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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].
BREAST SCREENING AND MANAGEMENT OF NON-PALPABLE LESIONS IS COMPLEX

The literature on the screening and management of non-palpable lesions appears to contain more incitements of high quality than any other care programme [5], which is also relevant for the communication between the various physicians involved, and between them and the worried healthy women, whose risk perception is often determined by 'worst case' scenarios. Therefore, screening for breast cancer, together with management of non-palpable lesions, comprises a complex set of medical activities with uncertain outcome, whose final measurement demands a long period of time. Also, in view of the subjective and paradoxical nature of medical and political decision making processes, the effectiveness and cost of breast cancer screening must be considered within a broader context of the health service and public health, taking the capacity of the health service and female life expectancy into account as well as 'competitive' breast cancer mortality lowering interventions. There may also be differences between screening as epidemiological research and in clinical practice, so future effectiveness may be different from past efficacy. The often-cited evaluation criteria of Wilson and Junger [6] are largely insufficient for this purpose. My evaluation occurs at different levels and comprises: desirability (values), efficacy (scientific proof), effectiveness (future efficacy in 'routine' practice), side-effects (positive and negative; for patients, doctors and care system) and, derived from this, efficiency. Finally, a screening programme, being initialised by care providers, can be weighed at these levels against other care programmes.

Most evaluations of mass mammographic screening show it to be an effective intervention against death from breast cancer in women above 50 years of age of which the cost per life-year saved seems reasonable. This is based on research programmes carried out in high breast cancer mortality populations within adequately functioning health care systems which were not too strained. Nonetheless, I have serious doubts about the short term side-effects and the long-term effects and costs, even in The Netherlands, with a relatively appropriate organisation and funding of the health service, in which a nationwide screening programme of biannual double view mammography was introduced for all women between 50 and 70 years of age. Despite many years of intensive policy-making, mass breast screening was considered in isolation, instead of being just one of the tools of increasingly complex breast cancer management in which breast cancer treatment was also introduced. First, the nature of screening in medical research and medical practice will be clarified.

SCREENING IS EPIDEMIOLOGICAL RESEARCH RATHER THAN MEDICAL PRACTICE

Screening is at the beginning of the systematic observation of determinants of the course of diseases with a long preclinical phase, usually by means of a population-based survey, with regular and long-term follow-up. Sometimes minimal interventions are carried out, preferably tested by means of controlled studies. This becomes difficult when new technologies and/or better tumour biology lead to a higher prevalence of less aggressive disease determined by more sensitive detection methods [7]. Diagnosis in chronic diseases is like uncovering the tip of an iceberg, which is always well illustrated in autopsy studies of most cancers [8]. The prevalence of (pre)malignant breast lesions was as much as 40% in women of 40 to 54 years who had died in accidents [9]. Only one in four of these women would probably ever have developed clinically relevant breast cancer and one in eight would have died from it. The study of disease progression and regression in screen-detected lesions is a virgin-like field, in which diagnoses of early phases or lesions of disease must repeatedly be revised. Apparently simple calculations of the sensitivity, specificity or predictive value of death of diagnostics are not only dependent upon the detection methods and skills of the practicing scientist (with learning curves), but also upon the shifting classification of potential lethal malignancy. Such subtleties do not work well in risk-shunning medical practice in which premanifest forms of breast cancer tend to be considered as lethal, if not by the pathologist, who unfortunately does not have the most appropriate terminology available [10], then by the surgeon and even more by worried women. This would be less of a problem if non-invasive, 'simple' treatments of DCIS lesions existed with few side-effects. Because of the long time-span needed for evaluation of mortality, the effects of screening are likely to be diluted rather than enhanced in the future by 'competitive' effects of a variety of other death-risk reducing interventions. One could argue that screening for breast cancer should not leave the research phase unless the threat of cancer (treatment) can be managed properly.

PREVENTION OF BREAST CANCER IS DESIRABLE

Should mass screening of a lethal disease, such as breast cancer, a complex and costly affair, in part due to overdiagnosis, be performed among postmenopausal women in industrialised countries whose life-expectancy has already improved dramatically in the last 50 years (at any age), and certainly compared to men? This phenomenon is even stronger among women of higher social classes. Will women, most of them already widowed for up to 15 years, not have other health worries? They are never asked. Alternatively, the desirability of preventing breast cancer, the most frequent cancer among women and a mutilating disease, is great, but the means are still far from perfect. Given current knowledge, primary prevention would have to start after menarch, but this is still in the distant future, and current knowledge of pathogenesis is insufficient for application of low-cost 'end' technologies. More research is thus desired. Avoiding breast cancer (death) in premenopausal women, i.e. by means of screening, would be more desirable because the relative mortality is high (Figure 1). However, mass screening has even less to offer women in middle age [11] when they are usually most needed by their (grand)children and/or partners and more life-years can be gained. Then there is the problem of resources: the extra expense of a screening programme must either by subtracted from other health-care activities or added to the—in the view of many policymakers—costs of the already overburdened, ever extending and unmanageable health-care system, with further risk of creating a precedent for introduction of other screening programmes, for example, for
Age-specific incidence of and (relative) mortality with increasing age, but the lower sensitivity and specificity colorectal and prostate cancer, which may be inefficient, as seen in cervical cancer screening.

**MASS BREAST SCREENING BECOMES LESS EFFICACIOUS WITH TIME**

Mass screening has proved to be gradually more effective with increasing age, but the lower sensitivity and specificity of mammography in premenopausal women and the non-significantly higher mortality in the first 5 years after screening in three studies (Two-country, Malmö and Canada) remains worrying [12]. Breast cancer screening of women over 50 years of age appeared to lower mortality by approximately 30% in the group invited for screening (only affecting those aged 55 years and over); this result was based on participation rates of over 70%, the target of most screening projects [13]. However, these research projects were mostly carried out at the end of the 1970s and in the early 1980s, when breast cancer awareness was less and stage-distribution improved substantially between 1975 and 1992: the proportion of patients with a less favourable stage distribution, which may explain the recent decline in England and Wales [16]. Based on the meta-analysis [4], a decrease in breast cancer mortality between 6 and 12% can be expected. Such decreases may be even larger in populations with a less favourable stage distribution, which may be expected to increase in the future, unless the programmes improve. In the Eindhoven Cancer Registry (as in many other areas in Europe), stage distribution improved substantially between 1975 and 1992: the proportion of patients with stage I (pTNM) tumours increased from 25 to 40% [3].

**SIDE-EFFECTS ARE NOT ONLY MEDICAL**

The afore-mentioned capacity problems either do not exist (because of ample supply of specialised care etc.) or they affect the effectiveness of the screening programme due to a lack of adherence to all guidelines. Unless efficiency increases, the access to care for other patients in need of the same doctors or facilities is affected, for example, remaining longer on waiting lists. The temporary increase (25 to 50%) in hospital-based activities for patients with early breast cancer, i.e. personnel working in pathological laboratories, surgical theatres and radiotherapy units, is often not accounted for. Although hard to verify, external side-effects are often related to breast cancer. The patient-related effects and side-effects of breast screening remain substantial, if related to prevented deaths (Table 1). Women are generally not aware of this, even within the Dutch programme, which will certainly lead to frustration later and malpractice suits. The patient-related effects and side-effects have been simulated extensively by means of elaborate models [18]. However, the care system-related side-effects are less well known and the extent of the effects remains unclear.

5% of postmenopausal patients would be involved, but also because of other risk factors.

### Table 1. Medical side-effects of biannual breast screening at age 50–69 years

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Number of women ‘bothered’ in order to save one life</th>
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<tr>
<td></td>
<td>Activity</td>
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<td></td>
<td>‘Best case’</td>
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<tr>
<td></td>
<td>Mammographies of healthy women</td>
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<td>Follow-up diagnostics</td>
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<td>Unnecessary treatment DCIS</td>
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<td></td>
<td>Patients with longer disease duration*</td>
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*The number of life-years with (useless) knowledge of having breast cancer would equal saved life-years. DCIS, ductal carcinoma in situ.
not only dependent on the performance of the programme, but also on the application of other death-reducing interventions. Side-effects may further diminish by unequivocal definition and/or 'benign' control (chemoprevention?) of in situ lesions.

**COST CALCULATIONS ARE VERY ARBITRARY**

The current cost calculations have in common not only that outcomes (expenses per gained life-year) vary according to incidence, type of screening programme and the prices for (or costs of) services, but also that they arbitrarily include and exclude items. Changes in stage-distribution and severity of the disease, birth cohort effects and the differences between efficacy and effectiveness, i.e. effects of 'competitive' interventions, can be substantial, but most of these tend to lead to less favourable effects and higher costs. Alternatively, future inflation may be lower than the used 5% discount rate. The cost per gained year-of-life in The Netherlands will probably vary between $5000 and $10 000 to which expenses for health-care during the gained life-years must be added, roughly equal to the costs of the screening programme [19]. It is debatable whether explicit provisions for these costs should be made; I would propose not to hide them, because public outcries against the ever-increasing costs of health services for the ever-increasing number of elderly are always likely to arise. Even if the estimated cost-effectiveness ratios were relevant, a direct translation into the budgets of hospitals and specialists who collaborate in screening programmes, for example, money for quality control, is difficult. The substantial overhead costs of the extensive policy-making and administrative processes not only remain hidden, other care programmes may suffer from lack of attention. Moreover, in health care systems confronted with lowering public expenses, political choices are certainly more influenced by pressure groups of (fewer and more modest) sick [20].

**CONCLUSIONS**

The research efforts of investigators of breast screening have contributed to uncovering the complexities of detection, classification, management and course of non-palpable breast tumours. Nonetheless, against the background of the very good life expectancy of postmenopausal women in industrialised countries, especially compared to men, the provision of a potentially life-saving but complex screening programme to women is less desirable than it seems. Moreover, screening is likely to yield lower results in the future, thanks also to competing, mortality-reducing interventions and a lower expected performance of 'routine' public health programmes compared with the past scientific projects. Mass screening will probably also yield smaller effects on mortality in areas with good access to 'dedicated' breast specialists. Screening should never be initiated before the management of early breast cancer, non-palpable lesions in particular, is properly organised for women of all ages, which could mean that screening may yield lower effects and become superfluous. Women should receive less alarming information on their health and of a disease which exhibits improved survival in most countries; if screening is offered, they should be better informed about the inherent complexities and side-effects. When proposals for mass single, preventive interventions for a chronic disease are put forward, politicians should rather ask for improvements, e.g. better access, of diagnostic care, including genetic screening. If the public still insists on mass screening (for women aged 50 to 70 years), the various medical disciplines should guarantee to offer screening without disturbing related health services or hampering other patients. Politicians should also verify whether research of pathogenesis and aetiology should not prevail, or be prepared to spend extra money on complex care for decades, as long as simple treatment methods are not available.

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When experts in health care are asked to give an opinion on so-called controversial themes, differences of ideas are restricted to personal appreciation of uncertainties and of imponderable pros and cons, or to personal predictions of future technical developments and/or social changes in the society. In fact, the messages of both the contributions of de Koning and Coebergh above are not too divergent.

Yet we have to give careful attention to the nuances in both views, to the subtle differences in their feelings, when decisions on the start or guidance of screening actions come up for discussion. Population-based screening programmes are very expensive and such complicated undertakings need great organisational skill and have complicated ethical aspects.

The decision making involved to start screening programmes or to continue financial support is often disturbed by improper political pressure. The medical world should have a standpoint based upon an unbiased interpretation of data and an ethical, sound view of the uncertainties. Thus, both the facts and hypotheses are important.

Coebergh challenges the benefits of screening considering other needs in health-care, which should have higher priority; he also suggests methods or mechanisms other than screening which might improve survival in breast cancer, such as better primary treatment or educational activities to increase the alertness of women on early self-detection. De Koning states that screening is cost effective, but only if the population to be screened is carefully chosen (specific age categories—in countries with high incidence of breast cancer) and if the quality of the screening process is high. Coebergh questions the theoretical benefits of screening: with early diagnosis survival will be better, but he argues that the gains claimed by the screening programmes might not be that substantial, with a strong negative effect on the cost–benefit analysis.

Assessment of the components constituting cost and benefit is complicated. The benefit should be a decrease in breast cancer mortality. This has been demonstrated in several ‘randomised’ trials as indicated by de Koning. We should keep in mind that methodologically optimal randomisation techniques, such as those used in testing a new pharmaceutical compound, are not possible to prove the benefit of screening. These imperfections influence the magnitude of the effect of screening, yet differences in favour of screening are seen in all these studies.

The gain in the very ‘civilised’ countries will be less substantial than postulated because of increasing alertness of women and better structured surveillance in risk groups. This is mentioned by de Koning, but is emphasised (used as main argument) by Coebergh. One should not forget, however, that the increased alertness leading to earlier detection outside screening programmes might also be seen as an (indirect) effect of screening programmes with their intensive publicity, and this secondary effect might fade away again when screening stops!

Better breast cancer treatment for the whole population might be seen as an indirect positive effect of screening with its quality assurance programmes. This might result in a survival benefit to an extent that surpasses that of the screening itself. To quantify all the benefit and to state what is caused by what in these inter-related systems is impossible and this leads to individual interpretations.

The costs are even more difficult to measure. The psychological harm caused by more years of ‘knowledge’ in the detected breast cancer cases, by overtreatment of borderline cases and by the anxiety produced by a ‘false alarm’ or after detection of false negative cases (‘missed’ or mammographically occult lesions) is fairly imponderable and difficult to quantify. These points are stressed by Coebergh and were also recently carefully described by Baum in his eloquent comment on his change of view on breast cancer screening in the U.K. [1]. It is clear that these items are difficult to weigh in the cost–benefit analysis and are certainly seen with a magnifying glass by those who are opponents of breast cancer screening, but these aspects should never be neglected. Personal feelings determine the weight to be given to such factors in the balance of pros and cons.

The pure economic costs are more easily visualised, but even this is complicated. The ‘cost’ per gained life-year is influenced by many details in the set-up of screening programmes; very sophisticated models have been designed to quantify all this, as is described by de Koning. The chosen interval between the screening rounds, the age limits of the...