Tuesday, 19 March 2002 10:00–17:00

EUROPEAN BREAST CANCER SCREENING GROUP MEETING

Breast cancer screening in Europe – current status

1 INVITED

Perspective of a sceptic

M. Baum. *CRC and UCL Cancer Trials Centre, London, UK*

A paper in the Lancet late last year, entitled 'Cochrane review on screening for breast cancer with mammography', suggested that screening by mammography does not save lives nor for that matter save breasts. The Cochrane includes all the available evidence much of which became available long after the NHS breast screening programme (NHSBSP) was established in 1988. No difference in cause specific or all cause mortality was detected after correction for flaws in the methodology of the trials was found. Furthermore, there was no evidence that 'catching it early' was associated with an increase in breast conserving procedures. On the contrary the field changes associated with duct carcinoma in situ (DCIS) often lead to mastectomy for a condition if left untreated might never have progressed to the invasive disease. If any of this is true then it is a cruel deception to continue to invite women for screening with the current formula of words used in the NHS leaflets. Yet within 12 hours of the press release spokesmen for the NHSBSP, the Cancer research Campaign and Breakthrough Breast Cancer were on the air or in the papers urging women to ignore the story. As if this wasn't enough the party line was that the Cochrane data was out of date and modern techniques were saving 1.200 lives a year. In fact the data used is the most complete available and if there have been improvements in techniques since the NHSBSP was launched then there is the need for further randomized controlled trials of this methodology with submissions to the National Institute of Clinical Excellence (NICE) before approval. For all we know the latest mammographic technology might be of greater sensitivity but with less specificity resulting from an increase in the detection of latent or low grade variants of DCIS.

I believe that there should be a period of careful reflection before these new data are dismissed and that the reasons for ignoring them also be explained to the lay public.

Women should be allowed to know that the estimates of benefit vary between a relative risk reduction of 25% and zero % as a public health measure also described in absolute terms as a 1/1,000 chance of life saved by ten years of screening with the best estimate. Against that they should be made aware of the hazards of false alarms, unnecessary biopsies, the overdiagnosis of borderline pathology and its overtreatment.

2 INVITED

Perspective of an enthusiast

Abstract not received.

3 INVITED

What age to start, what age to finish?

I. Vizcaino. [1] *Hospital Doctor Peset, Department of radiology, Valencia, Spain;* [2] *Public Health Office-Health Council, Valencia Breast Cancer Screening Program, Valencia, Spain*

Today, the most prominent risk factor for breast cancer is age. The incidence of breast cancer increases steeply with age, doubling about every 10 years. Maybe in the future, the risk for breast cancer will be able to be determined by genetic factors. The largest differences between the countries concerns about the age of groups invited. Generally the European screening programs start at 50 years and finish at 65-70 years. The reasons have been based in the Sweden randomized trials: reduction of breast cancer as underlying cause of death in the invited group compared to the control group in women 40-74 years at randomization (RR = 0.76; 95% CI: 0.66-0.87). The effect was more pronounced in women 50-69 years at randomization (29%), and lowest (13%) and non-significant in women 40-49 at randomization. Thus, if the number of life-years saved was given priority, the lower age limit for invitation to screening would be 40 years (Nystrom 2000). However, after the criticism about randomization (Gotzsche and Olsen 1999), we can only consider two studies (Malmo trials: RR=0.96 and CNBSS; RR= 1.36 in 40-49), in both the reduction of mortality in the group of 40-49 was not significant or increased. The cost/effectiveness of screening in women aged 40-49 is likely to be approximately 4 times higher than for women aged 50 and over (De Koning 2000). This fact is due to the lower detection rate, the need of more assessment studies, the lower PPV of mammography, and the lower PPV of surgical biopsy (Vizca'no 1998). On the other hand, the importance of exposure to ionizing irradiation in carcinogenesis depends on age at the time of exposure (Mansfield 1993). The Advisory Physicist Group of the Valencia Breast Cancer Screening Program have perform an Analysis of Detriment (European network project 2000/171) calculating the induced cancers by radiation in screening using the ASQRAD (Assessment System for the Quantification of Radiation Detriment). The projection models UNSCEAR 94 and NRPB 93, based in experimental models, perform the calculations. The study shows a greater probability of developing 1-breast-cancer/mSv received in 45-49 years. To take a decision, a public health perspective should always be applied when introducing an intervention in a healthy population. The new screening programs must be designed and the old screening programs must introduce the pertinent modifications based both in the scientific-evidence.

4 INVITED

Ten years of screening in Stockholm

G. Svane[1], H. Grundstöm[2], K. Leifland[3], K. Moberg[4], T. Sahlstedt[5], E. Azavedo[1], P. Sundén[2], H. Lundqvist[3], M. Wiege[4], L. Haverwall[5]. [1] *Karolinska Hospital, Department of Diagnostic Radiology, Stockholm, Sweden;* [2] *Danderyd Hospital, Department of Radiology, Stockholm, Sweden;* [3] *St: Göran Hospital, Department of Radiology, Stockholm, Sweden;* [4] *South Hospital, Department of Radiology, Stockholm, Sweden;* [5] *Skårholmen, Department of Radiology, Stockholm, Sweden*

The service screening programme in Stockholm started in 1989. Stockholm county is divided into five districts each with one independent mammography screening unit (The mammography units at Danderyd Hospital, Karolinska Hospital, St: G*ran Hospital, South Hospital and Sk*rholmen Radiology Department). In 1989, 152 000 women were aged 50 to 69 years. They were invited to the programme within two years. The first screening round was completed in June 1991. The screening interval has been 24 months for all age groups. In 1999, the number of women aged 50 to 69 years had increased to 195 000. The screening has been performed during 40 weeks per year. Each woman has received an invitation letter mailed to her home address with the date and time of the appointment. The women were offered to rebook her appointment. In the prevalence screening round all women were examined with two views, the medio-lateral-oblique (MLO) and the cranio-caudal views. In the following rounds the radiologists decided if one (MLO) or two views were necessary. All attending women were asked questions about previous breast disease and present symptoms from the breasts as well as previous mammography examinations. Women presenting with mammographic abnormalities or clinical symptoms of a lump were recalled for further investigations. Compliance during the prevalence round was 70%. The recall rate was 3%. The cancer detection rate was 6.3 cancers per 1000 screened women. Compliance during the four following rounds increased to around 75% and the recall rate decreased to 2.5%. Five cancers per 1000 screened women were detected. In the fifth screening round, 1997 to 1999, only 15% of the cancers had lymph node metastasis and around 50% were 10 mm or smaller.

5 INVITED

Biology and genetics of early breast cancer

S.R. Lakhani. *Institute of Cancer Research, The Breakthrough Toby Robins Breast Cancer Research, London, United Kingdom*

Breast cancer is thought to develop by a multistep process that involves transition through putative precancerous lesions. These lesions are being detected more frequently since the introduction of mammographic screening.

DCIS & ADH: Retrospective studies carried out in the 1980's demonstrated that a quarter to a third of patients with untreated DCIS develop invasive cancer in the ipsilateral breast. After local excision, up to half the recurrences involve an invasive component. Further evidence for precursor nature comes from molecular studies. LOH & CGH studies has revealed a large number of alterations in DCIS similar to those in invasive disease. Low grade DCIS exhibits different changes to high-grade lesions. The evidence indicates that DCIS, particularly high grade, shares features with invasive disease and is a precursor lesion.

ADH shows some of the morphological features of low-grade DCIS. Several studies have shown that ADH occurs more frequently in cancerous than non-cancerous breasts. Unlike DCIS, ADH rarely shows cerbB2 amplification or p53 mutations, but LOH on chromosomes 16q and 17p, has been demonstrated at a similar frequency to DCIS and invasive cancer. The data suggest that ADH is a clonal lesion and likely to be a non-obligate precursor.

LCIS & ALH:

LCIS is most frequently seen in premenopausal women. It is not clinically palpable and usually shows no mammographic changes. It is found in tissues excised for unrelated conditions. LCIS is often multifocal and bilateral. The relative risk of developing invasive disease is 8-10x. ALH shows similar morphology to LCIS but is less extensive. It carries a relative risk of 4-5x of developing invasive disease, but this risk is doubled in those with a family history of breast cancer. LOH has been detected at a number of chromosomal loci that are frequently involved in invasive disease. CGH analysis of LCIS and ALH demonstrates a similar pattern and frequency of changes. E-Cadherin mutations are common in invasive lobular carcinomas and the same mutations are also seen in LCIS, providing direct evidence that LCIS is a precursor of invasive lobular carcinoma.

Hyperplasia of usual type (HUT):

HUT is found more frequently in cancerous than non-cancerous breasts. It has a relative risk of 1.5-2 of developing invasive carcinoma. Some HUT's have been shown to be clonal. The data suggest that a small proportion of HUT may be non-obligate precursors.

6 INVITED

Detecting which invasive cancers at mammographic screening saves lives?

A.J. Evans, S.E. Pinder, H.C. Burrell, I.O. Ellis, A.R.M. Wilson. *Nottingham City Hospital, Helen Garrod Breast Screening Unit, Nottingham, NG5 1PB, UK*

Objectives: This study aims to demonstrate for which invasive breast cancers earlier detection by mammography screening is potentially beneficial by assessing the features of primary operable breast carcinomas arising in women known to subsequently develop metastatic disease and applying these data to a separate series of screen detected cancers.

Methods: Features associated with the development of metastatic disease after a previous operable breast cancer were ascertained, and in particular the incidence of nodal positivity and definite vascular invasion was determined. Trends in the frequency of nodal involvement and vascular invasion status according to histological grade, invasive size and tumour type were then examined in a further group of 573 screen detected invasive cancers to predict the likelihood of development of systemic disease in these women.

Findings: Of 173 women who developed metastatic disease after a previous operable breast cancer, 79 (72%) had nodal metastases and 62 (59%) had definite vascular invasion. 84% had either lymph node metastases or vascular invasion or both. The absence of vascular invasion and nodal involvement in invasive breast cancer indicated a low risk for subsequent metastatic disease.

In the screen detected group, grade 1 invasive cancers <20 mm in size and grade 2 and 3 cancers <10 mm in size had low rates of nodal involvement and vascular invasion. There was a gradual trend to small size, lymph node negativity and less vascular invasion when comparing screen detected ductal carcinoma of no special type, tubular mixed carcinoma and tubular carcinoma. Cancers with a lobular component tended to be larger and more frequently lymph node positive than ductal/no specific type carcinomas.

7 INVITED

Assessment of increased risk

Abstract not received.

8 INVITED

Review of pathological risk factors

I. Ellis. *Nottingham City Hospital, Department of Histopathology, Nottingham, United Kingdom*

The existing classification systems used to identify histological risk lesions for subsequent development of breast cancer are based on conventional morphological criteria. They include a range of epithelial proliferative lesions extending from the common epithelial hyperplastic process, ductal hyperplasia of usual type (UEH), to high grade ductal carcinoma in situ (DCIS). Intermediary forms include intermediate and low grade forms of DCIS and atypical ductal hyperplasia (ADH). The lobular neoplastic epithelial proliferations, atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) form a similar parallel spectrum of risk lesions. UEH carries a low bilateral 1.5 fold risk, ADH and ALH a bilateral 4 fold risk, which doubles when associated with a family history of breast cancer. DCIS has a unilateral risk of at least 10 fold and LCIS a bilateral risk of approximately 10 fold.

Distinction between these entities is based on evidence derived from a number of studies and their international acceptance reflects the relative consistency of data emerging from these various studies with respect to risk of subsequent development of invasive breast cancer. Problems have arisen with difficulty in achieving acceptable levels of concordance or consistency in diagnosis between pathologists for lesions such as ADH which is recognized largely on criteria of exclusion rather than positive criteria, i.e. recognition of some but not all features of DCIS and lack of the characteristics of usual type epithelial hyperplasia.

Ideally future classification systems for epithelial proliferative diseases of the breast will be reproducible between centres, and take account of clinical, morphological, phenotypic and genetic evidence. Clinical management will be based on the relevance and extent of these specific clinico-pathological entities. Hallmark genetic lesions will have been identified for many of the common and indeed uncommon lesions we currently recognize. These abnormalities will underpin the basis of the classification systems and disease sub classification will be based on acquisition of additional molecular genetic changes and disease extent.

9 INVITED

Review of familial breast cancer

Abstract not received.

10 INVITED

MRI – A role in screening?

F.J. Gilbert. *University of Aberdeen, Dept of Radiology, Aberdeen, AB25 2ZD, UK*

Women with greater than 50% chance of carrying the BRCA1 or BRCA2 or P53 gene are at 1–2% risk per annum of developing breast cancer, often this risk starting at a younger age than the general population. Breast MRI has the highest sensitivity for detection of breast cancer compared with conventional imaging techniques such as mammography and ultrasound. While MRI is the most expensive breast imaging modality it is postulated that it may be cost-effective in younger women at increased risk of breast cancer due to their family history where mammography may be less sensitive.

There are a number of ongoing studies examining the feasibility of breast MRI screening and comparing detection rates with mammography and ultrasound. In the UK the multi-centre MARIBS trial has recruited over 700 women age 35–50 who are BRCA 1 or BRCA 2 gene carriers or at 50% risk of having inherited the gene, to annual MRI, mammography and clinical examination. A Canadian study has reported results from 196 women at high risk where only MRI detected 2 of 6 invasive cancers found overall. In Germany preliminary findings from 192 high risk asymptomatic young women screened with mammography, ultrasonography and MRI showed that MRI detected all 9 cancers with only 4 detected on conventional imaging. In the Penn study from the USA all 5 cancers in 172 high risk women were detected by MRI. There is an ongoing multi-centre trial funded by the NCI aiming to recruit 420 women at more than 25% lifetime risk.

While these individuals studies are not able to prove conclusively the appropriateness of breast MRI as a screening tool further results are awaited. It is thought that a meta-analysis may give evidence to indicate best practice for these high risk women.

11 INVITED

Management of breast cancer risk – Screening versus prophylaxis

J.F. Forbes. *University of Newcastle, ANZ BCTG, Newcastle 2298, Australia*

All adult women are at risk of breast cancer (BC), and risk increases with increasing age. Risk management may include risk reduction and preven-

tion strategies. Risk reduction strategies are limited: age of menarche, and first birth cannot be changed for older women. Lifestyle changes such as increasing exercise remain of uncertain benefit, but avoidance of long term combined hormone replacement therapy may have value. Screening with mammography offers BC control through earlier diagnosis, and improved survival. Efficacy is well established from randomised controlled trials but its value depends on rigorous attention to high standards of mammography and reporting, and effective linkage of diagnosis to treatment.

The NSABP P1 trial demonstrated a reduction of BC incidence of close to 50% for women ages 35–49 years and 50 years and greater from daily tamoxifen with short term follow-up. The long term benefits remain unknown. Tamoxifen increased thromboembolic events and uterine cancer in women aged 50 or greater, and reduced the risk of osteoporotic fractures (wrist, hip, and lumbar spine). Two other trials of tamoxifen failed to detect a benefit and a fourth, IBIS I (International Breast cancer Intervention Study I), remains blinded to follow-up.

Raloxifene appears to have less uterine stimulating effect and may be able to preserve bone density and reduce BC incidence in postmenopausal women at increased risk. Prophylactic bilateral mastectomy may reduce the risk of subsequent BC by around 90% in women at increased risk. Bilateral oophorectomy may reduce the risk of BC and for women with BRCA mutations can reduce the risk of ovarian cancer. It may also reduce breast density and thus improve screening mammography sensitivity.

Outside of trials risk management strategies may vary with personal circumstance (age and risks of uterine cancer, thrombosis and osteoporosis) and preferences (attitude to surgery and importance of continued ovarian function). Tamoxifen may provide net benefit for a population of women who have atypical hyperplasia or who are ages 35–49 and have a Gail Model 5-year BC risk of $\geq$1.7%, but older women may require a prior hysterectomy and/or a higher BC risk for similar gains. Population strategies however aim to optimise risk-benefit and cost-benefit ratios and are not necessarily relevant to individual women.

12 INVITED

Imaging - digital mammography

Abstract not received.

13 INVITED

Computer aided detection

E. Azavedo. *Karolinska Hospital, Dept of diagnostic radiology, Stockholm, Sweden*

Computer Aided Detection or CAD is a new application of computer software to assist radiologists to minimise errors in film reading. Today we have access to commercially available systems that have shown to be a good help both for the experienced and the less experienced radiologists. The two main systems are Image Checker from R2-Technology, USA and Second Look from CADx, Canada.

Mammography films to be analysed by a CAD system have to be digitised first before the digitised information goes through a dedicated system of neural networks that have been taught to recognise patterns associated with pathology. CAD does not give us a diagnosis but only detects areas that the system thinks need further attention. A radiologist can then look at a selected area and then decide whether to take action or not. Areas of interest are marked with specific signs for calcifications and other fearues. Absence of computerised marks should not change a radiologists decision to work up a certain lesion.

CAD can detect calcifications with a sensitivity greater than 98%. Other type of lesions can be more challenging even to an experienced radiologist and therefore their sensitivity is lower than for the calcifications. When using a CAD system specificity is as important as sensitivity. We need to pick up more cancers without causing hazards to women who do not need actions including diagnostic interventions. This balance is one of the most important factors while determining success rates of any screening programs.

There are reports that we may have up to 20% of breast cancers that are overlooked on screening mammograms. Retrospective studies have shown that both radiologists and CAD systems could have perceived breast cancers on a screening examination prior to the diagnostic examination. Recent studies have shown that CAD could be used to help radiologists to look at mammographic features of which at least some are actionable. This will lead to an increase in breast cancer detection at an early stage since the ones that are overlooked are often those that have subtle signs of abnormalities.

CAD is not supposed to replace a radiologist but only assist one in not overlooking a possible area with pathology. Once a radiologist sees a mark then he or she should have enough knowledge to confidently make a decision about the area that the computer pointed out.

14 INVITED

Pathology perspectives

Abstract not received.

15 INVITED

Needle biopsy

R. Wilson. *Nottingham City Hospital, Breast Unit, Nottingham, United Kingdom*

Image guided needle biopsy is now well established as fundamental part of breast diagnosis as part of the triple test (clinical examination, imaging - usually mammography and ultrasound - and needle biopsy). Needle biopsy provides definitive diagnosis in a high proportion of cases avoiding the need for open surgical biopsy for diagnostic reasons. For benign conditions surgery can be avoided all together while for malignant disease sufficient diagnostic information can be obtained to allow for single stage therapeutic surgery. Image guided biopsy is more accurate than free hand techniques and ultrasound guided biopsy is often the preferred method for sampling both palpable and impalpable lesions, with x-ray stereotactic biopsy reserved for abnormalities not visible on ultrasound. Core biopsy has been shown to provide better sensitivity, specificity and predictive values than fine needle aspiration for cytology and a positive diagnosis of malignancy can be obtained in over 90% of cases. However in approximately 10% of cases conventional automated core biopsy does not provide sufficient or information because of sampling error or borderline patholoical findings. Calcifications and abnormalities such as papillary lesions, mucocele-like lesions and radial scars commonly cause diagnostic problems. Obtaining larger volumes of representative tissue by means of vacuum assisted mammotomy will provide definitive diagnosis in the majority of these borderline cases. Vacuum assisted mammotomy has the advantages of being suitable for both ultrasound and x-ray guidance, requiring single placement of the sampling probe to obtain multiple contiguous tissue specimens, and the ability to direct sampling in a particular direction making it easier to sample lesions behind the nipple and close to the chest wall. Vacuum assisted mammotomy can also be used to completely remove benign lesions. The equipment, technique and indications for ultrasound and x-ray guided vacuum assisted mammotomy will be debated.