Screening for Colorectal Cancer in British Columbia.

Iain G.M.Cleator, Robert Parson, Josefina Baker, Andrew Rae, Gregory McGregor, Gregory Hislop, David Klaassen, Walter MacDonald, Brenda Morrison, Andrew Coldman.

1. INTRODUCTION

The purpose of this paper is to describe the evidence for colorectal screening using the two tier test for fecal occult blood and to conduct a cost benefit analysis for an organized screening program as compared to current practice in the province. A decision analysis model is used for detection of colorectal cancer.

A demonstration project is planned to evaluate a two tier fecal occult blood test (2T) for the screening of colorectal cancer when offered to asymptomatic men and women between the ages of 50 and 74 years in the BC general population. Specifically information will be obtained on the acceptance of the 2T test by a sample of the BC population; the positivity rate of each tier of the test when offered to the general population; the positive predictive value (PPV) of the test when offered to the general population; the proportion of subjects recommended for colonoscopy by the second tier; and the polypl and cancer detection rate in the general population. In addition the staging distribution of colorectal cancer detected by the 2T test and the costs associated with the implementation of an organised colorectal cancer-screening program will be assessed.

2. BACKGROUND

Colorectal cancer (CRC) is the fourth most common cancer in BC and the third leading cause of cancer death [Coldman, 1997 #1]. Although the incidence of the disease is declining in women it is increasing in men and there is currently no reason to believe the impact of this disease will change substantially in the near future [Coldman, 1997 #1].

Effective treatment for CRC is available for early localised disease but approximately 855 of cases present with advanced disease where treatment is expensive and of limited effectiveness. Early diagnosis represents a substantial opportunity to lessen the impact of this disease. For those diagnosed with localized disease the 5-year survival rate is 91%, as compared to 60% in those with regional disease [Sugarbaker, 1985 #41]. The majority of new cases and deaths from colorectal cancer occur between the ages of fifty and eighty years. In British Columbia in 1994, 1901 new cases and 664 deaths were reported in men and women between these ages [Coldman, 1997 #1]. It is clear that a screening program which is effective in reducing mortality from colorectal cancer would be of great benefit.

A proven technology exists, the use of the fecal occult blood screening (FOBT) to reduce the mortality from this disease in a cost effective manner [Rae, 1994 #42;
three randomised trials have demonstrated that mortality reductions of around 30% occur in persons using FOBT [Hardcastle, 1996 #7; Kronborg, 1996 #11; Mandel, 1993 #13]. Screening for colorectal cancer (CRC) by FOBT is based upon the propensity for both polyps and cancers to bleed intermittently.

In 1993, Mandel [Mandel, 1993 #13] showed in a large prospective randomized trial that a 33% reduction in mortality from colorectal cancer was achieved using annual Hemoccult®II® testing. The predicted reduction in mortality for those fully compliant was 44%. Interestingly the two yearly screened group had a reduction in mortality of 6%. The rate of positivity in this study using HO II and slide rehydration was 9.8%. This resulted in a high colonoscopy rate of 8% which was not considered to be acceptable for widespread screening in asymptomatic persons [Mandel, 1993 #13]. Kronborg et al [Kronborg, 1996 #11] demonstrated an 18% mortality reduction using Hemoccult® II without rehydration in a two yearly screening program. Their colonoscopy rate was 4.3%. The predicted reduction in mortality for those fully compliant was 30%. Hardcastle et al [Hardcastle, 1996 #7] have reported a mortality reduction of 15% using the non-rehydrated Hemoccult® test on a two yearly basis. The colonoscopy rate in this study was 4.0%. The predicted reduction in mortality for those fully compliant was 29%. These three studies strongly support the implementation of colorectal cancer screening. The three studies have important differences in periodicity and methodology and are summarised in table 1.

In 1994, Rae and Cleator [Rae, 1994 #42] reported results showing that by combining the Hemoccult®¨Sensa test¨, (which is very sensitive but not specific for blood of human origin), with the immunological based HemeSelect® test, (which is specific for human blood), the specificity would be increased, resulting in a lower false positive and colonoscopy rate. Hence, the combination of these two tests known as the two tiered test (2T) should more effectively screen the population for colorectal cancer at more acceptable rates of positivity and colonoscopy [Rae, 1994 #42].

In 1996, Alison et al published data supporting the concept of two-tier testing. using non-rehydrated slides [Allison, 1996 #2]. The rate of positivity for Hemoccult®SENSA® was 13.6%. The combination of Hemoccult®SENSA® and HemeSelect® yielded a positivity rate of 3% as opposed to the 9.8% previously reported by Mandel [Mandel, 1993 #13]. This should reduce by two-thirds the number of colonoscopies required in a screening population, as compared to using Mandel’s technique of Hemoccult® II with rehydrated slides. The positive predictive value for the combination test was higher than for Hemoccult®SENSA®, Hemoccult® II or HemeSelect® individually.

Hardcastle [Hardcastle, 1996 #7] and Kronborg [Kronborg, 1996 #11] reported positivity rates of only 2% and 1% respectively for the initial screens. Together with the fact that they screened two yearly, this resulted in a lower mortality reduction than that seen in Mandel [Mandel, 1993 #13]. Because of the higher initial positivity
of the Hemoccult® SENSA® test, the two-tier test should result in higher reduction in mortality.

It is anticipated that annual screening using the two-tiered test may improve the mortality reduction to approximately that of Mandel while reducing the cost and morbidity from colonoscopy by 66%.

3. THE DIFFERENCES BETWEEN THE FOBT TESTS

The majority of the stool occult blood tests are based on guaicum impregnated paper which responds to an oxidising agent by turning blue when an activator is added. The commonest slides in use are: Hemoccult®, Hemoccult®11, Hemoccult® SENSA®. These three are in order from least to most sensitive. If the stool is fresh, or rehydrated there is a higher positivity than when it is dry.

Agglutination tests on the other hand show the presence of the globulin moiety of human hemoglobin.

The difficulty with the guaicum based tests is that they react positively to meat and other oxidizing substances in food and result, particularly when rehydrated in a high percentage of false positives, even with dietary restrictions.

The addition of a second tier to testing with a guaicum based test using an agglutination test results in fewer false positives and a higher positive predictive value for CRC (Table 2).

The results of this project will then provide information necessary for the planning of a population wide CRC screening strategy, including a centralized system of data collection, analysis and quality control.

4. PURPOSE

We will conduct a demonstration project for colorectal cancer screening. A two-tier fecal occult blood test (FOBT) will be utilized and this project will determine the acceptance rate of test, the positivity rate of the test, the positive predictive value (PPV) of the test, the proportion of screenees requiring colonoscopy, and the rates of polyp and cancer detection. The data produced in this project will be utilized in an economic model estimated to provide the third party cost of an FOBT based CRC screening program in BC. In addition, the demonstration project will design and test a centralized system of data collection, analysis and quality control. Whenever possible data collection activities will be integrated with the existing organized screening programs run by the BCCA: Cervical Cytology and the Screening Mammography Program of BC. It is anticipated that this, demonstration project will provide a vanguard for the development of an economically viable mass screening program which will ultimately extend and save the lives of British Columbians.

5. TREATMENT AND OUTCOME
Colorectal cancer (CRC) is a major cause of mortality in British Columbia. There were 1901 new cases and 664 deaths in 1994[Coldman, 1997 #1]. It is the fourth most common type of cancer and cause of cancer-related death in both sexes, accounting for approximately 12% of all invasive cancer cases, excluding nonmelanoma skin cancer, and 8% of all cancer related deaths[Coldman, 1997 #1]. Colorectal cancer results in an estimated loss of 8,400 years of life to British Columbians [Coldman, 1997 #1].

Treatment of localized CRC is successful with a 5-year survival rate of 91%, as compared to 60% in those with regional disease and only 2% in those with metastatic disease[Sugarbaker, 1985 #41] The precise stage distribution of CRC in British Columbia is currently unknown but with an overall survival of 50% [Coldman, 1997 #1] it is clear that few present with early disease. Data from the US suggests that 21% present with localized disease [Henson, 1992 #8], whereas European data using the control series in randomized trials suggest 11% will present with localized disease[Kronborg, 1996 #11; Hardcastle, 1996 #7]. In BC the proportion is probably intermediate between the US and European rates.

The primary mode of treatment for CRC is surgery for stage I–III (local + regional increase) with adjuvant chemotherapy for stages II & III rectal (regional) cancer and stage I/IIL regional colon cancer. Palliative radiotherapy chemotherapy and surgery are used in the treatment of metastatic disease (advanced)[BCCA, 1995 #44].

6. ORIGINS OF COLORECTAL CANCER

CRC incidence and mortality shows substantial variations between different geographic regions, with lower rates in Asia and higher rates in Western Countries[Shottenfeld, 1996 #46]. Studies of Japanese migrants to Hawaii and California have shown that environmental and not genetic differences appear to be the main reason for these geographic differences[Shottenfeld, 1996 #46]. Evidence from case control studies has implicated that diets rich in fat and low in fibre confer higher risk of the disease[Shottenfeld, 1996 #46]. It is not clear whether the current decline in rates of CRC among women in British Columbia is attributable to changes in dietary patterns, but it does coincide with similar declines in other diseases thought to be related to the same dietary patterns (e.g. heart and stroke).

Although lifetime diet may be important, migrants adopt local rates of CRC more quickly than for other cancers (e.g. breast) and the lower rates among migrants to BC from low risk regions can be expected to disappear over 20 years if patterns in other jurisdictions are repeated here[Shottenfeld, 1996 #46].

It is generally accepted that most, if not all, cancers of the colon and rectum develop from adenomatous polyps[Winawer, 1997 #20; Muto, 1975 #21]. Polyps are mucosal masses which develop on the wall of colon and rectum and can be classified into three types: adenomatous polyps, hyperplastic polyps and others. The prevalence of
polyps varies with age and by about 50 years of age about 50% of persons can be found to have polyps upon colonoscopic inspection. About 50% of these are of the adenomatous type. The evidence that carcinomas arise from adenomatous polyps is indirect but persuasive[Winawer, 1997 #20; Muto, 1975 #21].

1. Early CRS are found adjacent to adenomas in over 20%.
2. CRC and adenomatous polyps have a similar anatomic distribution;
3. CRC is rarely found without other adenomatous polyps being present;
4. adenomatous polyps have earlier age at onset than CRC;
5. persons with adenomatous polyposis have greatly increased risk of CRC;
6. persons with known polyps are at increased risk of subsequent CRC; and
7. removal of large polyps reduces subsequent risk of CRC.

Large polyps (≥ 1 cm.) are believed to progress more rapidly to cancer than are smaller polyps although there is little direct evidence about the speed with which cancer develops[Eide, 1986 #4]. The National Polyp study of 3371 adenomas from 1867 patients also found the adenoma size and the extent of the villous component were the major independent polyp risk factors associated with high-grade dysplasia [O'Brien, 1990 #35]. Follow-up studies of persons who have polyps removed indicates that the sequence from normal epithelium, through adenomatous polyp, to CRC takes at least 3 years[Winawer, 1987 #51].

Excision of polyps during colonoscopic examination is believed to be very effective and has been found to dramatically reduce subsequent cancer incidence with rates of 15% of that expected seen in one study of 21,150 individuals[Gilbertsen, 1978 #6].

7. SCREENING FOR COLORECTAL CANCER

Colorectal cancer is almost unique among cancers in that there are several available methods which can be used to screen for it. These fall into 3 distinct classes: palpation, visualization of the colon and rectum, and examination of the stool for occult blood.

Palpation: Digital rectal examination is often used as part of a physical examination with a view to detecting colorectal and prostate cancer. Only a small proportion (<10%) of colorectal cancers occur within the range of a finger[Winawer, 1997 #20]. It is therefore unlikely that this methodology would be of any significant benefit as a stand alone screening technology and it has not undergone any scientific evaluation.

Visualization of the colon and rectum: Three methods exist which can be used to visualize the colon and rectum: barium enema, sigmoidoscopy, and colonoscopy.

Barium Enema: Double contrast barium enemas provide a means to visualize the whole of the colon and rectum and have been shown to be effective at visualizing significant polyps and CRC's[Hixson, 1991 #9]. The reported incidence of serious side–effects with this procedure is low although there are few published follow–up studies. These observations have resulted in a recent recommendation that it be
considered as a screening tool [Winawer, 1997 #20] although there are no published studies of its effectiveness. At this time there is insufficient evidence for its recommendation as a screening tool for CRC in British Columbia.

Sigmoidoscopy: Modern flexible sigmoidoscopes can extend to 60 cm and have the potential to visualize anatomic sites where about 50% of CRC arise. Over this distance the instrument is believed to be as sensitive as any for the detection of CRC or, large polyps. Because sigmoidoscopy does not examine the complete colon, it is recommended that all individuals found to have polyps or CRC by the sigmoidoscope be subsequently examined by the colonoscope to exclude the existence of distant lesions. There are no published randomized trials assessing the effectiveness of the sigmoidoscope although one, the PLCO trial, is currently underway in the US. This trial is not expected to report findings of mortality for 10 years.. Case–control studies comparing subjects who died from colorectal cancer with controls (either deaths from other causes or living subjects) have found consistent reduced risks of death from CRC associated with a history of sigmoidoscopy and this effect was restricted to cancers located within the range of the device. The reduction in mortality was between 60 and 79% for tumors within the range of the sigmoidoscope which would translate to at least a 30% reduction overall. This estimate may be a lower estimate as current recommendations would require full colonoscopic examination of those in which polyps were found by the sigmoidoscope. Reliable estimates on the participation of subjects in screening with sigmoidoscopy are not available but rates as low as 1% [Petravage, 1988 #15] and as high as 100% [Stephenson, 1993 #55] have been reported.

Colonoscopy: Colonoscopy is the gold standard for the detection of CRC and polyps but has never been evaluated as a screening tool. Its use as the first follow-up procedure in other screening studies suggests that it is an effective means to reduce the risk of death of CRC. It's main drawback as a screening tool comes from its acceptability to the general population and the high incidence of major side-effects associated with its use. Published estimates indicate that 1 in 1000 subjects will suffer perforation [Winawer, 1997 #20], 3 in 1000[Winawer, 1997 #20] will have major hemorrhage and 1–3 in 10,000 will die as a result of the procedure[Winawer, 1997 #20] Data on participation in a screening colonoscopy are sparse but it may be as low as 15% [Rex, 1993 #16].

Examination of the stool for occult blood Testing stools for occult blood has long been proposed as a screening methodology for the early detection of CRC and polyps because of their tendency to bleed more than normal tissue. Currently it is not known whether all CRC's bleed but it is clear that most only bleed intermittently. Studies have also shown that when blood is present in the stool it is usually heterogenously distributed. These two circumstances make it necessary to utilize more than a single specimen in arriving at a screening result. Most current studies utilize 6 specimens taken from three consecutive stools. The most widely used tests (Hemoccult® and Hemoccult® II) are sensitive to peroxidase activity in the presence of hemoglobin. It is not specific for human hemoglobin or hemoglobin alone but also
reacts positively to a number of different dietary substances. The preceding observations imply that fecal occult blood testing will have significant false negative and false positive rates associated with it. Therefore follow-up of positive tests with colonoscopy is universally recommended. Despite the potential drawbacks of FOBT the observation that FOBT detected CRC's had a better prognostic profile than others led to the instigation of 4 population based randomized trials of this technique. Three randomized trials have now reported results in total representing data on nearly 260,000 subjects and all show a significant reduction in deaths from CRC[Mandel, 1993 #13; Hardcastle, 1996 #7; Kronborg, 1996 #11]. The mortality reductions range from 15% (every two years Hemoccult® without hydration, follow-up 8 years) to 33% (annual Hemoccult® with hydration, follow-up 13 years). There are no recognized risks associated directly with the FOBT screen itself but significant ones result from follow-up in test positive subjects. The degree of risk is highly related to the test used and is discussed further in the next section. Two of the trials were effectiveness trials and provided direct data on subject participation: the rates were 60% and 67% utilized at least one screen[Kronborg, 1996 #11; Hardcastle, 1996 #7].

8. RATIONALE FOR THE DEMONSTRATION PROJECT

We are proposing that the province fund the demonstration project for an organized screening program for the early detection of CRC and polyps. The rationale is as follows: the proposed program will draw upon existing expertise and resources at the BCCA and St. Paul's Hospital to efficiently operate the program CRC is a major cause of mortality and morbidity in British Columbia and its treatment is a significant cost to health care system of the province screening with FOBT has been clearly demonstrated to reduce the mortality from CRC within 5 years of the initiation of screening with FOBT already occurs within a minority of the general population in an uncoordinated sub optimal fashion.

The program proposed should overcome the major concern associated with FOBT viz. its high rate of false positives.

The two tier system proposed will seem to provide significant health benefits at a lower cost than the current one tier screen the proposed program will provide a single framework for participation facilitating recruitment, continued participation and consistent follow-up.

The proposed program will provide evaluation information for decision making around the system.

9. RESULTS OF RANDOMIZED TRIALS

The Canadian Task Force on the Periodic Health Examination [Soloman 1994] does not recommend the use of FOBT for colorectal cancer screening whereas the equivalent US Task F`orce report does support its use.[US Preventive Task Force 1995] The Canadian Task Force does not recommend FOBT primarily because of the
concern around high incidence of follow-up colonoscopy required for screening positive subjects reported in the single randomized trial published at the time of their decision. Table 1 summarizes the characteristics and findings of the three randomized trials which have now published their results[Kronborg, 1996 #11; Hardcastle, 1996 #7; Mandel, 1993 #13].

Table 1 shows that although the three studies had considerable similarities there were also substantial differences. Firstly the trial of Mandel was an efficacy trial[Mandel, 1993 #13] and all subjects agreed to participate prior to randomization. The trials of Kronberg and Hardcastle were effectiveness trials and populations were randomized and those allocated to the screening arm were invited to attend for screening. As may be expected the trials of Kronberg[Kronborg, 1996 #11] and Hardcastle[Hardcastle, 1996 #7] had lower initial and total participation rates than that of Mandel. The test used was slightly different in each trial. Rehydrated Hemoccult® is more sensitive and less specific than a non-rehydrated test so that we expect different operating characteristics of the test from the Mandel study compared to the other two studies. Mandel's study included two screening arms (annual and every two years) whereas the other two trials screened every two years. Age ranges differed somewhat but all included men and women aged 50–74.

It can be seen from Table 1 that a consistent pattern of reduction in CRC mortality in favor of screening exists in all three studies. The observed mortality reductions are somewhat different. The single potential anomaly is the rather small reduction in the two yearly screened group in the Mandel trial. Since the trial compliance rates with screening are very different adjusting for this has the potential to aid comparison between the trials. This can be done (approximately) by using published compliance rates and dividing the observed mortality reduction by the observed compliance rate. The resultant figure provides an estimate of the mortality reduction from CRC in actual users of the screen and is done separately for those complying with first screen and for all screens (Table 1: predicted CRC mortality reduction in those screened 1 +; predicted CRC mortality reduction in those fully compliant). This adjustment brings the Kronberg[Kronborg, 1996 #11] and Hardcastle[Hardcastle, 1996 #7] results into very close agreement with one another. After–such adjustment the Mandel annual screen results[Mandel, 1993 #13] appear better which probably results from the higher detection rates of cancer resulting from the greater frequency of screening, longer duration of screening and the use of a more sensitive test (i.e. rehydration). The smaller mortality reduction observed in the Mandel every two years screening arm[Mandel, 1993 #13] than in the other two trials[Hardcastle, 1996 #7; Kronborg, 1996 #11] appears to be the result of a chance maldistribution in incident and prevalent cancers at randomization. The arm with every two years screening in the Mandel trial[Mandel, 1993 #13] had higher cumulative incidence rates of CRC than the control arm in the first 7 years of the trial. It should also be noted that a mortality reduction of 25%, a value exceeding that seen in the two other trials, is not rejected for the every two years arm of the Mandel trial.
The evidence to date may be summarized as follows: FOBT screening reduces the mortality from colorectal cancer and annual FOBT appears to reduce it more than two yearly FOBT.

The three randomized trials [Mandel, 1993 #13; Kronborg, 1996 #11; Hardcastle, 1996 #7] do not provide a consistent picture of the effect of the removal of polyps, detected as a result of FOBT screening, on subsequent cancer incidence. This is not particularly surprising since the lead time between development of polyps and CRC is long (10 years) as shown by follow-up studies, and the sensitivity of the screen for polyps is significantly less than that for CRC. Coupled with harvesting of prevalent cancers by the screen it can be expected to be several years before any reduction in CRC incidence is seen by the use of FOBT. It seems reasonable to conclude that the ratio of incidence rates in screened subjects divided by control subjects of 1.03 [Hardcastle, 1996 #7], 0.99 [Kronborg, 1996 #11] and Mandel (0.90)[Mandel, 1993 #13] reflect the differing lengths of follow-up of 7.8, 10 and 13 years respectively. This is further supported by the results of the trial of Mandel[Mandel, 1993 #13] where incidence in the screened arms only began to fall behind that in the controls after 8 years. We conclude that FOBT screening will likely reduce the future incidence of CRC but that this will not occur until 10 years after the initiation of a program and the total magnitude of the reduction is currently unknown.

10. PROPOSED SCREENING TEST

Although it is clear that FOBT screening reduces the impact of CRC it is not as clear how this technique may be optimally used. The following questions need to be addressed:

1. What test should be used?
2. Who should be screened?
3. How often should they be screened?
4. How long should they be screened?

The demonstration project we propose will utilize the following answers to these questions.

What test should be used: The randomized trials previously referred to [Mandel, 1993 #13; Kronborg, 1996 #11; Hardcastle, 1996 #7] utilized tests which were available at their initiation (at least 10 years ago). New tests have since become available which offer new opportunities. In particular there are now two further tests: Hemoccult®SENSA® (a more sensitive version of Hemoccult® and HemeSelect® (an immunochemical test which is specific to human hemoglobin). Hemoccult®SENSA® has sensitivity and specificity more like that of hydrated Hemoccult®, so that although the test is quite sensitive it has a high false positive rate. HemeSelect® is a test designed to have high sensitivity and, because it is only sensitive to human blood, higher specificity than for guaiac based FOBTs. However, the higher processing cost associated with HemeSelect® reduces its attractiveness as a first line
screen. In 1994, Rae and Cleator [Rae, 1994 #42] reported results showing that, by testing with HemeSelect® in those reactive by the Hemoccult®SENSA® test, the specificity of the resulting combined test would be increased, with a lower colonoscopy rate than would be obtained from the use of Hemoccult®SENSA® test alone. Hence, the combination of these two tests should more effectively screen the population for colorectal cancer at more acceptable rates of positivity and colonoscopy. An additional advantage is that the first test can be done in a doctor's office or blood laboratory, and only the second test requires a special facility.

In 1996, Allison et al.[Allison, 1996 #2] published data supporting the concept of two-tier testing using Hemoccult®SENSA® and HemeSelect® for non-rehydrated slides (see Table 2) [Allison, 1996 #2]. This paper is particularly useful as it presents results of various tests in a single population thus allowing comparisons of the characteristics of tests. The rate of positivity for Hemoccult®SENSA® was 13.6%, for Hemoccult®II (non-rehydrated) 2.5% HemeSelect® 5.9% and for the combination of Hemoccult®SENSA® and HemeSelect® (both positive) 3%. In Mandel's study utilizing rehydrated Hemoccult® the positivity rate was 9.8% [Mandel, 1993 #13]. Due to the costs, both human and financial, of the colonoscopic follow-up in test positives it is necessary to minimize the number referred for investigation. The results presented in Table 2 argue against the use of either Hemoccult®SENSA® or HemeSelect® as single tier screening tests.

The results of Allison[Allison, 1996 #2] summarized in Table 2 did not include the uniform application of a gold standard for diagnosing CRC and polyps. The sensitivities quoted are based on the assumption that the disease indicated will become apparent within two years if missed by the screen. While this is mostly true for cancer, it is not true for polyps. In the section on “assumptions” we will discuss this aspect in detail. It thus seems likely that the test results quoted exaggerate the sensitivities but nevertheless the ratios between the indicated sensitivities probably provide valid estimates of the relative sensitivity of the tests or combinations. The same bias influences the specificity except that the magnitude of any effect will be much less. We therefore anticipate that it is possible, by using a combination of the HemeSelect® and Hemoccult®SENSA® tests to have a screen which will have 75% (65.6/37.1 – see Table 1) greater sensitivity for CRC (65% for Polyps or CRC) compared to non-rehydrated Hemoccult® 1103) with virtually the same specificity and an increased PPV.

It is not clear what the positivity rate of such a two tier test would be in the BC population. Hardcastle used (Hemoccult® II) with a more restrictive definition of positivity and found 1.5% testing positive[Hardcastle, 1996 #7] contrasting with the 3% in Allison's paper[Allison, 1996 #2] raising the possibility that the Allison study had a population with a higher positivity rate of all tests. We know that CRC and polyp prevalence varies with age so that the demographic profile of the study population will determine the positivity rates of the screen. Before embarking on a full scale program there is a need to determine these rates in BC in a representative sample of the population and this is one of the objectives of the demonstration project. We propose to utilize a two tier screen of Hemoccult®SENSA® and HemeSelect® as previously described. We believe a screen based on this two tier test
has the potential to deliver greater reductions in mortality than seen in the two trials which used unrehydrated Hemoccult® [Hardcastle, 1996 #7; Kronborg, 1996 #11]

Who should be screened: The three trials all included both men and women aged between 50 and 74. The trial of Kronborg[Kronborg, 1996 #11] also included persons age 45–49 and the trial of Mandel included persons aged 75–80 [Mandel, 1993 #13]. Persons with signs or symptoms of colorectal cancer are managed in accordance with local recommendations and are not included for screening. The Kronborg and Hardcastle trials both report a greater proportionate mortality reduction among persons younger at screening than those older. However, the positive predictive value increases with age so that, coupled with the increasing incidence of CRC and polyps with age, younger persons receive more investigations compared to their mortality gain than older persons. We would propose to make the screen available to all persons between the age of 50 and 74 in this demonstration project.

How often should they be screened: At present data on only two screening intervals are available: annual and every two years. The study of Mandel[Mandel, 1993 #13] included both frequencies and found the protective effect of annual screening significantly higher than that of biannual screening. The protective effect of two yearly screening in the studies of Kronborg and of Hardcastle[Kronborg, 1996 #11; Hardcastle, 1996 #7] was less than that of annual screening in the study of Mandel[Mandel, 1993 #13] even after adjustment for differences in the study compliance rates. The maximum estimate of the mortality gain of annual compared to every two years screening would be 47% (44/30–1) x 100 (Table 2) so that the gain from annual screening could be considerable, however other study differences could explain this. We intend to use annual screening in the demonstration project but will undertake modeling work, using data collected, to further explore this question. How long should they be screened: None of the studies are mature enough to assess the effect of continuing screening for a fixed length of time. Within the duration of the studies published cancers continue to be detected at the latest screens and thus we would anticipate that there is still benefit gained from persistent screening. Although this is not directly relevant to the conduct of this demonstration project. We would anticipate that individuals would continue to be screened until they reach the upper age limit for participation.

11. CURRENT ACTIVITY IN BRITISH COLUMBIA

Colorectal cancer detection is presently being done in an unorganized fashion. In 1995/96, 241,480 fecal occult blood tests were performed and approximately 20,569 colonoscopies were carried out costing $1,005,623 and $4,522,017 respectively[Plan, 1996 #43] It is unknown how much of this activity was for screening purposes.

Management of colorectal cancer is expensive. In 1994 in BC, there were 1901 new cases and 664 deaths from CRC. For the same time period, there were 33184 total
days of separation with the diagnosis –malignant neoplasm of colon” or –malignant
neoplasm of rectum rectosigmoid junction and anus.– [Canada, 1995 #45]. The
current cost of an acute care hospital bed at Vancouver Hospital is $970 per day.
This results in a price of $32,187,510 per year, for hospital care alone. This figure
does not include costs of consultation, colonoscopy, chemotherapy, radiotherapy, or
community based out-patient care.
The average length of stay for primary surgical resection is 11 days[Tartter, 1996
#18]. The minimum cost of surgery is therefore $10,670.00 ($970. x 11). Added to
this baseline cost should be costs of colonoscopy, anesthetic and surgical fees,
radiologic investigative fees including those for a CT Scan, barium enema, Chest X-
ray and Ultrasound. The overall cost is therefore at least $1000 more, giving a total
of $11,670.

The cost of terminal care for cancer patients is not well established and is difficult to
derive. Recurrence rates exceed 50%. Terminal care costs are again largely related to
hospital days. Looking at the figures for 1994, there were approximately 1,900 new
cases and approximately 600 deaths. Not every case would have required surgery,
but the majority would. Using a mean of 11 days per case, the maximum number of
days which could be related to primary surgical treatment for colorectal cancer would
be 20,900. Knowing there were approximately 33,000 days, one may assume there
were a minimum of 12,000 days devoted to palliative care for the 600 people who
died of disease. This means there were 20 days in hospital per cancer death with an
expenditure of approximately $20,000. Additional costs would be related to
chemotherapy, radiotherapy, diagnostic imaging, surgery and additional consultant
fees.
Other data suggests a much longer hospital stay of about 40 days[Geddes, 1996 #5].
The US Office of Technology states that the cost of caring for advanced cancer is
$45,000 US [Preventive Health Services under Medicare 1990] or $63,000 Canadian.
It was estimated that the cost of initial surgery was approximately $12,000. Hence,
costs of care of recurrent disease would be the difference between these two, or
$51,000.

Another study of economics related to colon cancer care suggests the cost of
recurrence is $10,000 US, and the cost of palliative terminal care is $24,148 US,
which is equivalent to a total cost of $47,800 Canadian.

It is therefore reasonable to estimate the cost of caring for patients with recurrent
colon cancer at $40,000. This figure is used in our subsequent cost/benefit analysis.

It is anticipated that there will be increasing pressure to initiate population–based
screening for colorectal cancer. It is anticipated that there will be increasing pressure
to initiate population-based screening for colorectal cancer. The United States
government is now developing plans for Medicaid to pay for colon cancer screening
utilizing fecal occult blood testing and/or sigmoidoscopy(15) [President's Report
1996] Hence, it is imperative that the costs and implication for two–tier screening
are known for the British Columbia population.
In conjunction with Smith Kline Diagnostics we have been developing a costing model of the two tier colorectal screening program for British Columbia. This is based on models developed by [Lieberman, 1995 #12; Wagner, 1996 #50] which have already concluded, using US costing data, that a program based on single tier FOBT screening is as cost–effective (cost per added year of life) as any other method for screening for colorectal cancer and at a rate comparable with that for some other medical interventions (e.g. mammography screening for breast cancer, renal dialysis). It is our belief that the two tier test proposed in this application will have a lower cost per year of life saved due to the superior characteristics of the test. However, in order to establish costs we need to determine BC specific estimates of participation rates, positivity rates and follow-up procedures and determination of these are objectives of this demonstration project.

As part of our costing analysis we will also determine the estimated cost of other screening scenarios using different age ranges for subject eligibility, different tests different frequencies, etc.

12. THE MODEL

The basis of the program for the pharmacoeconomic modeling is a paper by David Lieberman.(16) This analysis was prepared by Robert Parson of Hypertech Corporation in cooperation with Josie Baker of Smith Kline Diagnostics Inc. The screening logic flow for the cost effectiveness model is laid out in figures 1 to 7.

The model itself is an actuarial one, and therefore predicts the results of groups of sample size 100,000 as they progress through time – rather like looking at the risks of those entering an insurance agreement.

13. THE ASSUMPTIONS

Assumptions were taken from peer reviewed studies and referenced.(Table 1)The check on the system is an internal logic control – for illustration if the adenoma to cancer conversion rates and the treatment rate for cancers are correct, the cancer incidence rates should be at a rate that matches known data. In order to do this we incorporated the age specific data of Eide with respect to the increase in percentage adenomas with age(17) and the data from S.Winawer on cancer rates at different ages.(18)

14. THE MODEL PREDICTIONS

After using the model to test the cost/benefit of screening in the population, we used it again to answer the following questions:
1 is annual or biennial testing optimal?
2 what age span is optimal for the population?
3 what are the benefits of implementing a formal screening
program as compared to allowing the growth of current screening at an increment of 1% per year?
4 What effect would changing the terminal costs have on the model?

THE RESULTS

Table 2 through 8 shows the benefit of a screening program as compared to current practice. There is a reduction in deaths from CRC of 50% of the 1064 cumulative deaths per 100,000 projected for current practice over ten years. This is accompanied by a 76% reduction in the ten year cumulative prevalent CRC of 1091 per 100,000 in current practice. There is in fact a reduction of deaths as early as two to three years after the program starts.
All costs have been adjusted for 2% annual inflation, and 6% per annum discount (NPV). There is a saving of cost of $17 million over the projections for current practice per 100,000 over ten years ($62 millions) using the two-tier screening program.

There is also a much larger number of adenomas detected and treated in the organosed two-tier screening program: 10496 compared to the 5,287 projected on current practice over ten years per 100,000 persons.

Table 9 shows the effect of annual versus biennial testing on the screening program. Annual testing results in more colonoscopies (19,513 per 100,000 over ten years versus 9,288), but the costs are lower ($45 millions over ten years per 100,000) because of the lives saved and consequent reduction in terminal care costs.

Table 10 shows the slight effect of a 1% increment in testing as currently employed. There is a cost benefit (of $50,000 over ten years per 100,000) and an increased prevention of CRC (222 versus 185 over ten years per 100,000), and increased detection of CRC (318 versus 264 over ten years per 1000,000) and adenoma (6,353 versus 5,288 over ten years per 100,000)

Table 11 shows the cost/benefit at different ages. The younger ages have less cancer, and less terminal care costs which results in a low figure for screening younger people.

Table 12 shows that the two tier test shows greater cost advantages as the terminal care costs increase (the advantage increases from $11.5 to $34 millions versus the current practice over ten years per 100,000 as terminal care costs rise from $20,000 to $80,000 per patient).

Discussion. The model predicts a dramatic fall in the incidence and prevalence of colorectal cancer as a result of screening with the two tier test. This is the result of removal of the larger premalignant adenomas as well as the earlier staged cancers. The surprising feature is the cost effectiveness of the program with a greater
expense in the first three years of the ten year and diminished costs in the other years resulting in a saving of $32 million per 100,000 tested. The altered pattern of costs (figure 8) shows that the increased cost of screening arises primarily from the reduction in terminal care costs – surely a desirable outcome. There is an increase in the numbers of colonoscopies in the first three years, which then declines to slightly below current levels, and a similar pattern is true for surgery. There are studies which show that dying of colorectal cancer is much more expensive than other ways of dying.

Annual versus biannual testing shows a clear advantage in terms of deaths prevented, and cost. It is always difficult to change a one year program to a two year from the public perspective. We, however, recommend annual testing.

The cost benefit at different ages poses a problem. Usually the costs of screening in a lower risk population results in great expense for little benefit. Additionally the pathophysiology of colorectal cancer would indicate an age span of 50 to 75 as the likely optimal group. Others have selected the 45 to 70 or 75 age groups for their recommendations. Because of the low cancer rate in the 40 to 50 age group in our model and because so few require terminal care, the model shows that screening for CRC in this age group is cheap compared to the over eighties where the incidence of cancer is very high and the numbers of cancers and adenomas and terminal care costs are also high. The low cost of the two tier test and colonoscopy in our setting would seem to justify their inclusion particularly as this is a group with a longer expected life span than the older people and at a very productive time in their lives. We recommend inclusion of the 40 to 50 year group in the feasibility study.

The results of allowing increase in current screening at a rate of 1% increment per year are very disappointing in terms of cost or reduction in mortality from CRC compared to two–tier screening albeit an improvement on current practice.

15. PROJECT TEAM

A multi–disciplinary team has developed this proposal and will oversee its implementation and evaluation. The demonstration project will be conducted by persons from the BC Cancer Agency, St. Paul's Hospital and the University of British Columbia. A central laboratory and data bank of test results will be established under the direction of Dr. Iain Cleator at St. Paul's Hospital where knowledge and expertise regarding the two–tier test are already in place. The BCCA will develop and maintain a centralized database of all subjects, their test results and follow–up procedures using information downloaded from St. Paul's Hospital and direct contact with physicians' offices. The BCCA will provide overall coordination of the project and undertake the evaluation of the results. The BCCA will provide the necessary expertise on the implementation, data collection and evaluation of a population-based screening program. Overall responsibility rests with the BCCA. A schematic design of the infrastructure is enclosed in Appendix I.
16. PROJECT DESIGN

10.1 Project Objectives
A one year demonstration project is proposed to evaluate a two-tier fecal occult blood test for the screening of colorectal cancer when offered to asymptomatic men and women between the ages of 50 and 74 years in the BC general population. Specifically, information will be obtained on the following: the acceptance of the two-tier test by a sample of the BC population; the positivity rate of each tier of the test when offered to the general population; the positive predictive value of the test when offered to the general population; the proportion of subjects recommended for colonoscopy by the second tier; and the polyp and cancer detection rate in the general population.
In addition, information will be obtained on the staging distribution of colorectal cancer detected by the two-tier test and on the costs associated with the implementation of an organized colorectal screening program.

10.2 Project Design
The demonstration project will include designing and testing the feasibility of an organized colorectal cancer screening program using a two-tier fecal occult blood test when offered in a population-based setting. This will include a centralized system for laboratory analysis and data collection, and follow-up of investigations performed on patients with abnormal screening results.

Specifically, two-tier testing will be offered to eligible patients by a sample of general practitioners in the Greater Vancouver Regional District. The fecal sample will be collected on the specimen card by the patient and sent to their family physician or a private laboratory for the first tier testing. All specimen cards will then be sent to a central laboratory facility at St. Paul’s Hospital where the second tier will be tested for those with a positive first tier test result. A results letter will be sent to the general practitioner and the patient indicating the result of the two-tier screen.
Central office staff at the BC Cancer Agency will obtain information on the diagnostic workup and final diagnostic outcome for all patients with a positive second tier test result.
The schema for patient screening is shown in Appendix II.

10.3 Project population
The Vancouver Regional Health Board district will serve as the population from which the study sample will be drawn. 25,000 men and women between the ages of 50 and 74 years who are asymptomatic for colorectal cancer will be invited to participate from among the practices of general practitioners within this catchment area. Participation will initially be sought from general practitioners who will then invite their patients into the study. Assuming that an average of 150 eligible subjects are seen per practice [Hoogewerf 1987] 170 general practitioners will be randomly sampled from among practitioners in the Vancouver Regional Health Board and invited to participate. Those declining to participate will be replaced from the same pool of physicians.
A total study population of 25,000 will provide an anticipated accuracy of ~ .2% (with 95% confidence) for the overall test positivity rate. The recruited sample will be adjusted to have approximately 5,000 subjects in each age quintile (30–34, 35–59, 60–64, 65–9, 70–74) to permit the estimation of age specific acceptance rates, (estimated accuracy ~ 1.5% with 95% confidence) and positive predictive values (estimated accuracy ~ 7.5% with 95% confidence).

10.4 Data Collection and Analysis
Cooperation will initially be requested from general practitioners and the private and hospital laboratory facilities who provide fecal occult blood testing as they may need to increase their capacity for such testing. Participating general practitioners will provide information about the number of eligible patients within their practice. Demographic and patient identification information will be recorded by the patient on the specimen card designed so that the first tier (Hemoccult®SENSA® and the second tier (HemeSelect®) tests may be utilized on the same stool specimen.

The first tier testing will follow current practice patterns in BC and will be done by general practitioners and private and hospital laboratories. All specimen cards will then be sent to the central laboratory at St. Paul's Hospital where the second tier testing will be done on positive first tier specimen cards. The results of all screening tests will be obtained from this central laboratory by office staff at the BC Cancer Agency who will also obtain information on the diagnostic work-up and final diagnostic outcome for all patients with a positive second tier screen result. This will include information of the type of procedure received, the date of the procedure, the outcome, and for colorectal cancer patients, the stage of disease. This information will be obtained from the physicians responsible for the follow-up care of these patients.

In addition, all study participants regardless of their screening test result will be linked by name and date of birth with the provincial Cancer Registry one year after their screening test in order to identify subsequent cases of colorectal cancer.

Descriptive statistics will then be used to describe the acceptance rate, positivity rates for each tier of the test, positive predictive value of the test, colonoscopy rate as determined by the second tier, polyp and cancer detection rates, and staging distribution. This will be done by age and gender.
Costing information to implement the project will be collected throughout and costs will be subdivided into unit cost per cancer detected for screening test delivery and central office costs (for follow-up, data collection and analysis).

17. PROJECT BUDGET

The cost estimates for the one year demonstration project are projected in the accompanying Appendix 111. The estimates are based upon Allison's data which were applied to the proposed study sample. The central office costs for obtaining
follow-up data were calculated based upon the experience of the Screening Mammography Program of British Columbia.

The duties and responsibilities of the personnel, and other costs, are summarized below.

Medical Director. The medical director will provide medical direction throughout the project and oversight to the central laboratory at St. Paul's Hospital. This position will include communication with colonoscopists in the catchment area to ensure that appropriate follow-up is undertaken for patients with positive second tier testing results.

Project Manager (1 FTE). Under the direction of the research team, the project manager will be responsible for the supervision of staff at the laboratory centre of St. Paul's Hospital and the coordinating centre at BCCA. This will include subject recruitment, specimen card collection, ensuring second tier testing where appropriate, and collection of follow-up data.

Clerical support (coordinating centre) (0.75 FTE). Under the supervision of the project manager, to collect and enter into the computer data base study participant information from the specimen cards (n=25,000) and diagnostic workup information for participants with a positive second tier testing result (n=750).

Laboratory processing fees for the screening tests. The processing fee for the first tier testing of all 25,000 specimen cards is set at $2.00 each, totaling $50,000. The processing fee for the second tier testing (estimated at 13.6% of the total, or 3,400 specimen cards) is $10.00 each, totaling $34,000.

Programmer (0.33 FTE). Under the supervision of the investigative team and the consultant statistician, to conduct the evaluation and outcome analysis as described in the proposal. This will include computer linkage of the project database with the Provincial Cancer Registry in order to identify study participants with a subsequent diagnosis of colorectal cancer, and descriptive statistics for the study outcomes.

Consultants. Consulting fees are included for a statistician to provide work direction on outcome analysis for the programmer, and for an accountant to conduct a costing analysis for the project initiative.

Postal costs. Postage costs include informing the general practitioner and/or the patient (25,000 X 2 X $0.45) of the results, at $22,500, and the collection of follow-up information and other correspondence, at $15,750.

Equipment. A Sunserver, software and programming is required for data entry and analysis, totaling $56,000.
Office expenses. Office supplies, phone, fax and related expenses are estimated at $1,250.

Potential MSP costs for the initial office visit and diagnostic evaluation resulting from demonstration project. The professional fee of $4.16 (MSP billing # 9243) is included for the 25,000 subjects to be enrolled in this project. Also, an estimated 750 subjects are estimated to require colonoscopy (3% of all screened subjects) as a result of a positive second tier test result at a fee of $300 each, totaling $225,000. Of these, complications due to perforation are estimated at 1 due to surgical bleed (at a fee of $6,000) and 1 due to a nonsurgical bleed (at a fee of $2,000).

GLOSSARY
Fecal occult blood: blood in stool which can not be seen or detected by sight
Two–Tier test which involves two steps. In this case the first step is to collect as many potential subjects as possible and the second step is to wean out those who are most likely to have a polyp or cancer.
Polyp: small growth in the colon or rectum which may cause bleeding and may eventually become malignant if not removed.
Hemoccult®: a guaic based test which detects oxxidising agegents in stool (like human or animal blood, or meat)
Hemoccult® II: a more sensitive but similar test to Hemoccult®.
Hemoccult®SENSA® test which is similar to but more sensitive than the Hemoccult® II test
HemeSelect®: an immunochemical test which is very specific for human hemoglobin. This test is much more specific than Hemoccult® 11 or Hemoccult® SENSA®
Hydration: when stool samples are collected, a small smear of stool is placed on a semipermeable piece of paper. The specimen is sent to the lab in a dry state, and hydration refers to the act of placing a drop of water on the stool before the test chemical is added. This results in less false negatives than when the specimen is days old and has dried out.
Guaiac: a natural compound which is very sensitive to oxisising agents. It reacts to animal or human hemoglobin as well as myoglobin in muscle (meat).

THE MODEL
CONCLUSIONS
The colorectal cancer screening model described shows:
1 Massive reduction in the prevalence of CRC over ten years from 400/100000 to 86/100000
2 An overall reduction in cancer deaths over the ten years of 32.7%
3 A saving of $17 million per 100.000 screened over current costs. 3 A mortality and cost advantage of annual versus biannual testing.
4 A suggested age range of 40 to 75.
5 We recommend a feasibility study of this model.

REFERENCES
2) BC Cancer Agency Annual Report 1994/95; 29
4) Canadian Guide to periodic Health Exam
9) Medical Services Plan Data (present communication to Dr. Klaassen)
12) Barchielli A. Colorectal Lung and Breast Cancer Care During the 3 Years Following the Diagnosis – A Population Based Study. Tumori 1996; 82(3); 210–214

GLOSSARY

Fecal occult blood: blood in stool which can not be seen or detected by sight
Two-tier: Test which involves two steps. In this case the first step is to collect as many potential subjects as possible and the second step is to wean out those who are most likely to have a polyp or cancer.

Polyp: Small growth in the colon or rectum which may cause bleeding and may eventually become malignant if not removed.

Hemoccult® II: a guaiac based test for detecting traces of blood in stool samples

HO Sensa: A test which is similar to but more sensitive than the Hemoccult® 1I test

HemeSelect®®: an immunochemical test which is very specific for human hemoglobin. This test is much more specific than Hemoccult® II or Hemoccult® Sensa

Hydration: When stool samples are collected, a small smear of stool is placed on a semipermeable piece of paper. The specimen is sent to the lab in a dry state, and hydration refers to the act of placing a drop of water on the stool before the test chemical is added.

Guaiac: a natural compound which is very sensitive to the chemical make up of hemoglobin. It reacts to animal or human hemoglobin indiscriminately.