Summary

Breast cancer in Québec

Breast cancer is a major health problem in Québec. Each year nearly 4,000 new cases are reported, 25% of them among women under 50 years of age. Approximately 1,200 women die from this disease annually.

Basis for screening

The likelihood of treatment prolonging life is greater when the cancer is detected early in its course before the tumour has spread. Regular breast screening by clinical examination or mammography, or both, is a strategy increasingly used to lower the death rate due to breast cancer. There is now wide, but not universal, agreement that screening can produce a reduction in breast cancer mortality. There is, however, continuing controversy concerning the age at which screening should be initiated.

1990 Report of the Conseil

In November 1990, the Conseil d'évaluation des technologies de la santé du Québec completed a report on the benefits, adverse effects and costs which might be expected from the adoption of a screening program in Québec. It was concluded in that report that the greatest health gains could be expected for women aged approximately 50 to 69 years and the report suggested that, at least initially, any such program should be restricted to women in this age range.

Motivation for this report

Since publication of the report in 1990, new data from some of the earlier studies and from one completely new major Canadian study with substantial Québec participation, have been reported. Coincidentally, the ministry of health of Québec recently requested the Conseil to undertake a review of the evidence relating to possible health benefits, adverse effects and costs of screening women between the ages of 40 and 49 years. The report which follows is a review and analysis of this evidence.

Definitions

For the purpose of this analysis, “mammographic screening” is defined as two-view mammography and clinical breast examination carried out periodically in the absence of any reasons to suspect increased risk of breast cancer. Mammography carried out because of increased risk of cancer is not the subject of this report. The term “younger women” will refer to women between the ages of 40 and 49 years, and the term “older women” will refer to women aged 50 to 69 years.

Methods

Estimates of the health benefits of screening were based on an extensive literature review. The pertinent evidence was extracted and evaluated.

First, the direct epidemiological evidence of efficacy of screening younger women, was examined.

This evidence was supplemented by reviewing the indirect evidence bearing on the likelihood that screening younger women might be
beneficial. Five age-related determinants of screening effectiveness were examined to ascertain whether any of them suggest that screening younger women would be less effective.

The costs of screening were estimated on the basis of information obtained for the 1990 Report, updated where possible to reflect the experience of ongoing Canadian programs.

Finally, the recommendations and guidelines of seven Canadian provinces, the Canadian Task Force on the Periodic Health Examination and the Canadian Cancer Society, eight United States authorities, eight Western European countries, Australia, New-Zealand, and Japan were collected.

Methodological issues

It is extremely difficult to estimate the effects of screening from published data for several reasons:

All studies use the difference in cumulative mortality as the measure of effect. This obscures the effect of screening because there is a lag of several years between screening and the time that deaths would have otherwise occurred and, thus, mortality during these early years cannot be influenced by screening. To obtain more revealing estimates requires translating the reported figures to time-specific breast cancer mortality rates (incidence densities).

- An additional problem caused by the delay in appearance of any reduction in mortality is that conversion of such reductions to gains in life-expectancy cannot be based on the age at onset of screening. Thus, an age-deferral must be estimated, introducing additional uncertainty.

- In addition, quantitation of screening benefits is hampered by the small number of cancer deaths in younger women and the longer follow-up required.

Direct Epidemiological Evidence

HIP: The HIP study of New-York has produced evidence of a screening benefit for younger women. Of the 20,770 women who accepted screening in this study, 13,740 were below 50 years of age. The women in this trial were screened for four successive years using physical examination and mammography and have been followed for more than 18 years. The mortality rate was decreased by 31% in women aged 40 to 49 years, based on data from years 6 to 10.

Two-County: The Swedish Two-County study used single-view mammography without physical examination every two years. In this study, 19,844 women under 50 years of age were invited to screening. Participation was high, 83-89% over the first three rounds, but 13% of women in the control group also had mammography. Based on the data for years 6 to 10, no reduction is seen in the annual breast cancer mortality rate among younger women.

Malmö: Another Swedish study in the city of Malmö, offered two-view mammography every 18 to 24 months to 7,981 women younger than 55 years at onset of screening. Compliance was less than 70%, and 35% of women in the control group had at least one mammogram. An average increase of 13% in the annual breast cancer mortality in younger women was observed for years 6 to 10 of follow-up.

Stockholm: A third Swedish trial carried out in Stockholm offered 14,375 women under age 50 years at enrolment single-view mammography every two years without physical examination. Compliance was around 80% and an unknown number of women in the control group had mammography. A 71% reduction in the annual breast cancer mortality was estimated in younger women using data for years 6 to 8.

Edinburgh: In a trial in Edinburgh, approximately 23,000 women were offered clinical examination and two-view mammography every two years with an additional clinical examination each alternate year. Compliance rates were low and it is unclear whether any women in the control
group received mammograms. For women aged 45 to 49 years of age, there was a 2% reduction in cumulative mortality. Mortality rates could not be estimated from the data provided.

NBSS: The most recent report is that of the Canadian National Breast Screening Study which used annual two-view mammography and clinical breast examination. Approximately 25,000 women aged 40 to 49 years were screened and their outcome was compared to an equivalent number of women who received “usual care”. Participation was high, 85 to 89% in the first five rounds. After seven years of observation, however, no reduction in cumulative mortality was observed in the screened group. Annual breast cancer mortality rates cannot be calculated from the data provided. Although this study showed no benefit for screening younger women, it cannot be taken to exclude the possibility of benefit. The quality of screening for most of the study, although presumably representative of contemporary Canadian standards, seems to have been below the level necessary to detect early cancers consistently. Thus, the proportion of node-negative tumours was not increased among screened women, in marked contrast to all other screening trials. This study illustrates that a screening program that does not insist on exceptionally high screening quality throughout will not manifest a benefit.

Inference from direct evidence

Combination of the data from the 5 most recent trials produces an estimate of 1% increase in breast cancer mortality rate. The 95% confidence interval was wide, however, ranging from 26% reduction to 28% increase in mortality.

Thus, the available direct epidemiological evidence does not suggest that breast cancer mortality can be reduced by screening younger women. It is, however, inadequate to exclude the possibility that a substantial reduction in mortality could result.

Indirect Evidence

Faced with this uncertainty, the possible influence of 5 factors that might modify the efficacy of screening younger women was considered.

Breast cancer incidence: The lower incidence of breast cancer in younger women does not itself alter the proportional reduction in mortality but it does compel the study of larger numbers of women in order to observe an outcome.

Prognosis & tumour size: The impact of mammography depends on the detection of tumours when they are smaller. Tumour size at time of detection, is one determinant of effectiveness: the smaller the tumour the better the prognosis. The data reviewed indicate that this relationship is the same in younger women as in older women. Thus, increased detection of smaller tumours should have at least the same prognostic implications in younger women.

Breast density & tumour detection: Breast tissue density varies with the age of the subject. In the denser tissue of younger women, tumours can be harder to feel and to detect by mammography. A review of the evidence suggests that this factor must reduce, but not eliminate the effectiveness of screening in younger women.

Tumour growth rate: Evidence on relation of tumour growth rates to age is scanty. It appears that there may be a somewhat higher proportion of faster growing tumours among younger women. Hence, at any given interval, screening will be less effective in younger women. Participation: Participation in a program is another important determinant of a screening program’s success. Available evidence suggests, however, that younger women can be expected to participate more than older women.

Inference from indirect evidence

In summary, notwithstanding the lack of evidence of mortality reduction in clinical trials, there are reasonable a priori grounds to believe that a breast cancer screening program for younger women
might be successful. Furthermore, the negative impact of increased breast tissue density on the outcome of screening younger women might be reduced by use of optimal equipment, strict quality control, and an intentional lowering of the “diagnostic threshold”. The latter, would decrease the occurrence of missed cancers at the price of increased false positive mammograms. In addition, more frequent screening might lower the number of interval cancers in younger women.

Thus, the possibility cannot be excluded that a new Québec program, using modern improved equipment, high-quality two-view mammography, annual examination and strict quality control of all aspects of the program including film interpretation, combined with prompt and appropriate therapeutic reaction to positive findings, might produce a significant reduction of mortality in younger women after a delay, perhaps of 10 to 15 years.

**Range of Possible Benefits**

The need to establish policy requires that estimates of the effect of screening younger women must be made in spite of insufficient evidence. Review of the evidence suggests that optimal annual screening of younger women might result in an eventual reduction of annual breast cancer mortality, ranging from 0 to as great as 20%. A 10% reduction would translate into approximately 39 fewer breast cancer deaths per year, or nearly 1,000 additional years of life gained annually when the program reached steady-state. However, no confirmation of such benefits exists and, in practice, there may be no mortality reduction.

**Unwanted Health Effects**

Any health gains must be considered in the light of unwanted health effects.

False positive tests: Annual screening of younger women would result in approximately 22,500 false positive tests per year, leading to nearly 10,000 needle biopsies and 3,000 surgical biopsies in order to prove the absence of breast cancer. This effect is more certain than any gains and would occur immediately upon initiation of a screening program.

Radiation risk: Irradiation due to this program might cause some additional breast cancers, at a rate of perhaps one every 1 year, which could lead to death many years later. These deaths might translate to 17 years of life being lost across the entire screened population.

**Costs**

If an annual screening program were implemented at age 40 for Québec women, the cost would be about $25 million (CAD) per year. Beneficial effects of screening would be unlikely to appear before 10 to 15 years. During this time, an expenditure of approximately $250 million dollars (and 225,000 false positive screens) would be incurred.

**Cost-effectiveness**

If such a program were to yield a 10% reduction in the mortality rate at steady-state, an annual gain of nearly 1,000 years of life, the cost-effectiveness would be approximately $27,000 per life-year gained. A 20% reduction would correspond to a cost-effectiveness of $13,300 per life-year gained.

**Application of estimates to Québec**

It must be noted that all estimates of mortality reduction are based on comparing screening to total absence of screening. Since 21% of younger women in Québec already undergo mammography, any mortality reduction due to a screening program will be less than it would have been if no mammography were presently carried out.

**Public policy**
Public policy involving the lives of thousands of individuals and substantial resources should not normally be made in the absence of either direct evidence of benefit, or at least extremely powerful indirect evidence that benefit is likely. To extend screening to women in this age range in the absence of such evidence would require faith beyond what most individuals would consider reasonable. The only grounds on which the launching of such a policy might be considered reasonable, would be in the context of a research study. (Nothing said here relates to mammography carried out for clinical reasons such as family history of breast cancer nor to the conclusion of the previous report that screening of women 50 to 69 years of age could be effective.)