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Screening Strategies For Colorectal Cancer

Systematic Review & Recommendations

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TECHNICAL REPORT

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Screening Strategies for Colorectal Cancer
Systematic Review & Recommendations

Technical Report #01-2, February 2001

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ABSTRACT

Objectives: To make recommendations on the effectiveness of specific screening techniques for colorectal cancer in asymptomatic patients. Effectiveness in normal risk patients was reviewed for 1) multiphase screening with the Hemoccult test as first phase; 2) multiphase screening with sigmoidoscopy; 3) uniphase screening with colonoscopy. For above average risk patients, the specific screening maneuvers reviewed were: 1) flexible sigmoidoscopy and genetic testing for those with familial adenomatous polyposis (FAP); 2) colonoscopy for hereditary nonpolyposis colon cancer (HNPCC); and 3) colonoscopy for patients with family history (1st degree relative(s)) of polyps/colorectal cancer. This updates the 1994 review by the Canadian Task Force

Options: Multiphase screening that begins with testing for fecal occult blood or sigmoidoscopy, uniphase screening with colonoscopy or genetic testing were considered. Options included screening at different intervals and different procedures for patients with selected risk factors.

Outcomes: Rates of cancer detection, deaths from cancer, compliance, feasibility and accuracy of each manoeuver were considered. The highest value was assigned to manoeuvres that lowered the rate of death from cancer and had a low rate of false-positive results and acceptable cost and compliance.

Evidence: A MEDLINE search for articles published between January 1966 and January 2001 with the use of MESH terms "screening" and "colorectal neoplasia", a check with the reference sections of review articles published before January 2001 and a survey of content experts was performed. .

Benefits, Harms, and Costs: Colorectal cancer is an important cause of death in the western world. In Canada, it was estimated that there would be 17,000 new cases of and 6,500 deaths from colorectal cancer in 2000. Overall, colorectal cancer is the third most common cancer in Canada, accounting for more than 12% of cases of cancer in both sexes. The different screening manoeuvres were evaluated for their ability to detect cancer and prevent cancer mortality among normal risk and high risk individuals. Other factors, such as feasibility and compliance, were also assessed. Potential benefits were weighed against potential harms, such as direct harm from a manoeuvre (e.g. perforation), false positive tests, and poor compliance. Cost effectiveness was not directly assessed.

Values: The strength of evidence was evaluated using the evidence-based methods of the Canadian Task Force on Preventive Health Care.

Recommendations: *Normal risk individuals*: There is good evidence to support the inclusion of annual or biennial fecal occult blood testing (A recommendation) and fair evidence to include flexible sigmoidoscopy (B recommendation) in the periodic health examinations of asymptomatic individuals over age 50 years. There is insufficient evidence to make recommendations about whether only 1 or both of FOBT and sigmoidoscopy should be performed (C recommendation). There is insufficient evidence to include or exclude colonoscopy as an initial screen in the periodic health examination (C recommendation). *Above average risk individuals*: There is fair evidence to support either genetic testing (B recommendation) or

flexible sigmoidoscopy of at risk individuals in FAP kindreds (B recommendation) and screening with colonoscopy of patients in kindreds with the cancer family syndrome (HNPCC) (B recommendation). There is insufficient evidence to recommend colonoscopy for individuals who have a family history of colorectal polyps or cancer but do not fit the criteria for HNPCC (C recommendation). Development of better risk stratification for screening is a high research priority and further research, including randomized controlled trials, into the effectiveness and feasibility of other screening modalities is necessary.

Validation: The findings of this analysis were reviewed through an iterative process by the members of the Canadian Task Force on Preventive Health Care.

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Screening Strategies for Colorectal Cancer
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BACKGROUND

Colorectal cancer is the third most common cancer occurring in Canada.[1] It is well recognized that there are improved survival rates if the disease is treated in its early stages.[2] Furthermore, with advances in endoscopic techniques, which may be used both for detection as well as removal of precursor lesions, colorectal cancer is theoretically a preventable disease.[3] As a result, there is much interest in the various screening manoeuvers available for the early detection of both adenomas and carcinomas. In the past few years, several trials assessing the effectiveness of screening for colorectal cancer have been completed. Thus, the 1994 Canadian Task Force recommendations on screening for colorectal cancer were reviewed and have been revised to reflect recent evidence.[4]

The most common protocol for screening for colorectal cancer in average risk individuals is a multiphase manoeuvre with fecal occult blood testing initially followed by colonoscopy or flexible sigmoidoscopy and barium enema in patients with a positive test result for the presence of occult blood. The Hemoccult test detects the peroxidase-like activity of hemoglobin.[5] The HemoQuant test detects the porphyrin-like moiety of hemoglobin.[6] Immunochemical tests for fecal hemogolbin have been developed based on various techniques including radial immunodiffusion, latex hemagglutination, ELISA and monoclonal antibodies against hemoglobin.[7, 8] Of these, the HemeSelect test has been used most extensively.

An alternative to multiphase screening is screening with sigmoidoscopy alone or colonoscopy for average risk individuals.[9] In high risk groups, uniphase screening with colonoscopy has been recommended.

Burden of Suffering

Colorectal cancer is a leading cause of death in the western world. In Canada, it was estimated that there would be 17,000 new cases of and 6,500 deaths from colorectal cancer in 2000.[1] Overall, colorectal cancer is the third most common cancer in Canada, accounting for more than 12% of cases of cancer in both sexes. Rates of colorectal cancer in Canada, particularly among men, are among the highest in the world. Surgical resection remains the standard therapy for colorectal cancer but adjuvant therapy with radiation and chemotherapy has

also been shown to improve outcome in some patients.[10]

The etiology of colorectal cancer is unknown but most cancers arise from benign adenomas following the "polyp-cancer sequence".[11] Most cancers occur sporadically but it is estimated that up to 15% of cancers may have a genetic basis.[12] Thus, people with familial adenomatous polyposis, which account for 1% of all colorectal cancers and those with hereditary nonpolyposis colon cancer (HNPCC), which may account for another 5% of colorectal cancers, are at high risk for the development of colorectal cancer. Age is a significant risk factor. Less than 2% of cases occur in people under 40 years of age. The risk of colorectal cancer in a patient 50 years of age is 18 to 20 times that in a patient 30 years of age, and the risk doubles about every 7 years thereafter.[13] In Canada in 2000, it was estimated that there would be 940 cases of colorectal cancer in individuals between 40-49 years compared with 2400 individuals 50-59 years. The risk increased to age 80.[1] (See Table 1)

People with ulcerative colitis[14] and those who have had previous polyps or cancers are at increased risk for the development of colorectal cancer. These individuals have been excluded from this review since the management of those with identifiable disease is not generally part of the scope of a CTF review.

Objectives

This systematic review was to undertaken to make recommendations on the effectiveness of specific screening techniques for colorectal cancer in asymptomatic patients. Effectiveness in normal risk patients was reviewed for 1) multiphase screening with the Hemoccult test as first phase; 2) multiphase screening with sigmoidoscopy; 3) uniphase screening with colonoscopy. For above average risk patients, the specific screening maneuvers reviewed were: 1) flexible sigmoidoscopy and genetic testing for those with familial adenomatous polyposis (FAP); 2) colonoscopy for hereditary nonpolyposis colon cancer (HNPCC); and 3) colonoscopy for patients with family history (1st degree relative(s)) of polyps/colorectal cancer). This updates the 1994 review by the Canadian Task Force.[4]

METHODS

Extraction of Evidence

MEDLINE was searched for English language articles assessing screening for colorectal cancer published between January 1966 and January 2001 with the use of the MESH terms "screening" and "colorectal neoplasia." Review articles published between these dates were retrieved and their reference sections were used to cross-reference the MEDLINE search. Content experts were canvassed to ensure that no relevant articles were missed. Articles concerning Hemoccult testing or flexible sigmoidoscopy as the first step in a multiphase secondary prevention strategy or colonoscopy as a single-phase secondary prevention strategy in both asymptomatic and high-risk groups were included. Screening with digital rectal examination and double contrast barium enema were not considered because of the lack of direct evidence.

Critical Appraisal and Consensus Development

The evidence was systematically reviewed using the methodology of the Canadian Task Force on Preventive Health Care. The Task Force of expert clinician/methodologists from a variety of medical specialties used a standardized evidence-based method for evaluating the effectiveness of this intervention. Cost effectiveness was not directly assessed. A manuscript providing critical appraisal of the evidence was prepared by the lead author. This included identification and critical appraisal of key studies, and ratings of the quality of this evidence using the Task Force's established methodological hierarchy (Appendix 1), resulting in a summary of proposed conclusions and recommendations for consideration by the Task Force. This manuscript was pre-circulated to the members in January and June of 1999 and January, 2000 and evidence for this topic was presented by the lead author and deliberated at 3 Task Force Meetings in January and June of 1999 and January, 2000.

At the meetings, the expert panelists addressed critical issues, clarified ambiguous concepts and analyzed the synthesis of the evidence. At the end of this process, the specific clinical recommendations proposed by the lead author were discussed, as were issues related to clarification of the recommendations for clinical application, and any gaps in evidence. The results of this process are reflected in the description of the decision criteria presented with the specific recommendations. The group and lead author arrived at the final decisions on recommendations unanimously.

Subsequent to the meetings, the lead author revised the manuscript accordingly. After

final revision, the Task Force sent the manuscript to 4 experts in the field. Feedback from these experts was incorporated into a subsequent draft of the manuscript, which was then submitted to this journal.

Procedures to achieve adequate documentation, consistency, comprehensiveness, objectivity and adherence to the Task Force methodology were maintained at all stages during review development, the consensus process, and beyond. These were managed by the Task Force Office, under supervision from the Chair, and ensured uniformity and impartiality throughout the review process. The full methodology is described in Wolff et al.[15]

RESULTS

Screening Average Risk Individuals

Screening with the Hemoccult test

Four large RCTs have assessed the value of screening with the Hemoccult test.[16-27] As shown in Table I, death rates were derived from the most recent report from each trial. Sensitivity and specificity data were derived from the raw data. They report the accuracy of the screening program for each patient rather than of each Hemoccult test performed on one patient, as reported in some studies.

The University of Minnesota Colon Cancer Control Study began accruing subjects in 1975.[16-20] The 46,551 participants, who were between 50 and 80 years in age, were recruited from the American Cancer Society and fraternal, veteran and employee groups in Minnesota. They were randomly assigned to annual or biennial screening with the Hemoccult test or a control group and followed for 13 years. A high sensitivity of the Hemoccult test (88% to 92%) for detecting cancer, a high compliance rate (86%) and a cancer detection rate of 0.002 were originally reported. The high reported sensitivity may be a result of the method adopted for assessing sensitivity. However, if the sensitivity of the test is determined from the number of carcinomas detected through screening divided by the total number of carcinomas, then after 13 years, the sensitivity for the group screened annually is 49.5% and for the group screened biennially 38.3%. There were no differences in overall death rates among the three groups. However, the death rate from colorectal cancer was statistically significantly lower in the group

screened annually (82 deaths) compared to the control group (121 deaths) (RR=0.67 95% CI 0.51-0.89). Initially, in the group screened biennially, the colorectal cancer death rate was lower (117 deaths) but not significantly so (RR=0.95 95% CI 0.74-1.23). Thus, the cumulative mortality was 5.88/1000 (95% CI 4.61-7.15) in the annual screened, 8.33/1000 (95% CI 6.82-9.84) in the biennial screened and 8.83/1000 (95% CI 7.76-10.40) in the control group. However, in an updated report with 18 years follow-up, a significant reduction in colorectal cancer deaths in the group screened biennially was reported (177 deaths in the biennial screened group compared to 144 deaths in the control group, rate ratio, 0.79;95% CI=0.62-0.97). As well, for those in the annually screened group, the rate ratio at 18 years was 0.67 (95% CI 0.51-0.83).[20] Thus, this represents a cumulative benefit of annual screening of 2.95 deaths averted per 1000 people and for biennial screening 0.5 deaths averted per 1000 people over the 13 years.

In this trial, the rate of positive slides was 9.8% when they were rehydrated. As a result, 38% (5,917) of those in the annual screen group and 28% (4,365) of those in the biennially screen group had colonoscopic examinations to detect 646 cases of cancer. There were 15 major complications in the 12,246 colonoscopies performed at the university (0.1% complication rate). These included 4 perforations requiring surgery and 11 serious bleeds including 3 requiring surgery. There were no deaths.

A second population-based RCT conducted in Funen, Denmark, involved 61,933 people 45 to 75 years of age.[21-23] Patients in the screened group underwent the Hemoccult test at the outset of the study and biennially thereafter for 10 years. In the screened group, 481 cancers were detected compared with 483 in the control group. Of those in the screened group, 120 carcinomas were detected with screening and 148 were interval cancers. Therefore, the sensitivity of the test for detecting cancer was 45%. Overall, the tumors were at earlier stages in the screened group: significantly more subjects in the screened group had local (10% versus 5%, $p<0.01$) and curative surgery (69% versus 59%, $p<0.01$) for their cancers. In addition, 413 subjects in the screened group compared with 173 in the control group had adenomas >10 mm detected. Like the University of Minnesota study, overall mortality was not different between the 2 groups. However, there were 205 deaths due to colorectal cancer in the screened and 249 deaths due to colorectal cancer in the control group after 10 years, representing a 18% risk reduction (RR=0.86, 95% CI 0.74-0.99). Unlike the University of Minnesota study, the

Hemoccult slides were not rehydrated and overall only 4.3% of screened subjects had a colonoscopic examination. This may be the reason for the lower risk reduction in the screened group but also means that the financial costs of the program were less. The complication rate associated with colonoscopy was not reported.

A population-based RCT conducted in the Nottingham area of England examined screening with the Hemoccult test at study entry and every 2 years thereafter.[24, 25] Randomization was by household rather than by individual. Of the 75,253 individuals randomized to screening, only 44,838 (59.6%) completed at least one screening. In this study, slides were not rehydrated. For the initial test, subjects were not asked to restrict their diet. If the slides were positive, then the subject was asked to repeat the test after being on a restricted diet. The sensitivity of the test was similar to that reported in the previous trials with 236 of 485 (48.6%) cancers detected by screening and 249 in the interval between screening. After a median follow-up of 7.8 years, there were 360 deaths due to colorectal cancer in the screened group compared with 420 deaths due to colorectal cancer in the control group, representing a statistically significant risk reduction of 15% (RR=0.88, 95% CI 0.69-1.12). In this study, like the Danish study, only 4.0% of subjects underwent 1 or more colonoscopic examinations. Possibly because of the low compliance rate, almost half of the cancers in the screened group were detected in non-responders. (ie: those who were not screened despite randomization to screening) Overall, only one quarter (236) of the 856 cancers in the screened group were actually detected by Hemoccult testing. It is also interesting to note that 74% of the screen detected cancers were in the rectum or sigmoid which might have implications in considering a program of combined flexible sigmoidoscopy and fecal occult blood testing which has been suggested. In addition to the colorectal cancers, 1,001 subjects in the screened group were found to have adenomas, of whom 267 had adenomas over 2 cm in size. In comparison, 370 subjects had adenomas in the control group with 100 of them having polyps greater than 2 cm in size.

The fourth randomized controlled trial is a population-based study started in 1982 in Goteberg, Sweden involving 68,308 subjects between 60 and 64 years of age.[26-27] Subjects in the screen group were offered Hemoccult testing at the start of the trial and then 16-24 months later. Subjects were asked to follow a restricted diet before the tests. Furthermore, in order to decrease the false positive rate, subjects with a positive test were retested before undergoing follow-up

examinations. Those with a positive second test were worked up with proctoscopy, flexible sigmoidoscopy and double contrast barium enema. Colonoscopy was not performed initially. Overall 3.8% underwent workup after the first screen and 5.1% after the second screen. In this study, the sensitivity for the test was 81% (81 of 102 cancers). Mortality data have not been published in a primary report but mortality data were supplied so a meta-analysis could be performed.[28] To date, there have been 121 deaths in the screened group compared with 138 in the control group, representing a 12% risk reduction which is not statistically significant.

Towler and colleagues recently published a systematic review including the above mentioned trials plus 2 nonrandomized studies.[28] The first nonrandomized trial was performed at Memorial Sloan Kettering to assess the additional benefit of Hemoccult testing in patients already being offered sigmoidoscopy.[29-31] The second is a study from France which still has not reported mortality rates and therefore was not included in this analysis.[32] The meta-analysis included over 330,000 individuals from the RCTs and another 113,000 from the nonrandomized studies. The results from the 4 trials were combined and using a random effects model, there was a 16% risk reduction in mortality from colorectal cancer (RR 0.84, 95% CI 0.77 to 0.93). The overall relative reduction in mortality was 23% for those who were compliant (RR 0.77, 95%CI 0.57 to 0.89). They also estimated that if 10,000 people were offered screening, 8.5 (95%CI 3.6 to 13.5) deaths from colorectal cancer would be prevented over 10 years. The number needed to screen over 10 years would be 1173. As well, there is evidence from the University of Minnesota Trial that the detection and removal of adenomas decreases the incidence of colorectal cancer in the screened population. At 18 years, the cumulative incidence ratios for colorectal cancer in the screened groups as compared with the control group were 0.80 (95% CI 0.70-0.90) and 0.83 (95% CI 0.73-0.94) for the annual and biennial screened groups respectively. Thus, as follow up continues, it is likely that a further decrease in cancer related mortality will be realized.

In summary, there is now evidence from 4 RCTs that fecal occult blood testing with Hemoccult results in a significant decrease in mortality from colorectal cancer, but not in overall mortality. The relative risk reduction is in the order of 15% and in absolute terms, approximately 8.5 deaths from colorectal cancer would be averted if 10,000 people were screened over 10 years.[28] The relative risk reduction in mortality rates is fairly constant but the colorectal cancer detection rate is higher in older individuals. Thus, if screening were begun at a later age, the

absolute number of lives saved might be greater. The relative risk reduction may also vary depending on whether the test is performed annually or biennially and whether the slides are rehydrated. In the University of Minnesota trial, in the group screened annually and where the slides were rehydrated, the relative risk reduction was considerably greater (33% risk reduction compared with approximately 15% risk reduction in the other 3 trials). On the other hand, the positivity rate was highest in this group (9.8%) and 38% of subjects had a colonoscopy compared with approximately 4% of the screened subjects in the other trials. This has significant implications for the cost of a screening program. Significant adverse events, however, occurred in only 0.1% of individuals having colonoscopy in the University of Minnesota trial.[17]

While the trials have shown a significant reduction in colorectal cancer mortality with screening for fecal occult blood, there remain concerns about the sensitivity of Hemoccult testing and its value as a screening test. Overall, the sensitivity of the test for detecting colorectal cancer was approximately 50% in 3 of the trials. Lang and Ransahoff analyzed the data from the University of Minnesota trial and suggested that one third to one half of the mortality reduction was due to chance selection, simply due to colonoscopies being performed in a large proportion of subjects.[34] They questioned the need for fecal occult blood testing and whether colonoscopic examinations alone should be performed. Finally, none of these studies addressed the psychological issues of screening nor the acceptability of screening on a community basis.[35] The Nottingham trial perhaps provides the best data from the RCTs on the acceptance of mass screening and almost 60% of invited individuals participated.[25] However, other studies have shown much lower compliance rates both for the initial testing as well as the follow-up investigations.[36]

Screening with sigmoidoscopy

The Kaiser Multiphasic Evaluation Study was a RCT involving members of a medical care program 35 to 54 years of age who were encouraged (study group) or not actively encouraged (control group) to schedule a multiphase health checkup that included a sigmoidoscopic examination.[37] At each checkup, patients in both groups were offered sigmoidoscopic examination. Thus, this study determined whether compliance was improved

with encouragement rather than the effectiveness of sigmoidoscopic examination as a screening procedure for colorectal cancer.

The investigators re-analysed the data from these groups.[38] They retrospectively reviewed the charts of patients who had died of colorectal cancer and compared them with the charts of matched control subjects to determine the proportion of patients in each group who had been examined with rigid sigmoidoscopy in the preceding 10 years. Of the patients who had died of colorectal cancer 8.8% had undergone sigmoidoscopy within the preceding 10 years, as compared with 24.2% of the control patients. After adjustment, the odds ratio was 0.41, 95% CI 0.25-0.69. Another group of individuals with fatal colon cancer above the reach of the sigmoidoscope were compared with a control group. There was no significant difference in the proportion who had had a rigid sigmoidoscopy in the preceding 10 years. Although this study suggests that patients with fatal rectal cancer were less likely than matched control patients to have had rigid sigmoidoscopy in the preceding 10 years, adenomas were detected with sigmoidoscopy and removed in only 12 (1%) of the 868 control patients. Detection and successful treatment of neoplasia as a result of sigmoidoscopy is needed to infer that survival was due to screening with sigmoidoscopy. Since only a small proportion of patients had polypectomy, it suggests that there may be intrinsic differences between the groups resulting from the case - control design rather than a treatment effect.

A similar case control study was reported by Newcomb and colleagues.[39] All subjects in the study were members of a health plan during the study period 1979 to 1988. Individuals in the case group had died of cancer of the colon or rectum. This study included only 74 case subjects (of whom 66 had medical records available) and 206 control subjects (of whom 196 were included). There was no significant difference in the proportion of subjects who had had fecal occult blood testing (21% of case subjects compared with 16% of control subjects). However, 30% of control subjects compared with 10.6% of case subjects had had a sigmoidoscopy (OR=0.21, 95% CI 0.08-0.52). The reduction was in cases with cancers limited to the rectum and distal colon only. The proportion of subjects who had a polypectomy with the sigmoidoscopy was not reported.

A third case control study was reported by Muller and colleagues who studied over 30,000 individuals followed by the Veteran Affairs in the USA.[40] There were 8,722 individuals

who had died of a colon cancer and 7,629 who had died of a rectal cancer plus matched controls. The two groups were assessed for the proportion who had had an endoscopic procedure (flexible sigmoidoscopy, colonoscopy, polypectomy) between 1981 and the time of diagnosis of their cancer. The likelihood of a patient dying of a colon cancer having had an endoscopic procedure was 0.51 (95% CI 0.44-0.58) compared with the control subjects and the likelihood of a patient dying of a rectal cancer having had a sigmoidoscopy was 0.55 (95% CI 0.47-0.64).

Two large descriptive studies with adequate follow-up (level III evidence) have provided evidence that screening with sigmoidoscopy can decrease mortality from colorectal cancer compared with the normal population.[41-43] However, because both of these studies were uncontrolled, the effects of volunteer, lead-time and length-time bias cannot be measured.

Verne and colleagues conducted a small RCT comparing fecal occult blood testing, flexible sigmoidoscopy or both to determine the feasibility of such a study.[44] There were 3,744 patients between 50 and 75 years who were randomized by household to one of the 3 groups. Compliance was significantly higher in the group of patients randomized to flexible sigmoidoscopy compared to the other 2 groups (46.6% compared with 31.6% and 30.1%). Polyp and cancer detection data are available but no mortality data. Although polyps were detected in 17% of individuals, they were adenomas in only 6.8% and high risk adenomas in 2.4%. Cancers were found in 0.4%. The addition of fecal occult blood testing did not improve the detection rate. Eighty-one subjects who had a negative fecal occult blood test had polyps detected at flexible sigmoidoscopy including 30 with adenomas and 1 with an early cancer. Based on the histology of the polyps removed at flexible sigmoidoscopy, 7% of subjects required follow-up colonoscopy. Because not all patients had colonoscopy performed, the false negative rate cannot be calculated.

In another RCT, subjects were randomized to fecal occult blood testing or combined fecal occult blood testing and flexible sigmoidoscopy.[45] In total, 6,371 individuals between 50-74 years were randomized to the 2 groups. In both groups, the compliance with fecal occult blood testing was 48-50% whereas only 20% of individuals in the combined group agreed to have flexible sigmoidoscopy. Despite this, the neoplasia detection rate was 4 times higher in the fecal occult blood test (FOBT)/flexible sigmoidoscopy group (8.9 patients/1000 screened compared with 2.0 / 1000 screened). This difference was largely due to the addition of flexible sigmoidoscopy. Twenty-two patients (including 2 with cancers) were identified by flexible

sigmoidoscopy compared with only 6 or 7 individuals with fecal occult blood testing.

In a third trial, reported by Rasmussen et al, 5,495 individuals between 50-75 years were randomized to FOBT and flexible sigmoidoscopy and 5,483 to FOBT alone.[46] There was lower compliance in the FOBT/flexible sigmoidoscopy group (40% versus 50%). However, 12 colorectal cancers and 72 large adenomas were detected in this group compared with 4 colorectal cancers and 14 large adenomas in the FOBT only group. There are no data available on mortality.

Thus, there is evidence from 3 case control studies that sigmoidoscopy may reduce the risk of death from colorectal cancer. Three RCTs suggest that flexible sigmoidoscopy may be superior in detecting adenomas and possibly cancer than FOBT.[44-46] However, the latter trials are small and do not report mortality data. Therefore, the benefit of flexible sigmoidoscopy alone compared with FOBT or in combination with FOBT cannot be ascertained. However, there is fair evidence to suggest that sigmoidoscopy may reduce mortality from colorectal cancer. Flexible sigmoidoscopy may be preferable to rigid sigmoidoscopy, because the physician can examine the more proximal colon with the flexible sigmoidoscope than with the rigid one and thus detect more adenomas and carcinomas.[47] The flexible sigmoidoscope may be more acceptable to patients and safer.[48] Bowel perforations occur at a rate of only 1.4 per 10,000 flexible sigmoidoscopic examinations of asymptomatic patients.[49] It does require a more qualified examiner than rigid sigmoidoscopy.

Further data are required regarding frequency of examinations, compliance and feasibility, both of performing the screening flexible sigmoidoscopy as well as the colonoscopic follow-up examinations. As well, further data regarding the significance of small polyps identified at flexible sigmoidoscopy and the need for colonoscopic examination are required as there is controversy regarding the significance of polyps less than 0.5 cm. in size.[50-53] Finally, there is currently a RCT comparing once only screening with flexible sigmoidoscopy at age 60 years to no screening being performed in the UK (FLEXISCOPE trial).[54, 55] A second trial is the US NCI PLCO Trial.[56] The results of these trials will further elucidate the value of screening with flexible sigmoidoscopy.

Uniphase screening with colonoscopy

There is no direct evidence about the effectiveness of colonoscopy as a screening manoeuver in asymptomatic, average risk individuals. However, as stated previously, 38% of individuals in the annual screen group in the University of Minnesota trial underwent colonoscopic examination and there was a relative risk reduction in mortality from colorectal cancer of 33% (RR 0.67 95%CI 0.50-0.87) compared to control subjects.[17] Furthermore, after reanalyzing the data, Lang and Ransahoff, concluded that at least some of the reduction in mortality was due to chance selection of individuals for colonoscopy and if so, then perhaps less frequent screening with colonoscopy might be more appropriate than initial screening with Hemoccult testing.[33]

The National Polyp study was a RCT designed to determine the optimal frequency of colonoscopy in individuals who had previously had a polypectomy.[57] As a secondary analysis, the investigators compared the incidence of cancer in this cohort of patients to 2 historical control groups where polyps had not been removed (St. Mark's Hospital and Mayo Clinic patients) and 1 general-population registry (SEER data). In the 1,418 individuals in the National Polyp Study, there were 5 early asymptomatic cancers detected by colonoscopy within the mean follow-up time of 5.9 years. The predicted rates in the reference groups were 48.3, 43.4 and 20.7, for reductions in the incidence of colorectal cancer of 90, 88 and 76% respectively. This study is obviously limited by the biases of a study where patients are followed prospectively and compared to historical controls. Nevertheless, it provides some evidence (Level II-3) that colonoscopy may decrease the risk of cancer although it provides no evidence that mortality is reduced.

Four uncontrolled trials (level III evidence) involving asymptomatic patients over 50 years of age with no family history of colorectal cancer have been reported.[53, 58-60] Because there were no control groups or follow-up, there is no direct evidence for or against the effectiveness of screening asymptomatic patients with colonoscopy. Several important points were, however, noted in these studies. The incidence of carcinomas (0.01) and adenomas (0.22) was higher with colonoscopy than with the Hemoccult test. Compliance rates were variable ranging from 6%-49%.[53, 60]

Screening above average risk groups

Individuals belonging to familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPCC) kindreds have close to a 50% chance of developing colorectal cancer because of the autosomal dominant mode of inheritance of these syndromes. Similarly, individuals with a family history of colorectal cancer but do not fit the criteria for HNPCC or FAP may be at increased risk but that risk is less well defined. Finally, ulcerative colitis and a past history of adenomatous polyps or colorectal cancer increase the chance of developing a colorectal cancer. As mentioned previously, patients with ulcerative colitis and a history of polyps or cancer will be omitted from this review since both groups have identifiable diseases, although the latter may be asymptomatic.

Individuals at Risk for Familial Adenomatous Polyposis (FAP)

FAP is characterized by the progressive development of multiple adenomatous polyps occurring throughout the colon.[61] Generally, polyps first appear after puberty. If left untreated, 100% of individuals will develop a colon cancer, on average by 40 years. While colorectal polyps and cancer are the common manifestation of this disease, other benign and malignant lesions, including gastric and duodenal polyps, desmoid tumors, osteomas, retinal lesions (congenital hypertrophic retinal pigment epithelium) occur with variable frequency. FAP is transmitted through an autosomal dominant gene so that approximately 50% of at risk individuals will be affected. Approximately 10-15% of affected individuals give no family history and the disease is thought to arise because of a spontaneous mutation.

There are data from retrospective cohort studies of Registry data that the survival of screened individuals is significantly better than that of probands (Level II-3 evidence).[62] Because polyps almost always are present in the rectum prior to the development of a colorectal cancer, screening with flexible sigmoidoscopy in at risk individuals beginning at puberty and continuing at 1 or 2 yearly intervals has been the accepted routine.

With the identification of the APC gene on chromosome 5, it is now possible to perform genetic testing in at risk individuals.[63-65] In families where the genetic mutation has been identified, the sensitivity and specificity of genetic testing is 100%.[66] Furthermore, this strategy has been shown to be cost effective compared with surveillance with flexible sigmoidoscopy.[67]

The advantage of genetic testing is that it is noninvasive and may be more acceptable to patients. The disadvantage of genetic testing is that the gene mutation may be identified in only 70% of affected families. Furthermore, genetic testing may not be widely available.

Individuals at Risk for Hereditary Non-Polyposis Colon Cancer (HNPCC)

HNPCC is typified by the presence of multiple family members affected with cancer, including cancers of the colon and rectum as well as the endometrium, stomach, small bowel, pancreas, ovary and ureter and renal pelvis in some families.[68] Approximately 2-5% of all colorectal cancers fit the criteria for HNPCC.[69-72] Because HNPCC is inherited as an autosomal dominant trait with high penetrance, the risk of a family member of a HNPCC pedigree being affected nears 50%. In those affected, the risk of colorectal cancer is estimated to be approximately 70% by age 65 years.[73]

In HNPCC, colorectal cancers tend to be right sided, occur at an early age and there is an excess of synchronous and metachronous colon cancers. There is a greater incidence of polyps than in age matched controls although not the large numbers seen in FAP. Cancers tend to have poor prognostic histological features (poorly differentiated, mucinous) and be more advanced at presentation. Despite this, the prognosis is better than sporadic tumors of equivalent stage. Because the phenotype of HNPCC tumors is not as unique as with FAP, various criteria have been developed to define kindred with HNPCC. Of these, the Amsterdam criteria are most widely accepted.[74] Using the Amsterdam Criteria, an HNPCC kindred must have three individuals affected with colorectal cancer with two being in successive generations and at least one being under the age of 45 years. Familial adenomatous polyposis must be excluded. However, despite their value in standardizing reporting of HNPCC, these criteria have relatively low sensitivity and specificity in discriminating between families where there is clustering of sporadic cancers and HNPCC.[75, 76]

HNPCC cancers differ from sporadic cancers in that approximately 85%of cancers exhibit microsatellite instability compared to approximately 10-20% in sporadic cancers.[71] Six germline mutations (hMSH2, hMLH1, hPMS1, hPMS2, hMSH3 and hMSH6/GTBP) have been identified, all involving genes involved in DNA mismatch repair. These mutations are not unique to HNPCC.[68] Furthermore, germline mutations may be identified in only 50% of high risk

families suspected of having HNPCC.[75, 76] Thus, at the present time, genetic testing is not feasible to identify HNPCC families but is of value in testing members of HNPCC families where a mutation has been identified.

Since approximately 45% of cancers are right sided in HNPCC families, colonoscopy is the preferred method of screening. Based on expert opinion, colonoscopy, beginning at age 20-25 years and repeated at 1-3 yearly intervals has been recommended.[77] A short interval between examinations is based on evidence that the adenoma-cancer sequence may be shortened in HNPCC.[73] There are no randomized controlled trials showing that colonoscopy increases survival or decreases the incidence of colon cancer in at risk individuals in HNPCC families. The only evidence comes from retrospective observational data. Vasen and colleagues reported data from the Netherlands Registry where 388 asymptomatic first degree relatives underwent colonoscopy or double contrast barium enema and flexible sigmoidoscopy at 2-3 year intervals and compared the results to those of 238 individuals who did not undergo surveillance.[78] Cancers in the surveillance group were detected earlier (73% Dukes' A or B compared with 47% in the non-surveillance group) and had better survival (87% versus 63% respectively). Jarvinen and colleagues reported on 133 at risk individuals who had colonoscopy at 3 year intervals and 119 at risk subjects who did not have any screening.[79] Colorectal cancer occurred in 8 (6%) of screened individuals compared with 19 (16%) in the unscreened group ($p=0.014$). As well, the tumor stage of the cancers was more favorable in the screened group. There were no cancer deaths in the screened group compared with 9 colorectal cancer deaths in the unscreened group. ($p<0.001$) In addition, the overall mortality rate was significantly lower in the screened group (26 vs 10 deaths, $p=0.003$). With respect to the frequency of screening, 4 of the 8 cancers detected by screening by Jarvinen occurred in individuals who had been screened between 26 and 37 months earlier. In the Dutch study, 4 of 11 cancers occurred between 2 and 4 years after a negative screen. Lanspa and colleagues reported that 6 cancers arose in 225 individuals within 4 years of colonoscopic surveillance and another 17 developed a metachronous cancer within 5 years of resection of their first colon cancer.[80]

Vasen and colleagues constructed a model comparing a strategy of surveillance with colonoscopy every 2-3 years and no surveillance in individuals who were known to be gene carriers.[81] Their results showed that surveillance would lead to an increase in life expectancy of 7

years and the costs of surveillance under a wide range of assumptions were less than the costs of no surveillance.

Individuals with a Family History of Polyps or Colon Cancer

Several studies have indicated that individuals with a family history of colorectal cancer are at a higher risk for developing colorectal cancer. Family history data on colorectal cancer were collected in the Health Professionals Follow-up study and The Nurses Health Study.[82] Overall, a history of colorectal cancer in a first degree relative was reported by 9.4% of the 32,085 men in the Health Professionals Follow-up Study and by 10% of women in the Nurses Health Study. During the study period, colorectal cancer was diagnosed in 148 of the men and 315 of the women. Seventeen per cent of these had previously reported a family history of colorectal cancer. For men with a family history, the age adjusted relative risk of colorectal cancer was 1.64 (95% CI 1.04 to 2.58) and for women it was 1.77 (95% CI 1.32 to 2.37). The likelihood of a family history of colorectal cancer was higher in younger participants with colorectal cancer (RR for individuals 30-44 years=5.37 95%CI 1.98-17.4). There was also an increased risk of colorectal cancer as the number of affected relatives increased. Thus, with 2 or more affected first degree-relatives, the age-adjusted relative risk of colorectal cancer was 2.75 (95% CI 1.34 to 5.63).

Winawer and colleagues obtained a family history of colorectal cancer and analyzed the data from 1199 participants in the National Polyp Study.[83] The relative risk of colorectal cancer was 1.78 for parents and siblings of the patients with adenomas compared with spouse controls (95%CI 1.18 to 2.67). The risk increased if the proband was younger than 60 years (RR for siblings 2.59 95%CI 1.46 to 4.58) and continued to increase as the age of the proband decreased. The risk in siblings also increased if there was a parent with colorectal cancer as well as the proband (RR 3.25 95%CI 1.92 to 5.52). Similar results were reported by Ahsan et al who performed a similar study in patients found to have adenomas during an initial colonoscopy compared to a control group with a negative colonoscopy.[84] They also found the risk of colorectal cancer increased in first-degree relatives as the age of the proband decreased. St. John and colleagues performed a case control study with the cases being patients with colorectal cancers.[85] Again, the risk increased as the number of affected first degree relatives increased (RR

of 1.8, 95% CI 1.2 to 2.7 for those with 1 affected relative and 5.7, 95% CI 1.7 to 19.3 for 2 affected relatives). As well, the risk of colorectal cancer increased in parents and siblings as the age of the index case decreased (OR 3.7 95%CI 1.5 to 9.1 for case patients diagnosed before 45 years and OR 1.8 95%CI 1.2 to 2.9 for case patients diagnosed after 45 years).

Despite this increased risk, there is little evidence on how to screen individuals with a family history of colorectal cancer and whether a more intensive screening program is needed or effective. In particular, there are no randomized controlled trials or other studies comparing screening with FOBT to colonoscopy. Furthermore, the only published studies report detection rates but are too small to report survival data.

Rozen and colleagues initially screened 471 asymptomatic first degree relatives of patients with colorectal cancer with Hemoccult tests and sigmoidoscopy.[86] They compared the results with those from a group of 457 asymptomatic volunteers with no family history of colorectal cancer. The prevalence of neoplasia (both adenomas and carcinomas) was three times higher in the group with a family history than in the control group. However, only two invasive carcinomas were detected in the study group (for a detection rate of 0.004), as compared with one in the control group (for a detection rate of 0.002). There were three times as many colonoscopic examinations in the study group as in the control group despite there being no significant difference in the rate of positive results of Hemoccult tests or of positive results of sigmoidoscopic examinations. Hence, a diagnostic suspicion bias may explain some of the difference in the rate of detection of neoplasia.[87]

Pariente and colleagues offered colonoscopy to first degree relatives of 195 recently diagnosed individuals with colorectal cancer.[88] Two controls who had colonoscopy for a reason unrelated to colorectal cancer were selected from the same center. Adenomas were found in 43 (23.2%) of relatives and 64 (17.5%) of control subjects. No cancers were detected in either group. Compared with the controls, the odds ratios were 1.5 (95% CI 1.0-2.4) for detection of an adenoma and 2.6 (95% CI, 1.3-5.1) for a high risk adenoma (defined as a polyp greater than 1 cm or with a villous component) in the relatives group. Furthermore, the risk of a high-risk adenoma increased if the index case was under 65 or male, had a left side or advanced cancer.

Guillem and colleagues compared the colonoscopic results of 181 first-degree relatives to a control group without a family history of colorectal cancer.[89] Adenomatous polyps were

detected in 14.4% of the individuals with a family history compared with 8.4% of individuals in the control group. Again, no cancers were detected.

In a study from Scandinavia, the results of colonoscopy in 50 relatives were compared to that of 308 asymptomatic controls.[90] The risk of adenoma was twice as high in the first-degree relatives but this difference was observed only in females.

Finally, despite the increased risk for developing adenomas or cancers, compliance rates for screening colonoscopy among first degree relatives has been low in most studies. Only 39-42% of first degree relatives offered colonoscopy in the studies by Pariente and Guillem accepted the invitation.[88-89] Furthermore although 42% of the relatives offered colonoscopy accepted the invitation in the Guillem study, only 47% of individuals with cancer had agreed to have their relatives contacted. Thus, in fact, only approximately 20% of at risk individuals had a screening colonoscopy. The compliance rate reported by the Norwegian group was much higher (82%).[90]

INTERPRETATION

Canadian Task Force Recommendations (Table 3)

Average Risk Individuals

1) Screening with the Hemoccult test

There is good evidence to include screening with Hemoccult test in the periodic health examination of asymptomatic patients over age 50 with no other risk factors (**A recommendation**). However, there remain concerns about the high rate of false-positive results, feasibility and small clinical benefit of such screening (over 1000 individuals must be screened for 10 years to avert one death from colorectal cancer). For patients being screened with Hemoccult, it is recommended that they avoid red meat, cantaloupe and melons, raw turnip, radishes, broccoli and cauliflower, vitamin C supplements and aspirin and non-steroidal anti-inflammatory drugs for 3 days before fecal samples are collected. However, a recent meta-analysis of 4 RCTs found no improvement in positivity rates or change in compliance rates with moderate dietary restrictions.[91]

2) Screening with sigmoidoscopy

There is evidence from case control studies (level II-2), to recommend that flexible sigmoidoscopy be included in the periodic health examination of patients over age 50 (**B recommendation**). There is insufficient evidence to make recommendations about whether only 1 or both of FOBT and sigmoidoscopy should be performed (**C recommendation**).

3) Screening with colonoscopy

There is insufficient evidence to include or exclude colonoscopy as an initial screen in the periodic health examination (**C recommendation**). Although colonoscopy is the best method for detecting adenomas and carcinomas, it may not be feasible to screen asymptomatic patients because of patient compliance and the expertise and equipment required and the potential costs. On the other hand, if colonoscopy were an effective screening strategy when performed at less frequent intervals, these issues might be of less concern.

Above Average Risk Individuals

1) Individuals at Risk for Familial Adenomatous Polyposis (FAP)

The Task Force recommends genetic testing of individuals at risk for FAP if the genetic mutation has been identified in the family and if genetic testing is available (**B recommendation**). If the individual carries the mutation, then he or she should be screened with flexible sigmoidoscopy beginning at puberty (**B recommendation**). Individuals from families where the gene mutation has been identified but are negative themselves, require screening similar to the average risk population. For at risk individuals where the mutation has not been identified in the family or where genetic testing is not available, screening with annual or biannual flexible sigmoidoscopy should be undertaken beginning at puberty. In all instances, genetic counseling should be performed prior to genetic testing.

2) Individuals at Risk for Hereditary Non-Polyposis Colon Cancer (HNPCC)

Patients in kindreds with the cancer family syndrome (HNPCC) have a high risk of colorectal cancer and a high incidence of right-sided colon cancer. Thus, colonoscopy rather than sigmoidoscopy is recommended for screening such patients. Based on Level III evidence, the

Task Force recommends screening with colonoscopy in individuals from HNPCC kindreds (**B recommendation**). Although higher levels of evidence are usually required to give a B recommendation, the Task Force realizes that it is unlikely that more rigorous studies could be performed in this cohort of patients given the high risk of cancer and relative infrequency of HNPCC. The age when screening should begin and the frequency at which colonoscopy should be performed are unclear.

3) Individuals with a Family History of Polyps or Colon Cancer

Patients who have only one or two first-degree relatives with colorectal cancer should be screened in the same way as average risk individuals. There is insufficient evidence to recommend colonoscopy for individuals who have a family history of colorectal polyps or cancer but do not fit the criteria for HNPCC (**C recommendation**). While there is evidence that there is an increased prevalence of neoplasms in these individuals, there is insufficient information to recommend more intense screening than that of individuals at average risk. Further delineation of the risk for individuals with multiple affected family members and family members with early age of diagnosis of colorectal cancer is necessary.

Because most screening options are multiphasic, it is preferable that there is adequate infrastructure to support the implementation, assure quality control and optimal and timely follow-up of screened individuals.

Recommendations of Others

There are a number of guidelines available regarding colorectal cancer screening. Despite there being Level 1 evidence on the benefit of screening average risk individuals with Hemoccult testing, the recommendations are variable due to concern over test sensitivity. Of the 3 RCTs where mortality data were reported, only Hardcastle et al recommended institution of a national screening program with FOBT.[25] Kronberg and colleagues considered it to be a feasible option until better screening methods become available.[23] Mandel and colleagues made no recommendations but did cite concerns about the cost of a screening program.[17] After performing the meta-analysis, Towler and colleagues concluded that screening with Hemoccult is likely to result in a net benefit but stated that there are still some important issues to be answered

[and] these questions require further evaluation.[28]

In Canada, the Ontario Expert Panel on Colorectal Screening has recommended (1999) that a program of colorectal cancer screening for average risk individuals between 50 and 75 years using a multiphase program including initial screening with FOBT should be adopted.[92] To date, no recommendations have been made for individuals at increased risk.

The US Preventive Services Task Force also recommended (1996) screening for individuals over age 50 years with either annual FOBT or sigmoidoscopy (interval unspecified) or both.[9] A number of organizations in the USA, including the American Cancer Society, American College of Gastroenterology, American Gastroenterological Association, American Society of Colon and Rectal Surgeons, American Society for Gastrointestinal Endoscopy, Crohn's and Colitis Foundation of America, Oncology Nursing Society and the Society of American Gastrointestinal Endoscopic Surgeons, recommended (1997) screening with FOBT annually, flexible sigmoidoscopy every 5 years, combined FOBT and flexible sigmoidoscopy, double contrast barium enema every 5-10 years or colonoscopy every 10 years for individuals age 50 years or older, with no other risk factors.[93] This group also made recommendations for those with additional risk factors. Thus, they recommended genetic counseling and possible genetic testing for those at risk for FAP. For those who are positive, flexible sigmoidoscopy beginning at puberty is recommended. For HNPCC kindred, colonoscopy annually beginning between the years of 20 and 30 years is recommended. Finally, these groups made similar recommendations for individuals with a family history of polyps/cancer as those for average risk but beginning at age 40 years rather than 50 years.

The Australian Health Technology Advisory Committee has recommended (1997) the establishment of pilot and feasibility studies to assess screening programs in the Australian context.[13] They recommend screening with FOBT in the average risk population in individuals over the age of 50 years but given the uncertainties, the program should commence with preliminary testing.

The Italian National Committee for Colorectal Cancer Prevention (1996) found no evidence to support mass screening, and recommended a centrally coordinated intervention program to evaluate effectiveness of screening.[94]

In New Zealand, The National Health Committee Working Party on Screening for Colorectal

Cancer advised against population-based screening for colorectal cancer with fecal occult blood tests, or any other modality given the modest potential benefit by the former and lack of evidence for other modalities.[95]

Research Agenda

A screening test more sensitive than the Hemoccult, one less costly and invasive than colonoscopy and yet capable of detecting neoplasia in the entire colon and rectum is needed. Development of such a test is a high research priority, given that survival rates can be improved by screening even with an insensitive technique, that colorectal cancer represents a significant burden of illness in Western societies and that early detection is known to improve survival rates. Virtual colonoscopy is a promising screening test although further evaluation is required.[96]

More data regarding both the effectiveness and acceptance of colonoscopic screening are needed. Data on the timing (i.e. age of onset) and frequency of colonoscopy are also needed since it is possible that if screening with colonoscopy were effective if performed infrequently or even once only (for asymptomatic individuals), it might be feasible, acceptable and cost effective.[97]

Efforts to identify high-risk groups (through genetic counseling, for example) and to develop targeted strategies for these groups may be appropriate. More information on the genetic basis of HNPCC is needed, as is a better means of identifying high risk families requiring screening. Research efforts should also aim to determine the true risk of colorectal cancer in subgroups with family history of neoplasia, especially those with multiple family members where cancer occurred at a young age.

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Table 1: Rates of Colorectal Cancer in Canada by Age

Age	***# Cases***	***Population (x1000)***	***Rate/1000***
20-29	40	4249	0.01
30-39	250	5122	0.05
40-49	940	4995	0.18
50-59	2400	3653	0.66
60-69	4200	2417	1.74
70-79	5400	1832	2.95
80-89	3700	960	3.85

Table 2: Results of trials of multiphase screening for colorectal cancer with the Hemoccult test as the first stage

Study	***Colon Cancer Control Study***[18-21]	***Kronborg et al***[22,23]	***Hardcastle et al***[25]	***Kewenter et al***[24]
Level of evidence	1	1	1	1
Age of subjects	50-80	45-74	50-74	60-64
No. of subjects in screen group	31,157	30,967	76,466	31,144
No. of subjects in control group	15,394	30,966	76,384	34,164
% of patients who were compliant	75-78%	67%	59%	66%
Sensitivity of test, %	49.5/38.3%	48%		81%
No. of cancers (rate/10,000)	Annual screen 323 (207) Biennial screen 323 (207) Control 356 (231)	Screen 893 (117) Control 856 (112)	Screen 371 (108) Control 379 (111)	Screen 481 (155) Control 483 (156)
Positive predictive value	2.2%	10.2 - 17.0%	9.9 - 11.9%	4.6 - 5.0%
Follow-up (years)	13	10	median 7.8	median 8.3
No. of CRC deaths at latest follow-up (rate/10,000)	Annual screen 82(53) Biennial screen 117(75) Control 121(79)	Screen 360 (47) Control 420 (55)	Screen 121 (35) Control 138 (40)	Screen 205 (66) Control 249 (80)
Relative risk (95% CI) of CRC death with screening	Annual screen 0.67 (0.51 to 0.89) Biennial screen 0.95 (0.74 to 1.23) Total 0.81 (0.65 to 1.02)	0.86 (0.74 to 0.99)	0.88 (0.69 to 1.12)	0.82 (0.68 to 0.99)

CRC=Colorectal cancer

Table 3: Summary Table of Recommendations: Screening strategies to detect colorectal cancer in asymptomatic patients

Manoeuvre	*Effectiveness*	*Level of Evidence <refs>*	*Recommendation*
Average Risk			
Multiphase screening with the Hemoccult test for average risk adults > age 50.	Relative risk of CRC* death with screening with Hemoccult testing is 0.84 (95% CI 0.77-0.93) overall and 0.77 (0.57-0.89) in those who are compliant NNT=1173 over 10 yr	Randomized controlled trials and meta-analysis (I) <16-28>	Good evidence to include screening with annual or biennial Hemoccult test in the periodic health examination (PHE) of patients > 50 (**A**)
Sigmoidoscopy for average risk adults > age 50.	Patients with rectal cancers were less likely to have had a sigmoidoscopy in the previous 10 yrs	Case-control studies <37-40> (II-2), case series <41-43> (III)	Fair evidence to include screening with flexible sigmoidoscopy in the PHE of patients > 50 (**B**)
Hemoccult/sigmoidoscopy in combination for average risk adults > age 50.	Some evidence that the addition of flexible sigmoidoscopy increases the detection rate of adenomas and colorectal cancer. Nor mortality data	RCT (I) <44-46>	Insufficient evidence to make recommendations about whether only 1 or both of FOBT and sigmoidoscopy should be performed (**C**).
Colonoscopy	Indirect evidence from RCT showing decreased colorectal cancer mortality	(II-3) <19,57>	Insufficient evidence to include or exclude colonoscopy from PHE (**C**)
Above Average Risk			
Flexible sigmoidoscopy for those with FAP**	The risk of death from colorectal cancer may be decreased	II-3 <62>	Fair evidence to recommend flexible sigmoidoscopy, beginning at puberty, for those with FAP (**B**)
Genetic testing for those with FAP**	The risk of death from colorectal cancer may be decreased	II-3 <63-67>	Fair evidence to recommend genetic testing for those with FAP (**B**)
Colonoscopy for those with HNPCC*.**	The risk of neoplasia may be decreased	II-3 <78-80>	Fair evidence to recommend colonoscopy for those with HNPCC (**B**)
Colonoscopy for those with a family history of polyps/CRC (first degree relatives)	There is evidence of increased prevalence of neoplasms in these individuals, but insufficient information to recommend more intense screening.	III <82-90>	Insufficient evidence to recommend screening above that for average risk individuals (**C**)****

CRC*=Colorectal Cancer, FAP**=Familial adenomatous polyposis, HNPCC***=Hereditary nonpolyposis colon cancer; **** = for individuals with a family history of polyps/CRC but where mutation not identified in the family, or genetic testing not available, sigmoidoscopy may be considered.

Appendix 1:
Canadian Task Force on Preventive Health Care
Levels of Evidence and Grades of Recommendations

Levels of evidence	
I	Evidence from at least one well-designed randomized controlled trial
II-1	Evidence from well-designed controlled trials without randomization
II-2	Evidence from well-designed cohort or case–control analytic studies, preferably from more than one centre or research group
II-3	Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here
III	Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees
Grades of recommendations	
A	Good evidence to support the recommendation that the condition or manoeuvre be specifically considered in a periodic health examination (PHE)
B	Fair evidence to support the recommendation that the condition or manoeuvre be specifically considered in a PHE
C	Insufficient evidence regarding inclusion or exclusion of the condition or manoeuvre in a PHE, but recommendations may be made on other grounds
D	Fair evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE
E	Good evidence to support the recommendation that the condition or manoeuvre be specifically excluded from a PHE