50%, regardless of the population, setting, or publicity/public education campaigns.[63,100,103-105]

The highest rates of participation and compliance have been found in randomized trials (Table 12). This is not surprising, given that such interventions are closed, controlled and well-managed.

The following table highlights the reported participation and compliance rates of the three RCTs that evaluated screening for CRC with the FOBT. Note that participation in this context refers to completing the first screen.

Table 12. Participation and Compliance Rates in Randomized Controlled Trials of FOBT[abc]

	Participation Rate (i.e. completing 1st screen)	Compliance Rate (completing all screening events)
Funen Trial	67.0 %	45.9 %
Nottingham Trial	53.0 %	38.2 %
Minnesota Trial	89.9%	59.7 %

[a]Hardcastle JD, Chamberlain JO, Robinson MHE, Moss SM, Amar SS et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472-7.
[b]Kronborg O, Fenger C, Oslen J, Jøørgensen OD, Søøndergaard O. Randomized study of screening for colorectal cancer with faecal occult blood test. Lancet 1996;348:1467-71.
[c]Mandel JS, Church TR, Ederer F, Bond JH. Colorectal cancer mortality: effectiveness of biennial screening for fecal occult blood. J Natl Cancer Inst 1999;91:434-37.

Factors Affecting Participation

Factors associated with participation in FOB testing have not been consistent across all studies, although some have been reported with greater frequency. Individuals aged 70 years and older have lower participation rates[105], while those aged 50 to 69 years have the highest rates.[106] Women have typically completed FOB testing more often than men.[100,104-106] Individuals with higher socio-economic status also tend to participate more in FOB screening.[105] Few studies have investigated the effects of other factors, such as culture and ethnic status, marital status, or family and medical history.[105] Screening frequency has been reported to affect participation, in that longer intervals between FOB testing produce more desirable participation rates.[105]

Reasons for not participating in FOB testing are multifold and seem to be similarly inconsistent across studies. Two commonly cited reasons are the fear of further tests for diagnosis and/or surgery, and an individual's present state of health.[104,105] The fear of further testing was found to have a greater impact than the

concern for effective treatment should cancer be detected.[104] Colonoscopy and other diagnostic investigations, such as sigmoidoscopy and barium enema, are perceived as undignified, unpleasant and painful. If the person feels well at the time of recruitment and has no gastrointestinal symptoms, then he or she would be less likely to participate in testing. Other documented reasons for low participation are the unpleasantness of the test, embarrassment about collecting stool, and intercurrent illness.[102,104,105] Other studies have also reported that individuals are less likely to participate in testing because of conflicts with work, inconvenience, lack of interest or a negative attitude toward screening, a perceived low burden of disease, inaccessibility by telephone, and cost.[102,105,107] Religious reasons have not been reported to affect participation rates.[104]

Efforts to Increase Participation

Several interventions to increase participation in FOB screening have been evaluated. The most extensive strategies for well-defined populations have rarely exceeded a rate of 50%. Minimal and/or impersonal intervention strategies have resulted in participation rates ranging from 10% to 30%.[100,105] Dietary restrictions for the most part have not affected participation rates, and neither has the type of FOB test.[63,105,108]

Improved participation has been reported with physician involvement,[63] either through the signing of an invitation letter[105] or encouragement of the individual to participate.[59] Indeed, some authors have stated that a screening program will not be effective unless it is advocated by health care providers.[101,109]

Participation did not increase when the FOB screening was associated with a health check done by a nurse[100] but did increase when individuals were mailed an FOBT kit prior to a physician visit.[100,110] The response rate was highest when subjects received personalized invitation letters.[32]

Concerns About Participation Levels

Several concerns regarding participation in FOB testing warrant further consideration. The first is whether the participation and compliance rates observed in the controlled trials can be achieved and maintained over time in the general population.[63,105] The second is whether the population is willing to undergo the

recommended follow-up tests. This is crucial, given that the lack of proper follow-up will result in a diminished mortality benefit from the screening program. Screening with FOBT offers little benefit if there is no ensuing diagnosis and treatment.[76,111]

Trials have had higher rates of compliance with follow-up tests: both the Minnesota and Funen studies reported rates of over 90% in those who tested FOBT positive.[18] Nonetheless, other studies have indicated that, despite repeated attempts, up to one-third of all those who tested FOBT positive failed to respond to follow-up requests. Of those who did respond, only a minority agreed to undergo colonoscopy.[63] Furthermore, because the FOBT has a low positive predictive value, the majority of those who agree to subsequent diagnostic tests will not realize a benefit. These people may then be less likely to participate in future screening.[112]

Criterion 6

Evidence-based recommendations should be available to identify who should be offered further diagnostic investigation and/or treatment, and the choices available to them.

Investigation

Further examination of patients with a positive FOBT is required to determine the cause or source of bleeding. This investigation is typically conducted by means of either colonoscopy or a combination of double contrast barium enema (DCBE) and flexible sigmoidoscopy. These procedures have all been described in Criterion #3 and have been throughly evaluated in the literature.[38]

Diagnostic Tests

Colonoscopy

Colonoscopy is performed within hospitals primarily by physician specialists, such as gastroenterologists or general surgeons. A complete bowel preparation is required, and the patient is sedated for the procedure. Colonoscopy is unique in that it can find and remove pre-malignant lesions throughout the colon. Experienced endoscopists require 15 to 20 minutes to complete the procedure, and patients are able to go home after an hour or two. Colonoscopy appears to miss 25% of polyps < 5 mm in size and 10% of polyps > 1 cm. The cecum is reached in 80% to 95% of procedures. The greatest disadvantage of this procedure is that it is associated with complications of perforation, hemorrhage and death. Elderly patients or those with heart or lung disease are at increased risk of complications due to sedation.

All the randomized screening trials published to date that have shown a reduction in CRC mortality used colonoscopy as the investigative procedure for those who tested positive with the FOBT.

Flexible Sigmoidoscopy

Flexible sigmoidoscopy is performed within and outside hospitals. In addition to medical specialists, primary care physicians also perform this procedure, although less frequently.[113,114] In the United States, many centres use trained nurses, physician assistants and gastroenterology technicians to perform this procedure.[114] Non-physicians do not perform flexible sigmoidoscopy in Canada. Because only the lower bowel is being examined, there is less intensive bowel preparation. The procedure takes approximately 8 minutes to perform. Biopsy specimens can be taken with flexible sigmoidoscopy, but polypectomies cannot be done.

Barium Enema

Barium enemas are performed by radiologists either within or outside hospitals. After preparation of the entire colon, liquid barium is instilled into the rectum until it reaches the cecum. Air or carbon dioxide is also instilled to provide greater radiologic contrast (double contrast study). The examination takes 20 to 30 minutes. Sedation is not usually required.

About 5% to 10% of barium enemas are unsatisfactory and require either another attempt or a colonoscopy. The sensitivity of DCBE is estimated to be 50% to 80% for polyps < 1 cm, 70% to 90% for polyps > 1 cm, and 55% to 85% for early stage cancers (Dukes' stages A and B).[55] False positive findings are mainly caused by stool and non-neoplastic mucosal irregularities. Observed pathology (e.g. polyps) requires further colonoscopic examination.

Existing Guidelines/Recommendations for Detecting and Treating CRC

Some organizations in Canada have published guidelines or recommendations for various aspects of managing CRC. These organizations include the B.C. Cancer Agency (" Cancer Management Manual"), Cancer Care Ontario ("Practice Guidelines Initiative"), the Canadian Society for Surgical Oncology and the Canadian Society of Colon and Rectal Surgeons.[115]

The potential for adverse events with colonoscopy has been previously discussed (see Criterion #4), and various guidelines have been developed to ensure the competence of endoscopists. The College of Physicians and Surgeons of Manitoba has identified training standards with prerequisites.[116]

The American Gastroenterological Association (AGA) has guidelines for granting credentials and privileges for gastrointestinal endoscopy.[117] These guidelines make a strong statement that "performance of an arbitrary number of procedures does not guarantee competency" . The principles of re-granting of credentials and renewal of privileges are also described.

U.S.-based guidelines and recommendations for the follow-up of positive FOBTs, management and treatment of CRC are available from several organizations:

. The American Gastroenterological Association[38]
. The American Society of Surgical Oncology[118]
. The American Society of Colon and Rectal Surgeons[119]
. The American College of Physicians[111]
. The National Institute of Health[120]
. The National Cancer Institute[55]

Existing Guidelines/Recommendations for Polyp Removal

No guidelines for investigating or managing patients with polyps were found in the Canadian literature. In the AGA guidelines, individuals who have had previous adenomatous polyps are said to be at increased risk of developing polyps in the future. It is therefore recommended that a complete bowel examination be performed 3 years after the clearance of large or multiple adenomatous polyps.[121] Recent evidence showed that for patients who have undergone colonoscopic polypectomy, examination through colonoscopy is a more effective method of surveillance compared to double-contrast barium enema.[44] If the follow-up colonoscopy is negative, then a subsequent examination is recommended only in 5 years' time.

Patients found to have malignant lesions need to have their lesion staged to determine the best course of treatment. Nonetheless, debate continues over the clinical significance of small polyps (< 1 cm) and the effect or benefit of removing them.[66]

There is evidence indicating that follow-up of a positive FOBT in the United States is variable, despite current guidelines, and depends upon the individual's physician, the health plans, and the treatment centre.[122] Excluding the influence of the health plan, this likely holds true in Canada also.

Canadian data are not available on outcomes from investigations and treatment of CRC. Although existing administrative databases might be used for analysis in

Canada, the validity of the data would need to be ensured before any analyses were done. An Ontario study of colorectal surgical rates found a large range in these rates in hospitals.[123] Concern was expressed over whether surgeons in some of these facilities were performing sufficient procedures to maintain competency. Implementing a population-based screening program, which would entail ongoing data collection, would permit monitoring of critical performance measures and outcomes.

The scope of identifying all existing Canadian guidelines, standards, and recommendations surrounding the detection and management of CRC is beyond the breadth of this report. A separate study would need to be implemented to address this adequately.

Testing for Other Outcomes After Negative Investigation

Given that FOBTs detect the presence of occult blood, guidelines will need to be established for negative colonoscopies that are carried out after positive FOBTs. There is currently no consensus on whether a further endoscopic evaluation of the upper gastrointestinal (GI) tract is warranted in asymptomatic individuals.[124] Few studies have been done to determine the yield of esophagogastroduodenoscopy (EGD) in completely asymptomatic patients who have had a positive FOBT followed by a negative colonoscopy.[124,125]

One set of recommendations asserts that patients who are asymptomatic or who do not have iron deficiency anemia should be spared from further diagnostic work-up.[66,126] These recommendations stem from observations that relatively few individuals with a positive FOBT and negative colonoscopy have been found through EGD to have a truly serious or clinically silent condition. Ulcers and erosions frequently account for a large proportion of abnormal endoscopic findings.[66] Another set of recommendations proposes further endoscopic evaluation of the upper GI tract on the basis of study findings of significant GI lesions in asymptomatic individuals who had had a positive FOBT and negative colonoscopy.[124,125]

Criterion 7

Treatment or intervention that improves survival or quality of life (compared with not screening) should be available for patients with recognized disease.

Effectiveness of Treatments

CRC is a highly treatable and often curable disease when it is localized.[55] Surgery, the primary treatment, cures approximately 45% to 50% of all CRC. The prognosis is related to the degree of penetration of the tumour through the bowel wall and the presence or absence of nodal involvement, which is the basis of all staging systems. Stage I tumours invade no farther than the muscularis propria of the bowel wall. Stage II tumours are more invasive and may have directly invaded other organs or structures. Stage I and II tumours have no lymph node involvement or distant metastases. Stage III tumours have lymph node involvement but no distant metastases. Stage IV tumours have distant metastases. Randomized screening trials have clearly demonstrated the effectiveness of treating earlier stage disease. [38]

Standard treatment of localized colon cancer has involved open surgical resection with wide clearance of the primary tumour and wide removal of mesentery, lymph nodes and blood vessels. The use of chemotherapy for patients with Stage III disease has been shown to benefit survival. Along with surgical resection of the tumour in patients with distant metastatic disease (Stage IV), chemotherapy, radiation therapy and surgical resection of isolated metastases are treatment options. Nonetheless, recurrence following colon surgery is a major problem.[127]

Wide surgical resection of the tumour is the primary treatment for rectal cancer. The inability to obtain wide radial margins because of the presence of the bony pelvis is a major constraint in rectal cancer surgery. Combined radiation and chemotherapy have demonstrated survival benefit in patients with Stage II and Stage III disease. Patients with Stage IV disease are generally offered surgical resection of the primary tumour and isolated metastases, as well as chemo-radiation.

Variation in Treatment

There have been no published studies with respect to variations in treatment practices or outcomes for CRC in Canada. An Ontario report analyzed regional surgical rates and cancer incidence in the province, and projected surgical volumes based on the

number of reported new cases.[123] There appears to be evidence that treatment practices vary considerably in other countries.[128,129]

Key informants (see Appendix E) indicated that variation in practices is not likely to be a significant issue in Canada. Although baseline data are not currently available in this country, the development of a screening program and relevant system for data collection would help determine what information is essential in order to study the outcomes resulting from various treatments.

Staging and Survival

Prognosis and survival rates are related to stage at diagnosis. Staging data are not routinely collected or reported in Canada.[130] Only a few cancer centres routinely record stage, and no provincial population-based registries routinely compile and report on incidence and outcome by stage.

Table 13. Comparison of CRC Stage Distributions: Ottawa Regional Cancer Centre vs. US Surveillance Epidemiology and End Results (SEER) Program[a]

Summary Stage	Ottawa Regional Cancer Centre (1991-1992) CRC cases n = 700 (Ref.: see POHEM Appendix)	SEER CRC Cases (1988-1991), from Holowaty et al 1998 [a] n = 42,777
Stage I	13%	17.1 %
Stage II	33%	28.2 %
Stage III	27%	21.1 %
Stage IV	27%	17.1 %
Unknown	-	16.6 %

[a]Holowaty EJ, Marrett LD, Parkes R, Fehringer G. Colorectal cancer in Ontario: 1971-1996. Toronto: Cancer Care Ontario, 1998.

In Ontario, survival rates for CRC have been increasing overall since the 1970s, although they appear to have reached a plateau since 1991.[131] Five-year, cause-specific, survival rates from SEER[132] are shown in Table 14.

Table 14. Five Year CRC Survival, by Stage (US SEER 1989-95)

Stage of Disease	5-Year Survival CRC (US SEER 1989-95)
All stages	61.0%
Localized	89.5%
Regional	64.9%
Distant	8.3%
Unstaged	34.5%

Criterion 8

Adequate staffing and facilities for recruitment, testing, diagnosis and follow-up, treatment, and program management should be available

For the successful implementation of a population-based CRC screening program, the conditions achieved in randomized trials must be reproduced.[133] The resources associated with effective recruitment, testing, diagnosis, and treatment of patients must therefore be available.

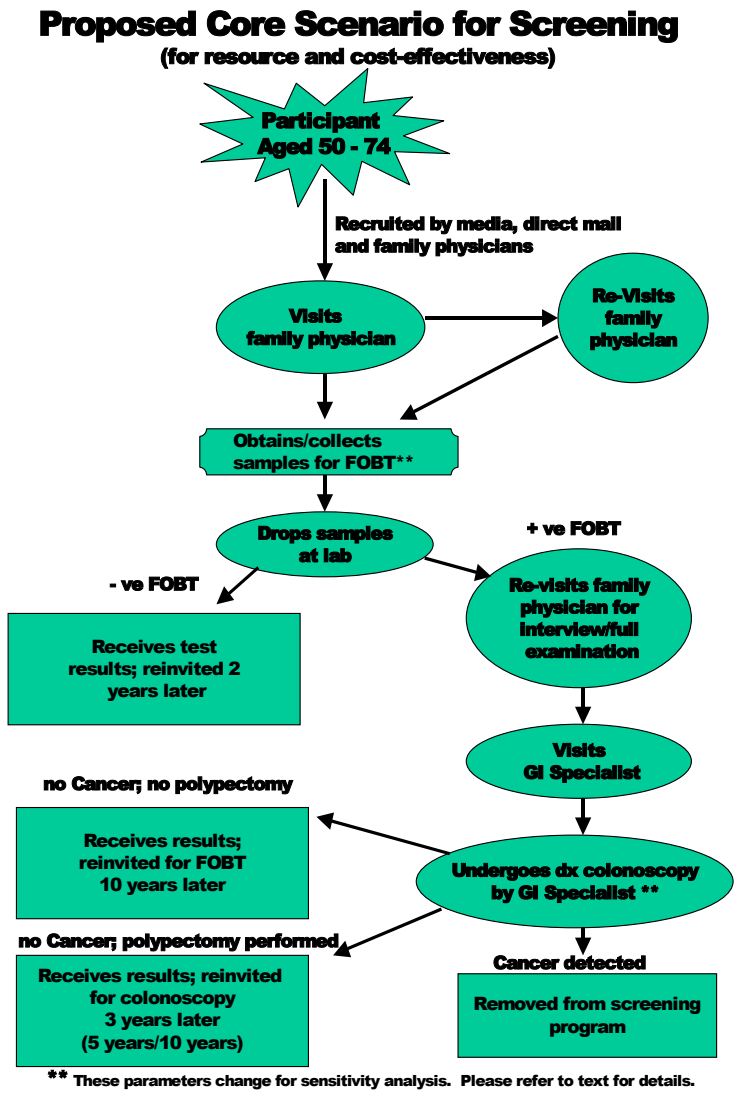
Resources are an important consideration for a population-based screening program, as the lack of sufficient services, personnel, and other resources will delay the achievement of the desired reduction in mortality. Participation is important to the planning process as it will be necessary to allocate adequate resources at the appropriate time.

The following section presents information on the current national and provincial capacity of the health care system to handle some of the interventions associated with a CRC screening program. Data describing use of colonoscopy were derived from the Canadian Institute for Health Information,[134,135] which publishes the annual number of colonoscopy procedures by province and year based on physician billing data. Statistical modelling using POHEM estimated the increased capacity that would be necessary over and above current resource utilization to accommodate a CRC screening program.

Figure 7 depicts a proposed scenario for a population-based screening program. The target population of individuals 50 to 74 years of age would be recruited by media promotion, letters of invitation, and visits to family physicians. It is assumed that 67% of the target population (those who would participate in screening) would visit a family physician, where the test kit would be distributed on the first or, in some cases, a subsequent visit. FOB kits would be taken home by participants, returned to a designated laboratory and processed. The results of the test would be communicated to the physician's office and subsequently to the patient. If the FOB is negative, participants will return to the screening pool and be re-invited 2 years later. If the FOB is positive, further investigation would be offered through consultation with a gastroenterologist followed by a colonoscopy. If no polyps are detected and cancer is not diagnosed, the participant would return for another FOBT in 10 years. If cancer is not diagnosed but polyps are detected and removed through polypectomy, the

participant would be re-invited for colonoscopy in 3 years and, if those results were negative, in 5 and then 10 years.

Figure 7 Proposed Core Scenario for Screening



I. Resource Implications Related to the Screening test (FOBT)

The resources associated with the screening test and diagnostic follow-up are described in two scenarios: a program that achieves full targeted participation rate (67%) at the onset (as in the Funen trial) and a program that achieves the full targeted participation rate only after 5 years, with an uptake of 20% of the targeted population entering the program each year. The second scenario is useful to envision the impact a delay in participation can have on resources.

Resources Related to Primary Care Physicians

The number of FOBTs that may be incurred from a biennial CRC screening program in the first year (year 2000) was projected from POHEM (Table 15). The primary resource considerations for the FOBT component of a screening program are the human resources, such as family physicians (as well as laboratory specialists, personnel for communicating results) and material resources (e.g. number of FOB test kits, including their processing and the communication of results). Although the family physician is likely to be an integral part of the process, it is difficult to accurately forecast the additional physicians that may be needed to accommodate a CRC screening program. This is because it is unknown what will be expected from physicians. An example using cardiovascular screening may provide some insight into the requirements for physicians.[136] If the decision were made that every adult in Ontario (10 million) required the family physician to provide a biennial cardiovascular screening examination, more than 500 additional family physicians would be required in Ontario to carry out that decision. Although this differs from FOB screening, it is likely to include similar activities for the physician, such as patient counselling on the individual risks/benefits of the screening test, relaying test results back to patients, ensuring follow-up for patients with abnormal tests, and recalling patients at the required screening interval.

The availability of extra physicians for a screening program in Canada is debatable. The number of family physicians per 100,000 in Canada dropped by 8%, from 101 to 93, between 1993 and 1997 at a time when there was a 4% increase in population.[137] Although 51% of graduates were trained as family physicians and general practitioners in 1993, only 40% of graduates were entering family or general practice by 1998; this is in the context of an increasing number of individuals entering retirement and an aging population.[137] For medical care delivery in Canada with the family physician as the first contact, Thurber and Busing conclude that the number of family physicians graduating in Canada will be insufficient to provide the needed level of primary care services for Canadians in the future.

The requirement from physicians to accommodate a CRC screening program will be largely dependent on the uptake of screening by the targeted population. This is

discussed in the subsequent section. (This section has addressed family physician requirements for personnel resource issues; however, it is acknowledged that added demand will be placed on laboratory personnel/services for the processing, interpretation, and communication of FOB test results.)

Resources Related to Screening Tests (FOBTs)

Table 15 depicts the projected average number of FOBTs that would be incurred annually in the first cycle of a biennial 25 year screening program, assuming that the targeted 67% participation rate is achieved at the onset as in the Funen trial.

Table 15. Estimated Number of Annual FOBTs Incurred in the First Year (2000) of a Biennial Screening Program, with 67% Participation (from POHEM)

Province	% Canadian Population* (aged 50-74)	Projected Number of FOBTs†
CANADA (Ages 50-74)	100% (7,001,322)	2485641
Newfoundland	1.8%	44741
PEI	0.5%	12428
Nova Scotia	3.2%	79540
New Brunswick	2.5%	62141
Quebec	25.7%	638809
Ontario	37.7%	937087
Manitoba	3.6%	89483
Saskatchewan	3.1%	77055
Alberta	8.4%	208794
British Columbia	13.4%	335561

*Provincial estimates based on 2,485,640 tests apportioned according to provincial populations. Numbers may not add up due to rounding.
†Estimate is the average number of FOBTs to be incurred in the first screening cycle (years 2000 and 2001), based on year 2000 census population projections (Statistics Canada). Numbers may not add due to rounding.

Table 16. Estimated Number of Annual FOBTs Incurred in the First Year (2000) of a Biennial Screening Program, with 67% Participation rate achieved (ramped up) over 5 years (from POHEM)

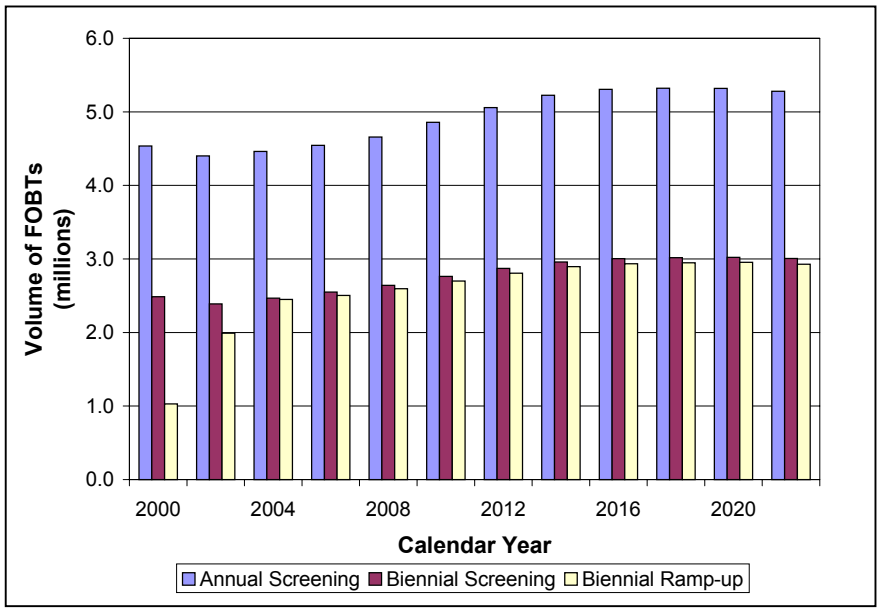
Province	% Canadian Population (aged 50-74)	Projected Number of FOBTs
CANADA (ages 50-74)	100% (7,001,322)	1029014
Newfoundland	1.8 %	18522
PEI	0.5%	5145
Nova Scotia	3.2%	32928
New Brunswick	2.5%	25725
Quebec	25.7%	264456
Ontario	37.7%	387938
Manitoba	3.6%	37044
Saskatchewan	3.1%	31899
Alberta	8.4%	86437
British Columbia	13.4%	137887

*Provincial estimates based on 1,029,049 tests apportioned according to provincial populations
†Estimate is the average of number of FOBTs to be incurred in the first screening cycle (years 2000 and 2001), based on year 2000 census population projections (Statistics Canada). Numbers may not add due to rounding.

Figure 8 depicts the number of FOBTs incurred over 25 years with and without attainment of full participation at the beginning of the program. It is apparent that

resource requirements will differ greatly in the first 5 years, depending on which scenario is the most realistic.

Figure 8 Number of FOBTs Incurred in a Biennial Screening Program, at Selected Years, With/Without Ramp-up of 67% Participation Rate (from POHEM)



II. Resource Implications for Positive FOBT Screens (with colonoscopy)

Data on resources related to diagnostic follow-up of the FOBT are equally sparse for Canada. Although flexible sigmoidoscopy and double contrast barium enema may be options for diagnostic follow-up of a positive FOBT, only current practices and projections related to colonoscopy will be described.

Table 17 depicts the estimated number of colonoscopies by province (column E) that would be expected given the current numbers of procedures (CIHI) in addition to those generated from a biennial screening program (POHEM).

Table 17. Projected Rates of Colonoscopy Procedures for the Year 2000 of a Biennial Screening Program, Based on Current Rates of Procedures (CIHI)[a] and Modelling Projections (POHEM)

	A Reported # of Colonoscopies 1995/96 (CIHI, 2000)*	B 1996 Population Estimates, Both Sexes and All Age Groups Combined (% of total Canadian population)	C # of Colonoscopies per 1,000 Population, 1996 (A /B)	D Projected # of Colonoscopies Resulting from Biennial Screening Program, 67% Participation, Year 2000† (POHEM)	E Total # of Colonoscopies, Year 2000‡ (Year 2000 population estimates§)
Canada	**303915**	29,862,700 (100%)	10.2	**46903**	**366,430** (31,397,000)
PEI	**1019**	134,200 (0.45%)	7.6	**211**	**1,254** (137,300)
NS	**8003**	936,300 (3.1%)	8.5	**1454**	**9,573** (949,900)
NB	**7881**	759,400 (2.5%)	10.4	**1173**	**9,131** (766,800)
NF	**9107**	582,100 (2.0%)	15.6	**938**	**9,995** (578,900)
QC	**87550**	7,413,700 (24.8%)	11.8	**11632**	**102,180** (7,667,600)
ON	**134942**	11,314,000 (37.9%)	11.9	**17776**	**161,890** (12,083,100)
MB	**7984**	1,132,100 (3.8%)	7.1	**1782**	**9,915** (1,153,300)
SK	**12861**	1,003,400 (3.4%)	12.8	**1595**	**14,486** (1,005,700)
AB	**14003**	2,789,500 (9.3%)	5	**4362**	**19,122** (2,940,300)
BC	**20565**	3,798,000 (12.7%)	5.4	**5957**	**28,235** (4,114,500)

[a]Canadian Institute for Health Information. National Grouping System Categories Report, Canada 1994/95 and 1995/96. National Physician Database. 2000.
*Reported number of colonoscopies, all ages
†Estimates of colonoscopies based on average of first cycle of screening (years 2000 and 2001). Numbers may not add due to rounding.
‡Total # of colonoscopies = current estimated colonoscopies + estimated colonoscopies due to screening
i.e. total # colonoscopies = (rate of colonoscopy use in 1996 x population projection for 2000) + projected # colonoscopies due to screening in 2000. Estimated provincial rate of colonoscopy use in 1996 for all ages.
§Numbers may not add due to rounding.

The rate of colonoscopy procedures is estimated using the most recent CIHI publication,[135] which reports the number of colonoscopies billed, by province, for the year 1995/96. Calculation of the estimated rates of colonoscopy use assumes that the rates for the latest year available (1995/96) remain constant to the year 2000, the year that implementation of the screening program will occur under the model. Further, it is assumed that the individuals captured in these rates do not take part in the screening program (and thus are not counted twice).

There is great variation in the crude per capita colonoscopy rates among provinces. Excluding Saskatchewan, there appears to be a gradient from west to east with the lowest per capita crude rate in Alberta (5.0 per 1,000 population) and the highest rate in Newfoundland (15.6 per 1,000 population). Although, there is a gradient of increasing CRC incidence from west to east, the rates of colonoscopy use show greater variability, which may be due to differences in reporting.

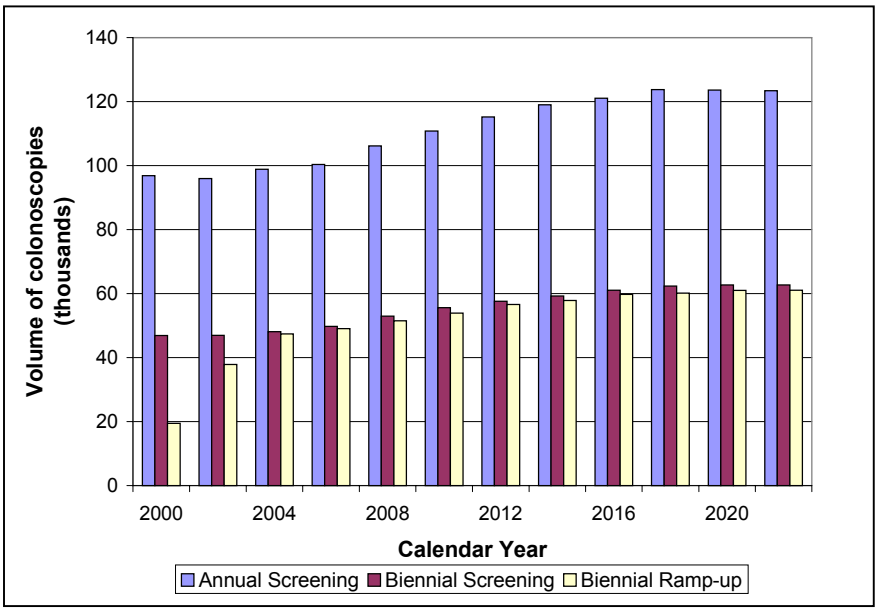
Demands on capacity will therefore depend not only on the "current" use of colonoscopy but also on the projected use of the test as part of a screening program. With 67% participation of Canadians aged 50 to 74, the first year of a national screening program (i.e. year 2000) could increase the number of colonoscopies performed, from 303,915 to 366,430 representing an overall increase of approximately 14.6% .

Colonoscopies are performed primarily by gastroenterologists and general surgeons. Gastroenterologists tend to be limited to larger urban centres, but general surgeons are often more frequently located in smaller communities in addition to urban areas. The most recent data from 1995/96 from the National Physician Database show that rates (per 100,000) of consultation in internal medicine range from 6,188 in P.E.I. to 13,274 in Ontario, with 11,445 consultations nationally.[135] Gastroenterology is one of the 13 sub-specialties included under the internal medicine specialty grouping. In contrast, the rates of consultation (per 100,000) in general surgery for these same provinces range from 8,942 in P.E.I. to 4,987 in Ontario with 4,415 consultations nationally. This may possibly indicate that some services provided by internal medicine specialists in Ontario are provided by general surgeons in P.E.I. and that access to certain specialties may differ in some geographic regions.

Interviews with key informants (Appendix E) indicate that published data groupings[134] may not be inclusive of colonoscopies performed in all provinces. For example, it appears that there were no billings for colonoscopy in P.E.I. from 1989/90 to1993/94,[134] when, in fact, the procedures were captured under "other endoscopies".[138]

Similar to FOBTs, the number of resulting colonoscopies will be dependent upon uptake of screening in the targeted population. Using both scenarios of full participation rate and ramped-up participation rate, the number of colonoscopies that would be incurred over 25 years of a biennial program was projected by POHEM.

Figure 9 Number of colonoscopies Incurred in a Biennial Screening Program, at Selected Years, With/Without Ramp-up of 67% Participation Rate (from POHEM)



Other Resource Implications

A CRC cancer screening program will result in an increased number of colonoscopy or other diagnostic procedures over and above those currently being performed. Many hospitals limit the hours of use of colonoscopy suites so that an increase in operating time as well as accompanying staff, equipment and endoscopist time may also be required. In addition, a proportion of colonoscopies will be followed by a biopsy, and thus the future demands on pathology services will need to be considered.

The current resources, both financial and human, necessary to run an endoscopy suite in Charlottetown, P.E.I. are reviewed (Table 18). The analysis is based on a 4 hour endoscopy session, 4 cases per session. Higher numbers of colonosopies may be performed in a different environment with other resources in place. Included are the expenses associated with maintenance, equipment breakdown, equipment and staffing costs for physicians and nurses. Physical space and equipment costs are not included.

Table 18. Colonoscopy Cost Analysis (4 diagnostic colonoscopies) - Endoscopy Suite in P.E.I.*†

Resource	Time Requirement and Cost
Equipment maintenance	$112.44
Supplies (including intravenous sedation)	$34.24
Nursing staff	$300.48 (salary and benefits: 2 full-time equivalent RNs and 1 full-time equivalent nursing assistant)
Admitting clerk	$11.85 (10 minutes. per patient)
Medical records	$6.56 (5 minutes per patient)
Endoscopists' fees	$569.40 ($142.35 per patient)
Total †	$1,034.97

*Estimates graciously supplied by Dr. Don Clark (Charlottetown, P.E.I.).
†Physical space requirements/costs and equipment costs excluded (estimated at $200,000/year and $75,000 respectively). With more procedures, expenses are projected to increase.

The costs for handling polypectomies were estimated by the Department of Laboratory Medicine at the Queen Elizabeth Hospital in Charlottetown. During a colonoscopy, many individual specimens are taken from different sites, and each specimen is cut to produce three histological slides. Between three and 24 slides could be generated from a single colonoscopy, all of which require processing, pathological interpretation, and filing. Each colonoscopy generates an average of four biopsy specimens at a cost of $184.00 ($37.00 per specimen x 4, including supplies and salary costs for technical and clerical functions + $36.00 for professional review).

As the aforementioned costs are specific to those at an endoscopy unit and laboratory in Charlottetown, costs may vary in other provinces. The cost per service for colonoscopy[135] is significantly higher in Manitoba ($149.34) and British Columbia ($219.07) than in P.E.I. ($138.69) (Table 19).

Table 19. Cost per Service for Colonoscopy, by Province, 1995/96 (CIHI, 2000)

Province	Provincial Cost per Service, Colonoscopy
Canada	**$ 122.78**
Quebec	**$ 76.23**
Saskatchewan	**$ 93.84**
Newfoundland	**$ 94.74**
Ontario	**$ 135.67**
Alberta	**$ 136.64**
PEI	**$ 138.69**
Manitoba	**$ 149.34**
Nova Scotia	**$ 150.13**
New Brunswick	**$ 166.10**
British Columbia	**$ 219.07**

The evaluation of an FOBT screening program in Canada is based on diagnostic follow-up of a positive test using colonoscopy. It is acknowledged that this may not be feasible in some geographic areas of Canada because of a shortage of specialists, lack of facilities, or patient preference. Thus, flexible sigmoidoscopy and double contrast barium enema could be considered as possible options.

Resource Implications Related to the Other Elements of a Screening Program

Issues specific to implementation of a CRC screening program are derived from literature related to the planning of screening programs in general, and not necessarily to screening for CRC. As previously stated by Garvican,[139] it is important to reiterate that no country at the time of this publication has implemented a national CRC screening program.

It has been recommended that screening works best if carried out in a structured "organized" environment rather than as opportunistic screening. Successful programs have essential elements in common: an identifiable target population; measures to guarantee high coverage and attendance; adequate field and laboratory facilities; an organized program for quality control of collection of material and laboratory interpretation; adequate facilities for diagnosis, treatment and follow-up of individuals; carefully designed referral systems; management of abnormalities; provision of information on normal screening tests; and provision for evaluation and monitoring of the whole program at the level of the target population.[140] Individual contact with the target population, education of the population, and encouragement of the primary physician are important factors in successful screening programs.[66]

Resources required to implement a screening program would include the following:

- resources for promotion of the program, recruitment of the target population, referral and management, reporting, maintenance of quality control;
- facilities for interpretation of FOB tests;
- facilities for diagnosis and treatment;
- physicians or health care providers: explanation of FOB test results, counsel, and arrangements for necessary follow-up;
- endoscopy suite and equipment: diagnostic follow-up of positive tests;
- GI specialists: colonoscopy and/or flexible sigmoidoscopy;
- radiologists: DCBE if required;
- pathologists: laboratory facilities and interpretation of biopsies;
- information systems: evaluation and monitoring.

Recruiting, collecting data on all participants, and ensuring timely follow through at all steps of the screening process must be considered in delivering an FOB screening program. Three basic models have been proposed by the Australian Health Technology Assessment Committee for implementing/organizing a CRC screening program:

1. A program that involves screening, follow-up and recall entirely managed by family physicians.

2. A program that involves screening by family physicians but with a central registry and recall system.

3. A totally "organized" or "centralized" screening program, which includes screening, follow-up, diagnosis and referral back to the family physician for further management.[2]

The first option has the inherent problem of reaching all of the targeted screening population. In Canada, there is no central registry of family physicians' practice. Furthermore, a percentage of the population aged 50 to 74 is unlikely to have a regular family physician whom they see on a regular basis. Analysis of the National Population Health Survey 1994-95 (NPHS) indicated that 67.5% of adults had "regular care from a family physician", 18.9% had "some regular care", and 13.6% had "no regular care" ("care from a family physician" defined by the authors). Further, those receiving regular care were more likely to have preventive services at the intervals recommended.[141]

The second option is a system similar to that typically seen with cervical cancer screening in the U.K. There are numerous reports of failure with this system, primarily because of the lack of adequate data collection, follow-up, and evaluation.[32] These two options are often referred to as unorganized or opportunistic screening: individuals enter a screening program when they visit their family physician for an unrelated problem or reason.

The third option, which typically occurs with screening mammography for breast cancer, has been reported to be the most effective. At minimum, the program should have a central registry to coordinate activities such as recall.[2]

Recruitment and education of the public and professionals will not be discussed in this report, but the reader should be aware that there are methods that have been evaluated and recommended.

Additional Considerations

Quality of Care

Physicians who will be involved in providing diagnostic follow-up need to be properly trained and periodically monitored to ensure that they can perform procedures such as colonoscopies and polypectomies safely and accurately. This is especially relevant given that most positive FOBTs will lead to lesions that subsequently will require removal.[142]

Management, Monitoring and Quality Assurance

With the organization of a screening program, there will be requirements for information. These requirements include the basic data designated for collection, the methods for storage and communication of the information, and the methods of analysis and presentation. These requirements arise from the need to maintain records; to communicate both with and about participants in the program or those eligible for inclusion in the program; to monitor the effectiveness and efficiency of the program; to enable future planning; to both assess and manage the laboratory and clinical

information; to implement quality control measures; to conduct research into the natural history and epidemiology of the cancer; and, if appropriate, to address payment for service issues.[143] While the need to maintain records and undertake communication is essential to the functioning of the screening program, at the very least an attempt should be made to monitor the effectiveness and efficiency of the program. For smaller programs, it may not be possible to address the remaining needs noted above.[143]

Total Costs of a Screening Program

To estimate the total costs of running a biennial FOBT screening program for Canadians aged 50 to 74 years with a participation rate of 67% and re-screen rate of 93%, POHEM used the following assumptions.

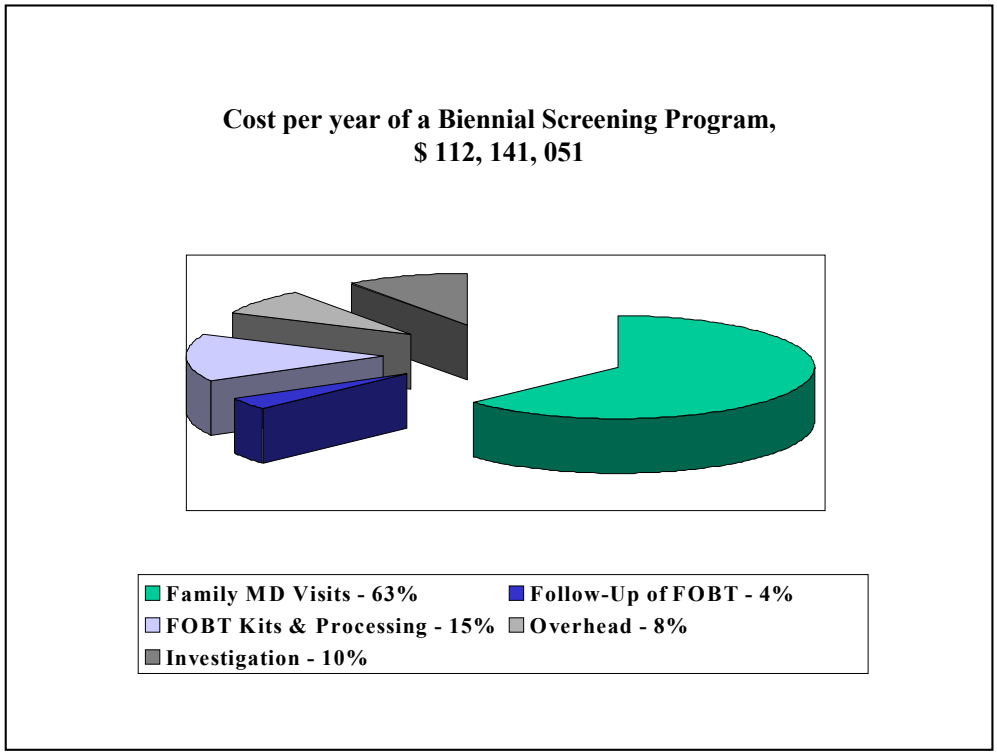
Table 20 illustrates the estimated costs of the various screening components and the source of the data that were included in POHEM.

Table 20. Estimated Costs of Screening Program Components for Core Scenario*†

Screening Program Component	Cost for Core Scenario	Rationale
Head office, satellite branches, recruitment and promotion strategies (OVERHEAD)	$15,000,000/ yr	Based on estimate for Ontario of $3.5M (ON only‡);
Physician visits	$43.58	Based on 1½ visits to family physician for each participant (1999 OHIP fee schedule for A004 "reassessment" of $29.05§)
FOBT - slides (kit)	$4.65	Based on OHIP reimbursement (June, 2000) of $1.55/ slide x 3
- processing, interpretation, data entry, communication of results (both negative and positive results)	$6.00	Based on fee estimates ranging from $2.50 to $8.00 (quoted by 3 Ontario private laboratories)
Follow-up consultation (for positive FOBTs)	$123.70	Based on every participant with positive FOBT revisiting family physician for interview and physical exam (1999 OHIP for A003 of $ 52.05), similar to Funen Trial. Every participant would subsequently have minor consultation with a gastro-intestinal specialist (1999 OHIP A416 or A545 of $ 71.65)
Diagnostic investigation - using colonoscopy (includes equipment and maintenance, overhead, intravenous sedation, endoscopist's fee and support staff)	$350.00	Based on estimates from Charlottetown, PEI (Dr. Don Clark) and estimates from Manitoba* and Alberta† cost lists of DPGs ("endoscopy - gi")
Polypectomy (part of diagnostic investigation)	$147.00	Based on estimates from Queen Elizabeth Hospital, Charlottetown, PEI: removal of three polyps

*Manitoba: "DPG"Day Procedure Group (cost list for Manitoba Health Services)
†Alberta: "DPG"Day Procedure Group costs (an Alberta Standard Cost List for Health Economics Evaluations)
‡CCO: Cancer Care Ontario (estimated screening cost for Ontario using FOBT, unpublished)
§OHIP: Ontario Health Insurance Plan

Figure 10 Cost per Year of a Biennial Screening Program (from POHEM)



POHEM estimated the total costs for a 25 year program with allowances for the changing population (i.e. aging of "baby boomers") and for the entry and exit of individuals who become eligible at age 50 and ineligible at age 75. Based on the core scenario, the cost per year to run a 25 year biennial FOBT screening program with a 25 year follow-up was estimated at $**112,141,051**. This translates into an average cost of **$40 per screen**. The largest component of this overall cost is that associated with physician visits (Figure 10), which represent 63% of the total cost. The next largest cost component is that associated with FOBT kits and processing (16%) followed by the cost of diagnostic investigation (through colonoscopy with or without polypectomy). Follow-up costs for positive FOBTs through consultation and the costs associated with the program overhead account for less than 10% of the total overall cost.

Because the 63% allocated to family physicians represents only those visits at the onset of the screening pathway and does not capture the cost of revisiting a family physician after a positive FOBT, it is a slight underestimate. The costs per year associated with running an annual FOBT screening program for 25 years was estimated at **$194,521,993**. The distribution of costs approximate those of a biennial screening program.

Criterion 9

The resources allocated to the screening program (including testing, diagnosis, and treatment of patients diagnosed) should be economically balanced in relation to other health care priorities

The National Committee recognizes that the allocation of resources for health care will ultimately lie with policy decision-makers. This section therefore attempts to provide adequate information about the resources (human and economic) that would be required for a screening program in order to support appropriate decision-making. It is important to note that the calculation of cost-effectiveness will depend not only on screening per se, but on the organizational structure that will be put in place for screening.

Cost-effectiveness analysis addresses "the comparative cost of two interventions per outcome" and is measured as the cost per case prevented, the cost per life saved, or the cost per year of life saved".[144,145] Cost-utility analysis is identical to cost-effectiveness analysis except that the outcome (cost per year of quality-adjusted life expectancy) takes into consideration the preference of the individual or society.[144]

The cost of population-based screening will always be relative, especially in developed countries; the issue is really one of competing priorities.[66] There is more theory than data with respect to the cost-effectiveness of CRC screening programs, and the acceptable cost of CRC screening has never really been defined. Thus, responses to costs are purely subjective and consequently may not be solely reliable for making a decision for or against CRC screening.[66]

Modeling has shown that screening average-risk individuals for CRC is as cost-effective as screening for other cancers,[146] although rates of compliance significantly affect incremental cost-effectiveness ratios. It has been estimated that CRC screening costs approximately $20,000 (US) per life year saved regardless of the strategy; this falls within the range of cost-effectiveness for commonly accepted screening programs.[38] Costs per year of life saved for screening mammography and hemodialysis have been estimated at $34,500 (US) and $36,000 (US) respectively.[59] Although the short-term cost-effectiveness of CRC screening is comparable to that of breast cancer, some believe that it is even more cost-effective in the long term. A modelling exercise using 60 different CRC screening programs suggested that annual CRC screening (using Hemoccult II) for those 50 to 74 years appears to be more cost-effective than biennial mammography for those 50 to 59 years. Similarly, in Denmark, where programs for

cervical cancer screening are already in place, the cost-effectiveness of screening for CRC is more favourable than that for cervical cancer.[147]

Effectiveness and Cost-effectiveness of Population-based Colorectal Cancer Screening in Canada (POHEM)

This section will focus on the effectiveness and costs associated with biennial screening. For further estimates regarding annual screening, please refer to Appendix D.

Core Scenario
Biennial screening of the Canadian population aged 50 to 74, with a participation rate of 67% and a rescreen rate of 93%. See Figure 7 of Criterion #8 for the proposed screening pathway.

The costs of the program elements used in POHEM are summarized in Table 20 of the previous criterion. On the basis of the above core scenario and the proposed program pathway (Figure 7), the overall cost per life year gained from a 25 year screening program with lifetime follow-up was estimated to be **$11,907** (discounted at 5%). This finding is comparable with the "price"of health benefits determined by the U.S. Office of Technology Assessment in its review of a number of screening strategies for colorectal cancer for average-risk adults, and is also well below the benchmark value of approximately $40,000 (US) per added year of life that is often applied to preventive technologies.[148]

Sensitivity Analyses

Sensitivity analysis involves varying one parameter across the range of uncertainty to determine what impact a specific component has on the final result.[149] The programmatic costs for the core screening scenario were altered as part of the sensitivity analyses, as some costs are truly unknown and are best estimated by a range of possible values. Table 21 includes the costs that were used for the sensitivity analyses.

On the basis of these costs, POHEM estimated the cost per life year gained for biennial screening with a 25 year program with lifetime follow-up to be **$18,445** (discounted at 5%).

Table 21. Estimated Costs of Screening Program Components for the Sensitivity Analyses

Screening Program Component	Cost for Sensitivity Analysis	Rationale
Head office, satellite branches, recruitment and promotion strategies (OVERHEAD)	$30,000,000/ yr	Doubling overhead costs of core scenario†
Physician visits	$58.10	Based on two visits to a family physician for each participant (1999 OHIP fee schedule for A004 "reassessment"of $29.05)
FOBT - slides (kit)	$9.30	Based on OHIP reimbursement (as of June 2000) of $1.55/slide (for 6 slides), as per Funen Trial, which reported 2 fecal samples from each of 3 consecutive stools
- processing, interpretation, data entry, communication of results (both negative and positive results)	$8.00	Higher fee to accommodate processing, cost of communication etc.
Follow-up consultation (for positive FOBTs)	$161.10	Based on every participant with positive FOBT revisiting the family physician for interview and physical examination (1999 OHIP for A003 of $52.05), similar to protocol in Funen Trial. Subsequently, thorough consultation with a gastrointestinal specialist (1999 OHIP A415 of $109.05) for every participant.
Diagnostic investigation using colonoscopy (includes equipment and maintenance, overhead, medication, endoscopist's fee, support staff)	$425.00	Based on Alberta cost lists of DPGs ("endoscopy - gi") ($427.41)
Diagnostic investigation using barium enema (includes technical and professional fees)	$101.25	Derived from cost analysis for radiology services, Charlottetown, PEI (includes technical and professional fees)
Diagnostic investigation using flexible sigmoidoscopy	$125.45	Based on 1999 OHIP fee schedule for Z580 + E717 + 4 units of anesthesia (@ $11.20 each
Polypectomy (part of diagnostic investigation)	$147.00	Based on estimates from Queen Elizabeth Hospital, Charlottetown, PEI: removal of 3 polyps

CCO: Cancer Care Ontario (based on estimate using FOB screening from Cancer Care Ontario); DPG: Day Procedure Group "DPG"- Day Procedure Group Costs (an Alberta Standard Cost List for Health Economics Evaluations); OHIP: Ontario Health Insurance Plan

As the Committee recognized that there may be issues of personal preference and access that determine the test used for diagnostic follow-up, it suggested that barium enema be modelled as part of the sensitivity analyses. To model this, the core scenario was used but altered so that 50% of individuals would undergo barium enema and 50% would undergo colonoscopy as diagnostic follow-up investigations. Of those individuals undergoing barium enema, 80% would go on to have a flexible sigmoidoscopy, 10% would have a colonoscopy, and the remaining 10% would go directly to surgery. In this scenario, the estimated cost per life year gained was **$11,683** (discounted at 5%) for biennial screening with a 25 year screening program and a lifetime follow-up. When the costs were changed to those found in Table 21, with barium enema and colonoscopy as diagnostic tests, the estimated cost per life year gained was **$18,074** (discounted at 5%) for biennial screening.

Based on the modelling results using different cost estimates, POHEM indicates that biennial population-based screening using FOBT is cost-effective in Canada. (The same is true for annual FOBT screening (refer to Appendix D)).

Incremental Cost Effectiveness — Ages to Start and Stop Screening

In an environment of rationed health care, the cost-effectiveness of screening different age groups needs to be carefully evaluated.[18] POHEM was used to estimate the incremental cost effectiveness (extra cost incurred divided by the incremental life years gained between two scenarios) of starting and stopping at different ages.

Costs were discounted to indicate that the costs or benefits in the future will have less value than they have in the present. For example, $1 today has more value than $1 next year even if the dollar is returned with inflation factored into the value. Discounting is especially important for costing interventions that incur later benefits and, like inflation, is calculated in percentages. The rate used is debatable, but often 3% or 5% per year is used.[145]

The age at which biennial screening should begin was modeled by taking a large simulated cohort of 40 to 44 year old people in the year 2000 and following them until death. Starting at this age range is appropriate given literature findings that propose cost-effectiveness be considered with respect to screening individuals aged 40 to 50, because the prevalence of occult lesions will probably be comparatively low in this age group.[2] To determine the most cost-effective age at which to start screening, the ages to start screening were varied by 5 year increments while a fixed age of 74 was maintained to end screening. There was no statistically significant difference in life years gained between starting to screen at ages 40, 45, or 50 years (95% confidence intervals overlap) (Figure 11).

The incremental costs per life year gained associated with starting screening at different ages are depicted in Table 22. The incremental cost associated with starting screening at age 40 versus waiting until age 45 with 5% discounting was very high ($133,325) compared with starting screening later. This is consistent with other findings[150] that concluded screening at age 40 rather than age 50 did little to increase the effectiveness and delaying screening to age 50 reduced costs approximately by a factor of 2.

Figure 11 Change in Life Expectancy Due to Screening, by Starting at Different Ages

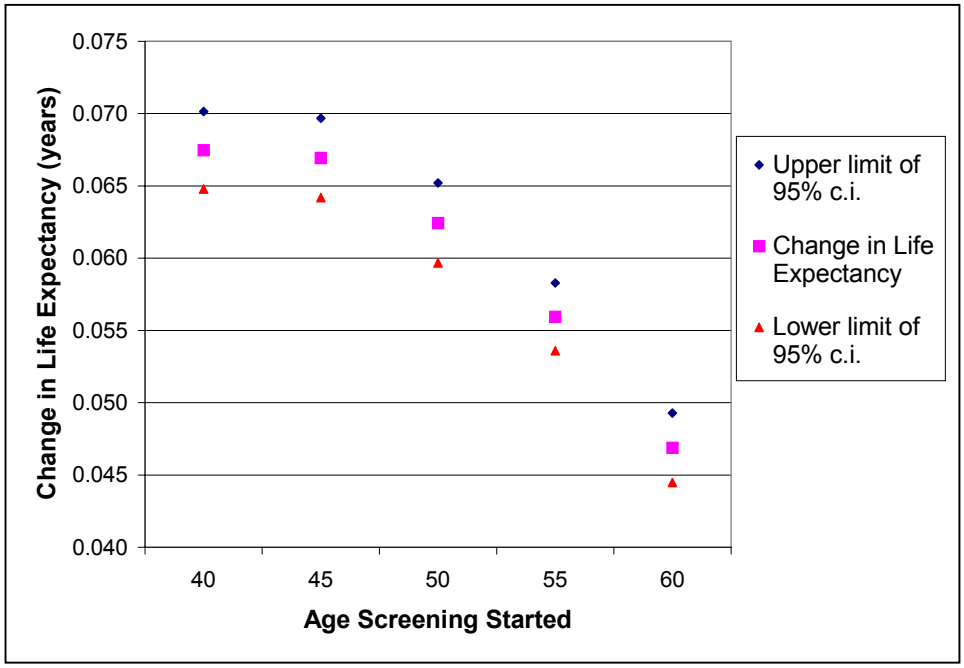


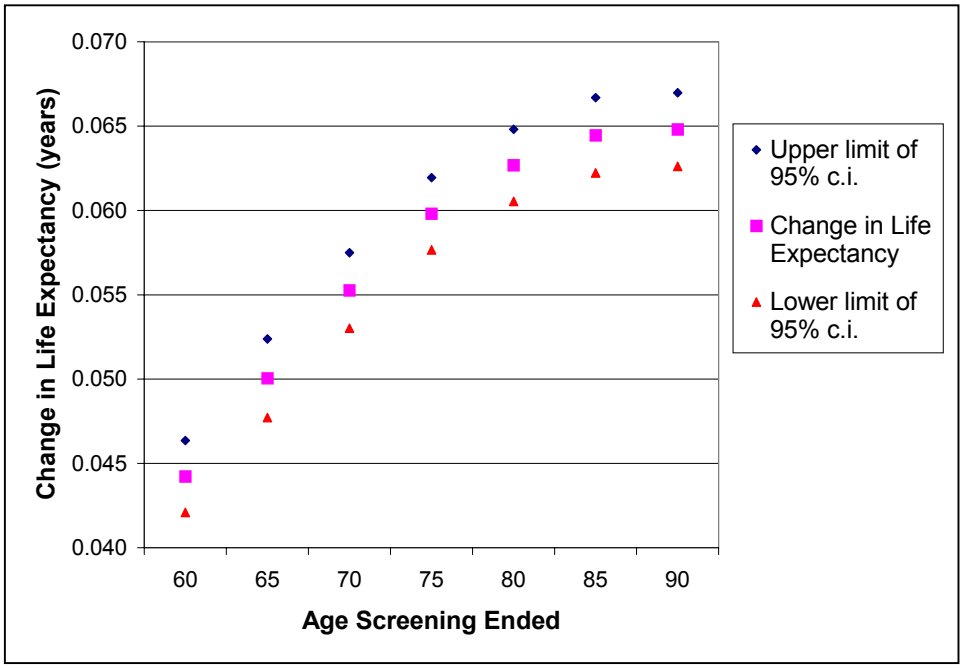
Table 22. Incremental Cost Per Life Year Gained with Biennial Screening Starting at Different Ages* (ending at age 74)

Age at which Screening is Started	Cost and Outcome Discounted at 0%	Cost and Outcome Discounted at 3%	Cost and Outcome Discounted at 5%
40 vs 45 yrs	$90,239	$112,385	$133,325
45 vs 50 yrs	$21,175	$ 36,096	$ 49,647
50 vs 55 yrs	$10,946	$ 18,458	$ 24,643
55 vs 60 yrs	$ 9,907	$ 14,155	$ 17,681

*Based on a simulated cohort of 40-44 year olds recruited in the year 2000 and followed until death, n = 1,503,578.

The age at which screening should stop was also modelled. In this analysis, the ages at which to end screening were altered, while a fixed age to start screening was maintained at 50 years. Regardless of the cost, there was no apparent benefit in terms of life expectancy by screening beyond age 80 (Figure 12) as there was no statistically significant difference between ending screening at ages 80, 85, or 90. Ending screening at age 75 or 80 also appeared to be statistically the same.

Figure 12 Change in Life Expectancy Due to Screening to Different Ages



Extending screening beyond the age of 80 years does not significantly increase life expectancy (see Figure 12) . Table 23 represents the incremental costs of screening to various ages.

Table 23. Incremental Cost Per Life Year Gained with Extending Screening to Different Ages (starting at age 50)

Age at which Screening Ends	Cost and Outcome Discounted at 0%	Cost and Outcome Discounted at 3%	Cost and Outcome Discounted at 5%
65 vs 60	$15,993	$23,538	$29,681
70 vs 65	$14,341	$20,103	$24,691
75 vs 70	$16,378	$21,620	$25,701
80 vs 75	$19,396	$24,012	$27,516
85 vs 80	$27,938	$31,622	$34,328
90 vs 85	$63,099	$65,454	$66,944

Based on a simulated cohort of 50-54 year olds recruited in the year 2000 and followed until death, n = 1,195,134.

The prevalence of occult lesions will increase with age[88], and although age is important as a risk factor for colorectal cancer, the benefits of screening will be diluted at older ages because of competing causes of morbidity and mortality. [60]

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APPENDIX A

National Committee on Colorectal Cancer Screening
Terms of Reference

Purpose:

To explore the scope and determine the issues of national importance with respect to population-based colorectal cancer screening in Canada. To develop recommendations for population-based colorectal cancer screening in Canada.

Roles and Responsibilities:

1. To facilitate communication between member agencies/foundations, organizations, and associations for the development and dissemination of consensus-based policy recommendations for population-based colorectal cancer screening in Canada.

2. To review the existing recommendations/guidelines regarding colorectal cancer screening including those developed by the provinces as they develop.

3. To identify gaps in knowledge regarding colorectal cancer screening and propose actions to remedy the gaps (e.g. target group, frequency, cost analysis).

4. To develop recommendations for the promotion of organized colorectal cancer screening in Canada.

5. To report on the status of colorectal cancer in Canada, and propose recommendations that could be taken at a national level.

Membership:

The National Committee on Colorectal Cancer Screening will be chaired by Dr. Heather Bryant, Director, Epidemiology, Prevention and Screening and Vice-President of the Alberta Cancer Board and supported by Health Canada. Membership will include nominees from the provincial cancer agencies/foundations, the Canadian Cancer Society/ National Cancer Institute of Canada, professional and non-professional organizations, and Health Canada.

Dr. Heather Bryant (Chair)	Alberta Cancer Board
Dr. Christofer Balram	Provincial Epidemiology Service - New Brunswick/rep. Public Health Working Group
Ms. Frances Barnes	Consumers' Association of Canada
Dr. Jean-François Boivin	Conseil québécois de lutte contre le cancer/Conseil d'évaluation des technologies de la santé du Québec
Dr. Françoise Bouchard	Health Canada

Dr. Fred Burge	College of Family Physicians of Canada
Dr. Gregory J. Butler	Canadian Association of Radiologists
Dr. Don Clark	Province of Prince Edward Island
Dr. Andrew Coldman	British Columbia Cancer Agency
Ms. Ann Coombs	Health Canada
Dr. A.L.A. Fields	Canadian Cancer Society/National Cancer Institute of Canada
Dr. Alan Kwan	Newfoundland Cancer Treatment and Research Foundation
Dr. Robin McLeod	Canadian Task Force on Preventive Health Care
Dr. Liam Mulroy	Cancer Care Nova Scotia
Dr. Eric Nicholls	Health Canada
Mr. Hussein Z. Noorani	Canadian Coordinating Office for Health Technology Assessment
Dr. Daniel C. Sadowski	Canadian Association of Gastroenterology; Royal College of Physicians and Surgeons of Canada
Dr. Richard Schabas	Cancer Care Ontario
Dr. Chandrakant P. Shah	Canadian Medical Association
Dr. Ross Stimpson	Cancer Care Manitoba
Dr. M. Jane Thomas	Canadian Association of Pathologists
Ms. Sandra Thompson Bednarek	Colorectal Cancer Association of Canada
Dr. M.R.B. Tria Tirona	Saskatchewan Cancer Agency - Allan Blair Cancer Centre
Dr. Carol-Ann Vasilevsky	Canadian Association of General Surgeons/Canadian Society of Colon and Rectal Surgeons

APPENDIX B

Primary Prevention of Colorectal Cancer

A document prepared for the National Committee on Colorectal Cancer Screening

By Elaine Jones-McLean
April 2000

Prevention of disease occurs at different levels, with primary prevention being aimed at preventing disease in a population at risk.[1] This Appendix provides a snapshot of what is currently reported on the primary prevention of colorectal cancer (CRC), including chemoprevention.

1. Dietary Lifestyle Factors

Comparison of international cancer rates and studies of migrants have long suggested a potential role for diet in the etiology of various cancers, including CRC. Although there has been extensive research in this area with respect to CRC, much still remains unclear about the level of risk and the possible mechanisms for most dietary constituents.

The hypothesis that dietary fiber may be related to CRC risk stems from Burkitt's ecological observation in the 1970s that Africa had lower rates of CRC than other areas of the world. Although analytic studies have been fairly consistent in showing that high intakes of fiber are inversely related to CRC risk, [2,3,4] a large prospective study [5], two small randomized controlled trials (RCTs) [6,7] and two larger recent RCTs have all failed to establish this relationship.[8,9] In the latter trials, the fiber intakes (13.5 gms and 18 gms) were low, especially in view of recommended levels of 25 to 30 gms. In addition, the follow-up periods of three and four years may have been too short to observe an effect. An ongoing European trial looking at fiber and CRC risk is still underway.[10] The purported biological mechanisms for fiber's potential preventive role are several-fold. Fiber increases fecal bulk, which decreases transit time and diminishes contact with potential carcinogens, and it acts to dilute fecal concentrations of bile acids through binding of the acids. Bile acids have been shown to promote colon carcinogenesis in animal models.[11] There is still uncertainty about whether the observed effect is actually due to fiber itself or to other nutrients and non-nutrients present in high-fiber foods, which themselves have been shown to be chemopreventive. [12] These constituents, such as vitamin E, flavonoids and lignans, vary in presence and concentrations depending on their source. Studies which have reported or studied the effect of fiber on CRC have varied according to the amount of fiber supplied, as well as whether the fiber was consumed from food sources or by supplement. This may be important since fiber is not a specific chemical entity and various fibers can affect the colonic mucosa in different ways.[13] It is also important to stress that the fiber for which a protective role is suggested is the insoluble fiber. Soluble fiber (such as oat bran) has been promoted for hypercholesterolemia prevention; it does not have the same properties as insoluble fiber in terms of interfering with bile acids.

Although CRC rates are higher in countries where there is a high fat intake, analytic studies have failed to establish consistent or significant elevated risk of CRC with high fat intakes, and there have been no accounts of an associated decreased risk.[2,14,15,16] Intervention studies, which have counselled subjects to reduce their total fat intake to 20-25% of their total energy intake, have further failed to demonstrate a consistent risk reduction in CRC.[17,6,9] It is probably not only the total amount of fat, but also the type of fat, which is important. Saturated fat, compared to the unsaturated fats found in vegetable oils and fish, may increase CRC risk by increasing the concentration of bile acids.[11,16] It is therefore important to account for the effect of meat (typically high sources of saturated fat) and for total caloric intakes.[14,18]

Heterocyclic amines (HCAs) have been shown to be carcinogenic in animal models. These compounds form when high protein foods, such as meat and fish, are exposed to very high temperatures or are cooked to a well-done state.[19,20] Any positive association between meat intake, especially fried meat,[21] and CRC may be explained by the intake of HCAs.[15,19] Some epidemiological studies have indicated an increased risk for CRC with high intakes of HCAs,[22,23,24] while others have not.[19,21]

Nonetheless, many studies have relied on indirect measures of mutagenic activity, such as the level of browning on the meat's surface or the level of doneness. This is less than ideal as HCA levels vary across meat types using the same cooking method, and across cooking methods for the same meat type.[20] A recent case-control study which attempted to separate out cooking method and doneness from red meat consumption found an elevated risk of CRC with high HCA intake.[24] Although it may be difficult to separate the effect of HCAs from meat consumption (including its protein and fat content), most studies have not examined the risk with fried fish or meats other than beef.[20,25] Also, the association between HCAs and CRC could be highly influenced by certain genotypes.[21,26]

It has been proposed that calcium may form insoluble soaps by binding to potentially carcinogenic bile acids, thereby reducing the latter's concentration and thus decreasing the risk for CRC.[27,28,29] Results from observational studies appear to support a protective role for high calcium diets or calcium supplementation; most studies have reported decreased colorectal cell proliferation, changes in bile acid composition, and an overall decreased risk of CRC or colorectal adenoma.[4] Nonetheless, the associations have not always been significant, nor replicated.[2,4,29,20,31,32,33,34,35,36] Part of the reported inconsistencies from calcium studies may stem from the inability to accurately capture calcium intake [4] and to separate out the effects of fat and phosphorus, two nutrients typically found in high calcium foods. High phosphorus and fat intakes have been associated with increased bile acid concentrations.[29] If there is a protective role for calcium, it is likely that it is early in the pathway of colon carcinogenesis [4] and that it may be more beneficial to the rectum than to the colon.[27] Vitamin D has often been paired with calcium when examining the latter's potential role in reducing the risk of CRC. Unfortunately less is known about vitamin D.[27,31,37] Randomized clinical trials (RCTs) with supplements of calcium have looked at different outcomes (e.g., bile acids, rectal mucosal proliferation, bowel adenomas, adenoma recurrences and CRC), and have shown conflicting results with supplementation.[27,28,29,30,37,38,39,40] Several trials looking at changes in rectal mucosal proliferation rates have not reported any decreases among those receiving 1200 to 1500 mg of elemental calcium.[30,39,40] Nonetheless, a recent trial showed a modest reduction in colorectal adenoma recurrence with calcium supplementation, independent of fat intake.[28]

Individuals who consume higher amounts of fruits and vegetables appear to have lower rates of CRC according to the majority of observational studies. [28,41,42] Accordingly, researchers have speculated that antioxidant compounds found in these foods, such as vitamins C and E and beta-carotene, may be responsible for this protective effect. Antioxidants are compounds which act to inhibit free radicals and thereby reduce DNA damage and mutation.[43] Nonetheless, intervention studies have failed to offer convincing support for a beneficial role of these compounds with respect to preventing CRC.[2,14,41,42,44,45,46] The longest running trial so far followed subjects for 12 years and failed to establish a beneficial effect from beta-carotene in preventing CRC occurrence.[41] The only RCT to evaluate the effect of all antioxidants also failed to report a significant risk reduction in the treatment arm.[42] Other RCTs have been similarly disappointing.[4]

Few studies have specifically investigated the role of folate with respect to CRC. Three prospective studies, two of which included only men and the other a large cohort of female American nurses, have suggested that inadequate levels of folate may increase the risk for CRC.[47.48] Supplements of folate, or vitamin supplements containing folate, have been shown to protect against CRC particularly if taken over the long term; furthermore, this inverse relationship was stronger for supplement use than for intake of folate through food sources.[47] Any benefit from folate supplementation is also more likely to occur in those genetically at higher risk for CRC.[4] When examining the benefits of folate, it is critical to control for intakes of alcohol, methionine or red meat,since they may confound any observed effects.[14,37] To date, there have been no intervention studies examining the effect of folate on the risk for CRC.

Alcohol has been widely studied in relation to risk of CRC, but conclusions are limited by very different methodologies and insufficient evidence.[49] A review of descriptive and observational studies suggest a positive association between alcohol and risks for CRC.[50,51,52,5354,55] While some indicate a small increased risk,[49] other studies have found nothing definitive with respect to CRC.[56] Some reports suggest the risks may be different for men and women,[50,51,52,57,58] for the different sites (rectum vs. colon)[52,55] and for different the types of alcohol (i.e., beer, wine or spirits).[50,52] Beer consumption has been associated with a moderate increase in risk for rectal cancer among male brewery workers in one study[55] and a significant increased risk for rectal cancer among women in another study.[52] The exact role of alcohol in carcinogenesis is not clear,[49,57] but it is probably more likely to be a co-carcinogen or tumour promoter.[49] Low rates of colon cancer have been reported in Mormons and Seventh Day Adventists.[59,60] Although this reduced risk may be related to the restriction of alcohol use, it may also be attributable to other lifestyle factors such as diet and non-smoking. Colon cancer has been reported to be higher in non-vegetarian Seventh-Day Adventists than in vegetarian Adventists.[61]

The risk of CRC as it relates to diet has recently been looked at from the food group level, rather than from the constituent or nutrient level. This seems appropriate given that it is still unclear whether it is a single aspect of diet, such as a particular vitamin [62] or cooking practice, which accounts for any of the observed risk estimates. Fruits, vegetables and red meat have frequently been discussed in relation to CRC. The observational evidence surrounding a beneficial role for fruits and vegetables,[63] more specifically for vegetables, is consistent. Decreased risk seems to be more pronounced for women, particularly for the colon, with a diet including raw, green and cruciferous vegetables.[54,64] There have been fewer studies examining the role of fruits alone. The role of red meat as a risk factor for CRC is very unclear. Several epidemiological studies have found an increased risk with red meat, but others have not.[15,21,45,65,66] The majority of cohort studies and five prospective studies on vegetarians (the closest perhaps to a non-randomized controlled trial) have failed to support a link between red meat intake and increased risk for CRC.[67] Some researchers believe red meat may simply be a marker for something else which contributes to a higher risk for CRC, such as overall eating patterns. Interestingly, American-based studies have reported an increased risk with red meat intake, while studies done in Europe, where there are higher fruit and vegetables intakes, have failed to observe an association with red meat.[65]

In another study, the risk for CRC was assessed in relation to five identified eating and lifestyle patterns. Although the risk was not significant, the "Western" eater who had the highest intake of total energy and cholesterol and the highest body mass index (BMI), was found to be at the greatest risk. The prudent eater, whose lifestyle included a high-fiber, high-folate diet and vigorous exercise, had the lowest risk.[68] This coincides with the hypothesis that some foods (eg., meat) may be associated with increased risk of CRC if their intake is jointly associated with a decreased intake of protective foods, such as fruits and vegetables.[65] This point might apply to Finland where the typical diet contains high amounts of both fat (approximately 40%) and fiber (30 gm), but where the rates for CRC are lower than those found in North America, where the intake of fat is similarly high but the intake of fiber is low.[11]

Other foods or diet-related components which have also been cited or examined in relation to CRC include: sugar, methylxanthine-containing beverages (such as coffee, tea and colas), garlic, soybeans, tea, eggs, phenols, dithiones, flavones, thioethers, iron and iron stores, as well as meal frequency.[58,69,70] Other components have been less investigated. For example, selenium supplementation (200 µg) has been reported in one RCT to be associated with a decrease in CRC incidence.[71] However, the sample size was small (27 subjects in total), and the primary endpoint of the trial was skin cancer. A case-control study looking at serum levels of selenium did not find an overall association between decreased risk for CRC tumour and higher levels of selenium.[72]

2. Other Lifestyle Factors

Physical activity has consistently been linked, in both occupation and recreation-related studies, to lower risk for colon cancer in both men and women.[54] The greatest impact seems to be imparted by life-long activity.[58,73] Despite a seeming dose-response relationship, the required level of activity to bring about a benefit is not well established.[73] Studies also suggest that energy intake does not necessarily confound the protective effect of exercise.[45] One study showed that overweight men who were physically active were at less risk for colon cancer than their overweight, inactive counterparts, suggesting that perhaps lean body mass may be somehow involved or that body mass index (BMI), the standard for determining obesity, may not accurately reflect adiposity.[54] The evidence for cancer of the rectum alone is not as well established.[58]

Body mass is related to exercise insofar as an imbalance in energy intake and energy output contributes to obesity. Obesity has been inconsistently associated with an elevated risk for CRC, especially in men.[54,58] Besides potential problems with using the BMI, biases have been found in self-reported weights and heights. In general, men tend to report higher weights than their actual, while women tend to report lower weights.[74,75] One hypothesis is that the mechanisms behind physical activity and obesity may lie with the condition of hyperinsulinemia. The latter has been linked with tumour growth and is controlled by physical activity and by maintaining a healthy weight.[73] Independent of body mass, higher stature has been associated with greater risk for colon cancer.[45] Obesity also appears to influence the risks for rectal cancer, but to a less certain degree.[58]

Although the evidence linking CRC and smoking is inconclusive,[13] cigarette smoking has consistently been associated with the development of colorectal polyps.[76] Some studies have demonstrated an elevated risk for CRC among smokers who have a long smoking history. More specifically, cigar and pipe smokers seem to be at an increased risk for CRC.[58] Confounding any possible association between tobacco smoking and CRC are the observed differences in dietary intake between smokers and non-smokers. Some studies note that smokers have higher intakes of energy and fat (including saturated fat) and lower intakes of fiber, vitamin C and beta-carotene.[77]

3. Chemoprevention

Chemoprevention has been defined as the use of natural or pharmacologic agents to disrupt the process of carcinogenesis.[2] With respect to CRC, chemoprevention involves the long-term use of such oral agents to prevent the development of adenomatous polyps and their subsequent progression to CRC.[4]

Indomethacin, piroxicam, sulindac and aspirin have all been found to decrease the incidence and multiplicity of tumours in animals studies, and have thus been identified as chemopreventive agents for animal CRC.[78] Non-steroidal anti-inflammatory drugs (NSAIDs) are thought to inhibit enzymes, specifically prostaglandin H synthetase, which are involved with the initiation and promotion of carcinogenesis.[78] Another likely mechanism of NSAIDs is through the inhibition of cyclo-oxygenase (COX). COX activity, particularly COX-2, has been reported to be higher in colorectal cancers, but lower in colorectal adenomas or normal colonic epithelium.[4,37] Inhibition of COX-2 activity has decreased the formation of tumours in experimental models[79] and has arrested apoptosis in familial adenomatous polyps.[37] Randomized trials in the early 1990s showed that sulindac successfully regressed colorectal polyps in individuals with Familial Adenomatous Polyposis (FAP).[80] Observational studies with non-FAP

subjects have demonstrated a 30%- 50% reduction in CRC incidence and mortality with aspirin[4,78,81] and with another non-aspirin NSAID.[82] Among the limitations in these observational studies is the recall bias, since most aspirin and salicylate are not obtained by prescription.[82] With respect to interventions, The Physicians' Health Study is the only completed RCT to date that examines the effect of aspirin use on CRC incidence. The study was originally designed to assess the impact of aspirin on the risk of coronary heart disease. Two publications arising from the study, including the original RCT and an historical cohort, failed to support a beneficial role for aspirin use.[81,83] Lack of clarity about both dosage and duration of use may have contributed to the absence of any protective effect. This is not surprising given that there appears to be poor understanding surrounding NSAIDs (including non-aspirin ones), specifically in relation to optimal doses, duration of use,[4] and the effects of different NSAIDs on different sites. Another historical cohort, however, did find a lower risk of adenoma recurrence among those who reported a consistent use of aspirin in comparison to those who reported no previous use of aspirin.[84]

Observational studies have consistently shown an approximate 20% reduction in CRC in post-menopausal women who have used hormone replacement therapy (HRT). These have included large cohort studies such as the Nurses' Health Study and an American Cancer Society prospective mortality study.[85] The risk reduction was strongest in women currently on HRT.[85,86] Since there have not been any RCTs with hormone use, the observed risk may be due to associated bias. For example, women who use hormone therapy may engage in healthy behaviours which protect against CRC, such as being more physically active and consuming less alcohol.[85] Nonetheless, the biologic evidence that estrogen reduces the synthesis of bile acids and may inhibit colonic epithelial proliferation[73,85] likely confirms a beneficial role for estrogen. There remains some uncertainty about how duration of HRT use may affect the risk for CRC. Based on the likely mechanism of estrogen, it is thought that HRT affects colorectal carcinogenesis at a later stage.[4] The benefit of hormones through oral contraceptive (OC) use is less clear. There appears to be a decrease in risk with OC use, but the results have not always been significant.[43,73]

4. Conclusion

The inconsistencies reported in the literature surrounding primary prevention of CRC are difficult to explain. Case-control and cohort studies have inherent biases which make them less reliable than controlled trials for ascertaining true risk estimates. With respect to diet, the inability to pinpoint the exact dietary constituents or behaviours often stems from difficulties in accurately assessing current and past dietary patterns, especially with constituents such as fat.[11,16] While RCTs minimize confounding elements and are often viewed as the standard, they are also subject to problems of subject compliance, assessing long-term effects and consistent findings when the treatment effects are small.[62,87] Specific to CRC, it may be that the RCTs have failed to provide a consistent picture because of problems associated with using surrogate end-points. Adenomatous polyps have been described as reasonably valid surrogate end-points for CRC based on the polyp-to-carcinoma causal pathway. Nonetheless, RCTs which have chosen polyps as their only end-point could be missing the potential effect of a treatment which may act by another pathway.[87,88]

We still need to acknowledge the potential impact of certain preventive practices on CRC risk. Two decades ago, Doll and Peto reported that a 90% reduction in CRC mortality could be achieved with practicable dietary modifications.[89] More recently, an international expert panel stated that dietary factors are the principal causes of CRC, and that 65-75% of CRC cases could be prevented by diet, exercise, and maintaining a healthy weight.[64] Controlling these lifestyle factors has also been associated with decreased risk for other chronic conditions such as coronary heart disease and hyperinsulinemia. The hypothesis linking hyperinsulinemia to increased risk for CRC may also explain some of the positive associations

found with obesity, alcohol consumption, inactivity and a typical Western diet. Insulin is an important growth factor for colonic mucosal cells and is a mitogen of colonic carcinoma in vitro.[90]

While lifestyle modifications have a potential preventative role with respect to CRC, the ability to implement change at the population level, to the degree that benefits will be realized, can be challenging. Some primary prevention interventions have been evaluated and found to be more successful than others, and should be judged in conjunction with any screening program for CRC.

(The author wishes to acknowledge the contributions of Ann Coombs, Dr. Carol-Ann Vasilevsky and Dr. Heather Bryant who provided valuable feedback for this document).

Table 1. Published Interventions for CRC (excl. trials consisting solely of subjects with FAP)

Study/ authors	Intervention *	Subjects (# and place)	Compliance	Follow-up/ end-point	Results
1988 McKeown-Eyssen (Ref #7)	vitamins C+ E (400 mg each) vs placebo for 2 yrs.	185 men & women Canada	75%	2 yrs recurrence of colorectal adenomas	small, non-significant reduction in # of adenomas with vitamin gr.
1993 Alder et al (#29)	calcium supplement (3g) vs placebo for 1 week	68 men Canada	87.5% in intervention gr. 80 % in ctl gr.	1 week bile acid concentration	no reduction in faecal bile acid levels
The Physicians' Health Study 1993 Gann et al (#83)	325 mg aspirin (alternate days), vs placebo for 5 yrs.	22,071 male physicians United States	not indicated	5 yrs incidence of colorectal tumours	small, non-significant decrease in incidence in NSAIDS group
1993 Roncucci et al (#91)	vit A (30,000 IU), vit C (1 g) & vit E (70 mg) vs lactulose vs no treatment for 5 yrs.	209 men & women Italy	85 %	18 mos recurrence of colorectal adenomas	sig. reduction in # adenomas in both vitamin and lactulose group
1995 Armitage et al (#40)	calcium carbonate supplement (3000 mg) vs placebo for 1 yr	79 patients with adenomas United Kingdom	95%	1 yr recurrence of new adenomas and changes in rectal mucosal proliferation	no significant reduction in rectal mucosal proliferation results on adenoma recurrences not available for this publication

Study/ authors	Intervention *	Subjects (# and place)	Compliance	Follow-up/ end-point	Results
The Polyp Prevention Study Group 1994 Greenberg et al (#42)	combination of beta-carotene (25 mg), vit C(1 g), vit E (400 mg) vs placebo for 4 yrs.	864 men and women (mainly men) United States	87%	1 & 4 yrs recurrence of colorectal adenomas	no reduction after either period with any treatments
The Toronto Polyp Prevention Group 1994 McKeown-Eyssen et al (#17)	9fat (20%), 8fiber (50g/d) diet with counselling vs normal Western diet (8fat/ 9 fiber) for 2 yrs	201 men & women Canada	82.1%	2 yrs recurrence of colorectal adenomas	no overall reduction (But a reduction in adenomas in women & dec. in bile acid levels and opposite for men)
1995 Bostick et al (#38)	one type of calcium suppl. (1 or 2 g) vs placebo for 6 mos	193 men & women (mainly men) United States	84.5%	1, 2, 4 & 6 mos colorectal cell epithelial proliferation	no significant difference appears to be a decrease in proliferation with the higher calcium supplement
The Alpha-Tocopherol Beta-Carotene Cancer Prevention Study 1995 Albanes et al (#46)	combination of beta-carotene (20 mg) suppl., vitamin E (50 mg) suppl. vs placebo for 8 yrs.	29, 133 male smokers Finland	99%	5-8 yrs incidence of cancers, including CRC	non-significant decrease in CRC with vitamin E supplementation. no difference with beta-carotene
1995 Baron et al (#30)	calcium carbonate supplement (3000 mg) vs placebo	333 men & women (mostly men) United States	96%	approxima-tely 1 yr rectal mucosal proliferation	no significant difference
The Australian Polyp Prevention Project 1995 MacLennan et al (#6)	combination of 9fat (25%), 8fiber suppl. (25 g) or beta-carotene (20 mg) vs placebo for 4 yrs.	424 men & women (mostly men) Australia	74.5% at 4 yrs	2 & 4 yrs recurrence of colorectal adenomas	no reduction with any intervention sig. decrease in # of large adenomas with 9fat/8fiber diet (only partially double-blinded)

Study/ authors	Intervention *	Subjects (# and place)	Compliance	Follow-up/ end-point	Results
1996 Clark et al (#71)	selenium supplement (200 ug) vs placebo for approx. 3 yrs	1312 men & women in total (mostly men) with a history of skin cancer only 27 in CRC intervention study United States	82%	6.2 yrs (treated for 4.5 yrs) primary end point was skin cancer. Secondary endpoints were all cause of cancer incidence/ mortality	significant decrease in CRC cancer incidence in treatment arm
The Physicians' Health Study 1996 Hennekens et al (#41)	beta-carotene (50 mg) suppl on alternate days vs placebo for 12 years	22,071 male physicians United States	100%	12 yrs incidence of colorectal malignant neoplasms	no reduction in incidence
1997 Alberts et al (#39)	combination of fiber suppl (2.0 or 13.5 g), calcium suppl (250 or 1500 mg) vs placebo for 9 mos	144 men and women United States	64.6%	3 & 9 mos rectal mucosal proliferation	no significant effect
The Physicians' Health Study 1998 Sturmer et al (Historical cohort from original RCT) (#81)	aspirin (325mg) on alternate days vs placebo for 5 yrs. (aspirin intervention arm discontinued prematurely)	22,071 male physicians United States	71%	12 yrs. incidence of CRC tumours	- no decrease in incidence of CRC
The Calcium Polyp Prevention Study Group 1999 Baron et al (#28)	calcium suppl (3g) vs placebo for 4 yrs	930 men & women United States	89.5%	1 & 4 yrs recurrence of colorectal adenomas	slight reduction in recurrence

Study/ authors	Intervention *	Subjects (# and place)	Compliance	Follow-up/ end-point	Results
The Phoenix Colon Cancer Prevention Physicians' Network 2000 Alberts et al	8fiber suppl (13. 5g) vs 9fiber suppl (2 g) for 3 yrs.	1429 men & women United States	91.2%	3 yrs recurrence of colorectal adenomas	no reduction in recurrence
The Polyp Prevention Trial Study Group 2000 Schatzkin et al	9fat (20%), 8fiber (18 g), 8fr/veg vs usual diet for 4 yrs	2079 men & women United States	91.6%	4 yrs. recurrence of colorectal adenomas	- no reduction in recurrence

Notes:
* unless indicated otherwise, treatment is per day.

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APPENDIX C

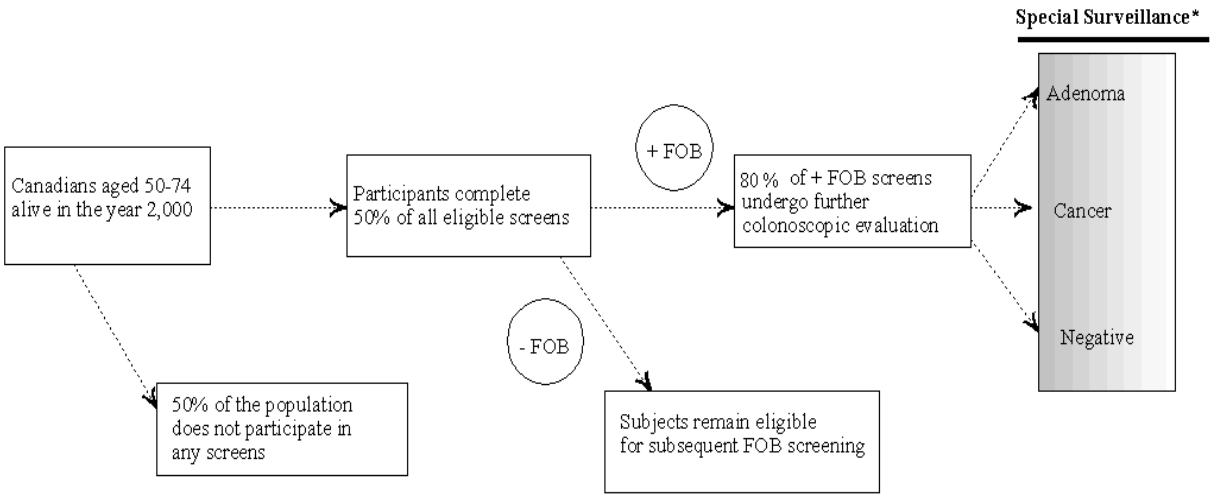
Screening for Colorectal Cancer Using the Fecal Occult Blood Test: Assessing the Impact of a Canadian Population-based Program Using an Actuarial Model

Summary of a Report by Paul J. Villeneuve

Screening for Colorectal Cancer Using the Fecal Occult Blood Test: Assessing the Impact of a Canadian Population-based Program Using an Actuarial Model

The impact of implementing a population-based colorectal cancer screening program using the fecal occult blood (FOB) test was evaluated using actuarial lifetable methods. The purpose of the analyses was fourfold. The first objective was to provide an estimate of the impact of implementing a Canadian population-based colorectal cancer screening program using annual and biennial FOB testing on the subsequent colorectal cancer (CRC) mortality experience a cohort of Canadians aged 50-74 in the year 2000 with follow-up extending to 2010 (Figure A).

Figure A : **Flowchart of actuarial model that evaluates the impact of annual and biennial FOB screening for colorectal cancer in the cohort of Canadians aged 50-74 alive in 2000 with follow-up extending to the year 2010**.



* these participants no longer eligible for FOB screening program

The impact of the program was assessed by calculating the number of colorectal cancer deaths in three hypothetical populations; those not participating in screening, those undergoing annual FOB screening, and those undergoing biennial FOB screening. It was assumed that as in the Minnesota, Nottingham and Funen trials, positive FOB tests were followed-up with colonoscopy. The second objective was to present estimates of the number of FOB tests, colonoscopies, complications due to colonoscopy, and number of incident CRC cases by stage so that economic costing of a "base scenario" for the screening program could be applied. Third, lifetable analyses were to be used to characterize the risks of developing and dying from colorectal cancer using recent population-based rate data. The final and most important objective was to provide a reference point from which POHEM [1] microsimulation outputs could be compared. The added flexibility of the POHEM model enables the effects of differing compliance rates, eligible screening age, and polyp dwell time to be more easily assessed [1].

The primary assumption of the underlying actuarial model was that screening for colorectal cancer (CRC) using the FOB test would confer similar reductions in mortality as reported in three randomized control trials. The model assumes that the screening program influences mortality by detecting CRC at an earlier stage, thereby making it more amenable to treatment. The improvement in survival is taken into account by applying reductions in mortality rates as observed in the Funen, Minnesota, and Nottingham randomized controlled trials. The mortality experience of the cohort was modelled by assuming that 50% of the population would participate in the screening program. A list of the assumptions is included in Table A. Furthermore, among participants it was assumed that eligible subjects would participate in 50% of the screens. Participants in the modelled screening program consisted of Canadians who were between the ages of 50 and 74 in the year 2000, with follow-up extending to the year 2010. The size of the modelled cohort was defined by population estimates for the yar 2000 by five-year age groups supplied by Statistics Canada. The number of person-years of follow-up were calculated by five-year age groupings, for both sexes separately, for the 10 years of the proposed program. Canadian all-cause mortality rates for 1997 were used to characterize the mortality experience of the cohort and Canadian age-specific CRC incidence rates for 1994, were then applied to the number of person-years to estimate the total number of incident cases expected to develop between 2000 and 2010. Similarly, Canadian CRC mortality rates for 1997 were used to calculate the number of CRC deaths expected to develop in this period. These mortality projections are those that would be expected in the cohort without any FOB screening program in place. The screening program was based on FOB testing using nonrehydrated Hemoccult® II and results for annual and biennial screening intervals were provided. The assumptions listed above form the framework of a "base model" that was developed by the Colorectal Modelling Steering Group.

Given an overall compliance rate of 50%, it was assumed that biennial FOB screening would reduce colorectal cancer mortality rates among screening participants during the 10-year follow-up by 14% (based on Funen RCT); the corresponding decrease for annual FOB was 22% (based on Minnesota RCT).

In the cohort of individuals aged 50-74 in the year 2000, the projected number of colorectal cancer deaths that would be averted with annual and biennial screens during this interval were 4,444 and 2,828 deaths, respectively (Table B). It was assumed that the total number of incident cancers did not vary between the screened and unscreened groups. During the 10-year follow-up it was

estimated that approximately 120 thousand incident cases of colorectal cancer would occur within the assembled cohort.

Table A Assumptions of Actuarial Model

Parameter	Assumption
Compliance	• 50% of population does not participate in screening program and participants attend half of all eligible screens.
CRC Mortality reduction	• 14% biennial screening (cumulative reduction) • 22% annual screening (cumulative reduction)
Proportion of cancers in screening group detected with a Positive FOB:	• annual screening: 50% • biennial screening 40%
Number of FOB tests	• the annual screening: calculated by multiplying the total number of person-years of follow-up among those eligible for screening by 50% • biennial screening: calculated by multiplying the total number of person-years of follow-up among those eligible for screening by 50% and dividing this product by two
Number of Colonoscopies	• first, the number of screen detected cancers was calculated. It was assumed that each of these screen detected cancers were identified using colonoscopy • the number of screen detected cancers and data describing the distribution of outcomes from colonoscopy from the Funen and Nottingham trials were used to estimate the number of colonoscopies performed between 2000 and 2010 • the Nottingham trial provided a lower bound on the number of colonoscopies while the Funen trial provided an upper bound
Number of adenomas detected by screening	• calculated by first estimating the number of colonoscopies that were performed during the follow-up of the screened group and applying the polyp detection rates observed in the Funen and Nottingham trials
Death from complications of colonoscopy	•2/10,000 individuals die as result of complications arising from colonoscopy
Reduction in the incidence of CRC following polypectomy	• it was assumed that the CRC incidence rates were unchanged due to polypectomy
Reduced mortality due to identification of cancers at an earlier stage	• number of cancers by stage determined for both screened and unscreened populations. •change in stage distribution based on results from randomized control trials.

Table B Summary of modelling a population-based FOB screening program, annual vs. biennial screening, Canadians aged 50-74 in 2,000 followed until July 1, 2010

Parameter/Output	Biennial FOB testing	Annual FOB testing
Eligible screening population	7,081,422	7,081,422
Person years of follow-up	64,702,052	64,710,132
Projected # incident cancers	119,681	119,681
Projected # cancers by stage		
Stage I	20,884	27,706
Stage II	40,272	38,597
Stage III	29,282	31,057
Stage IV	29,143	22,321
Projected # CRC deaths (with screening)	37,575	35,959
Projected # CRC deaths (no screening)	40,403	40,403
Total CRC deaths avoided during 10 year follow-up	2,828	4,444
Estimated # colonoscopies†	141,844 to 166,513	177,304 to 208,139
# "negative" colonoscopies	80,142 to 89,751	100,177 to 112,187
# screen-detected cancers	19,149	23,936
# colonoscopies - adenomas detected	42,553 to 57,613	53,191 to 72,016
Complications due to colonoscopy† Death (2/10,000 procedures)	28 to 33	35 to 42
Estimated # FOB tests	7,609,016	15,058,770
# FOB tests to avoid one CRC death (during 1st 10 years)	2,690	3,389

† the lower and upper bounds are defined by difference in the outcomes of colonoscopy that were observed in the Nottingham and Funen trials.

Canadian pilot data on rates of participation for population-based screening are urgently required to more accurately model the impact of participation on the effectiveness of the screening program. Results from the POHEM model demonstrate that low participation rates can compromise the effectiveness of a FOB screening program in reducing CRC mortality. A greater understanding of potential differences in participation across age groupings, gender, ethnicity, subsequent re-screens, and across background risk profiles would provide some more accurate estimates of model outputs.

The results from several studies indicate that lifestyle factors, particularly, diet and physical activity, play an important role in the etiology of colorectal cancer. Dramatically reduced colorectal cancer incidence rates (~40%) have also been observed with non-steroidal anti-inflammatory drugs [2]. An integrated approach that combines efforts in screening, primary prevention and improved treatment regimens should be pursued to reduce the health burden associated with CRC.

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Modelling colorectal cancer screening in POHEM

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Introduction

A National Committee on Colorectal Cancer Screening (NCCCS) was established by Health Canada in 1998 with the mandate to evaluate the potential impact and feasibility of establishing a population based screening program for colorectal cancer in Canada. Randomized controlled trials had shown efficacy of screening for colorectal cancer with faecal occult blood testing (Hemoccult II, nonrehydrated) followed by colonoscopy for positive test outcomes. However, follow-up periods in these trials were relatively short and conditions in a trial setting are not necessarily the same in a population-based setting. Statistics Canada's microsimulation model, the Population Health Model, was used to evaluate the potential effectiveness of population-based screening of colorectal cancer in Canada. The disease module of colorectal cancer was already in place in the model; a screening module was developed in close collaboration with the committee and was validated against one of the randomized controlled trials before being applied to the Canadian setting.

The Population Health Model (POHEM) is a micro-simulation model developed by the Health Analysis and Modelling group of Statistics Canada since the late 1980's. POHEM generates a synthetic sample of people with demographic characteristics, risk factor exposures and health histories typical of Canadians. Life paths are simulated continuously over time through a series of competing events. Events are scheduled according to the probability of their occurrence using random number techniques (see Addendum for an example). Over a large number of cases, the observed distributions are reproduced relatively well and estimates of the monte carlo error provide confidence limits. POHEM includes detailed modules on lung cancer, breast cancer, heart disease and osteoporosis, among others. A detailed module for the diagnosis, treatment, cost and disease progression of colorectal cancer was developed between 1997 and 2000.

The colorectal cancer module of POHEM models the disease incidence by age, gender and site (colon or rectum), the disease progression to local recurrence, distant recurrence (metastasis) and/or death, treatment options and cost. Incidence data were obtained from the Canadian Cancer Registry (1995). Stage distribution and survival data were derived from a chart review of 700 patients diagnosed at the Ottawa Regional Cancer Centre (ORCC) in 1991-1992. Treatment options and costs were obtained from hospital discharge abstracts, surveys of oncologists and numerous consultations. Details of this module are being documented in the manuscript "Lifetime Costs of Colon and Rectal Cancer Treatment in Canada" (Maroun, Ng, et al.).

The screening module was developed for faecal occult blood testing (FOBT) (Hemoccult II, nonrehydrated) followed by colonoscopy for positive tests. It was adopted as the screening modality because it had been shown to be efficacious in randomized controlled trials. In particular, FOBT-based colorectal cancer screening was shown to significantly reduce mortality from CRC in clinical trials conducted in Funen[1] (Denmark),

Nottingham[2] (UK) and Minnesota[3] (USA). The Funen trial was population-based and had a clearly defined recruitment strategy that could be reproduced in the model to generate similar follow-up periods (10 year). The module was therefore built on and validated against the Funen trial. Results were taken from the other trials as needed to complete the screening model.

Methods

In the model, a sample reference population of approximately 3.6 million cases was built from synthetic individuals meeting the eligibility criteria. The reference population was cloned to generate identical samples of 3.6 million cases. Each cloned sample population was evaluated under a different screening strategy and compared to the reference population (not screened). Screening strategies evaluated for Canada were biennial and annual screening as well as alternative participation scenarios. The main outcomes were the reduction in mortality from CRC, life expectancy, cost-effectiveness and volumes of FOBTs and colonoscopies.

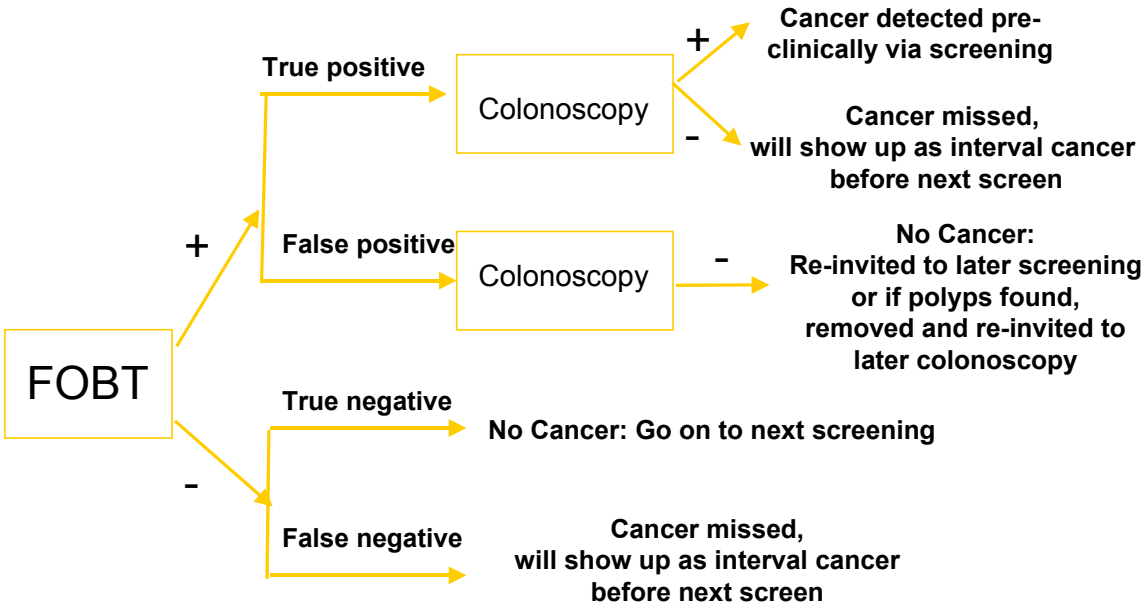
Simulating a screening programme

Synthetic individuals within a specific target age range during the period of recruitment were eligible for FOBT screening, provided they had no history of CRC. The recruitment period was either the year 2000 to generate a fixed cohort or the period 2000 to 2024 to generate a dynamic cohort. Fixed cohorts were used to simulate clinical trial conditions, to evaluate mortality reduction and to perform cost-effectiveness analyses. Dynamic cohorts take into account the changing population structure and were used to determine the impact on resources, such as the volumes of FOBTs and colonoscopies that might be required from an implemented screening program.

The screening module simulated participation for first and subsequent invitations to FOBT screening and to colonoscopy following positive FOBT results. Participation was simulated by random assignment such that the overall participation rate was reproduced. Only candidates participating at the first screen round were re-invited to subsequent rounds. Participation in subsequent screening rounds was independent of each other. For instance, it would be possible to participate at screening rounds three and five without having participated at screening rounds two and four. Other participation features were built into the model to be able to gradually ramp-up participation to the target rate over a period of five years.

The recruitment strategy plays an important role in the overall participation rate and cost of a screening program. While a mixed recruitment strategy can be envisioned for the implementation of a program, for practical reasons the modelling was limited to one type of recruitment. The strategy agreed upon by the resources subcommittee of the NCCCS consisted of physician-based recruitment. It was estimated that those complying with screening would have an average of 1.5 physician's visits at which the FOBT test kit would be distributed and consultation provided. A further assumption was that all the test kits were returned. Once processed, the results of the FOBT would be communicated to the doctor's office, which would then forward them to the participant. If the FOBT were negative, no further visits would be necessary. If it were positive, then further investigation would be offered, in the form of a consultation with a gastroenterologist and colonoscopy. The possible pathways are summarised in Figure 1.

Figure 1: Screening Paths



In the simulation, the four outcomes of the FOBT (true and false positives and negatives) were generated using the sensitivity and specificity estimates of the clinical trials. The sensitivity measured the test's ability to detect a cancer when one was present whereas the specificity measured the test's accuracy at identifying that no cancer was present. The presence of pre-clinical cancer potentially detectable by FOBT was simulated by calculating the probability of incidence of CRC into the future, two years for biennial screening or one year for annual screening. When pre-clinical cancer was present the sensitivity estimate was applied to generate a true positive or false negative outcome. If no cancer was present, the specificity was applied to generate true negative and false positive outcomes.

Follow-up investigation of positive FOBTs was by colonoscopy. All colonoscopies were assumed to be complete and would not require secondary investigation by other techniques. The colonoscopy was assumed to be 95% sensitive and 100% specific (would never report a cancer when none was present). Table 1 shows the complication rates for colonoscopy used in the model[4].

Table 1: Complication rates used for colonoscopy

Perforation	*Hemorrhage*	*Infection*	*Cardiopulmonary*	*Death*
0.17%	0.03%	0%	0%	0.02%

Participants were exempt from screening for 10 years after a negative colonoscopy provided that no polyps were found. After that period, they were offered screening again and their participation rate was assumed to be the same as that of others re-invited to screening. When the colonoscopy was negative and polyps were found, the surveillance protocol was to perform a colonoscopy after 3, 5 and 10 years following a subsequent

negative colonoscopy, based on recommendations from the American Society of Clinical Oncology[5] and American Gastroenterologists Association guidelines[6]. It was assumed that colonoscopy could detect polyps greater than 1 cm and that removal of polyps had no impact on incidence of CRC, consistent with findings in the Funen trial over the 10-year follow-up period. Table 2 shows the prevalence of polyps used in the model[7].

Table 2: Prevalence of polyps

Age	*50*	*60*	*70*	*80*
Any polyp	30%	40%	50%	55%
Large polyps (> 1 cm)	3%	4%	5%	5.5%

All cancers detected in the screened sample population were assigned a stage according to the estimated distribution for Canada. For biennial screening, the stage distribution of cancers detected in a screened population was estimated from the change in stage observed between control and screen groups in the Funen trial (Table 3). For annual screening, it was estimated from outcomes of the Minnesota trial (Table 4). Note that the stage distribution for the Canadian reference population (control) was taken from the ORCC chart review.

Table 3: Estimated Canadian stage distribution for biennial screening (Funen-based)

Stage	*Control*	*Screen detected*	*Interval cancer*	*Non responders*
I	13%	38%	22%	14%
II	33%	38%	29%	32%
III	27%	17%	28%	20%
IV	27%	7%	21%	34%

Table 4: Estimated Canadian stage distribution for annual screening (Minnesota-based)

Stage	*Control*	*Screen detected*	*Interval cancer*	*Non responders*
I	13%	22%	22%	22%
II	33%	32%	32%	32%
III	27%	31%	31%	31%
IV	27%	15%	15%	15%

The improved stage distribution accounted for part but not all of the improved survival observed in the trials. Table 5 shows the improved survival after controlling for stage as reported in the Nottingham paper. In the model, these relative risks were applied to all survival paths of the disease for both biennial and annual screening.

Table 5: Relative risks for survival

Group	*Relative Risk*
Control	1.0
First Screen	0.53
Re-screen	0.62
Interval cancer	0.88
Non-responders	1.04

Costs related to colorectal cancer screening were difficult to estimate since no program already existed in Canada. Costs could vary depending on the structure of the program, the size of the population targeted, and the recruitment strategy. To take into account this uncertainty, two sets of costs were estimated, a base estimate of expected costs and a higher estimate. For each, costs were broken down into several components relating to overhead, the FOBT test or follow-up. Fixed yearly overhead costs (overhead, satellite and promotion) were estimated from Cancer Care Ontario's report. The cost of physician visits and consultations, FOBT kits and follow-up procedures were estimated from OHIP data. The cost of processing the FOBT slides was based on quotes from private labs and other costs were based on the expert opinion of committee members. Table 6 summarises the costs used for each component of the screening programme (these have been discussed in more detail earlier in the main report).

Table 6: Summary of screen costs by component

Unit Screening Costs	*Base Cost ($)*	*High Cost ($)*
Head Office, Satellite & Promotion	15,000,000	30,000,000
Extra Physician Visits	43.58	58.10
FOBT kit	4.65	9.30
Processing	6.00	8.00
Consultation (positive FOBT)	123.70	161.10
Colonoscopy	350.00	425.00
Polypectomy	147.00	147.00

The cost-effectiveness ratio has been calculated as the incremental cost incurred divided by the incremental life-years saved due to screening. Both screening and treatment costs were included, but no indirect costs such as loss of productivity were modelled. Cost-effectiveness ratios less than $40,000 per life-year saved were considered cost-effective in this analysis. Discounting was performed at 0%, 3% and 5%. Both costs and life-years were discounted equally in the calculation of cost-effectiveness.

Canadian screening scenarios

After much discussion, the modelling subcommittee of the NCCCS decided that participation rates observed in the population-based Funen trial could be achieved in Canada. Furthermore, the mortality reduction observed in the trial was based on the trial participation patterns and there was no good evidence that the relationship would extend to other participation rates. Moreover, the model was validated with Funen parameters

offering the best starting point for a scenario for Canada. Consequently, biennial screening with FOBT Hemoccult II (nonrehydrated) was adopted as the Canadian core scenario, with 67% participation in the initial screening round and 93% participation in subsequent rounds. The target age range was shortened to 50-74 (N=7,001,322 in the year 2000) and the estimated stage distribution of cancers detected by screening for Canada was used (Table 3). All other parameters and assumptions remained the same as in the Funen validation scenario (described below).

Alternative scenarios were created to assess the impact of screening annually and of screening biennially with alternative participation rates. For annual screening, parameter estimates for sensitivity (80.7%) and specificity (97.7%) were taken from the Minnesota trial results for annual screening with FOBT (nonrehydrated). The stage distribution was also estimated from the Minnesota trial results (Table 4). For biennial screening, three alternative participation scenarios were evaluated: (1) participation in the initial screen was reduced from 67% to 50%; (2) target participation of 67% was reached gradually over a period of five years; and (3) full participation was simulated from age 50 to age 74 to assess the full potential life expectancy gains. Canadian scenarios were evaluated for fixed and/or dynamic cohorts to evaluate mortality reduction, cost-effectiveness and impact on resources.

In addition, sensitivity analyses were performed on other parameters deemed hard to estimate or that could take more than one value depending on the implementation of the screening program. This included stage distribution, participation, and target age group.

Validation of the screening module

In order to validate the screening module implemented in POHEM, we used the input parameters provided in the publications related to the Funen trial and reproduced their observed outcome, specifically their mortality reduction. The protocol used was biennial screening with FOBT Hemoccult II, nonrehydrated, for the population aged between 45 and 75 years old. The length of the follow-up period was 10 years. The participation rate was 67% for the first screen, while the participation rate for subsequent screens was 93% on average. Each participant with a positive FOBT was offered further investigation in the form of colonoscopy and 89% complied. The sensitivity of the FOBT was 51% and the specificity was 98%. Once a cancer was detected, the stage was assigned from the distribution reported in the Funen trial according to how the cancer was detected. The results were standardised to the age group and gender of the population structure of the Funen trial.

The Funen trial observed, after 10 years of follow-up, a mortality reduction of 18%, with a 95% confidence interval from 1% to 32%. Using the input parameters from the Funen trial in POHEM, the model produced a mortality reduction of 17.9%, with a 95% confidence interval of 16.9% to 18.9%. While the Funen trial recruited approximately 60,000 participants, the output of the model is based on approximately 7.2 million synthetic lives. This explains why the confidence interval from the model is much narrower.

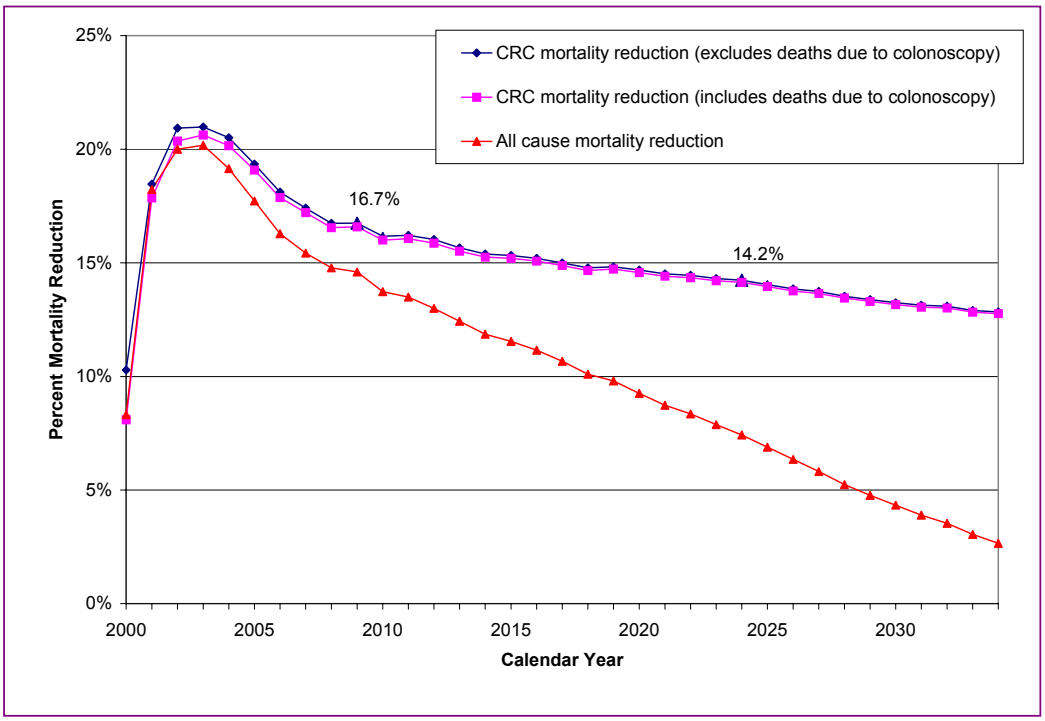
Results

CRC mortality reduction

For a cohort of synthetic individuals aged 50-74 recruited in the year 2000 subject to the assumptions of the Canadian core scenario, the colorectal cancer mortality reduction after 10 years of biennial screening was estimated to be 16.7%, with a 95% confidence interval of 15.8% to 17.6%. This is lower than the Funen result due to the shortened target age range. The mortality reduction peaked in the first few years of screening due to the increased detection of the disease. It then steadily declined since improved survival did not necessarily preclude mortality. When all causes of death were taken into account, the decline in mortality reduction is much more pronounced as illustrated by the lowest curve in Figure 2. Deaths due to complication to colonoscopy did not have much impact on the estimated mortality reduction. For every 178 CRC deaths avoided in this simulated cohort, one death due to complications of colonoscopy was incurred. The overall impact of the life-years gained and lost is reflected in the estimate of life expectancy. Biennial screening for CRC increased the life expectancy by an estimated 0.040 years (95% confidence interval, 0.038 to 0.042) which is approximately 15 days (Table 7).

Similar trends in mortality reduction were observed for the alternative scenarios. Annual screening further reduced the 10-year CRC mortality reduction to 26% and increased life expectancy to 0.065 years (24 days). When participation in biennial screening was reduced to 50%, the CRC mortality reduction dropped to 10.0% and life expectancy to 0.025 years (9 days).

Figure 2: Percent mortality reduction over time for Canadian core screening scenario



Cost-effectiveness

When screening biennially as per the core scenario assumptions, the cost per life-year-gained discounted at 5% was $11,907 and rose to $18,445 under the high cost option (Table 7). Screening annually increased the cost per life-year-gained to $13,497 ($19,893 in the high cost option). Interestingly, reduced participation in biennial screening was also less cost-effective. This is explained by the fixed yearly costs incurred regardless of participation, coupled with the lower gain in life expectancy.

Table 7: Mortality reduction and cost-effectiveness of screening biennially, annually and with reduced participation compared to no-screening option

Scenario	*Cohort of eligible 50-74 year olds recruited in the year 2000*			
		Core	*Alternatives*	
	Frequency	**Biennial**	**Annual**	Biennial
	Participation to 1st screen	**67%**	67%	**50%**
CRC Mortality	10-year CRC mortality reduction	16.7%	26.0%	10.0%
	25-year CRC mortality reduction	14.2%	22.5%	8.7%
	CRC deaths avoided (lifetime)	23 668	40 110	13 964
	Death from complication to colonoscopy	133	265	106
Discount 0%	Years (days) of life saved for the cohort	0.040 (15)	0.065 (24)	0.025 (9)
	Cost per life-year gained	$ 6 202	$ 7 129	$ 8 262
	High cost option	*$ 10 001*	*$ 10 750*	*$ 13 502*
Discount 5%	Years (days) of life saved for the cohort	0.016 (6)	0.025 (9)	0.009 (3)
	Cost per life-year gained	$ 11 907	$ 13 497	$ 15 688
	High cost option	*$ 18 445*	*$ 19 893*	*$ 24 635*

Impact of target age range

To model the impact of the age at first screen, a simulated cohort of 40-44 year-olds in the year 2000 (N=1,503,578) was followed until death under five different screening scenarios. The age to start screening was set at 40, 45, 50, 55 or 60 while keeping the end age fixed at 74. Figure 3 shows the gain in life expectancy (with upper and lower points of the 95% confidence interval) for each of the five screening scenarios as compared to a reference population that was not screened. The life expectancy gain from screening started at age 40 was approximately 0.067 (0.064-0.071) compared to 0.066 (0.064-0.069) when screening was started at age 45. Since these are not significantly different, no advantage would be gained from starting to screen at age 40. Likewise, no statistically significant difference was observed when screening was started at age 45 compared to age 50. A statistical difference was observed between start ages 50 and 55. Furthermore, starting to screen at age 50 versus waiting until 55 was cost-effective at $ 24,643 per life-year gained (discount at 5%) (Table 9).

To model the impacts of age at final screen, a simulated cohort of 50-54 year- olds in the year 2000 (N=1,195,134) was followed until death under seven different screening scenarios. In each case the screening began at age 50, but ended at age 60, 65, 70, 75, 80, 85 or 90. Significant differences in life expectancy were observed until age 75 as shown in Figure 4. It was also cost-effective at $ 25,701 per life-year gained (discounted at 5%) to continue to screen until age 75 compared to stopping at age 70 (Table 9).

Figure 3: Change in life expectancy due to screening by age at first screen

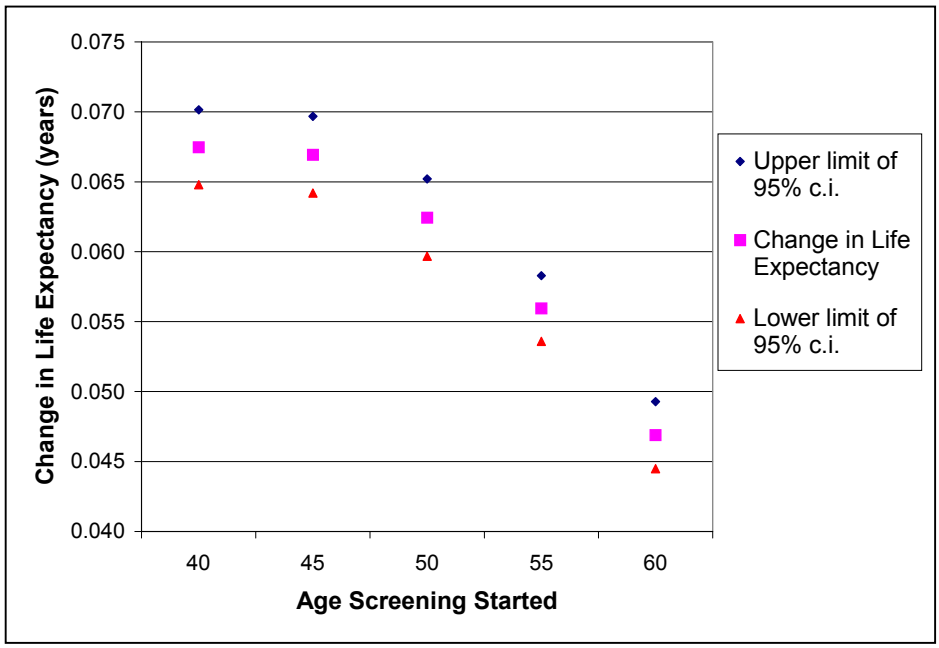


Figure 4: Change in life expectancy due to screening by age at final screen

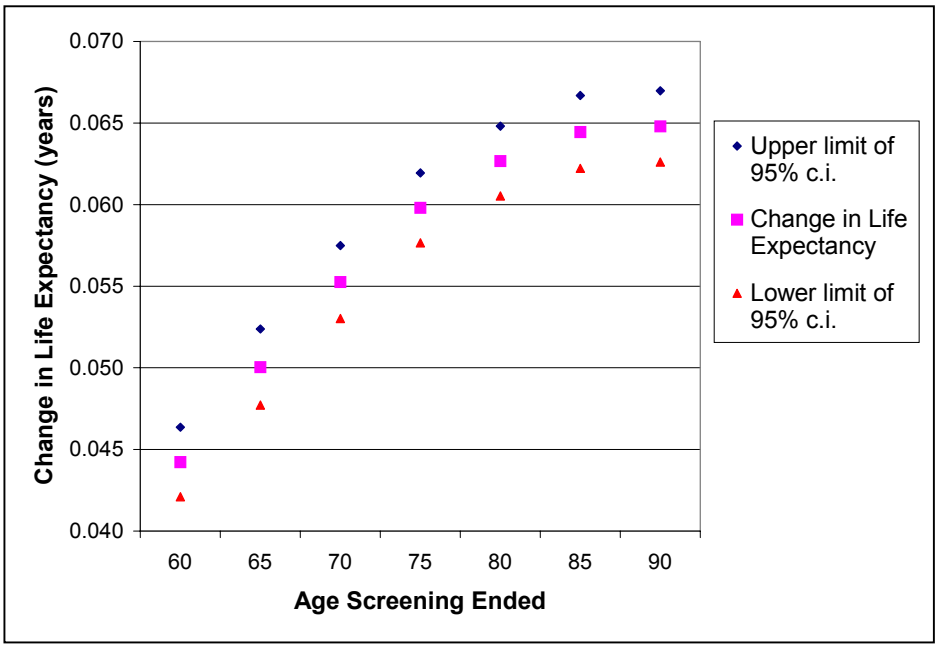


Table 8: Cost-effectiveness of starting colorectal cancer screening at different ages

	Cost per life-year gained		
Age at first screen	*Not discounted*	*Discounted at 3%*	*Discounted at 5%*
40 versus 45	90,239	112,385	133,325
45 versus 50	21,175	36,096	49,647
50 versus 55	**10,946**	**18,458**	**24,643**
55 versus 60	9,907	14,155	17,681

Table 9: Cost-effectiveness of ending colorectal cancer screening at different ages

	Cost per life-year gained		
Age at final screen	*Not discounted*	*Discounted at 3%*	*Discounted at 5%*
65 versus 60	15,993	23,538	29,681
70 versus 65	14,341	20,103	24,691
75 versus 70	**16,378**	**21,620**	**25,701**
80 versus 75	19,396	24,012	27,516
85 versus 80	27,938	31,622	34,328
90 versus 85	63,099	65,454	66,944

Impact on Resources

A cohort of synthetic individuals aged 50-74 recruited in years 2000-2024, subject to the assumptions of the Canadian core scenario, would require an average of 2.8 million FOBTs and 55,845 colonoscopies per year. An estimated 841 FOBTs and 17 colonoscopies were required to pre-clinically screen detect one colorectal cancer case, while 1,278 FOBTs and 27 colonoscopies were needed to avoid one colorectal cancer death over the lifetime of the cohort. The average cost of screening, discounted at 5%, was $112 million per year over 25 years of screening, which was 24% of the total cost associated with colorectal cancer. Screening led to a 4.8% reduction in the cost of treating colorectal cancer (Table 10).

Annual screening nearly doubled the demand on resources as illustrated in Figures 5 and 6. The average number of FOBTs rose from 2.8 million to 4.8 million and the average number of colonoscopies increased from 55,845 to 111,654. The change in volume over time reflected the changing population structure and the impact of the aging baby boomers. In the other alternative scenario, the target participation of 67% was reached gradually over a period of five years. This delay in screening led to a small drop in the demand for resources, because the overall follow-up period was shorter and because 1,519 cancers occurred before the first scheduled screen. Correspondingly, a decrease in the number of screen detected cancers was observed.

Table 10: Impact on resources per year for biennial, annual and ramp-up screening scenarios
Outcomes averaged over 25 years of screening programme

Scenario	*Cohort of eligible 50-74 year olds recruited from year 2000-2024*			
		Base	Alternatives	
	Frequency	**Biennial**	**Annual**	Biennial "ramp-up"
	Participation rate in 1st screen	67%	67%	67% over 5 years
FOBT	Screenings offered per year (millions)	3.2	8.2	3.0
	FOBTs completed per year (millions)	2.8	4.9	2.6
	FOBTs testing positive	59,267	118,434	54,932
	True Positives	3,900	5,286	3,605
	False Negatives	3,732	1,257	3,457
Colon-oscopy	Number of colonoscopies	55,845	111,654	51,632
	Death due to complications	12	23	11
	Polyps >1cm detected (no cancer)	2,061	4,134	1,910
CRC incidence	CRC incidence	16,769	16,694	16,752
	Screen detected	3,301	4,469	3,052
	Interval detected	7,986	6,743	7,160
	Non-responder	5,482	5,482	4,971
Cost	Cost of screening per year (millions), discounted at 5%	$ 112	$ 194	$ 100
	Screening as proportion of total cost	23.6 %	35.1 %	21.5%
	Reduction in treatment cost (lifetime)	4.8 %	5.8 %	4.2 %

Figure 5: Volume of FOBTs by calendar year for biennial, annual and ramp-up screening scenarios

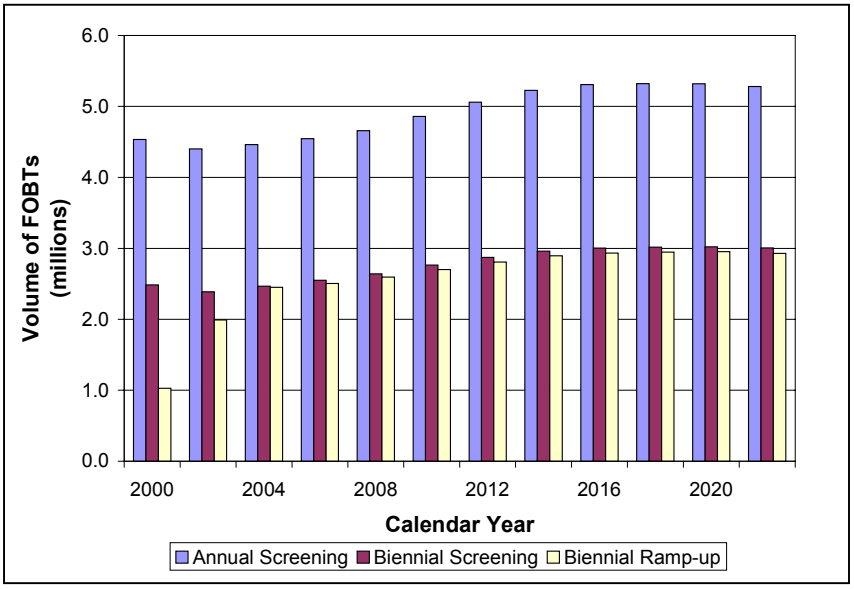
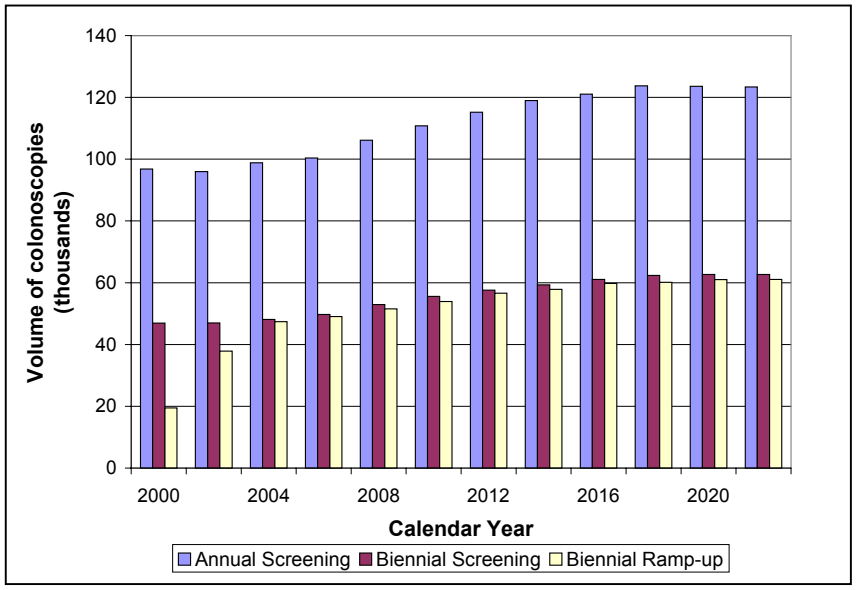


Figure 6: Volume of colonoscopies by calendar year for biennial, annual and ramp-up screening scenarios



Potential life expectancy gains

The potential increase in life expectancy of a cohort fully participating to biennial screening from age 50 to 74 was estimated at 0.10 years (37 days). The average life expectancy gain for a synthetic individual diagnosed with CRC was approximately 1.75 years. The lifetime incidence of CRC rose from 5.88% to 5.91% because screening detected cancer in some individuals who otherwise would have died from another cause

prior to clinical detection. The lifetime mortality from CRC dropped from 3.06% to 2.30% (25% reduction). The probability of dying due to complications of a colonoscopy was 0.005%, 0.043% suffered a perforation and 0.008% hemorrhaged as a result of the colonoscopy. Over the 25 years of screening, the probability of having a colonoscopy was 25%.

Parameter Sensitivity Analyses

Sensitivity analyses were performed as follows to evaluate their impact on 10-year CRC mortality reduction:

- replaced the stage distribution from Funen with Canadian estimates;
- reduced participation in initial screen from 67% to 50%;
- reduced participation in subsequent screen rounds from 93% to 80%;
- reduced participation for colonoscopy from 89% to 80%; and
- shortened the target age group from 45-75 to 50-74.

The parameter changes were cumulative: for instance, the Canadian stage distribution introduced in the first sensitivity analysis remained in all subsequent analyses. A reference population of approximately 1.2 million eligible cases was generated and cloned for each of the sensitivity analyses. The main driver of CRC mortality reduction was the change in participation for first screen, where the mortality reduction dropped from 17.5% to 10.5% (Table 11).

Table 11: Sensitivity of 10-year CRC mortality reduction to parameter change

Type of Run	*10-year CRC Mortality Reduction*
Funen validation parameters	17.20%
Canadian stage data	17.50%
From 67% to 50% FOBT compliance	10.50%
From 93% to 80% re-screen rate	9.90%
From 89% to 80% colonoscopy compliance	9.30%
From 45-75 to 50-74 age group	8.90%

Discussion

The major drivers of reduction in mortality due to colorectal cancer were the participation in first screen and the frequency of screening. Screening of 50-74 year olds was shown to be an optimal target age range. Screening was cost-effective under all scenarios simulated including the high cost option. Although annual screening remained cost-effective, it nearly doubled the demand for resources. In fact, biennial screening already increased the demand for colonoscopies by 15% over current use (2000) estimates (projected from 1995/96 CIHI estimates). In short, screening for colorectal cancer with faecal occult blood testing followed by colonoscopy for positive test results was shown to be effective under the Canadian scenarios tested, but depends strongly on reaching the targeted participation rate of 67% and finding the resources to complete the increased number of colonoscopies.

There are a number of limitations of the model that should be recognised. First, the model was validated with the assumption of 67% participation for first screen in a biennial screening programme; therefore Canadian results under these assumptions should be considered the most reliable. Second, while sensitivity of some parameters was performed, full parameter uncertainty was not modelled. For instance, the CRC mortality reduction in the Funen trial was reported with a 95% confidence interval of 1% to 32%, but the model was developed to reproduce the point estimate of 18%. Third, follow-up in clinical trials may be more rigorous than would occur in a population-based screening programme. Consequently, not all of the benefits observed in the trial may be realised. Finally, life expectancy estimates were not adjusted for quality of life.

The best available evidence was incorporated into the model, however certain limitations remained. Even though randomized controlled trials were a strong source of evidence, follow-up periods were relatively short. Modelling intentionally projected beyond these follow-up periods to determine the intervention's effectiveness. Projecting forward necessarily carried with it assumptions about the long-term behaviour of the observed outcomes for which no data existed. In other cases, the best available evidence was taken from guidelines. The follow-up surveillance protocol to polyp detection is an example. The protocol adopted would impact on the number of colonoscopies required, but would have little impact on survival outcomes in the model since polyp removal was not linked to incidence of CRC. This latter assumption may itself be an underestimate of benefit since some evidence, such as the National Polyp Study[8], suggests that polyp removal leads to lower incidence of CRC. Finally, complications for colonoscopy were modelled but the potential for harm to otherwise healthy patients and the community's willingness to accept it remain major concerns.

Addendum

POHEM example:

In this example, a synthetic individual was generated in POHEM with a date of birth of August 22, 1950 and the gender was determined as male. He was aged continuously through time while being exposed each year to the risk of developing disease and dying. At age 50 his probability of being diagnosed with colon cancer (0.00035) was compared to a random number between 0 and 1 to determine if he would develop colon cancer. He did not develop colon cancer because the random number (0.046) was greater than the probability of the event. (This is a simplification of the random number technique used to schedule events, since most probabilities are converted to hazards from which waiting times are generated.) At age 65 he developed stage I colon cancer. The stage was determined using a similar random number technique on the Canadian stage distribution. Waiting times to local and distant recurrence and to death were generated (using random numbers) according to the modelled survival parameters for stage I colon cancer (implemented as a piecewise Weibull). He remained free of further colon cancer events for five years so at age 70 was considered cured in the model. He later developed CHD and died of a cardiac arrest at age 77.

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Appendix E

Summary of key informant* interviews regarding national capacity for colonoscopy as diagnostic follow-up to FOBT, for population-based colorectal cancer screening

	Summary of Key Informant Responses/ Comments	
Current Volumes of Colonoscopy	•Some key informants felt that data from CIHI** accurately reflected current volumes of colonoscopies for their provinces; others felt that reported volumes were underestimations or overestimations. •Published grouping category not reflective of actual volumes •One province - although a proportion of procedures billed as colonoscopy, are performed to only a limited distance in the bowel.	
Capacity	Procedure:	•concern over attempting to comment on future demands when current volumes unclear •increase in volume with increased access but relative increase will depend on the actual current volumes
	Manpower: •Frequent concern was lack of anticipated manpower:	•stretched to current capacity and difficulty recruiting and retaining GI specialists •few new graduates and imminent retirements •current waiting lists •one province noted provincial restriction on number of MDs •funds to hire more MDs • need for availability of increased endoscopy time; extra funds for support (nurses, clerical, etc...), equipment, and extra physical space •also potential shortages of radiologists
Training/ Competency	•need for adequate training and assurance of competency of physician through reference checks, observation, audits, accreditation, possible probationary period, sufficient volumes, recognized standards (fellowship in endoscopy) •monitoring outcomes; average time to complete, completion rates, complication rates, patient comfort and satisfaction, patient recovery time •flexible sigmoidoscopy performed by non-specialists?	

	Summary of Key Informant Responses/ Comments
Guidelines/ Standards	•several existing guidelines (e.g. AGA for screening; American Society Colon & Rectal Surgeons for rectal surgery; Manitoba College for scoping) •guidelines needed and important; perhaps should develop nationally •guidelines needed for small cancers (re: extent of surgical intervention)
General Comments	•extra funds would be necessary to support screening program •concern re: use of barium enema as alternative; availability of barium enema also limited - delays exist and one province noted that caps exist •oneprovincial informant: hospital incentives for more barium enemas •flexible sigmoidoscopy and colonoscopy essentially done by same physicians

* Key informants were chosen from each of the ten (10) provinces and represent GI specialists, radiation oncologists, and surgeons.

** Canadian Institute for Health Information. Data supplied from the National Grouping System Categories Report, Canada 1994/95 (National Physician Database) and 1995/96 (National Physician Database, 2000).

APPENDIX F

Comparison of Three Randomized Controlled Trials of FOBT Screening for Colorectal Cancer

Table 1 Study Design

Parameter	Minnesota, USA	Funen, Denmark	Nottingham, UK
RCT Period	Recruitment: 1975-77	August, 1985 - August, 1995	February, 1981- January, 1991 Recruitment to Pilot: February, 1981 - June, 1983 Recruitment to main trial: February, 1985 - January, 1991
Aim of RCT	To evaluate the effectiveness of fecal occult-blood screening in the context of a randomized controlled trial in reducing mortality from colorectal cancer	Comparison of deaths from CRC after biennial screening by FOB tests with deaths from CRC in similar unscreened population (controls) during 10 year period	Randomized controlled trial to assess effect of biennial FOB screening on CRC mortality in general population of Nottingham, UK
Exclusion Criteria	At time of enrollment: •history of CRC •familial polyposis •chronic ulcerative colitis •persons bedridden/disabled	•individuals with CRC or precursor adenomas •distant spread from all types of malignant disorders •individuals who had taken part in previous pilot study • (as per New Zealand Working Group: participants diagnosed with adenomas or CRC between randomisation and first screening invitation)	Exclusions by family physicians: •serious illness including those diagnosed with CRC in previous 5 years
Study Population	3 groups of 15,000; volunteers (American Cancer Society and fraternal organizations, veterans and employee groups in Minnesota)	2 groups of 31,000 •population-based	2 groups of 76,000 • population-based •living in Nottingham area and identified according to general practice where registered •1.7% could not be traced and excluded from analysis

Parameter	Minnesota, USA				Funen, Denmark			Nottingham, UK		
Randomization	•stratification according to age, sex, place of residence followed by random assignment of individuals to annual screening (15,570), biennial screening (15,587) or control group (15,394)				•137,485 randomized in blocks of 14 allocated 3 per 14 to screening group (30,967); 3 per 14 to control group (30,966) and 8 not to be enrolled in study (75,552). •married couples allocated to same group			•random allocation by household to FOB screening (76,466) or no screening controls (76,384) •before randomization, individuals sorted by household; households stratified by size, sex (male only, female only, mixed) and average age of eligible members (in 5 yr. age-groups).		
Sex of Participants at Time of Randomization	Women: Men:	Annual 8,081 7,489	Biennial 8,143 7,444	Control 7,960 7,434	Women: Men:	Screening 16,103 14,864	Control 16,116 14,850	Women: Men: 36,130	Screening 39,123 36,130	Control 38,956 36,042
Study Population: Age-range	50-80 years				45-75 years			50-74 years (Pilot study: 45-74 years)		

Table 2 Characteristics of the Test

Parameter	Minnesota, USA	Funen, Denmark	Nottingham, UK

Type of Test	Hemoccult® (6 guaiac-impregnated •paper slides; slides contained 2 smears from each of 3 consecutive stools)	Hemoccult-II •2 samples from each of 3 consecutive stools	Hemoccult (Rohm Pharma, Weiterstadt, Germany) •2 samples from each of 3 consecutive stools (cohort within screening group asked to test 6 consecutive stools at prevalent screen)
Hydration of Slide	Rehydration (beginning 1977) All slides rehydrated 1982-92 *82.5% of slides rehydrated	No rehydration	No rehydration
Definition of Positive FOB	One or more slides testing positive in set of 6	One or more blue slides	Pilot study: 1 or more test squares positive on FOB card 6 DCBE + Flex sig Main study: repeat test sent to participants with up to 4 positive squares + request for diet restriction for 2 days prior to taking 2 samples from 6 consecutive stools *only those with 5+ positive squares at 1st test and those with 1 or more positive squares at retest offered colonoscopy (supplemented by DCBE when full colonoscopy not possible) Negative Retest: asked to repeat test (with dietary restriction) 3 months following retest and offered colonoscopy if test positive

Test Parameters	Both screening groups combined (1976-1982)		
Positivity	Positivity: Rehydration: 9.8% No Rehydration: 2.4%	Positivity: 1st Screen: 1% Rescreen round 2: 0.8% Round 3: 0.9% Round 4: 1.3% Round 5: 1.8%	Positivity: 1st Screen: 2.1% Rescreen within 27 months: 1.2% (allowing for 3-month delay in invitation for screening)
Sensitivity	Sensitivity: Rehydration: 92.2% No Rehydration: 80.8% number of true positive results divided by sum of true positive results and false negative results under assumption cases of CRC true positives if discovered within one year after positive screening and false negative if discovered within one year after negative screening (NEJM Aug. 1993; 329:672).	Sensitivity: 51% (Some sources cite 48%)	Sensitivity: 53.6% (*not able to calculate sensitivity of FOB tests used in study because 2 years had not passed since final screening round; earlier analysis (based on >50,000 FOB tests) found sensitivity of 53.6%
Specificity	Specificity: Rehydration: 90.4% No Rehydration: 97.7%	Specificity: 98% (estimate)	Specificity: 96-98% (estimate)
Positive Predictive Value(PPV)	Positive Predictive Value of testing for colorectal cancer: both screening groups combined results from 1976-82 Rehydration: 2.2% No Rehydration: 5.6% <60 yrs.: 1.6% >70 yrs.: 3.6%	Positive Predictive Value of FOB for CRC: 1st round: 17% final screen: 9% Predictive Value of Pos. test for detection of large adenomas: 1st round: 32% Final round: 21%	Positive Predictive Value for cancer: 1st Screen: 9.9% Rescreen within 27 months: 11.9% (allowing for 3-month delay in invitation for screening)

Restrictions to Participants Prior to Testing	•abstinence from red meat, poultry, fish, certain raw vegetables and fruits, Vitamin C and aspirin for 24 hours before and during sample collection	•dietary restrictions: no red meat, fresh fruit, iron preparations, Vitamin C, aspirin or other non-steroidal antirheumatics during 3 days before samples taken	•no dietary restrictions. Dietary restrictions imposed only for retesting borderline results.
Frequency of Screening	Annual Biennial	Biennial	Biennial
Median Period of Follow-up	13 years	10 years	Median: 7.8 years Range: 4.5-14.5 years
Screening Protocol	•Initial Protocol: 5 yrs. screening; 5 yrs. follow-up (screening phase to end '82; screening reinstated Feb.'86-Feb.'92)	•only those completing first screening round invited for further screening; 5 rounds during 10-year period	•Negative FOB tests at 1st screen and those testing positive but with no neoplasia found on colonoscopy invited to screening every 2 years
Follow-up of Pos. Screen (Diagnostic Protocol)	•One or more slides positive: history and physical exam; rigid procto-sigmoidoscopy (discontinued in 1982), single column BE radiography (discontinued in 1978; thereafter DCBE administered to approximately 5% of patients when colonoscopy incomplete or suboptimal), CBC, urinalysis, routine blood chemistry, upper GI series (discontinued in 1982), chest radiography, electrocardiography, colonoscopy - biopsy and removal of lesions	•Pos. tests (one or more blue slides): full examination: Interview, physical exam, full colonoscopy (DCBE offered when full colonoscopy could not be obtained	•Pos. test: participants offered full colonoscopy

Table 3 Results of Minnesota, Funen and Nottingham Trials

Parameter	Minnesota, USA	Funen, Denmark	Nottingham, UK
% of Screenings Completed of Screens Offered (total screens/total eligible screens)	Annual Group: 75.2% Biennial Group: 78.4%		
% Participants Completing 1st Screen	Annual: 90.2% Biennial: 89.9%	67% of screening group - completion of 1st screening round	1st Screening round: 53% Completion of at least one screen: 59.6%
% of Participants Completing all Screens	Annual: 46.2% Biennial: 59.7%	46% complete all 5 screening rounds	all screening rounds completed by 38%
Follow-up of Negative FOB test			Screening every 2 years
Follow-up of Positive FOB (no neoplasia or colonoscopy)			Screening every 2 years
Reinvitation to Screening			•those who did not accept 1st invitation for screening not initially reinvited; September/90, reinvited non-responders every 2 years
% of Patients Testing Positive Completing Colonoscopy	Annual: 80.9% Biennial: 81.7%	>85% of those with positive tests	
Colonoscopy rate	Completing at least 1 colonoscopy: Annual: 38% Biennial: 28%	Participants screened at least once and undergoing colonoscopy: 4.3%	Screenees undergoing colonoscopy at least once: 4%
Complications of Colonoscopy	Of 12,246 Colonoscopies: Perforation, diagnostic: 4 (all requiring surgery) Bleed, major: 11 (all requiring surgery)	1000 procedures: 1 death	1,778 procedures: Perforation, diagnostic: 1 Perforation, therapeutic: 4 Bleed, major: 1 Snare entrapment: 1

Parameter	Minnesota, USA	Funen, Denmark	Nottingham, UK
Cases of Colorectal Cancer	Over first 13 Years of Follow-up: 1,002 cases of CRC Annual: 323 Biennial: 323 Control: 356	During 10-year study: 481 cases of CRC in screening group compared with 483 unscreened controls	Screened: 885 (1.49 per 1000 person years) Control: 856 (1.44 per 1000 person years)
Number of Deaths from Colorectal Cancer (total in group)	Over first 13 Years of Follow-up: 320 Annual: 82 (15,570) Biennial: 117 (15,587) Control: 121 (15,394)	Screened: 205 (30,967) Control: 249 (30,966)	Screened: 360 (75,253) Control: 420 (74,998)
Mortality rate (Control Group)	67 per 100,000 PY	89 per 100,000 PY	70 per 100,000 PY
Mortality rate (Intervention Group)	After 13 years: Annual: 45 per 100,000 PY Biennial: 64 per 100,000 PY	After 10 years: 73 per 100,000 PY	After 7.8 years: 60 per 100,000 PY
Cumulative Annual Mortality from CRC	Over first 13 Years of Follow-up: Annual: 5.88 per 1000 (95% CI 4.61-7.15) Biennial: 8.33 per 1000 (95% CI 6.82-9.84) Control: 8.83 per 1000 (95% CI 7.26 - 10.40)		
Rate Ratio (Relative Risk) for Mortality (mortality rate in each screened group/mortality rate in control group) from CRC	Annual: (after 13 years of follow-up): RR= 0.67(95% CI = 0.50-0.87) Annual: (after 18 years of follow-up): RR= 0.67 (95% CI = 0.51-0.83) Biennial (after 13 years of follow-up): RR= 0.94 (95% CI = 0.68-1.31) Biennial (after 18 years of follow-up): RR= 0.79 (95% CI: 0.62-0.97)	RR= 0.82 (95% CI = 0.68 - 0.99) CRC mortality ratio including deaths from complications of treatment for CRC: men: 0.80 (95% CI=0.61 - 1.02) women: 0.85 (95% CI=0.64-1.11) >60 years at start of follow-up: 0.84 (0.68 - 1.05) <60 years: 0.77 (0.54-1.10)	RR= 0.85 (95% CI = 0.74-0.98)
Relative Reduction (%) in Mortality from Colorectal Cancer	Annual: 33% (13 years of screening and follow-up) Biennial: 21% (18 years of follow-up)	Biennial: 18%	Biennial: 15%

Parameter	Minnesota, USA	Funen, Denmark	Nottingham, UK
Distribution of colorectal cancers by Stage (Dukes)	Annual: Stage A: 107 (30.2%) Stage B: 101 (28.5%) Stage C: 80 (22.6%) Stage D: 33 (9.3%) Unstaged:33 (9.3%) All: 354 Biennial: Stage A: 98 (26.6%) Stage B: 95 (25.8%) Stage C: 100 (27.2%) Stage D: 41 (11.1%) Unstaged: 34 (9.2%) All: 368 Control: Stage A: 88 (22.3%) Stage B: 120 (30.4%) Stage C: 82 (20.8%) Stage D: 65 (16.5%) Unstaged: 39 (9.9%) All: 394	Total: Screening Group: Dukes' A: 105 (22%) Dukes' B: 164 (34%) Dukes' C: 90 (19%) Distant spread: 98 (20%) No classification: 24 (5%) Total CRC: 481 Controls: Dukes' A: 54 (11%) Dukes' B: 177 (37%) Dukes' C: 111 (23%) Distant spread: 114 (24%) No classification: 27 (5%) Total CRC: 483	Turnbull modification of Dukes' Staging Total: Screening Group: Dukes' A: 181 (20%) Dukes' B: 286 (32%) Dukes'C: 215 (24%) Dukes' D: 192 (22%) Not known: 19 (2%) Total CRC: 893 Controls: Dukes' A: 95 (11%) Dukes' B: 285 (33%) Dukes' C: 264 (31%) Dukes' D: 179 (21%) Not known: 33 (4%) Total CRC: 856
Five-Year Survival	Stage A: 94.3% Stage B: 84.4% Stage C: 56.6% Stage D: 2.4% Unstaged: 87.0% All: 70.0%		

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