Summary

Screening Mammography for Women Aged 40 to 49 Years: Update

Introduction

In Québec, breast cancer is the leading cancer in women and the second most common cause of cancer-related mortality, after lung cancer. It affects roughly 5,900 Québec women per year, and 1,350 die from it. It is well established that mammographic screening helps reduce breast cancer mortality among women aged 50 to 69 years. Recent data indicate that annual screening starting at the age of 40 years may also be effective, but its effectiveness is lower.

In light of these new data, including the published outcomes of a major clinical trial conducted in the United Kingdom (UK Age Trial), Québec's Ministère de la Santé et des Services sociaux (MSSS) asked AETMIS to review the new mortality reduction estimates for screening starting from the age 40 years. It also asked for an assessment of the magnitude of screening-related adverse effects, especially those associated with radiation exposure, additional diagnostic tests, and overdiagnosis. This analysis aims to enable both the MSSS and women and their physicians to make informed decisions regarding the possibility of participating in screening mammography starting from the age of 40 years.

Methods

Breast cancer screening is designed to reduce mortality by detecting early-stage breast tumours. We pooled the results of the UK Age Trial with those of the other randomized mammography trials conducted with women younger than 50 years. We present these results by comparing the expected outcomes for a cohort of 1000 women aged 40 years assumed to participate in annual screening for 10 years, with the outcomes of unscreened women. We examined the amount of radiation absorbed during a mammogram and its carcinogenic effects, according to different modelling analyses, and also looked at the additional adverse effects arising from diagnostic investigations and overdiagnosis. Lastly, we compared the conditions and parameters of Québec's organized breast screening program, the Programme québécois de dépistage du cancer du sein (PQDCS), with those of breast screening programs implemented during the major clinical trials from which we derived our estimates. This comparison was done to evaluate the extent to which these outcomes may be reproduced in the Québec program.

Results

Mortality reduction through screening

The UK Age Trial is one of the best among trials of variable quality. It showed a 17% mortality reduction, and a meta-analysis including these results indicated a mortality reduction ranging from 10% (the three best trials) to 14–15% (including the poorest trials). These results were obtained despite the fact that many women invited to screening did not participate in it, thereby diluting the measured effect. Adjusting for this non-participation allows us to estimate that mortality is reduced by 25% among regularly screened participants.

However, this reduction, which may be deemed a relative reduction, applies to a population that already has a lower incidence of breast cancer. Applying the 25% reduction to a cohort of 1000 women screened over 10 years yields an estimated reduction of **0.9 deaths** for women screened annually[1] from the age of 40 years, while the reduction is 2.7 deaths for women screened every two years from the age 50 years, and 4.2 deaths for women who start biennial screening from the age of 60 years.

Adverse effects

Apart from the benefits derived from the timely diagnosis of cancers, which can be treated better at early stages, screening inevitably has its own

1. Published studies on the effectiveness of mammographic screening in women aged 40 to 49 years are based on annual screening, while those on the effectiveness of screening in women aged 50 to 69 years are based on biennial screening. Screening programs for women of that age group have adopted this interval.

share of adverse effects, especially those produced by ionizing radiation linked with mammography itself and the iatrogenic effects associated with the different diagnosis and treatment stages.

- Radiation-induced cancers

  Different models help estimate the magnitude of the effect of radiation on cancer development, and the estimations greatly differ according to the data selected to estimate the model parameters. Recent analyses, adjusted to be applied to an annual mammography with a radiation dose of 4.5 mGy per examination, produce results ranging from 0.1 to 0.7 deaths caused by mammography among 1000 women screened annually for 10 years starting from the age 40 years, with a central estimate of **0.5 deaths**.

- Overdiagnosis

  Of the screen-detected early-stage cancers, it is likely that some would not have produced symptoms in a woman during her lifetime, either because the cancer would have regressed or because another disease would have caused her death before the onset of breast cancer symptoms. Assuming a 20% overdiagnosis rate, it is estimated that **4 cases** of overdiagnosis would occur among 1000 regularly screened participants for 10 years starting from the age 40 years, such cases generally being associated with unnecessary treatments.

- Diagnostic tests associated with screening

  Most positive screening results (around 19 out of 20) will be false-positives and will result in a large number of diagnostic imaging investigations (mammography, ultrasound) or biopsy investigations (cytology examination, core needle biopsy, open biopsy), most of which will lead to the conclusion that the woman is free of cancer. We estimated the number of imaging and biopsy investigations that would be performed on 1000 screened participants and on 1000 non-participants. These calculations required estimating several uncertain parameters, such as the frequency of biopsies in a population of unscreened women. These are therefore interim results likely to be improved through further research using clinical databases.

The table below summarizes the screening benefits (prevented deaths) and harms (radiation-induced mortality, overdiagnosis, diagnostic tests) for three hypothetical cohorts of 1000 women starting screening at ages 40, 50 and 60 years, compared with an equivalent cohort of unscreened women.

For the two older groups, mortality benefits outweigh the disadvantages, and the other effects, while numerous, may be justified by these gains. However, for women starting screening at age 40 years, everything depends on the estimated radiation effects selected, with estimates reported here ranging from 0.1 to 0.7 deaths per 1000 women. In a worst-case scenario, radiation effects alone cancel out almost all the benefits, without factoring in the other harmful effects associated with diagnostic and therapeutic procedures. In a best-case scenario, these harmful effects are much less significant than the targeted gains. In a middle-case scenario, harmful radiation effects alone cancel out more than half of the expected gains.

Main expected effects in 1000 women participating in mammographic screening for 10 years, compared with the effects in 1000 unscreened women (absolute differences)

	MORTALITY EFFECTS		OVERDIAGNOSIS EFFECTS	DIAGNOSTIC TEST EFFECTS* (NUMBER OF TESTS)	
Ten-year screening regimen	Number of deaths prevented through early diagnosis	Number of radiation-induced deaths	Number of cases	Imaging†	Biopsies‡
40–49 years, annual	**0.9**	**0.5**	**4**	**800**	**160**
50–59 years, biennial	2.7	0.2	5	350	70
60–69 years, biennial	4.2	0.1	7	325	65

* The number of diagnostic procedures is the total procedures for 1000 women; however, given that the same woman may undergo several procedures, the number of women undergoing diagnostic procedures would therefore be lower.
† Additional diagnostic mammograms and ultrasounds following screening mammography.
‡ Cytology examinations, core needle biopsies, open biopsies.
Note: Effects represent the difference between the expected effects in 1000 screened participants and the expected effects in 1000 unscreened women. Desirable effects are shown in the pale grey cells; adverse effects in the dark grey cells.

Comparison of the Québec program with the trials and other programs

The outcomes of major clinical trials, particularly those in Sweden, motivated the adoption of quality standards in Europe, Australia and Canada. With regard to program structure and processes, several of the quality standards required in the clinical trials and adopted by national programs are not met in Québec. This is especially true for the annual volume of examinations required for x-ray film production or interpretation, audit methods and the double reading of films. In these respects, Québec compares unfavourably, given its minimum standard of 1,000 films read per year relative to standards ranging from 2,000 to 5,000 films read in effect elsewhere. The Québec program also differs from other programs in that it does not employ double reading of films and it does not have a provincial program director, clinical expert committees and formal methods for auditing screening centres or for reviewing interval cancers.

Nevertheless, in terms of early cancer detection, the interim statistics on tumour detection rates and tumour size detected by the PQDCS are reassuring. The Québec program may achieve the same mortality reduction as the research trials, but it gives rise to excess diagnostic investigations and possibly overdiagnosis associated with false positives. These drawbacks will tend to reduce the net benefit of screening participation, especially for younger women who start off with more modest benefits.

The emergence of new technologies, especially digital mammography, 3D mammography (breast tomosynthesis) and magnetic resonance imaging, clearly shows how quickly the balance between benefits and harms can shift. Mammography-associated radiation, once much higher, could decrease with digital mammography or increase with 3D mammography, but we still do not know the extent to which the improved detection promised by these technologies will translate into mortality reduction. Today, the benefits seem to clearly outweigh the risks for women aged 50 to 69 years, although less so for younger women; however, that balance will need to be re-evaluated when these techniques are tested in comparative studies.

Conclusions and Recommendations

Mammographic screening starting from the age of 40 years helps reduce breast cancer mortality on the order of 15% for all women invited to screening, but the reduction is on the order of 25% for screened participants alone, which is the relevant consideration for women weighing the benefits and harms of screening. In absolute numbers, this reduction corresponds to 0.9 prevented deaths among 1000 women aged 40 years screened annually over a 10-year period. In comparison, screening among women aged 50 and older, which is credited with a relative reduction of 35%, yields significantly greater benefits: 10 years of biennial screening would cause a reduction of 2.7 deaths among 1000 women screened between the ages of 50 and 59 years, and a reduction of 4.2 deaths among 1000 women screened between the ages of 60 and 69 years.

To avoid this **0.9** mortality, women aged 40 to 49 years face three main disadvantages: absorption of radiation inherent in mammography, potential overdiagnosis, and diagnostic investigations subsequent to screening. It is estimated that, among 1000 women participating in annual screening over 10 years, there will be **0.5** deaths due to radiation, **4** cases of cancer overdiagnosis and overtreatment, **800** additional imaging tests and **160** additional biopsies.

While a consensus exists on screening benefits after the age of 50, the guidelines regarding women younger than 50 years fall into two categories: those from organizations, mostly U.S., that advocate systematic screening starting from age 40 years, and those that propose targeted screening for women at higher risk of breast cancer. This dichotomy is also found in the choices offered in large screening programs. All offer systematic screening to women aged 50 to 69 years, generally every two years. A few also offer systematic screening starting from age 40 years, while the others do not systematically invite these women to screening but provide access to women on physician referral.

1. Should screening be systematically offered starting from age 40 years?

For women aged 40–49 years, the adverse effects of routine mammographic screening are greater than generally recognized. First, the number of deaths from radiation-induced cancer is close to the number of screening-prevented deaths. Second, other

screening-associated harms, meaning false positives, diagnostic investigations and unnecessary treatments, are greater.

***Recommendation**: Routine screening for women younger than 50 years is not desirable. New evidence confirms that routine screening among women aged 40 to 49 years reduces breast cancer mortality, but this reduction, in absolute numbers of prevented deaths, is substantially lower than that documented among women aged 50 and older. For many women, screening at that younger age may even present more harms than benefits.*

2. Should some women younger than 50 years be invited to screening?

No population-based clinical trial on screening for at-risk women has been conducted, but clinical guidelines, including those issued by the Collège des médecins du Québec, recommend offering screening to women at higher risk of breast cancer.

***Recommendation**: Individual risk-based breast cancer screening for women younger than 50 years should continue to be offered on referral by primary care physicians. Such targeted screening for women aged 40 to 49 years requires evaluation of screening benefits and harms based on individual cancer risk and an informed decision about whether or not to participate. The MSSS should therefore ensure that risk assessment protocols be established and risk assessment services be available.*

3. How can women decide whether or not they want to participate, and if so, at what age?

There is an ethical and medical consensus in favour of providing all women with an explanation of screening benefits and harms so that they can make an informed choice whether or not to be screened and, if so, at what age to start. This information should include estimates of absolute mortality reduction among women, not the percentage of reduction. It should also be based on the reduction that applies to screened participants, not on the average expected reduction for all the invited population. The other effects to take into account are the number of diagnostic tests resulting from screening, overdiagnosis and radiation-induced cancers.

***Recommendation**: The PQDCS, in conjunction with continuing medical education organizations, should ensure that primary care physicians receive appropriate training that enables them to provide women of all ages with complete information on the benefits and harms associated with screening, including the magnitude of radiation effects, so that these women may make an informed decision about the best time to start and stop mammographic screening. The Program should also ensure that expert referral services are set up for women younger than 50 years.*

4. Should we include younger women in the program as do other provinces?

Including women of all ages who undergo screening as part of the program would offer the advantage of standardizing aspects such as transmitting the results to the woman and her physician and evaluating screening quality and performance for all age groups.

***Recommendation**: The PQDCS should formally include all women who have undergone screening mammography, regardless of their age, while maintaining different aged-based screening invitation modalities. Feasibility studies should be undertaken in this regard.*

5. How can screening quality be enhanced?

Any program expecting to achieve the outcomes documented in the major clinical trials must at least equal their quality standard levels. The Québec program, like the other programs in place in Canada, should aim for the standards of excellence achieved during the trials and applied in the European and Australian programs. While the quality of the films produced by the PQDCS likely meets international standards, the same cannot be said for its film reading standards. The indicators measured in Québec suggest that the program performs well in detecting breast cancer but generates too many additional tests. These harms significantly counterbalance the benefits of screening, especially for women younger than 50 years, who face more modest benefits.

***Recommendation**: The PQDCS should ensure that its quality standards match the higher international standards of excellence. In particular, it should develop structures to help professionals achieve the performance of their counterparts involved in well-organized programs in other countries, where recall rates are two times if not three times, lower. Raising quality standards would allow us to maximize the chances of achieving the potential of mammography, while minimizing its harms.*