SUMMARY

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer death in industrialised countries. Québec does not escape this general trend. As part of its mandate, the Comité consultatif sur le cancer, which was set up by the Ministère de la Santé et des Services sociaux du Québec to examine the entire issue of cancer and ways to combat it, has naturally devoted special attention to colorectal cancer, given its extent. In its 1997 report, the committee could not, at that time, recommend the development of systematic screening activities, one of the reasons being the lack of convincing data. However, it did recommend that the *Conseil d'évaluation des technologies de la santé du Québec* undertake an in-depth examination of the efficacy and efficiency of CRC screening in terms of mortality reduction.

Since the *Conseil* had already begun work on the comparative efficacy of different techniques for diagnosing colorectal lesions and decided to include within the scope of this problem their impact on the prevention of mortality, it was quickly able to accommodate the Comité consultatif sur le cancer's request. This report examines the evidence regarding the efficacy of different strategies for identifying and treating both precancerous lesions and malignant lesions that are still in their early stages. This examination is based on an in-depth, critical literature review but first provides basic information on the epidemiology and carcinogenesis of colorectal cancer. Special attention is also given to the different models for determining both the efficacy and cost-effectiveness of various screening strategies. Lastly, an overview of colorectal cancer in Québec and different scenarios are followed by conclusions and recommendations.

This report focuses specifically on colorectal cancer in average-risk, asymptomatic people, since it is assumed that people at higher risk (familial and genetic factors) are already being taken care of by other mechanisms. However, as part of the overall work on the transfer of human genetics research findings to clinical practice, the *Conseil* has already decided to prepare a report on the usefulness of instituting screening based on genetic susceptibility to colorectal cancer.

Colorectal cancer

The number of new cases of colorectal cancer in Québec in 1998 is estimated at 4,200, with 2,200 cases in men and 2,000 in women. Colorectal cancer ranks third in terms of the incidence of cancer in men after lung and prostate cancer and in women after breast and lung cancer. The comparative incidence rate (per 100,000 population) of colorectal cancer is higher in men (62) than in women (41). The incidence of colon cancer is higher than that of rectal cancer by about 1.6-fold in men and about 2.3-fold in women.

The number of deaths from colorectal cancer in Québec in 1998 is estimated at 1,990, with 1,000 in men and 990 in women. It ranks second in terms of mortality in men, together with prostate cancer, after lung cancer, and third in women after breast and lung cancer. The comparative mortality rate (per 100,000 population) is higher in men (30) than in women (19).

With a ratio of 0.47 for the number of deaths to the number of new cases, the prognosis in

colorectal cancer is fair, differing both from the favourable prognosis in prostate (ratio, 0.25) and breast (ratio, 0.34) cancer and from the poor prognosis in lung cancer (ratio, 0.81).

In terms of the potential years of life lost due to cancer, colorectal cancer ranks third, with close to 10%. It comes after lung and breast cancer and before prostate cancer, which ranks sixth.

For all cases of colorectal cancer, relative survival decreases from about 72% after one year to about 52% at five years. Survival is strongly associated with the stage of the malignant lesions at the time of treatment. In the early stages, when lesions are well circumscribed, survival is approximately 90% at five years. It is less than 5% in advanced cases, when metastases have spread.

People with colorectal cancer very often remain asymptomatic during the early stages of the disease. Screening is therefore targeted at individuals whose cancers are still in their early stages, when survival is the highest.

There are many CRC risk factors. They are individual, familial and genetic factors. Inflammatory bowel disease, familial adenomatous polyposis, hereditary non-polyposis colorectal cancer syndrome and family history are high risk factors and reportedly account for 10 to 30% of new cases each year.

Between 70 and 90% of colorectal cancers occur in asymptomatic individuals aged 50 and older in whom there is no identifiable risk other than age. They are considered to be at average risk and are the target of the screening discussed in this report. Genetic screening will be dealt with in a subsequent report.

The annual cancer-related hospitalisation costs in Québec in 1994-1995 can serve as point of comparison for expenses attributable to the main cancers. Colorectal cancer ranked second, with $45.8 million, after lung cancer, $59.8 million, and was followed by breast cancer, with $27.1 million, lymphomas, $25.3 million, and prostate cancer, with $17.8 million.

In another connection, comparing the major cancers after lung cancer in terms of incidence and mortality reveals that research grants obtained in Québec between 1994 and 1998 for breast cancer amounted to $15.8 million, prostate cancer $6.8 million and intestinal cancer $4.6 million, for a total of $27.2 million (Medical Research Council of Canada and Fonds de la recherche en santé du Québec). If, proportionately, for each new case of cancer in 1998, $1.00 was granted for intestinal cancer research, then $1.70 was granted for prostate cancer research and $3.38 for breast cancer research.

Efficacy of treatments

Surgery is the main treatment with curative intent for colorectal cancer. Tumour excision is the only intervention for early-stage tumours (TNM classification), specifically, stage I and stage II colon cancers and stage I rectal cancers. In more advanced cases, chemotherapy and radiation therapy may be added, chemotherapy for stage III colon cancers and stage II and stage III rectal cancers. For these rectal cancers, radiation therapy is added to chemotherapy. For stage IV cancers of both the rectum and colon, the treatments are palliative in nature, being surgery, chemotherapy and radiation therapy, if need be. The 5-year survival rate is higher if the tumours are in their early stages. It is greater than 90% for stage I lesions; 60 to 80% for stage II lesions: 30 to 60% for stage III lesions and less than 5% for stage IV lesions.

It takes several years for cancerous colorectal tumours (carcinomas) to progress from premalignant lesions consisting, for the most

part, of adenomatous polyps. Several case-control studies showed that excising polyps reduced the occurrence of carcinomas, that excising carcinomas in their early stages reduced mortality and that excising polyps ultimately resulted in a reduction in mortality. In light of these favourable results of intervention during one of the stages in the adenoma-carcinoma sequence, adenomatous polyps and early-stage cancers are the target of screening aimed at reducing CRC mortality.

Efficacy of screening

Only recently was evidence of the efficacy of screening from randomised controlled trials in asymptomatic individuals obtained. Two randomised controlled studies conducted in the United Kingdom and Denmark were published in November 1996. One randomised controlled trial conducted in United States had been published three years earlier. The findings of the three studies were generally identical: fecal occult blood (FOB) testing leads to a reduction in the relative risk of CRC mortality. An update of the American study published in March 1999 confirmed these findings.

The American study was conducted in average-risk, asymptomatic volunteers aged 50 to 80 years. It revealed a significant reduction (33%) in the risk of CRC mortality through annual screening with a rehydrated, guaiac-type chemical FOB test. After 13 years of follow-up, biennial screening resulted in a non-significant reduction (6%) in the risk of CRC mortality. After 18 years of follow-up, the reduction was 21% and was significant.

The British and Danish studies involved average-risk, asymptomatic subjects. They were recruited from the population aged 45 to 74 years in the United Kingdom and 45 to 75 years in Denmark. The screening was conducted every other year using a non-rehydrated guaiac test. The reductions in the risk of CRC mortality, which were significant, were 15% and 18%, respectively.

In all three studies, a positive FOB test result was followed by a medical examination and a diagnostic procedure. The latter consisted of a colonoscopy or, failing that, a barium enema, preferably double-contrast, with or without a complementary sigmoidoscopy.

This new evidence resparked the debate over instituting mass screening of average-risk, asymptomatic individuals and using diagnostic procedures for screening purposes.

Controversy over test equivalence

Only screening by guaiac-type chemical FOB tests has been shown to be effective. Yet the uncertain performance of guaiac tests (low sensitivity, poor specificity and low predictive value, especially in the case of polyps) has several ramifications, one being that a considerable number of positive results lead to expensive diagnostic colonoscopies. Also, in the British and Danish trials, the number of cancers diagnosed after a negative test was higher than the number of those detected following a positive test result, which means that the sensitivity of such screening is less than 50%. This explains the many efforts being made to find FOB tests with a higher level of performance or to use diagnostic procedures for screening purposes, especially colonoscopy, which is the gold standard both for screening and diagnosis.

The advantages and limitations of each of the different diagnostic procedures used for screening

purposes have not yet been demonstrated in randomised controlled trials. Following proposals regarding the preventive potential of a "one-time sigmoidoscopy" at age 55, various feasibility studies have been carried out, are in progress or are scheduled. Other studies are evaluating various chemical and immunological FOB tests or various screening strategies involving sigmoidoscopy alone or in conjunction with an FOB test.

In the meantime, assessment needs have led to increasingly refined models for determining the efficacy and cost-effectiveness of different screening strategies.

Models

Models of a number of screening strategies have been constructed. Some of them, the monophasic ones, involve a single screening test, such as FOB ***or*** a type of endoscopy (sigmoidoscopy or colonoscopy). The others, the multiphasic ones, involve a combination of tests, such as FOB ***and*** a screening endoscopy. Depending on their characteristics, certain techniques, such as colonoscopy and sigmoidoscopy, can be used both for screening and diagnostic and therapeutic purposes.

The choice of modelling parameters is varied. Specifically, it is based on the natural history of the disease (e.g. the rate of adenomatous polyp-to- carcinoma transformation), the complication rates of the different tests or procedures, the life expectancy of the target populations, the likelihood of having cancer that will or will not be detected, depending on the test, and the costs. In some models, the costs are limited to those of the screening activities, while others include the treatment costs and those associated with the complications.

On the whole, the compilations are not thorough enough to take into account all the costs to the health-care systems concerned. Thus, some models include the costs of the screening and diagnostic tests, but not the treatment or surveillance costs, while others include them. In the latter models, some authors make a distinction between the cost of curative-intent treatments and the cost of palliative care. This cost disparity between the different models makes it difficult to compare them.

However, the nature and extent of the differences between the parameters seem to be within compatible limits, with the result that attention can be directed toward the concordance of the results yielded by the models of various strategies rather than the disparity between their premises. Thus: All the strategies that have been modelled, whether they involve a single screening test (monophasic) or a combination of two (or three) tests (multiphasic), lead to a reduction in CRC mortality.

- Colonoscopy could prove to be one of the more effective screening strategies. Its cost is usually prohibitive, although sensitivity analyses show that it is competitive in certain plausible conditions of utilisation.

- Double-contrast barium enema (DCBE) could constitute an alternative to screening colonoscopy.

- Sigmoidoscopy often has a lower level of performance than colonoscopy or double-contrast barium enema, mainly because it can detect only between 50 and 60% of all colorectal cancers. Consideration is often given to performing a sigmoidoscopy in conjunction with a DCBE.

- FOB testing is often the least expensive and least effective strategy.

- The costs of all the strategies are within the upper limit usually accepted in the United States for other preventive technologies, i.e. about $40,000 US per life-year saved. Most of the strategies involve a cost of under $20,000 US per life-year saved.

- In terms of the cost per QALY (quality-adjusted life-year), simulations show that CRC screening compares favourably with breast cancer screening.

These models, in which the parameters are often theoretical, reveal that each strategy has certain advantages and disadvantages. From a practical and operational standpoint, the parameters used in these models should reflect the actual conditions in the health-care systems in which these parameters apply. Otherwise, the conclusions drawn from the models will remain hypothetical.

Efficacy and cost of a colorectal cancer screening program tailored for Québec

Conditions similar to those of the British and Danish study designs have served as the basis for the following estimates, which are preliminary and need to be validated. Using 1993 Québec data, it can be estimated that a biennial screening program based on a non-rehydrated, guaiac-type FOB test and targeted at asymptomatic individuals aged 50 to 79 years could have prevented approximately 192 deaths, if the program had been in place long enough to achieve a 16% reduction in mortality. This figure was derived by combining, by meta-analysis, the result of 15% obtained in the United Kingdom and that of 18% obtained in Denmark.

When calculating the costs of FOB testing and, if need be, of the medical examinations followed by diagnostic procedures (including, if necessary, polypectomies or biopsies), the cost of implementing and managing the program was not taken into account.

For a screening campaign, this cost would be, on average, $17.3 million. In calculating the number of potential years of life lost that would be gained with a 16% mortality reduction, we obtain 2,927 life-years gained for the 192 deaths prevented, or a screening cost of under $6,000 per life-year gained. With the results of the American models estimating the average number of life-years gained through screening, we could, however, place this cost at close to $11,000 per life-year gained. The cost is that of biennial screening, which implies that the annual cost would be considerably lower.

Although these preliminary estimates were not subjected to a sensitivity analysis, they do provide enough information in favour of conducting feasibility studies and pilot trials to validate, from an operational standpoint, what has been learned over the past few years.

Conclusions

The *Conseil d'évaluation des technologies de la santé du Québec* believes that a CRC screening program would significantly reduce mortality from this type of cancer.

In principle, the program would be modelled on the designs of the British and Danish studies. It would target asymptomatic people aged 50 to 79 years and would involve biennial FOB screening with guaiac-type specimen-collection and test

kits containing mail-in slides. Two stool samples would be collected from each of three consecutive bowel movements, with no prior dietary or medicinal restrictions. The slides would not be rehydrated before the actual tests are performed in designated laboratories. A single positive finding would result in an invitation for an interview and a medical examination followed by a diagnostic and, if need be, therapeutic colonoscopy.

This program is based on the existing evidence of efficacy and can serve as a basis for implementing CRC screening. In light of ongoing research, it would be advisable to explore other screening strategies, such as colonoscopy, sigmoidoscopy and double-contrast barium enema (DCBE). Sigmoidoscopy could be used alone or in conjunction with other tests, such as a chemical or an immunological FOB test.

However, the following preconditions should be applied both to the institution of the proposed program and to the exploration of other screening strategies:

- The screening and diagnostic tests should first be validated in the operational context in which they would be performed.

- A computerised model for comparing the cost-effectiveness of different strategies applicable to the Québec population should be developed.

- Feasibility studies and pilot trials should be conducted in order to validate the operational parameters and the costs associated with these strategies.

Specifically, the objectives of these feasibility studies and pilot trials would be to:

- Define the optimal conditions for soliciting and training the target population in obtaining and mailing in stool samples.

- Determine the criteria for recognising laboratories designated for FOB testing (training of personnel, equipment, etc.).

- Validate FOB tests with a higher level of performance (e.g. immunochemical tests, whether automated or not).

- Estimate the cost of purchasing additional colonoscopes to meet the increased demand generated by screening and the cost of earlier replacement caused by their increased utilisation.

- Assess the feasibility of sigmoidoscopy in hospitals where colonoscopy is not practicable on a large scale, or of using DCBE in its place.

Standardising the classification of pathology reports for describing the stages of the colorectal cancers at diagnosis and during follow-ups.

- Ensure that the stages of the lesions at diagnosis are recorded in the Québec tumour database.

Some feasibility studies or pilot trials would require research teams whose task would be to examine different aspects of CRC screening, such as models applicable to different strategies, the target population's acceptance of the tests, the evaluation of intermediate and global indicators of the program's efficacy, and ethical aspects. These teams could be part of the networks that receive grants from the *Fonds de la recherche en santé du Québec*.

The task of coordinating the research and intervention activities should be assigned to a core committee bringing together all the different types of expertise necessary for conducting the research and for ensuring that the screening program proceeds smoothly. Adjustments could thus be made to the program (e.g. targeting certain age groups, new screening strategies) as new knowledge is acquired through evaluative research carried out while the program is in operation.