Benefits and Risks of Breast Cancer Screening

Pro: Achim Wöckela  Wolfgang Jannib

a Department of Gynecology and Obstetrics, University Hospital Würzburg, Würzburg, Germany  
b Department of Obstetrics and Gynaecology, University of Ulm, Ulm, Germany

Contra: Franz Porzsoltc,d  
c Versorgungsforschung, Klinik für Allgemein-und Viszeralchirurgie, Universitätsklinikum Ulm, Ulm, Germany  
d Institute of Clinical Economics e.V., An-Institut der Hochschule Neu-Ulm, Hochschulschloss Vöhlín, Illertissen, Germany

Comment: Rita Schmutzleré  
é Zentrum Familiärer Brust- und Eierstockkrebs, Universitätsklinikum Köln, Köln, Germany

Breast Cancer Screening: Pro

Achim Wöckel (Würzburg); Wolfgang Janni (Ulm)

Worldwide, breast cancer remains the most common form of cancer affecting women. In Germany, more than 70,000 women are diagnosed with breast cancer annually, 17,000 of whom die each year from their disease [1]. Nationwide, mammography is used in the group of 50- to 69-year-olds for early detection of breast cancer. Unlike curative mammography, screening examinations are performed at highly specialized centres with a sophisticated quality management programme in place. To be able to participate in the programme, the corresponding qualifications must be verified by annual audits. The outcome rates are verified by special higher-ranking bodies, called reference centres. In total, Germany has 94 screening centres around the country. By definition, the objective of screening mammography is not just to lower overall breast cancer mortality. Rather, the paramount aim is also to discover tumours at an early stage and thereby improve survival and quality of life of the women affected. This definition by itself makes it obvious that numerous different endpoints need to be analysed in order to evaluate the benefits of this type of screening intervention. Besides direct parameters like breast cancer mortality, a more complex analytical approach must also address other rapidly changing surrogate parameters such as increases in incidences and staging shifts in favour of smaller and thus prognostically more favourable tumours. These surrogate parameters also include changes in tumour therapies trending towards less radical locoregional treatments or less aggressive systemic regimens. The above highlights the importance of the current debate surrounding these surrogate parameters, given that mortality effects can only be estimated over relatively long observation periods. Since such a broadly comprehensive and functioning screening programme was not implemented nationwide until 2006, evidence for any specific effects on mortality in Germany is still lacking.

Impact of Screening on Prognostic Surrogate Parameters and Treatment Modalities

Breast cancer is not a singular illness, but comprises a very heterogeneous group of various subtypes with differing prognoses. In general, the survival rate is dependent on specific prognostic factors. These include tumour size, axillary lymph node metastases, distant metastases (TNM classification) and histological differentiation grade. Hypothetically, it should be possible to favourably influence these prognostic surrogate parameters with effective screening interventions. Furthermore, changes in tumour stages and prognostic factors have had a considerable impact on locoregional and systemic therapies, which also might be one reason for an association between certain trends and screening interventions. Recently published studies have impressively demonstrated these effects: As early as 2003, a screening mammography programme was commenced in Bavaria, which was turned over to the national screening programme in 2006. On a total of 75,575 registered breast cancer cases (primary diagnosis 2000–2008) in this Bavarian cohort, an initial analysis of the trends in prognostic factors and standard therapies for the 3 age groups (up to 49 years, 50–69 years, >70 years) was conducted based on annual percentages and 95% confidence intervals (CI) for the percent difference between the year of...
In all age groups, the rate of poorly differentiated carcinomas (G3) showed a constant decline, the strongest being in the age group of under 49 years (2000: 40.1%; 2008: 30.2%). Among the up to 49-year-olds, the reduction was weaker and not significant; in the elderly patients, there was essentially no identifiable trend over time. In all age groups, the rate of poorly differentiated carcinomas (G3) showed a constant decline, the strongest being in the screened cohort with 11.1 percentage points (95% CI 15.0; –7.1) (2000: 37.9%; 2008: 26.8%). These analyses moreover revealed for the trends in standard therapies that the observed increasing more favourable stage distributions might have contributed to the fact that it was the 50- to 69-year-old women in particular who avoided radical surgical procedures like mastectomy (2000: 32.6%; 2008: 19.6%) or axillary lymph node dissection (89 vs. 37%) significantly more frequently. The increase in the number of radiotherapies performed in this cohort (59.7 vs. 66.6%) was attributable to the higher rate of in-situ carcinomas in the age group of screened women, whereas a constant time curve of incidence rates was registered in the unscreened cohorts. Since 2004, a continual and significant decline in the rate of advanced invasive carcinomas (tumour size > 2 cm) has been registered in the age groups up to 49 years and 50–69 years, whilst this rate remained stable in the group of over 70-year-olds. Concerning the rate of lymph node metastases (pN+) verified by pathology, the data on the screened cohort showed a statistically significant decrease of 9.9 percentage points (95% CI 13.9; –5.9) (2000: 40.1%; 2008: 30.2%). Among the up to 49-year-olds, the reduction was weaker and not significant; in the elderly patients, there was essentially no identifiable trend over time.

**Analysis of Survival and Breast Cancer Mortality**

In the past, various individual studies demonstrated a positive effect of mammographic screening examinations on survival [3–6]. A synopsis of several papers suggests a ‘likely’ advantage for the age group between 50 and 69 years. However, this effect strength diverges strongly across the individual data collections. According to current knowledge, mammography screening does not confer any benefit for women under 40–50 years of age because the percentage of false-positive findings is proportionately higher the younger the women are. Among others, one explanation for this is that younger women have a higher breast density which encumbers the general readability of the mammogram. Current data from clinical trials suggests that screening does not lower mortality in elderly women (>70) either, i.e. due to their age, the women no ‘longer’ benefit from mammography [7].

Past meta-analyses and appraisals have repeatedly addressed the methodical deficiencies in these study populations, some of which were monitored over a decade ago, show differences in risk profiles, and can only be followed up within cohort studies. A recent paper published in the Cochrane Database examined the benefit-harm relationship based on the available evidence [8], thereby updating a systematic review from the year 2011: In sum, the overall analysis only included 7 randomised trials that were methodologically robust and published up to 2012. The data were available from an aggregate total of 600,000 women aged between 39 and 74 years. 4 of these trials showed a significant reduction in breast cancer mortality (relative risk 0.75 (95% CI 0.67–0.83)), whereas 3 studies showed no benefit despite adequate randomisation. The authors did show, however, that the endpoint ‘breast cancer mortality’ in the individual trials had been interpreted variably. This was because there is no uniform classification for the cause of the patients’ deaths. Similarly, other research groups attribute the difficulties associated with interpreting screening interventions to multifactorial effects [2]: The implementation of quality-promoting interventions (e.g. guidelines), the use of modern therapeutic methods (e.g. antibody therapy), and modified surgical techniques all make it very difficult to quantify the impact of screening both on the changes in therapies and on oncologically relevant endpoints. This fact highlights the importance of methodically stringent reviews in the Cochrane Database, as illustrated above, which nevertheless were able to show survival benefits. However, the extent to which more effective therapeutic modalities will overshadow the survival benefits conferred by screening mammography for the endpoint analysis moving forward remains to be seen.

Obviously, these survival benefits cannot be viewed in a vacuum, but must be contrasted against the potential harms that can be incurred through screening interventions. The authors of the Cochrane review estimated the reduction in breast cancer mortality to be around 15% and showed that 1 woman (only) could be saved from death by breast cancer in a cohort of 2,000 women who were screened over a period of 10 years. This contrasts with the 200 healthy women forced to suffer the enormous psychological stress caused by false-positive findings. Other authors have also aggregated the current evidence and interpreted the data to quantify the benefits and harms. One paper recently published in *JAMA Intern Med*, which analysed data from the Surveillance Epidemiology and End Results (SEER) Program and a number of randomised trials [9], gave a similar estimation of this effect: In 1,000 American women in the 50-year age group receiving screening over a 10-year period, 0.3–3.2 women avoided breast cancer death because of the screening interventions, whereas 490–670 women received at least one false-positive result that led to further needless interventions. These analyses undertaken by Welch and Passow [9] also clearly illustrate that the effect strengths which, in turn, prove the benefits, vary greatly between the individual age groups (table 1).
the endpoint analysis moving forward remains to be seen. Obviously, these survival benefits cannot be viewed in a simplistic way of thinking in medicine [10]. When reading this book one feels like holding a brand-new story in his hands which tells current problems of modern medicine. The same person will be surprised when realizing that this booklet is 50 years old and in fact suggests a serious lack of progress in medical thinking. One of these lacks of progress is represented by the expression assigned to Benjamin Franklin (1706–1790) ‘An ounce of prevention is worth a pound of cure’. Most of us still agree with this 300-year-old saying and cannot believe that this traditional ‘rule’ could be wrong.

About 30 years ago, we started to realize that the resources for healthcare are not unlimited. We began to think about optimizing the use of healthcare resources, which means to use minimum resources to gain maximum health. When discussing the costs of health for others, most people would think about monetary costs. The same person would consider non-monetary costs such as the burden of a treatment, side effects, and impairments when they have to make decisions about their own health or the health of their family. Hence, there are two perspectives which may be used to balance input and output or costs and consequences or harm and benefit in healthcare. Health economy (HE) considers the societal perspective of an economic analysis in healthcare while the science of clinical economics (CE) considers the individual perspective of an economic analysis in healthcare [11–13].

When we discuss the health of others, which is the job of economists, we will apply the perspective of HE. When discussing our own health or the health of our family, which is the job of a medical doctor, we take the perspective of CE. Despite both HE and CE trying to balance costs and consequences, i.e. any costs we must incur to get more health, there is an important difference between them. HE counts monetary units to describe the costs of healthcare while CE describes the non-monetary values a person has to give away (hospitalization instead of being at home) or accept (side ef-
Table 3. Description of goals and effects of screening, diagnosis or treatment under ideal or real-world conditions

<table>
<thead>
<tr>
<th>Methods</th>
<th>Goal of action</th>
<th>Potential effects</th>
<th>Actual effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>confirmation of a suspected but specified disease without signs or symptoms</td>
<td>will be suspected but not confirmed</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td>confirmation of an existing but not yet specified disease with signs or symptoms</td>
<td>confirmation of sensitivity and specificity</td>
<td>confirmation of the significance of the test result</td>
</tr>
<tr>
<td>Therapy</td>
<td>intervention to prevent unwanted consequences in patients with confirmed disease</td>
<td>confirmation of efficacy of the intervention</td>
<td>confirmation of effectiveness of the intervention</td>
</tr>
</tbody>
</table>

Persons who decide to participate in a screening programme will barely agree not to be screened as members of the control group.

Table 4. Examples of systematic errors (bias) which may occur in treatment, screening, or diagnostic studies

<table>
<thead>
<tr>
<th>Conception/Performance</th>
<th>Treatment study</th>
<th>Screening study</th>
<th>Diagnostic study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sampling bias</td>
<td>healthy volunteer bias and incentive bias</td>
<td>pre-test bias (sampling bias)</td>
</tr>
<tr>
<td></td>
<td>selection bias</td>
<td>performance bias</td>
<td>performance bias</td>
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<tr>
<td></td>
<td>performance bias</td>
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<td></td>
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<tr>
<td></td>
<td>attrition bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evaluation</td>
<td>detection bias</td>
<td>detection bias</td>
<td>detection bias</td>
</tr>
<tr>
<td>Interpretation</td>
<td>lack of intent-to-treat analysis</td>
<td>sensitivity/specificity bias</td>
<td>sensitivity/specificity bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lead time/length bias</td>
<td>threshold bias</td>
</tr>
</tbody>
</table>

Effects of a treatment) to solve a health problem (e.g. to avoid death from breast cancer). The misunderstanding of the differences between these two necessary perspectives, HE and CE, often generates unnecessary conflicts and an avoidable waste of resources.

Prevention from the Perspective of Clinical Economics

From the perspective of CE, we allocate any health service to one of three strategies, namely primary, secondary, or tertiary prevention (table 2). The aim of primary prevention is to prevent the emergence of a disease, e.g. by avoiding risks such as smoking which trigger various forms of disease. The aim of secondary prevention is to prevent death from a disease such as breast cancer by detecting a suspicious lesion at a very early stage, confirming the suspected lesion by making a diagnosis, and finally treating the patient suffering from the confirmed early-stage disease with the goal of cure. The aim of tertiary prevention is to confirm a suspected diagnosis mostly in a non-curable (advanced) stage of disease and treating the patient to prevent new clinical problems or to stop the deterioration of already existing clinical problems [14]. This classification and description of healthcare strategies demonstrates that secondary prevention is the most complex strategy as it employs three different methods to achieve the final goal (table 3).

The aims of screening are probably identical under ideal and real-world conditions as participants of screening programmes will barely agree not to undergo a screening programme in a control group. Attempts to consider the influence of participants’ preferences on the results of randomized trials were unsuccessful because these results were either ethnically unacceptable or could not be interpreted due to two unknown variables (preference and treatment) in a single experiment [15–17].

The aims of diagnostic studies are different under ideal or under real-world conditions. Under ideal study conditions, the aim is to investigate the sensitivity and specificity of a test. Under real-world conditions, the clinical significance of the test result should be demonstrated. A test has no clinical significance at all if the derived consequences are completely independent from the test result. On the other hand, the clinical significance of a test may be considered high if the derived consequences strongly correlate with the test results. In relation to therapy, the aim of studies conducted under ideal conditions is the assessment of efficacy, while effectiveness can be assessed in studies conducted under real-world conditions.

Risk of Bias in Prevention Studies

From the perspective of CE, it is essential to avoid bias in prevention studies. It is demonstrated in table 2 that secondary prevention is the most complex of all prevention strategies and inherits the largest number of potential forms of bias (table 4). This evidence could only be derived from a structured analysis of different prevention strategies. In several ongoing projects, we are analysing studies to prevent glaucoma and cancer of the lung, colon, prostate and breast. In these projects, we are identifying a huge number of systematic errors in diagnostic and screening studies. Some of these errors are due to lack of intent-to-treat analysis in randomized trials, which cause systematic errors.

However, the absence of these variables is insufficient because we may also need to consider the influence of preference and treatment in randomized trials. Thus far, the evidence is insufficient to derive the influence of these variables in randomized trials.
are identical with the well described forms of bias which affect the internal [17] or external [18] validity of treatment studies. However, there are other forms of bias, such as the healthy volunteer bias (or healthy screenee bias), lead time bias, and length bias, which are described in the literature to affect the validity of screening studies [19, 20]. In addition, there is an 'incentive bias' which is introduced by health insurance tariffs that include 'grey services'. These services influence the competition between health insurances but cannot be considered as evidence-based health-promoting measures. It is impossible to discuss all possible forms of bias; however, it is essential to avoid all of them because treatment, screening and diagnosis are jeopardized by these systematic errors.

Selection of an Appropriate Goal

The most powerful form of bias in any type of management is related to imprecise or inappropriate goals. The example of secondary prevention of breast cancer shows that inadequate endpoints are used in a large number of studies to confirm the effectiveness of mammography screening. A high compliance rate with mammography screening or high sensitivity and/or specificity of a detection method or an impressive mammography-related increase in breast cancer incidence are no reliable indicators to demonstrate effectiveness of screening. A high compliance rate with screening indicates a convincing quality of the screening campaign, and a high sensitivity/specificity indicates a high correlation of imaging methods with the results of histopathologic examinations. Any of these results are important and describe a necessary but not sufficient prerequisite to demonstrate effectiveness of mammography screening. Screening cannot be considered effective unless the number of breast cancer-related deaths can be reduced by it. Unfortunately, the sensitivity of disease-specific death is hard to confirm as the prevalence of both conditions, death and disease, are each 100% in a diseased person. Instead of assessing disease-specific death, we suggest the assessment of advanced stages of the disease. Advanced stages of a disease can be assessed much more reliably than ‘disease-specific death’. The reliability is high because advanced stages of disease can be confirmed by signs while disease-specific death is an assumption which may or may not be true.

Reliable Screening Studies

Screening studies which measure the incidence of advanced stages of disease are more reliable than screening studies which measure other indicators such as compliance with the screening programme or incidence of early-stage breast cancer. All of the mentioned results, compliance as well as incidence of early-stage and late-stage disease, were reported in a recent study on 30 years’ experience with breast cancer screening [21]. This study demonstrated that the only indicator which did not change at all during the last 30 years – despite an increasing compliance with screening – was the incidence of late-stage distant disease. The authors of this publication did not discuss the possible consequences from this important finding [21]. Our letter to the editor which expressed the need to discuss the absence of reduction of advanced-stage distant disease was rejected. The editor did not want to publish a minority opinion. Even if the New England Journal of Medicine did not want to grasp this nettle, I strongly encourage the discussion about appropriate endpoints of screening programmes.

Screening – A Conflicting Topic of Science and the Public/Politics

Politicians and a considerable part of the public [22] believe in the effectiveness of screening programmes despite a considerable volume of contradictory observations. There is probably only a single reason which feeds this belief and the associated discussions: the induced perception of safety.

Most doctors favour screening programmes for two reasons. First, they are convinced that screening programmes generate patient benefit. This conviction can be explained by the doctors’ lack of ability to assess the validity of screening studies (table 4) and the lack of knowledge to distinguish final endpoints or their surrogates (e.g. reduction of the incidence of late-stage disease) from intermediate endpoints (e.g. increased incidence of detected early-stage breast cancer). Based on this lack of understanding, doctors would even feel unsafe when not offering screening. Second, doctors who offer screening programmes generate earnings from the offered programmes and react predictably to an economic incentive. As long as our society is offering this incentive, doctors cannot be blamed for acting accordingly.

Patients are overwhelmed with information provided by doctors and other players on the beneficial effects of screening although it is clear that this information is often imbalanced [23, 24]. Following this information, patients feel unsafe without screening and consequently request screening programmes.

Politicians would most likely compromise their career if they did not support strong public demand.

Another group of players who promote screening programmes are the health insurance companies. These companies reimburse the costs of screening and so do achieve two important effects: they satisfy the demands of the patients as well as the demands of the doctors. Hence, it would be absolutely counterproductive not to support screening programmes.

In summary, there are four powerful players – doctors, patients, politicians and health insurances – who disagree with scientists concerning the value of screening. We have to decide whether the opinion of these four players or that of the scien-
The healthy volunteer bias will probably persist in the future, i.e., healthy people will continue to accept screening programmes more often than others. The conflict of interest of any players of the system will also persist. It will stay the same as long as the education of doctors and the information of the public about the effects of screening does not change. Both the education of doctors and the information of the public cannot change unless more people understand how to assess the validity of scientific publications and how to collect real-world data which describe the actual and not only the potential outcomes of screening programmes. Theoretically, both aspects are easy to achieve.

We offer courses to teach medical students how to assess the validity of scientific papers [25]. These courses get accepted by students as they can earn good money with the assessment of the validity of scientific publications instead of doing night shifts in hospitals or accepting jobs in pubs. Healthcare professionals working with scientific associations or guideline groups will not accept these courses for three reasons: they probably lack the time which is necessary to complete a conscious critical appraisal; they also lack the experience that grows with learning by doing; and, finally, they lack the necessary interest in doing this type of work.

Healthcare professionals should care about the legal framework supporting the collection of real-world data. Methods to collect these data were recently published [26], and are presently tested in pilot studies. Without these data, we will be able to improve the prognosis of those 1–2 women that develop breast cancer, Porzsolt misinterprets this as a lack of effect of mammography screening on the reduction of all breast cancers that may eventually metastasize.

The crucial question of this debate is whether we should call screening mammography into question at this moment. Although more precise data on the effects of screening mammography have become available, the main facts have not changed since its introduction. As outlined by Porzsolt, the introduction of this programme was a value judgement that emerged out of an intensive debate between self-help groups, doctors, health insurers, and healthcare professionals. I do not see, however, that this decision thwarts scientific findings. It is rather mandatory to guarantee that women who consider participation in screening mammography get all the information on hand to be able to make an informed decision. Although this is recognized by all parties involved and strongly recommended by the position paper on informed decision making of the National Cancer Plan, there is still a sore lack of knowledge and ability on the doctors’ side to communicate the relevant facts of screening mammography as stated by Porzsolt. Even going through the papers of Wöckel and Porzsolt, it is challenging to extract the important information. For instance, can all readers understand table 1 in the Wöckel paper and communicate these data in layman’s terms to their patients?

In the updated analyses of screening mammography commented on by Wöckel and Porzsolt, the following facts and absolute risks are calculated for women between 40–70 years of age, who participate for 10 years in screening mammography:

i) The risk of getting a false-positive result is 1/2; hence, women should be advised to stay calm if they are called for a revisit as approximately 90% of suspicious findings turn out to be harmless.

ii) The risk of getting a breast cancer diagnosis is doubled. This means that the absolute risk of being diagnosed with breast cancer increases by approximately 1.2%, i.e., 23 instead of 11 women out of 1,000 women within 10 years.

iii) In the case of a breast cancer diagnosis, 1/3 of women would never have required treatment. That means that approximately 8 of 1,000 women who participate in screening mammography eventually metastasize.
Benefits and Risks of Breast Cancer Screening

Benefits

- Improved diagnosis and treatment
- Reduction in breast cancer-specific mortality
- Increased survival rates

Risks

- False-positive results
- Overtreatment
- Psychological distress
- Financial burden

Beyond the conflicting debate on the benefits and harms of screening mammography, we are facing an even bigger challenge in dealing with risk prediction and preventive options in the post-genomic era. Already, numerous genetic risk factors have been identified for most common solid tumours, i.e. breast, colon, and prostate cancer. Based on these data, risk prediction models have already been established and will be further refined that will ultimately allow individual risk prediction on a continuous risk scale in the near future. This raises numerous questions, e.g. what are the requirements for the introduction of genetic risk factors into clinical risk prediction and consequently clinical prevention? How can genotype/phenotype studies be performed under the assumption of an extreme genetic heterogeneity and therefore small cohorts of patients? Who decides what risk factor should be tested and sets threshold levels for offering risk-adapted preventive measures? Can screening mammography and other cancer screening programmes then be abolished for the general population? Is there a right or an obligation to undergo risk prediction and prevention? How does this effect non-directive counselling, the right to not know, and the legally guaranteed protection against discrimination? The National Cancer Plan has approached this new field of action in a position paper on risk-adapted prevention that provides a meta-level concept for the translation of genetically driven risk prediction into clinical prevention. On this basis, players in healthcare politics now have the chance to frame this field of action before opportunistic screening activities gain ground, with the introduction of structured programmes based on the principles of mutual solidarity.

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RS: Nothing to declare.

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