Breast Cancer Screening with Mammography

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Few, if any, medical interventions are as evidence based as mammography screening. More than 500,000 women have been entered into randomised trials to investigate the effect on breast cancer mortality. A reduction of the breast cancer mortality in the order of 20–30% has been demonstrated in women who were aged 50 years and older at entry into the trials [1–3]. This effect is due to earlier detection which also means less mutilating surgery and less drugs and radiotherapy in addition to less suffering from metastatic disease. Another benefit is the reassurance that many women experience after testing normal.

More controversial has been the effect of screening women aged 40–50 [4]. Subgroup analysis of some of the randomised trials has suggested a similar effect in this age group. However, it has been argued that part of the effect might have been due to screening after the age of 50 (due to the design of the randomised trials). Also, one study in Canada, specifically designed to investigate this age group, did not show any effect [5]. A recently published study from the UK, the so-called Age Trial, was designed to overcome the problem of bias from screening after the age of 50 by inviting women 39–41 years old and following them for 10 years [6]. A reduction of the breast cancer mortality of 17% (not statistically significant, $p = 0.11$) was seen which increased to 24% when adjusting for non-compliance (also not statistically significant, but close). For various reasons the effect may be somewhat underestimated in the Age Trial. Thus, the bulk of the evidence indicates an effect of screening women aged 40–50 which, in relative terms, may be similar to that seen in women aged 50–70. Over the years the results of the randomised trials have been questioned on the basis of methodological deficiencies, most fiercely by Goetzsche and Olsen [7]. Extensive analysis of the critique by several expert groups suggested that none, if any, bias was present that could have affected the overall results [1, 2].

Results from randomised trials do not necessarily translate into a service screening situation. However, there is accumulating evidence from several national service screening programmes that the effect in terms of breast cancer mortality reduction is at least as good as in the trials [8–10]. Nevertheless, it should be kept in mind that changes in breast cancer mortality due to screening may be difficult to distinguish from other trends in breast cancer mortality related to factors such as therapy and public attitudes to seeking advice early for breast symptoms.

To put the above data in perspective some statistics might be of interest. Breast cancer is a fairly common disease and the incidence has increased substantially in many countries over the last few decades. In Sweden the annual incidence in women aged 50–70 is approximately 33 new cases per 10,000 women. Fortunately, and in stark contrast to the impression often given in the lay press, the risk of dying from breast cancer is much less than the risk of developing breast cancer. In the age group 65–74 the risk is about 7 per 10,000, while all-cause mortality is about 140 cases per 10,000. The figures would be similar in many European countries. A 30% breast cancer risk reduction would mean 2 prevented deaths per 10,000. Thus, relative risks have to be considered in relation to the underlying absolute risk. A 30% reduction in a younger age group is a smaller number in absolute terms. As an example, in the Age Trial the breast cancer mortality reduction corresponded to 1 prevented death in 2,000 women attending the screening after almost 11 years of follow-up.

In addition to strong evidence of benefit a preventive intervention should carry little or no risk. Mammography screening does carry some distinctive risks. The principal negative effects of screening are false positive and false negative screening results as well as overdiagnosis of breast cancer. There is also a loss of quality of life due to the fact that women have to live longer with a diagnosis of breast cancer due to

the earlier diagnosis. Furthermore, there is a minute radiation hazard. Attempts have been made to quantify in easily understandable terms the pros and cons of screening [11].

In most programs, between 2 and 5% of screened women have to be recalled to undergo additional examination before they can be cleared of the suspicion of breast cancer. This means that during a 20-year period of screening with a 1.5 year interval up to 50% of the screening population run the risk of a false positive screening, resulting in anxiety in most women, albeit usually of short duration.

False negatives refer to breast cancer cases appearing after a normal screening examination before the next scheduled screening, often called interval cancers. There are multiple explanations, such as rapid growth rate, atypical radiographic presentation and, in a minor proportion of the cases, the radiologist overlooking or misinterpreting the cancer signs.

Overdiagnosis may be defined as the detection of breast cancer that would never have been detected, had the screening not been performed [12–15]. The magnitude of this problem has been estimated by several investigators with markedly discrepant results, varying from 3 to more than 30% of screening-

detected cancers. In the Malmö Mammographic Screening Trial we had a unique opportunity to study this issue, as the control groups were never invited in the cohort aged 55–69 at entry into the trial. We found 10% higher cumulated breast cancer incidence when we compared the whole invited group (including the non-attenders) with the control group 15 years after the end of the trial. If one looks at the attenders only, which may be more appropriate, the figure is over 20%. We conclude on the basis of our experience that for every life saved between 1 and 2 women were overdiagnosed through screening. The data on overdiagnosis also suggests that the risk of overdiagnosis is age dependent, being greater in the older screening ages (>55 years) and a minor problem in the younger (<50–55 years).

Breast cancer is a frightening disease to most women. The most important way to reduce the risk is regular mammography screening. However, this comes at a price and the balance between benefits and risks is delicate. Therefore, high-quality screening is mandatory. Also, understandable information about benefits and risks should be easily available as a basis for informed decision.

References

- 1 International Agency for Research on Cancer: Breast Cancer Screening. Oxford, UK, Oxford University Press, 2002.
- 2 Nyström L, Andersson I, Bjurstam N, Frisell J, Nordenskjöld B: Long-term effects of mammography screening: updated overview of the Swedish randomised trials. *Lancet* 2002;359:909–919.
- 3 Tabár L, Vitak B, Chen HH, et al.: The Swedish two-county trial twenty years later: updated mortality results and new insights from long-term follow-up. *Radiol Clin North Am* 2000;38:625–651.
- 4 Andersson I: Mammographic screening under age 50: a review. *Breast* 2000;9:125–129.
- 5 Miller AB, To T, Baines CJ, Wall C: The Canadian National Breast Screening Study 1: breast cancer mortality after 11 to 16 years of follow-up. *Ann Intern Med* 2002;137:E305–315.
- 6 Moss SM, Cuckle H, Evans A, Johns L, Waller M, Bobrow L; Trial Management Group: Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet* 2006;368:2053–2060.
- 7 Goetzsche PC, Olsen O: Is screening for breast cancer with mammography justifiable? *Lancet* 2000;355:129–134.
- 8 Blanks RG, Moss SM, McGahan CE, Quinn MJ, Babb PJ: Effect of NHS breast screening programme on mortality from breast cancer, England and Wales, 1990–8: comparison of observed with predicted mortality. *Br Med J* 2000;321:665–669.
- 9 Otto SJ, Fracheboud J, Looman CWN, et al.: Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. *Lancet* 2003;361:1411–1417.
- 10 The Swedish Organised Service Screening Evaluation Group: Reduction in breast cancer mortality from organized service screening with mammography: 1. Further confirmation with extended data. *Cancer Epidemiol Biomarkers Prev* 2006;15:45–51.
- 11 Barratt A, Howard K, Irwig L, Salkeld G, Houssami N: Model of outcomes of screening mammography: information to support informed choices. *BMJ* 2005;330:936.
- 12 Duffy SW, Agbaje O, Tabar, Vitak B, Bjurstam N, Bjorneld L et al.: Overdiagnosis and overtreatment of breast cancer: estimates of overdiagnosis from two trials of mammographic screening for breast cancer. *Breast Cancer Res* 2005;7:258–265.
- 13 Paci E, Miccinesi G, Puliti D, et al.: Estimate of overdiagnosis of breast cancer due to mammography after adjustment for lead time. A service screening study in Italy. *Breast Cancer Res* 2006;8:R68.
- 14 Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP: Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. *BMJ* 2006;332:689–692.
- 15 Zahl PH, Strand BH, Maehlen J: Incidence of breast cancer in Norway and Sweden during introduction of nationwide screening: prospective cohort study. *BMJ* 2004;328:921–942.