

Colon cancer screening in Ontario in 2016

E. Lalor

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This review was prompted by the report of the Canadian Task Force on Preventive Health Care, on screening for colorectal cancer, published in February, 2016, in the Canadian Medical Association Journal.

I was, and remain at this time, concerned that due to this report, patients will be confused about why they are being, or have been, referred for colonoscopy.

Disclaimer/disclosure

I am a gastroenterologist who, amongst many other services, provides screening colonoscopy, to asymptomatic patients over age 50, as a publicly-funded service in Ontario. I have followed the colon cancer screening literature for more than 20 years, and I am firmly convinced that a high-quality colonoscopy (definitions available in the literature), provided by myself, and other expert colonoscopist colleagues, provides those patients with the most effective and appropriate method to reduce colorectal cancer incidence and mortality, and this intervention is highly cost-effective and very safe.

Executive summary (short “take-home” version) of this review.

Colon cancer screening is very important for all Canadians aged 50-75. The choice continues to be, for the individual patient, between colonoscopy and fecal occult blood testing.

This CMAJ report has chosen a selected literature to review, and has ignored a large body of evidence, and a very large body of expert opinion, concerning the value of screening at ages 50-59, and also concerning the value of colonoscopy screening from 50-75. The paper contains a few strengths, which add to the ongoing discussion, and a number of weaknesses. Until this area is legislated, I will continue to offer colon cancer screening (a high-quality examination performed by myself) to people aged 50-75, and I will offer them a choice, and a discussion, between colonoscopy, and fecal immunochemical testing (also known

as FIT), which is not currently available in Ontario. Until the FIT stool test is available, I would also discuss my “weak recommendation” for guaiac-based fecal blood testing. I also offer screening to patients age 75 and older, with a more detailed discussion about the risks, benefits and alternatives.

Introduction

With the recent publication (February 22, 2016), in the Canadian Medical Association Journal (CMAJ), of the Canadian Task Force on Preventive Health Care recommendations, titled “Recommendations on screening for colorectal cancer and primary care” there is now increasing interest, and controversy, surrounding the patient choice for, or availability of, colonoscopy for screening.

This topic is important, as colorectal cancer is the second most common cause of cancer-related death in men and third most common in women. Since lung cancer is the commonest cause in both men and women, and more than 80-85% of those cases are related to cigarette smoking, colon cancer becomes the commonest cause of cancer-related death in men who do not smoke, and the second most common cause of cancer-related death in women who do not smoke.

In addition, Canada is in the top five countries in the world for colon cancer incidence, along with Australia, New Zealand, United States, and Britain. Colorectal cancer has a mortality rate of between 20 and 50%, except when it is diagnosed in early-stage. Obviously, screening for cancer is based on the evidence, which is very clear and strong in colorectal cancer, that early detection has a significant increase in survival/cure rates, ie reduction in mortality. This evidence is much stronger than similar evidence for breast, lung or prostate cancer.

In Canada, and in North America in general, there has been a plateau or slow decline in the rates of colon cancer incidence, but curiously, an increase in the rates in patients under age 50.

Background

For several decades, screening for colorectal cancer has been recommended, in countries where the disease is felt to be common (North America, Great Britain, New Zealand, Australia, Europe) and has generally consisted of a choice between:

- Fecal/stool tests (fecal occult blood test, also known as FOBT) to find small amounts of blood, not visible to the naked eye (ie occult)
- sigmoidoscopy, which is an endoscopic evaluation of the lower part of the colon
- colonoscopy, which is an endoscopic evaluation of the entire colon.

Screening refers to the testing of people, not patients, and does not concern the investigation of symptoms. Screening can be opportunistic, based on an individual's interactions with a primary healthcare provider, or programmatic, which is independent of any interaction between a patient and a primary healthcare provider, and is organized by a provincial public health authority or government.

The literature related to colorectal cancer screening is large, and various guidelines have been proposed by taskforces on preventive or primary health care, and also by many special interest and expert groups, in North America and also in Europe. In general, screening is strongly recommended, between ages 50 and 75, although some countries (Great Britain in particular) have suggested screening commencing at age 55 or 60. Some guidelines, including most American ones, rely more heavily on modelling studies, and longterm observational studies. Other guidelines, like this most recent Canadian one, ignore those data and restrict their concern to "randomized controlled trial" (RCT) evidence.

The highest level of evidence in medicine is considered the RCT, and there have been four large and well-done such studies of fecal testing, and a smaller number of sigmoidoscopy studies, but unfortunately, no randomized controlled trials of colonoscopy screening. The lower levels of evidence include large cohort and observational studies. These studies suggest a significant reduction in colorectal cancer incidence and mortality, at least from left-sided colon cancer, in patients undergoing colonoscopy, but some recent reports suggest reduced or even

absent protection from right-sided colon cancer, despite colonoscopy. There is a body of literature describing possible reasons for this, and ways to mitigate this potential problem.

While colorectal cancer is linked to various “modifiable” risk factors, including obesity, alcohol, smoking, lack of exercise, and dietary intake, in particular of red and processed meats, there is very little, if any, evidence that these risk factors can be successfully addressed, and secondly, even if they are successfully addressed, that they can result in significant declines in colorectal cancer incidence or mortality.

Most of the debate, once it is accepted that screening is indicated in a certain asymptomatic population (ie people not patients), concerns the choice, between the fecal tests, and the endoscopic tests. There is no controversy that colon cancer screening is strongly recommended, especially in the countries where it is a major health care problem.

The evidence for screening for any disease, but especially cancer, can be analyzed and assessed, or weighed, according to the disease-specific mortality, or the overall mortality of the group, or other features, including, but not limited to, cost, cost-effectiveness, real-life effectiveness as opposed to study efficacy, and also factors including patient values and preferences.

It should be pointed out that most cancer screening modalities (colorectal, breast, prostate), even though strongly supported by evidence, are unable to show a reduction in overall mortality of the screened group, but clearly a reduction in disease-specific mortality has been shown in those studies of fecal testing and sigmoidoscopy.

Finally, it must be pointed out that there will obviously be differences based on healthcare systems and healthcare system funding that will drive differences between United States, Canada, and Great Britain, for example, and in Canada, there may also be differences between provinces. It is however overly simplistic, in my opinion, to state (as do the authors) that “wait lists for colonoscopy are long in Canada and have increased over the years”, and “because of higher human resource requirements and greater potential for harm, ongoing randomized trials would have to show greater efficacy of colonoscopy before its routine use for screening could be recommended”.

Summary of the new CMAJ paper

The recommendations are as follows:

- Screening from age 60-74 should be with fecal/stool tests every two years or sigmoidoscopy every 10 years (*strong recommendation; moderate quality evidence*)
- Screening from age 50-59 should be with fecal/stool tests every two years or sigmoidoscopy every 10 years (*weak recommendation; moderate quality evidence*)
- Screening from age 75 and older is not recommended (*weak recommendation; low-quality evidence*)
- Screening using colonoscopy is not recommended (*weak recommendation; low-quality evidence*)
- No other screening tests are currently supported by published literature
- These recommendations are considered “consistent with those of the previous task force guideline”, published in 2001
- Gaps in knowledge are identified, with recommendations made

Support for the conclusions of this paper

It is true that there have been no randomized controlled trials of colonoscopy, published or completed, as of 2016. It is noted in the paper that there are four randomized trials currently investigating the mortality benefit of screening colonoscopy, their completion dates are 2021, 2026, 2027, and 2034.

It is true that fecal occult blood testing has been proven to reduce colon cancer mortality, the risk ratio (RR) reported is 0.82, which is an 18% reduction from control, and the incidence of late stage colorectal cancer is reported as 0.92, which is an 8% reduction in the outcome compared to controls. The best outcome from one of the studies quoted showed a RR of 0.68 with annual testing over 30 years, and a RR of 0.78 of biennial testing.

The reduction in colon cancer mortality for sigmoidoscopy, is a RR of 0.74, and late stage colorectal cancer RR of 0.73, which translates into a 26-27% reduction in the baseline (unscreened) mortality.

It is noted that the fecal studies and sigmoidoscopy studies were underpowered to detect an effect below age 60 or over age 70. It should be noted that the absence of proof of an effect does not mean that the effect does not exist - these studies did not include enough patient's below 60 and above 70 to draw any statistically significant conclusion.

The paper discusses in some detail the harm following sigmoidoscopy or colonoscopy, identified as the rates of perforation, minor bleeding, major bleeding, and death.

A section in the paper entitled "values and preferences" notes that a Canadian survey about patient preference indicates that there are concerns about invasiveness, level of preparation required, and pain. A US study revealed that patients' highest priorities for screening were preventing cancer, avoiding test adverse effects, minimizing false positive results, and the combination of screening frequency, test preparation and test procedures. When patients are choosing between different screening tests, factors that may influence the decision include sedation needs, perceived test accuracy, confidence in completing the test, bowel preparation, and frequency of tests.

Concerns with the conclusions of the current paper

There are general concerns with the overall philosophy, perhaps specifically that the absence of evidence indicates a lack of efficacy. It is recognized however that high quality evidence should be available to support a screening procedure, which is applied to healthy people who are not patients, ideally by a programmatic approach, and an increased level of evidence could be demanded if the intervention has a risk for harm or even death.

The focus on randomized controlled trials ignores that colorectal cancer screening programs may in fact reduce the incidence of colon cancer (i.e. the development of malignancy and premalignant lesions, i.e. polyps), which is quite different from any other screening program. This requires the detection and removal of polyps, which are not well-detected by fecal tests, and quite poorly detected by

sigmoidoscopy (and not detected at all in the colon that is not examined beyond the reach of the sigmoidoscopy). Removal of adenomatous polyps is the mechanism by which colorectal cancer incidence can be reduced, and this is apparent in some recent American reports, and may be one of the causes of the decline in colorectal incidence and mortality recently described in the United States. Unfortunately, the definition and philosophy of screening is generally applied to detecting and then curing early-stage cancer, but it is clear that fecal tests, in particular the guaiac-based fecal blood tests, are very poor at detecting adenomatous polyps. The main debate is really now concerning the best method of detecting “high-risk” polyps, since the incidence of polyps is probably 10 times greater than the incidence of colorectal cancer, and by definition this implies that perhaps 90% of polyps will never develop into cancer.

The paper states on page 2 that because “sufficient evidence was available on these [previously defined] clinically important outcomes, polyps (an intermediate outcome) were not considered in the development of this guideline...”. This is a significant weakness, since it is well-accepted that the vast majority of colorectal cancers arise from polyps. It is also clearly outlined that colon cancer “screening” tests can now be divided into early-detection tests, and cancer-preventing tests.

The statistics for the effectiveness of the screening modalities recommended, while reported in the previous section on the “strengths of the report”, are in fact underwhelming. In particular the absolute reduction in deaths, and the number needed to screen to prevent one death, for both fecal testing and sigmoidoscopy, is disappointing. Of course there is currently no evidence, in the absence of a randomized controlled trial, for the absolute reduction in deaths, or the number needed to screen, for colonoscopy.

On page 3, the rationale behind making separate recommendations for the two age groups (50-59, and 60-74) is expanded, and ranks the different balance of benefit to harm, higher than the disadvantage of added complexity by having recommendations based on different age groups. There is no discussion about the “cost” to those patients age 50-59 who will develop colorectal cancer, that might have been detected by screening.

On page 4, a rationale is proposed for recommending a screening interval of two years, despite the well-accepted fact that the only study that compared one year

and two year (biennial) screening intervals, showed a significantly higher reduction in mortality in the annually screened group, and in the group age 70 and older, only the annual testing showed a statistically significant reduction in mortality at all. The relative risk in this older age group, for annual screening was 0.47, but the relative risk for biennial screening was 0.66, with the confidence interval significantly overlapping 1, implying that this relative risk reduction (with biennial screening) is not statistically significant at all in this age-group.

The task force recommends two-year screening as “less burdensome”, and recommends that “additional studies are required to determine whether annual testing would lead to incremental clinical benefit”, which of course is recommending research studies that will never be done. Experts have stated in public that only one of the four screening fecal occult blood studies showed an advantage in the annual screening group, but often omit to point out that only one of the four studies had an annual arm. This is another example of assuming that the absence of evidence is equivalent to the absence of efficacy.

The biggest and most serious weakness of this guideline is that the expert panel appears to have completely ignored the real-life effectiveness of fecal testing, or even sigmoidoscopy, compared to the efficacy determined under randomized controlled trial circumstances. There is extensive literature showing that the compliance with fecal testing programs is very poor, first time around, and drops off significantly even if the patient complies the first time. Compliance with sigmoidoscopy is also poor, especially if the test is being offered without sedation. Most experts feel that sigmoidoscopy should not require sedation, but most patients, as outlined previously and to be discussed subsequently, have a great interest in avoiding discomfort and perceived likelihood of pain.

Despite a section describing patient’s values and preferences, there is really no discussion of how the recommendations of the task force take into account the patient’s values and preferences.

In summary, in the best possible circumstances, biennial fecal testing has been shown to reduce colorectal cancer mortality by 18-22%, and sigmoidoscopy, under the best possible circumstances, by 26%.

The expert panel has avoided a discussion of the extensive literature suggesting that colonoscopy, followed by stratification into “low risk” (one or two small

adenomatous polyps less than 1 cm) and “higher risk” (three or more adenomatous polyps, or any one adenomatous polyp greater than 1 cm) can dramatically predict subsequent incidence and mortality of colorectal cancer in those groups.

Concerning harm

The background systematic review referenced by this paper includes a section on harm. All of the numbers presented are described as “very low” quality of evidence.

The statistics provided for harm from flexible sigmoidoscopy are somewhat controversial. The reference provided indicates perforation in .001% of patients, which is a much lower figure than generally accepted, and implies one in 100,000. The death rate is quoted as .015%, and the comparable death rate for “diagnostic colonoscopy” is .035%, with the perforation rate of .061%, and yet the comment is made that the harm for diagnostic colonoscopy is based on all colonoscopies performed in symptomatic patients. They state “Although important, distinguishing harms from therapeutic versus non-therapeutic colonoscopies was beyond the scope of the... systematic review and would not have influenced our recommendations”. Under the colonoscopy screening section, they quote the harms of “screening colonoscopy”, to include perforation at .05%, and death at .002%, which of course is dramatically lower than the death rate (above) following sigmoidoscopy, and a perforation rate of screening colonoscopy of .05%, which is one in 2000, which is certainly accepted as a reasonable estimate.

It is highly unlikely that the death rate of screening sigmoidoscopy is seven times higher than the death rate of screening colonoscopy, and it is inadequate, and perhaps cavalier, to quote numbers for “harm of colonoscopy” as being based on colonoscopies performed for symptomatic patients, and including “therapeutic” (which implies removal of various sizes of polyps, treatment of bleeding, endoscopic dilation of obstructing strictures, etc., or do they mean followup?, i.e. colonoscopy performed as a result of a positive screening fecal blood test) and nontherapeutic colonoscopies, and then, to state that it “would not have influenced... recommendations”.

It should be emphasized that the recommendation against colonoscopy is “a weak recommendation; low-quality evidence”, in their own words. It is stated that

there is a higher value placed on the lack of randomized controlled evidence, and opportunity costs of using colonoscopy for population screening, and a lower value on the “indirect evidence suggesting that the clinical benefits of colonoscopy could outweigh its clinical harms”. They also place a lower value on economic modeling, despite previous published and robust evidence that the most cost-effective screening modalities are fecal blood testing, sigmoidoscopy, or colonoscopy every 10 years.

In the section on patient values and preferences, it should be noted that a US study identified the patient’s highest priority being “preventing cancer”, and when patients are choosing between different screening tests, the perceived test accuracy, and frequency of tests are some of the factors that may influence the decision. It is not mentioned in this report that colonoscopy is recommended every 10 years, (and remains cost-effective for that reason, as well as allowing the removal of polyps and the stratification of patients into low risk and higher risk groups).

In the conclusion of the paper, it is unfortunate, in my opinion, that a “weak recommendation” to screen people age 50-59, requires a “nuanced discussion about harms and benefits in this population”. Screening at any age, of a person who is by definition not a patient, requires a detailed discussion about harms and benefits, and choices, and that discussion would not be any “less nuanced” in age 60 to 74, just because the expert panel has provided a “strong recommendation” in that age group, as opposed to the “weak recommendation” under age 60.

Conclusion

Beginning with an awareness of the incidence and significant mortality of colorectal cancer in Canada, , and then considering a test which may detect premalignant polyps in 20-30% of patients over age 50, with a published perforation rate of 1 in 2000 and a death rate of approximately 1 in 20,000, and considering the alternative testing strategies, and the evidence on patient preference and reasons for choosing various tests, it is clear that colonoscopy continues to play a crucial role, and in fact is a leading strategy for early detection and for colorectal cancer prevention for Ontario patients aged 50-74.

Appendix (background statistics):

Taken from the 2015 report of the Canadian Cancer Society :

(<https://www.cancer.ca/~media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2015-EN.pdf>):

Lifetime probability of developing colorectal cancer in 2010, for males was 7.2%, and for females, 6.3%. This was the third highest for both genders.

Starting from the mid-1980s, overall incidence rates for colorectal cancer declined for both sexes until the mid-1990s (although this decline was more prominent for females).(14) Incidence rates then rose through 2000, only to decline slightly thereafter, most likely due to increased use of colorectal cancer screening, which can identify and remove precancerous polyps, which can in turn reduce incidence. The decline in colorectal cancer incidence rates appears confined to older adults as rates are increasing among young adults under the age of 50 years in Canada and in the United States.(15-17) Diabetes may also increase risk for colorectal cancer.(10) As of 2014, nine provinces had organized screening programs available, and the remaining province has announced the intention to implement one.(18,19) Participation rates vary within and between the existing organized programs and do not meet the target of 60%.(18) Colorectal cancer is linked to several modifiable risk factors including obesity, physical inactivity, consumption of red and processed meat and smoking.(20,21).