14 INVITED

Is overdiagnosis of serious concern in breast cancer screening?

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Overdiagnosis at screening may be defined at the detection of cancers that would never have been found if the screening had not taken place.

Breast cancer represents a wide spectrum of diseases from fast growing tumors to slow or even non progessive disease. In the latter category are some highly differentiated tubular carcinomas and above all a proportion of ductal carcinoma in situ (DCIS). It is known that the introduction of mammography and screening leads to the detection of an increased number of patients with DCIS. The question is what proportion of DCIS would have progressed to invasive disease in the absence of screening. This question can be rephrased: Is the incidence of invasive carcinoma reduced by the detection of DCIS? Overdiagnosis can be estimated in randomized trials. Also, national cancer incidence data over time may provide useful information in relation to the introduction of mammography and screening. A third source of information is provided by the prevalance of disease observerad at autopsy.

From these data it seems clear that screening leads to overdiagnosis of breast cancer, but opinions differ on the magnitude of the problem.

15 INVITED

Should screen detected breast cancers be treated differently from symptomatic breast cancers?

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The surgical treatment of screen detected breast cancers should follow the same principles for treating symptomatic breast cancer. However the widespread development of screening programmes have made it easier to diagnose small sized tumors often not palpable invasive and non invasive. This requires a rigorous diagnostic process and a rational methodology. Close cooperation between the radiologist, surgeon and pathologist is essential. Surgical treatment may cure a high percentage of cases nowadays and this is due to early diagnosis. However, early diagnosis does not mean underestimating the risks and problems connected with breast cancer. The target is full excision of the lesion i.e. a quantity of tissue must be removed around the tumor to achieve good local control and cosmesis. Modern imaging, morphological and biological characterization of the lesion and many other factors require a more flexible attitude from the surgeon. The integration of reconstruction and remodelling procedures can guarantee good cosmetic results. A decrease in the average size of breast cancer is accompained by a decrease in axillary lymph node metastases. However the introduction of the sentinel node biopsy with the examination of several sections of axillary lymph nodes has almost doubled the incidence of positive lymph nodes in T1a and T1b tumours. This greater incidence is almost always due to the presence of micrometastases, the prognostic impact of which is uncertain at present. A correct treatment nowadays is the result of the correct blending of the surgical, radiotherapeutical and pharmacological techniques that are available. This demands great knowledge of the problems. From 1990 to 1996 in Florence 59947 women aged 50–69 years were invited to a prevalence screen and to subsequent screens at two year intervals. The rate of breast conserving surgery has increased significantly with the advent of screening and the rate of radical surgery has declined drastically.

16 INVITED

Can prognostic factors be used to reduce treatment intensity of screen detected breast cancer?

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Mammography screening not only leads to a reduction in breast cancer mortality, it also contributes to a shift towards earlier breast cancer stages upon presentation. Breast cancers detected by screening will be smaller and mostly node-negative (N0). In addition, the percentage of non-invasive lesions will increase. Only about 30% of early stage invasive N0 breast cancers will eventually relapse. Nevertheless, following international guidelines based on established prognostic factors (e.g. size, grade, receptor status, age), more than 90% of N0 patients are candidates for adjuvant systemic therapy. Surgical procedures on early-stage, small breast cancers can usually be limited; novel prognostic markers based on tumor biological properties are needed to avoid systemic overtreatment. Only a few of the many proposed markers are already suited for clinical routine. Invasion factors uPA and PAI-1 were the first novel markers to be validated. N0 patients with low uPA and PAI-1, comprising about 50%, have a very low risk of disease recurrence and are thus candidates for being spared the burden of adjuvant chemotherapy. For screening detected lesions, markers must be measurable in limited tissue amounts. The standardized, quality controlled uPA/PAI-1 ELISA requires only 100 μg tumor tissue (about 1 μg protein extract) and is thus feasible for core biopsies or cryostat sections. Proliferation, measured by thymidine labeling index, is validated for clinical relevance, but its radioactive determination method precludes widespread use. Disseminated tumor cells in the bone marrow also seem to identify low-risk patients, but unfortunately lack of methodological standardization has restricted this marker to experienced centers. Recently, novel molecular technologies have been shown to discriminate risk groups in early-stage breast cancer; methodological standardization and clinical validation on larger patient collectives are still needed before these promising assays can be used for patient management. In conclusion, conventional prognostic factors are insufficient for avoiding systemic overtherapy, especially in screen-detected early stage breast cancers. Novel tumor-biological factors need to be used for individualized therapy concepts. So far, only a few novel markers such as uPA/PAI-1 have been recommended for treatment decisions, but with the advent of molecular array technology, promising approaches toward tailored therapy are available for the future.

17 INVITED

Ultrasound in the assessment of screen detected lesions

Abstract not received.

18 INVITED

The influence of breast density on the sensitivity of mammography screening

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Mammographic breast cancer screening in postmenopausal women has been shown to be effective, although breast cancers still escape detection. High mammographic breast density partly account for these 'missed' carcinomas. Uncertainty about the presence of breast cancer because of high breast density may also lead to more women being unnecessarily referred and given a biopsy.

It is investigated to what extent high breast density still has an impact on screening performance. Participants from the SVOKON-region in the Netherlands, N=54,500, are screened biennally with mammography. A random sample of 2000 screening mammograms from SVOKON participants (repeat screening) were collected. Breast density was automatedly classified into 'dense' (if >25% of the breast was composed of density) or 'lucent' (≤25% density). Also, random samples from referred women and cancer patients among participants were taken.

In the age-group 50–69 years dense mammographical breast pattern was frequently seen: 25%, ranging from 44% in women aged 50–54 years to 17% if aged 65–69 years. The actual HRT use was low in the perimenopausal age period: <10%, and almost non-existing in the elderly. Additionally to the standard oblique one-view screening examination 23% two-view (oblique and cranio-caudal) examinations in the youngest group were performed, decreasing to 11% in the oldest group.

The ratio of screen-detected cancers to the total number of screen detected plus interval cancers was calculated as a proxy for sensitivity of the mammographical screening test. The sensitivity in the dense group was 59%, and 67% in those with lucent breasts.

Nowadays, in postmenopausal women the presence of dense parenchymal mammographic patterns is to a large extent persistent with potential bearing on screening outcomes.

19 INVITED

Hormones and the radiological density of the breast

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Several of reports have indicated that HRT is associated with an increased mammographic density in a significant proportion of postmenopausal women. We, and also the ongoing PEPI trial, have reported that different regimens for HRT have different impact on the mammographic breast density pattern. Data suggest that an increase in breast density is more frequent among women on combined estrogen/progestogen treatment than in those receiving estrogen alone. During treatment with common continuous combined regimens about 40–50% of women respond with an increase in mammographic density whereas in women receiving estrogen only treatment the number of women with increased density is only a few %.

Mammographic breast density may be a surrogate marker for the development of breast cancer. Epidemiological studies have found increased mammographic breast density to be a strong and an independent risk factor for breast cancer. At present there is no consensus about the Interpretation of these data and there is a lack in our understanding of the histological correlates to mammographic density. It seems that the increase

in mammographic density is an early event which occurs during the first months of therapy and thereafter remains stable during long term treatment with the same regimen. Still in many women no apparent increase in density will be detected. The individual response may be related to dose, type of regimen, route of administration but also to individual factors like age, BMI and individual sensitivity and enzymatic activity within the breast.

20 INVITED

Ultrasound as additional screening modality

Abstract not received.