## Tuesday, 16 March 2004 09:00–17:00

EUROPEAN BREAST CANCER SCREENING GROUP MEETING

# Breast cancer screening in Europe – current status

1 INVITED

### Detection of an increased breast cancer risk

B. Kuschel. *Klinikum rechts der Isar, Department of obstetrics and gynaecology, München, Germany*

About 15–25% of breast cancer patients report about a positive family history. Highly penetrant germline BRCA1 and BRCA2 mutations account for ~20% of familial breast cancer clustering. The remaining 80% is likely genetic in origin and the result of the combined effects of many genetic and environmental variants, which individually have little effect. By analysing pedigree data of breast and/or ovarian cancer families, individual breast and ovarian cancer risk can be estimated. Genetic testing for genes as BRCA1/2 (in exceptionally rare cases for other genes like PTEN,P53,CHK2) is available. The cumulative lifetime-risk for BRCA1 mutation carriers is 65% for breast-, 40% for ovarian cancer. BRCA2 mutation carriers have got a 45% risk for breast-, 11% for ovarian cancer. Elevated risk estimations and/or genetic testing may lead to intensified surveillance and prevention strategies.

2 INVITED

### Mammography/ultrasound in women with an increased risk for breast cancer

H.M. Zonderland[1], C.T.M. Brekelmans[2], G.H. de Bock[3]. *[1]Leiden University Medical Centre, Department of Radiology, Leiden, The Netherlands; [2]Erasmus Medical Center Rotterdam, Department of Epidemiology, Rotterdam, The Netherlands; [3]Leiden University Medical Center, Department of Medical Decision Making, Leiden, The Netherlands*

A familial predisposition is the most important factor that increases the cumulative life time risk (CLTR) of breast cancer. CLTR may vary from 15–30% in women with moderate risk to 60% CLTR at age 75 in carriers of a BRCA1 or BRCA2 germline mutation.

The Nation-wide Breast Cancer Screening Program in The Netherlands provides breast screening by mammography in women 50–75 years old; if the CLTR of a woman under this age is the same or higher, annual examination by mammography and physical examination is recommended. A simple table with Dutch guidelines in primary care is shown in Table 1.

Table 1

| No. of relatives affected | Breast cancer < 50 yrs of age in at least one relative | Breast cancer ⩾ 50 yrs of age in all affected relatives |
|---|---|---|
| 1 first degree | Annual examination | No further research and follow-up |
| 2 first degree | General practitioner should consult a clinical geneticist | Annual examination |
| 3 first degree | Referral clinical geneticist | Referral clinical geneticist |
| 1 second degree | No further research and follow-up | No further research and follow-up |
| 2 second degree | General practitioner should consult a clinical geneticist | Annual examination |
| 3 second degree | General practitioner should consult a clinical geneticist | General practitioner should consult a clinical geneticist |

Source: Dutch College of General Practitioners

Table 2

| Age group | Cancer rate/1000 | | Sensitivity | |
|---|---|---|---|---|
| | No High Risk[a] | High Risk[a] | No High Risk[a] | High Risk[a] |
| 30–39 yrs | 1.6 | 3.2 | 69.5 | 63.2 |
| 40–49 yrs | 2.7 | 4.7 | 77.5 | 70.2 |
| 50–59 yrs | 4.6 | 6.6 | 80.2 | |

[a] Based on Family History.

Several large studies provide screening parameters separately for women with and without a familial predisposition. Cancer detection rates in women with a first degree relative with a history of breast cancer were similar to those in women a decade older without such a history. The sensitivity of screening was influenced primarily by age (Table 2).

3 INVITED

### MRI for screening women with an increased risk of breast cancer

C. Kuhl. *Medizinische Universitätsklinik Bonn, Radiologische Klinik, Bonn, Germany*

While the majority of breast cancer cases is due to sporadic cases, about 5%–10% are associated with or due to a genetic predisposition for the disease. Accordingly, familial (or hereditary) breast cancer accounts for at least 9100 new breast cancer cases in the United States per year (it should be well understood that the term "familial breast cancer" does not necessarily refer to a specific breast cancer type or to an actual breast cancer case, but it describes a *genetic condition* that puts the carrier at high risk to *develop* breast cancer). The breast and ovarian cancer susceptibility genes identified thus far, BRCA1 and BRCA2, account for only about 50% of the genetically induced breast cancer cases; for the remaining cases, other, yet undefined BRCA genes are suspected.

The lifetime risk to eventually develop breast cancer accumulates to 80%–90% and 60%–80% for carriers of the BRCA1- and BRCA2-mutation, respectively. Moreover, if a gene carrier already survived breast cancer, she faces a 65% risk to develop a second primary breast or ovarian cancer. As opposed to patients with sporadic breast cancer, women with familial breast cancer tend to develop the disease at a significantly younger, i.e. at a pre-menopausal age; according to recent data, about 50% already had breast cancer by the age of 50. In addition, breast cancers arising in mutation carriers exhibit adverse histopathologic features and prognostic factors; with respect to sporadic breast cancers, they are more likely to be high grade, receptor-negative, such that an early diagnosis seems even more crucial. Accordingly, the current screening recommendations (that refer to sporadic breast cancer) may not be sufficient (and will most probably not start early enough) for gene carriers.

Due to the high risk to develop breast cancer, and due to the early onset of the disease, a close screening of proven or suspected gene carriers should start at a substantially earlier age than is recommended for the general population, i.e. at the age of 25–30. On the other hand, BRCA-related gene products have been implicated in cell cycle regeneration and DNA repair. Accordingly, a pathogenic mutation in a BRCA gene can be expected to increase a carrier's vulnerability towards mutagenic agents, like e.g. ionizing radiation. The possibly increased radiosensitivity of mutation carriers should mandate the careful use of mammography in these women. To further investigate the effectivness of different breast imaging modalities in this subset of women, several multicenter screening trials are underway in Europe, Canada, and the US. This talk serves to summarize the current status of these trials, including our own results.

4 INVITED

### Breast biopsy techniques and protocols: Core/Vacuum

A.R.M. Wilson. *Nottingham City Hospital, Breast Institute, Nottingham, UK*

**Introduction:** The triple test – the combination of clinical examination, imaging and needle biopsy for cytology or histology – is the gold standard for the diagnosis of breast disease; image-guided breast biopsy is an integral and essential part of this process.

**Rationale for the triple test:** Needle biopsy is highly accurate in determining the nature of most breast lesions and should be preferred to open surgical biopsy. Patients with benign conditions avoid unnecessary surgery; carrying out open surgical biopsy for diagnosis should be regarded as a failure of the diagnostic process. For patients who prove to have breast cancer needle biopsy provides accurate understanding of the type and extent of disease so ensuring that patients, and the doctors treating them, are able to make informed treatment choices. Needle biopsy not only provides accurate information on the nature of malignant disease, such as histological type and grade, but also facilitates the assessment of tumour biology and genetics.

**Which biopsy technique?** The current methods available for breast tissue diagnosis are:

- Fine needle aspiration for cytology (FNAC)
- Needle core biopsy for histology (NCB)
- Vacuum assisted mammotomy (VAM)
- Open surgical biopsy FNAC verses Needle Core Biopsy

There has been much debate about the comparative benefits of fine needle aspiration of cytology and core biopsy. In general terms 14 gauge 20mm throw automated core biopsy provides significantly better sensitivity, specificity and positive predictive values. Results with core biopsy are particularly better than FNA for stereotactic biopsy of microcalcifications

and architectural distortions. The overall better performance achievable with core biopsy compared to FNA is illustrated in the performance of the National Health Service Breast Screening Programme in the UK. In 1994 using FNA as the primary diagnostic technique fewer than 10% of 90 units were able to achieve the target of 70% preoperative diagnosis cancer. In 1996 the majority of units swapped to core biopsy and within three years all units were easily achieving this target.

**Vacuum Assisted Mammotomy:** The predominant reasons for failure to achieve accurate diagnosis by needle biopsy are sampling error and failure to retrieve sufficient representative material. These problems have been largely addressed by the development of larger directional core techniques that yield significantly greater volumes of tissue. Vacuum assisted mammotomy (VAM) is proving to be a very successful method for improving the diagnostic accuracy of borderline breast lesions and lesions at sites in the breast difficult to biopsy using other techniques. VAM has been shown to under stage both in situ and invasive cancer approximately half as often as conventional core biopsy (typically 10% compared to 20%). The VAM technique has a higher sensitivity because it allows sampling of lesions at sites that are difficult to biopsy using either FNA or core biopsy and because the amount of tissue harvested is at least five times greater per core specimen. The indications for vacuum assisted mammotomy are listed below:

- Very small mass lesions
- Architectural distortions
- Failed "conventional" core biopsy
- Microcalcifications
- Papillary and mucocele like lesions
- Diffuse non-specific abnormality
- Excision of benign lesions
- Sentinel node sampling

Core biopsy and vacuum assisted mammotomy are now the recommended techniques for sampling calcifications and mammographic architectural distortions. For calcifications it is imperative that there is proof of representative sampling with specimen radiography. If calcification is not demonstrated on the specimens radiograph and the histology is benign then the management cannot be based on this result as there is a high risk of sampling error; the procedure must either be repeated or an open surgical biopsy carried out.

**Guidance techniques for breast needle biopsy:** Ultrasound guidance is the technique of choice for biopsy of both palpable and impalpable breast lesions; it is less costly, easy to perform and more accurate than free hand or other image-guided techniques. Ultrasound provides real time visualisation of the biopsy procedure and visual confirmation of adequate sampling. Eighty to 90% of all breast abnormalities will be clearly visible on ultrasound and amenable to biopsy using this technique. For impalpable abnormalities not visible on ultrasound stereotactic x-ray guided biopsy is required. A few lesions are only visible on magnetic resonance imaging and require MR guided biopsy. The negative predictive value of combined normal mammography and ultrasound is extremely high; where there is a clinically palpable abnormality and mammography and ultrasound are entirely normal the likelihood of malignancy is low (less than 1%). However, in these circumstances it remains prudent to carry out freehand biopsy to exclude the occasional diffuse malignant process, such as classical lobular carcinoma or low grade DCIS, that may be occult on both mammography and ultrasound.

**Vacuum assisted mammotomy:** Mammotomy is usually carried out using an 11-gauge probe, which provides 100mgs of tissue per core specimen. Unlike conventional core biopsy the needle remains in the breast at the sampling site and contiguous core biopsies can be obtained. The probe can be rotated through 360o and wide sampling can be achieved and VAM should be preferred where there is expected to be diagnostic uncertainty. Because the probe does not have to pass directly through the area being sampled and a satisfactory sample can be obtained from placing the needle adjacently, this technique is also preferred for biopsy of abnormalities at sites in the breast that are difficult to reach using FNA or core biopsy (i.e. close to the chest wall).

**Number of samples:** A simple rule for satisfactory sampling using needle techniques is to obtain sufficient material to achieve a diagnosis. For ultrasound guided core biopsy this may simply be a single core. By knowing on ultrasound that the needle has passed through the centre of the abnormality and looking at the sample with the naked eye it is usually possible to tell if a satisfactory sample has been obtained. It is unnecessary to obtain multiple cores as a matter of routine. The number of core specimens obtained should reflect the nature of the abnormality being sampled. For ultrasound guided biopsy where there is a suspicion of carcinoma it is recommended that a minimum of two core specimens are obtained. As stereotactic biopsy is used for abnormalities that are difficult to define on ultrasound and are therefore more difficult to sample a minimum of five core specimens be obtained. Ensuring that calcification is present in at least three separate cores and/or five separate flecks of calcification are retrieved from the area of suspicion will provide accurate diagnosis. When there is still diagnostic uncertainty 8gauge vacuum assisted mammotomy can be used to obtain larger tissue volumes (approximately 300mgs per core). The 8g mammotomy probe is preferred for therapeutic removal of breast lesions such as fibroadenomas.

**MR guided biopsy:** A few breast lesions are only visible on MR and therefore have to be localised and biopsied under MR guidance. A number of different approaches have been developed for this procedure using both closed and open magnets. FNA, core biopsy and vacuum assisted mammotomy may all be used for MR guided sampling.

**Conclusions:**

- The aim should be to achieve as near as possible 100% non-operative diagnosis of breast problems
- Both palpable and impalpable breast lesions are best sampled under image guidance
- Automated core biopsy is the technique of first choice
- Ultrasound is the guidance technique of first choice
- Digital stereotactic core biopsy should be reserved for sampling lesions not visible on ultrasound
- FNA is not recommended for calcifications or stellate lesions
- 14g core biopsy can provide a definitive diagnosis in 90% of cases and should be the preferred method
- Mammotomy can provide the diagnosis in the remainder
- Stereo-guided mammotomy is particularly effective for small clusters of indeterminate microcalcifications and calcifications in sites difficult to access with core biopsy.
- Vacuum assisted mammotomy is an effective and well tolerated problem solving device for breast diagnosis and can also be used to completely excise benign lesions

It is important that the result of needle breast biopsy is always correlated with the clinical and imaging findings before clinical management is discussed with the patient. This is best achieved by reviewing each case at multidisciplinary meetings.

**5** INVITED

## Fine needle biopsies of breast lesions

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

Fine Needle Aspiration (FNA) technique has been used at the Karolinska Hospital as a routine in the evaluation of especially palpable breast lesions since 1955. This technique proved to be fast, reliable and inexpensive. The technique confirmed a malignancy diagnosis pre-operatively and this helped for proper management of a case right from the beginning. The other benefit was to exclude suspicion of malignancy and thereby avoid unnecessary surgery.

Breast imaging techniques experienced a revolution in image quality during the last 30 years and this lead to the detection of many non-palpable breast abnormalities of which some represented non-malignant pathology. The need to differentiate malignant from the non-malignant mammographically detected breast lesions led to the development of the SFNB technique, Stereotaxic Fine Needle Biopsy Technique. SFNB has thus been used at our hospital since 1975 and to date we have performed more than 16.000 procedures. The technique has always had a technical precision of $\pm 1$ mm to reach a target.

Sampling with FNA yields single or groups of cells that have to be diagnosed with a microscope after special staining techniques. Unlike core biopsies, that yield tissue fragments that can be read by most if not all the pathologists, the cytology specimens of FNAs demand special training of the cytomorphologists to give us proper diagnosis of the retrieved cells. One factor that is often underestimated is the technique to obtain cellular material from a non-palpable breast lesion. This very important step in the overall success of an intervention needs high volumes to attain acceptable skills. Even the preparation of the cytology smears needs special skills so that the obtained cellular material is spread on a glass slide as a single layer of cells for proper assessment.

When above-mentioned factors are optimised than the procedures show high sensitivity and specificity that lie in the upper nineties. On the other hand both sensitivity and specificity can vary depending upon both the interventionist and the microscopic reader. One morphologic detail that cytology cannot answer is whether a tumour is invasive or not. This particular aspect can on the other hand be reliably answered when both radiology and cytology is integrated. Again unlike histopathology on a core biopsy, a cytology report should always be integrated together with the radiological assessment of a lesion in order to get a correct final diagnosis. The material used for a FNA is inexpensive but access to trained specialists could be a challenge.

To conclude, when all criteria are satisfactory then the outcome is fully usable in routine diagnostics.