Organised mammographic screening – more benefits than harms

Recent European pooled analyses indicate that mammographic screening reduces breast cancer mortality, but entails a certain risk of overdiagnosis and false positive screening results. In Norway, as I see it, we lack valid results concerning mammographic screening and breast cancer mortality. Norwegian figures for overdiagnosis vary, while the risk of false positive test results appears to be at the same level as the European pooled analysis.

In September 2012 the *Journal of Medical Screening* published a supplement of eight articles from European mammographic screening programmes (1–8). The articles are pooled analyses conducted by researchers from nine countries in the Euroscreen Working Group. The effect of screening on breast cancer mortality, increased incidence and false positive screening results is the main focus of the analyses. I was part of the working group and in this commentary I provide a brief description of the main results and discuss these in relation to Norwegian conditions.

Mortality

The purpose of mammographic screening is to reduce breast cancer mortality. Randomised controlled studies are considered the most stringent study design, followed by cohort analyses. With incidence-based cohort analyses it is possible to separate out deaths among women who were diagnosed with breast cancer after they were invited/attended as part of the programme (2). The working group assessed these types of studies as very well suited to evaluate the effect, both for invited and attending women in the organised screening programmes, provided that there was adequate follow-up time and adjustment for selection bias. The meta-analysis with cohort analyses showed 25 % (RR = 0.75; 95 % CI 0.69–0.81) lower breast cancer mortality among invited versus non-invited women and 38 % (RR = 0.62; 95 % CI 0.56–0.69) lower breast cancer mortality among those who attended versus those who did not attend.

Case-control studies were also assessed as suitable, provided that there was ade quate adjustment for selection bias (3). Analysis of studies with this type of design showed that breast cancer mortality was 31 % (RR = 0.69; 95 % CI 0.57–0.83) lower for invited versus non-invited women and 48 % (RR = 0.52; 95 % CI 0.42–0.65) lower for women who attended versus women who did not attend, respectively (3).

Trend studies are not able to take account of whether the women were diagnosed with the disease before or after they were invited to/attended the screening programme. According to the working group, results from trend studies should principally be discounted (1).

Overdiagnosis

Overdiagnosis is defined as breast cancer that would not have been diagnosed in the woman's lifetime if she had not been invited to/did not attend for screening. This is a theoretical concept, and the estimates are based on mathematical calculations with a number of assumptions. There is currently no agreement on which method is best or which assumptions should be included in the calculations (4, 9). An adequate follow-up period after the women are no longer invited to screening as well as adjustment for natural increase in incidence and lead-time bias are regarded as crucial to be able to assign the most exact estimate possible. If overdiagnosis is defined as a percentage of the expected incidence in the absence of screening, the adjusted estimates in the meta-analysis are 1–10 % (average 6.5 %) for women who were screened from the age of 50 until the age of 69 and were followed for ten years after their last invitation (4).

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False positive screening results

A positive screening test resulting in a recall for further assessment that ends up negative is called a false positive screening result. Women who are recalled for further assessment may experience temporary worry and anxiety (10, 11). Pooled analyses showed that the risk of a recall assessment including additional X-ray and/or ultrasound examinations with a negative result in the course of ten screening tests over 20 years was 17 %. The cumulative risk of undergoing supplementary X-rays and/or ultrasound and a subsequent biopsy with a benign result was 3 % (5).

Benefits versus harms

The working group calculated that if 1 000 women in the age group 50–69 years are screened biennially and followed for ten years thereafter, until they are 79, one would expect to diagnose 71 cases of breast cancer, against 67 cases without screening. It was further calculated that 30 women would die of breast cancer without screening, against 21–23 with screening. Of the 200 women with a false positive screening result, 30 would undergo a biopsy with a benign outcome (8).

An independent UK panel has also evaluated different effects of mammographic screening. Their results (9) were published immediately after the supplement in the *Journal of Medical Screening*. While the Euroscreen working group based its analyses on results from service screening programmes (1–8), the UK panel used results from randomised studies (9). The conclusion was that breast cancer mortality was 20 % lower for invited than for non-invited women. Overdiagnosis was calculated to be 11–20 %. The panel assessed the benefits of mammographic screening to be greater than its harms, and recommends further mammographic screening in the UK. The facts that the randomised studies were conducted 20–50 years ago and were not designed to calculate the extent of excess breast cancer incidence were described as weaknesses of the study. Furthermore they described trend studies to be of limited value for evaluating mammographic screening, while cohort and case-control studies, which adjust for differences between attended and non-attended women, were evaluated as acceptable. However, the panel chose not to calculate the effect of these types of studies. Their justification was that the adjustments in question possibly result in estimates in favour of screening. It is therefore considered evident that no study design is faultless, either for calculation of mortality, increased incidence or false positive screening results.

The situation in Norway

The Mammography Programme started in four counties in 1996 and became nationwide in 2005 (12). Women in the age group 50–69 years are invited to mammographic screening biennially. The Cancer Registry of Norway is responsible for administration, quality control and evaluation of the programme.

Cancer statistics in Norway are currently updated through 2010. In other words we have limited follow-up time, particularly for women resident in the counties that were late in implementing the programme. To evaluate breast cancer mortality after introduction of the Norwegian Breast Cancer Screening Programme (NBCSP) , it is important to have individual-level information from a sufficient number of invited women who have been invited to/have attended the programme more than once. It is further claimed that 10–15 years' follow-up time is necessary to obtain the most exact estimates (9). Until now results from two analyses have been published on breast cancer mortality since the introduction of the programme (13, 14). Neither of the analyses used individual information on when the women were invited to or attended the screening, and the follow-up period is inadequate. Both analyses showed approximately 10 % lower breast cancer mortality among the presumably invited women. Given the shortcomings of the studies, both analyses may have underestimated the effect of the screening programme (15).

Another challenge in Norway is the fact that there is no information on the use of mammography outside of the programme. New data show that 32 % of breast cancer tumours that were diagnosed in women who did not attend the programme in Møre og Romsdal were asymptomatic and therefore may have been diagnosed through screening at private clinics (16). If this finding is representative for all the counties, it is possible that the reduction in mortality is underestimated among the attendees and overestimated among the invitees.

To calculate the extent of overdiagnosis of breast cancer tumours, a follow-up time of ten years has been proposed, but recently published studies imply that 10–15 years'– even lifelong – follow-up might be necessary (9, 17). Several studies have been published with figures from Norway, with estimates of 10–67 % (17–20). A number of the studies have been criticised for methodological weaknesses (21, 22), and only the one with the lowest estimate (17) uses individual data for invitation and attendance. The latter study shows 10–20 % excess cancer incidence, depending on the inclusion criteria.

The risk of false positive screening results in the Mammography Programme has previously been calculated to be of the same order of magnitude as the meta-analysis, 17 % for additional examinations with supplementary X-rays and/or ultrasound, and 3 % for those including a biopsy (23).

Important documentation

The European group chose to draw attention to the effect of organised screening programmes in Europe (1–8). As I see it, the supplement therefore represents an important addition to the debate on the benefits and costs of organised mammographic screening. The results are somewhat more in favour of screening than was shown by the independent UK evaluation panel (9). While the Euroscreen group concluded that two women's lives are saved for each that is overdiagnosed, the independent UK panel concluded that three women were diagnosed for each woman whose life was saved. Neither the *Journal of Medical Screening* supplement (1–8) nor the article in *The Lancet* (9) discusses interval cancer or stage-specific incidence, which is a weakness.

Based on results from quality parameters, we have previously found that the screening programme in Norway meets the recommendations given in the European guidelinesr (12). It is thus anticipated that analyses based on individual data and with an adequate follow-up period will identify a reduction in mortality corresponding to the meta-analyses in the *Journal of Medical Screening* and the results from the independent UK panel. The results from such studies are expected during 2013.

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