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Current Controversies in Cancer

Is Mass Screening for Breast Cancer Cost-effective?

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WHY IS THE EFFECTIVENESS OF BREAST CANCER SCREENING STILL DISCUSSED?

Curative therapy for breast cancer detected at an advanced stage is insufficient. Breast cancer screening is designed to detect tumours at such an early stage that they can still be treated effectively. The chance of dying of breast cancer is thus reduced for those women who participate in high quality screening. Various trial projects, in which women were invited to participate in mammographic screening, have shown that a reduction in breast cancer mortality is, indeed, achieved. In 1963 the randomised Health Insurance Plan (HIP) trial was set up in New York [1]. More than 60 000 women aged 40–65 years who were insured under the Health Insurance Plan of Greater New York were randomly divided into two groups. Half the women were invited for mammographic screening and clinical examination (the study population). The other half were not, acting as the control population. Women in the study group were offered screening a total of four times, at yearly intervals. After 10 years, the mortality from breast cancer of patients (diagnosed within 5 years after entry) aged 50 years and over was 32% lower in the study population than in the control population.

Swedish trials with new technology (film-screen mammography and media-lateral oblique views) were set up towards the end of the 1970s. The Kopparberg/Östergötland trial covered two rural areas in the south-east and mid-west of Sweden [2]. Randomisation was carried out by dividing each of nineteen homogenous social-economic areas into (one or more) areas with a control group and a study group. After an average follow-up period of 6 years for each woman offered screening, the first results were published showing a significant reduction in mortality from breast cancer of 39% in the study population for women aged 50–74 years. Randomised screening trials were also started in a number of Swedish urban areas: Malmö, Stockholm and Göteborg. In two areas in the United Kingdom, women were invited for mammographic screening; women were encouraged to carry out breast self-examination in a further two areas, and there were four control areas. Some element of randomisation was added at the beginning of Edinburgh, one of the two areas where mammographic screening was carried out: 84 general practices were randomly distributed into practices where women were invited and those where they were not.

To date, all these randomised trials, and also non-randomised projects in the United Kingdom, The Netherlands and Italy, and a project in Canada which randomised volunteers, have proven to reduce breast cancer mortality for women invited aged 50–69 years.

They, therefore, confirm the theoretical concept of screening and some of the clinical evidence. Clinical studies had shown that, for breast cancer, the size of the primary tumour at initial treatment and, therefore, the time of detection correlates strongly with the probability of metastatic dissemination. The greater the clinical volume, the higher the proportion of metastases appearing later during the course of disease following primary treatment [3]. In a more recent study on 103 primary breast cancers, it was found that significantly higher degrees of vascularisation (by counting of microvessels) were found in tumours than in normal tissue and this was significantly associated with node metastases [4]. The results suggested that angiogenesis is closely linked to metastasis, that metastasis is only acquired at a critical density of vessels, and that this process occurs as tumours enlarge (or become poorly differentiated). The detection and treatment of cancers before a critical number of blood vessels has been induced could then, theoretically, lead to a reduction in cancer mortality.

BREAST CANCER MORTALITY REDUCTION: NO DIMINISHING RETURN WITH TIME

Since the publication of the first European results in 1985 showing a 39% mortality reduction [2], no other trial has ever published such a large difference in effect. The first results from Malmö were published in 1988 [5], showing a seemingly more unfavourable 21% reduction in women aged 55 and over after an average study period of more than 8 years. This then, has consistently led to discussions on the 'real' efficacy of mammographic screening. It is suggested that the high quality in the earlier trials is either not sustained in the more modern situations or that changes

outside of the screening programme influence the effect of screening between the invited (for screening) group and the control group as time goes by.

Although both explanations should not be ruled out, important characteristics of the screening policies in the two aforementioned Swedish trials, and all trials in general, such as screening interval, attendance rate, follow-up period and age groups, should first be considered, since these markedly differ.

A combined analysis of all five randomised Swedish trials with more than 250 000 women and 10 years of follow-up has confirmed the earlier publications: at the end of December 1989, a 29.5% statistically significant difference in breast cancer mortality was found for women aged 50–69 years invited for screening [6]. Weighted for trial sizes, the Kopparberg, Östergötland and Malmö trials had earlier shown a 32% average reduction [7]. So, are the critics right? [8]. Is there a diminishing return with time in breast cancer mortality reduction due to screening?

The newest results include the Stockholm and Göteborg trials with substantially shorter follow-up, less broad age ranges, intermediate attendance rates, and other screening intervals than the earlier started and reported three Swedish trials. Computer modelling using one underlying model that incorporates both the natural history of breast cancer and the performance of mammographic screening for all five trials, but taking into account as many relevant differences in screening policy between the trials, have made it plausible that the more recently observed results are indeed more favourable with regard to the effect of screening than estimated earlier [9]. If the earlier experience in the effect of screening (the improvement in prognosis for early screen-detected cancers) from the three Malmö, Kopparberg, Östergötland trials had been the reference value for all five Swedish trials, one would even have expected a smaller overall reduction of 26.5% compared to the 29.5% observed, only due to the different policy characteristics in the most recently started trials. There is no evidence from the trials for a diminishing return with time for women aged 50–69 years.

EFFECTIVENESS IN PROGRAMMES

Large European nationwide programmes, targeting all women in a certain age group at national level, have been initiated on the basis of the positive initial results from the trials. The United Kingdom launched its programme for women aged 50–64 years at 3-yearly intervals around 1987 [10], followed by The Netherlands in 1988 with a programme for women aged 50–69 at 2-yearly intervals [11] and Finland for women aged 50–59 years initially at 2-yearly intervals. Apparently, the policy-makers agreed on only one thing, the lower age limit of 50. The United Kingdom predicted a 25% breast cancer mortality reduction rate for the invited group aged 50–64 years with the U.K. screening programme, emphasising the Kopparberg/Östergötland results [12]. In The Netherlands, predictions have been based on the reductions seen in the five Swedish randomised trials and the experience achieved in the previous Nijmegen and Utrecht projects (regarding detection rates, interval cancers and stage distributions) [7, 9]. A 17% reduction in the annual total female breast cancer mortality rate seems realistic, which is the same as approximately 23% in the invited group (50–69 years). The age range in The Netherlands is, however, broader, and the screening interval shorter, which would make the U.K. estimates too optimistic according to the Dutch research [9, 13]. Recently, researchers from the U.K. have also challenged the predictions [14]. Still, these possible reductions for women aged 50 years and over are tremendous substantial figures. In The Netherlands, each year 700–800 women will no longer die from breast cancer (metastases), in the U.K. this figure may possibly be 3–4 times more. The question is, therefore, no longer whether screening is effective, but how effective it is?

Of course, the change in population breast cancer mortality, being the ultimate goal, cannot yet be seen, but both from the U.K. and the Dutch programme, nationwide results of the first years of the screening programmes are becoming available, on approximately 2.7 million and 1.0 million screens, respectively [10, 11]. In general, the first results are good. An attendance level between 70 and 80%, on average, is being reached, the number of women who need further assessment after screening is limited to 1.5–7% and the detection rates at first screening are 6 to 7 per thousand screened women (in these populations with a relatively high background incidence). There is a substantial shift towards earlier detection reflected in favourable size distributions for tumours detected at screening, as well as in the more favourable axillary lymph node status. In the Dutch situation, these data are comparable or even better than initially anticipated; in the U.K. the anticipated size distribution for screen-detected cancers was suggested to be more favourable than the Dutch anticipation, and appears now to be generally the same as in the Dutch programme. Furthermore, the suggestion is that social-economic differences do not influence the attendance rate in The Netherlands [15].

The interval cancer rates are not yet known at the national level, but regional data from the U.K. suggest that these are higher than seen for instance in the Kopparberg/Östergötland trial [14, 16]. It is especially these data and the preliminary data on subsequent screens that might suggest a lower mortality reduction in the nationwide programmes than seen in the Kopparberg/Östergötland trial. Day and associates have estimated a 19% reduction in East Anglia, given the current rate of interval cancers [14]. Dutch investigators estimated a 21% reduction in the specific age group 50–64 if the U.K. policy had been chosen for The Netherlands [13]. The message from the nationwide programmes is, therefore, 2-fold: on the one hand, the initial process has been put in place with substantially important achievements in the countries involved. While, on the other hand, much effort should still go into improving the nationwide results up to the highest standards possible. One must admit that the Kopparberg/Östergötland trial has shown the most favourable point estimate of all five Swedish trials [6, 9]. In fact, all five Swedish randomised trials might be used as a reference in forecasting the expected reduction in other programmes, since these can be considered to give the most conclusive evidence on the effect of mammographic screening. However, detailed data on detection rates, interval cancers, stage distributions and the background situation are not (yet) available from each Swedish trial to give a correct interpretation of the impact

of any quality differences between the trials, and to make comparisons with the nationwide screening programmes. Meticulous monitoring of the nationwide programmes and comparisons with the predictions made will remain crucial.

AGE CATEGORIES TO BE INVITED

The discussion on the age categories of women to be invited for screening sometimes seems preoccupied with younger women. The upper age limit is as interesting but under-rated. Stating that breast cancer screening is clearly beneficial for women aged 50–69 years challenges one to make the statement that the same will apply at higher ages too. There is no ground to assume a substantial different natural course of disease nor a substantial different quality of mammography regarding the higher age groups. Scientifically, we are facing a problem, since randomised trials including older women is limited to the Kopparberg/Östergötland trial, which included women up to 74 years of age at entry. Did women not live long enough at the start of the trials to include them? In the Swedish 'overview', the reduction in women aged 70–74 years at entry was limited to 6%, and confidence intervals were wide, but no major differences were found in ages 65–74 years at entry or 50–64 years at entry [17]. Non-randomised results are available from Nijmegen and the U.S.A. only. The possible lower attendance rate has initially been put forward as a reason not to include women aged 65 years and over in the U.K. programme. The Dutch results now show no reason to support this with attendance levels only 5% less in women aged 65–69 years than for younger women. The U.K. Health Select Committee recently recommended that the upper age limit for inclusion in the call and recall system should be extended to 69 years [18].

Boer and colleagues have shown that the number of breast cancer deaths prevented and life-years gained will increase substantially when extending the upper age limit of screening [19]. The counterpart is an increase in lead time years, which are the extra number of years after the diagnosis of breast cancer due to the earlier diagnosis by screening for some of the women. The higher probability of women dying from other causes (after screen-detection) and the possible larger increase in lead time years at older ages, makes screening programmes with upper age limits higher than 80 years of age unequally balanced towards unfavourable effects of screening. A small loss in quality of life for the women involved, during such years in follow-up, can be assumed due to the experience of several medical follow-up procedures and by the negative impact on a woman's quality of life resulting from treatment and the knowledge that she has had breast cancer [20], although research has shown that with long follow-up, prevalence of anxiety and depression is not increased [21]. When starting a nationwide programme, an upper age boundary of 75 years has to be carefully considered. For the already existing programmes, emphasis should be put on establishing a high quality screening programme for the already invited age group, comparable to the earlier screening trials, before extending the programme to more women.

Contrary to all the positive results for the older women, there was no hard evidence for a possible effect of breast cancer screening in women aged under 50 years of age. No single trial has shown a significant mortality reduction in this age group, and neither did the first 'overview' of the five Swedish trials combined including 800 000 person-years of follow-up [22]. It did show a 10–13% mortality reduction, but only after 9 years of follow-up for women aged 40–49 years at entry. Part of the observed mortality reduction in these women is likely to have been a result of detecting the cancer earlier in later rounds when the women were 50 years or older [9]. With longer follow-up of the trials, this might lead to observed mortality reductions that are significant in this age group entering the trial, merely due to the beneficial effect of screening at older ages. True data on age at detection and mortality differences were not available until recently. Tabár and colleagues have shown that, in the women aged 40–49 years at randomisation, 36% of the breast cancers were indeed diagnosed at age 50 years and over. They could not find less benefit in the women with screen-detected cancers before age 50 than for cancers detected at later ages [23], but the other trials have not yet answered this question. The newest results from Sweden are again promising, showing a 23% reduction in the younger age group [24]. Before we value this as an equally effective programme in younger versus elderly women, it is crucial to have a reasonable estimate with regard to the amount of reduction achieved for these women entering the trials at younger ages on the basis of screening in later rounds (for all trials).

Thus, it is possible that benefit may also be achieved in younger women under the age of 50 years. However, sensitivity of mammography is lower and the period that the cancer might be detected by screening before clinical diagnosis is shorter. A shorter interval in the younger age group is thus needed, which brings us to cost-effectiveness.

IS SCREENING COST-EFFECTIVE?

Published cost-effectiveness ratios on breast cancer screening range remarkably. In a review of 16 such studies, the predicted cost per life-year saved ranged from US$ 3400 to 83 830 for screening women over the age of 49 years [25]. This seems no real advertisement for cost-effectiveness analyses, in general, one would say. However, many factors influence the final ratio. The estimated cost of providing the direct screening services is probably the most obvious one and is related to the price of screening and the frequency at which it is delivered to the population. If the 16 studies are adjusted for this factor alone, the range becomes smaller, between US$ 9500 and 35 500. However, when examining two representative studies in detail, the Office of Technology Assessment-study [26] and the Dutch [7], the results reported are not as arbitrary as they seem. When comparably defined programmes are evaluated using similar assumptions about consequences, very similar results are obtained in the overview of approximately US$ 7000 per life-year saved in both analyses. It is estimated that in the long-run, 47% of the annual cost of screening might be offset by savings due to a decrease in the number of women with advanced disease. If costs generated by screening are taken into account, one third of the cost of screening will be countered by savings in a 2-yearly programme for women aged 50–69 years.

Thus, there is much evidence and well described research on the cost-effectiveness of breast cancer screening and for women aged 50 and over, high quality screening can be

considered to be cost-effective compared to other health-care programmes. The cervical cancer screening in The Netherlands, for instance, is three times more costly to gain one life-year. A 2- or 3-year interval breast programme is almost equally cost-effective, although the number (and %) of deaths prevented is substantially lower with a 3-year programme. Including women aged 40–49 years in a nationwide programme was initially estimated to lead to a marginal cost-effectiveness ratio of approximately seven times higher cost for the same amount of life-years gained than for a nationwide programme inviting women aged 50 years and over [7]. The newest results from Sweden will make the difference certainly smaller.

ONE UNIFORM DECISION FOR ALL COUNTRIES WOULD BE INAPPROPRIATE

The positive findings described above on the (cost-) effectiveness of screening women aged 50 years and over apply, in principal, to all countries with a similar population of women with breast cancer to that of the trials or those used in the cost-effectiveness analyses. It is, however, far from evident that each country should, therefore, start a nationwide programme. In countries with relatively low incidence and mortality rates of breast cancer, even in Europe, the cost-effectiveness ratio may be up to five times less favourable than for the U.K. or The Netherlands [27], simply because less absolute benefit is to be gained from screening if the burden of disease is less. A less frequent programme might be more appropriate comparing other health-care needs. Furthermore, there may be large differences in cost in so-called decentralised systems, especially if related to the total health-care budget. In developing countries, the use of less costly screening services should be seriously considered. Even more important, estimates are based on potentially high quality programmes, considering the experience already present in parts of some countries. The critics may, of course, be right, in stating that high quality interpretation has to be taught and that high quality performance needs a well-established system with involvement of all disciplines and quality and evaluation assurance. Pilot projects in other countries should, therefore, be a guide in estimating more precisely the possible effects and cost of screening in other countries. German data showed a clear indication that improvement was needed in attendance and quality in order to achieve the same cost-effective ratios as seen in The Netherlands and the U.K. [28].

Therefore, while breast cancer screening is effective, this is dependent on the quality of the screening programme. Furthermore, the balance between favourable and unfavourable effects for the woman is delicate. For 30% of women with screen-detected cancer, the screening programme will result in cure—they would otherwise have died of breast cancer. For each breast cancer death prevented, almost 1000 screens will have to be done in countries with a high incidence. In particular, for those women with a positive test result needing further diagnostic assessment, quality of life is temporarily reduced. Furthermore, an increased incidence of 2% in breast cancer is expected from cancers detected in the programme that would not have been detected during the womens' life time without the programme [29].

Finally, the most recent reduction in breast cancer mortality in England and Wales has led to some discussion: Is this due to the benefit of the nationwide screening programme, the benefit of (adjuvant systemic) treatment, or the earlier diagnosis of breast cancer outside the screening [30], or a cohort effect? The still relatively high incidence in the U.K. and especially the high mortality:incidence ratio makes a U.K. breast screening programme still highly cost-effective. It is difficult to interpret the intermingling with adjuvant systemic treatment for screen-detected cancers. Does the early detection mean detecting the cancer before important micrometastases have occurred (adjuvant treatment no additional benefit) or at a time when micrometastases can still be cured (additional benefit of treatment)? The trend towards earlier clinical diagnosis has also been used in postulating that the effect of the nationwide screening programmes now being introduced is less than seen in the trials. If we assume that the general shortening of the delay between onset of disease and clinical diagnosis leads to a rather high and immediate 25% decrease in the chance of a breast cancer patient, not diagnosed via screening, dying of her disease, the cost-effectiveness ratio will be US$ 6500 instead of US$ 4000; an important difference, but still a very favourable ratio to base your health policy upon. However, we are then forgeting the cost and effort needed and the unfavourable effects induced by achieving an earlier diagnosis outside of a regular screening programme.

Unless the future tells us otherwise, high quality mass screening for breast cancer for women aged 50–75 years is relatively cost-effective.

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FEMALE HEALTH AND BREAST CANCER RISKS AND TRENDS

NEVER BEFORE in history have women in industrialised countries had a more favourable life expectancy than today; for those over 55 years of age, mortality for the major diseases is generally two to three times higher for males, so male life expectancy is 5 to 7 years shorter. Although breast cancer is the most frequent female cancer, 9 out of 10 women ultimately will not develop breast cancer and 19 out of 20 will not die from it in North-Western Europe and the U.S.A. Whereas the incidence of breast cancer in most of these countries has increased at all ages according to birth cohort, and since the mid 1970s, upon the introduction of mammography, age-adjusted mortality rates have either increased slightly or remained unchanged. They started to decline among premenopausal women (especially those born after 1950) in the high-incidence populations in the U.K., Switzerland, Holland, Scandinavia except Norway, and the U.S.A. [1]. For women over 70 years of age an increase was generally observed, while life expectancy rose by a few years. In Southern and Eastern Europe, the breast cancer rates are generally lower, but on the increase. In high incidence populations, relative 10-year survival for patients 45–74 years of age with clinically detected cancer was more than 50%, being lower in populations with low incidence rates and/or a less favourable stage distribution [2]. Smaller and less aggressive cancers have increasingly been detected since the 1970s, even without organised screening programmes [3], which probably lowers the gain of screening in the future. Moreover, wide application of effective hormonal and cytotoxic therapy is likely to affect mortality from breast cancer [4].

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