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Symposia

286

Breast cancer predisposition genes

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Greater than 10% of breast cancer cases are attributable to mutations in susceptibility genes. *BRCA*1 and 2 mutations are rare, with population frequencies of between 0.002 and 0.001. However, these genes are associated with a particularly high risk of breast cancer, each having mutant alleles with greater than 80% penetrance. The *BRCA*1 and 2 genes account for the vast majority of families with multiple cases of breast cancer. Mutation carriers are also at increased risk of other malignancies. Loss of function *BRCA*1 and 2 susceptibility mutations have been identified in many families, allowing for the presymptomatic screening of potential carriers. As these are large genes, screening using conventional techniques is both labour intensive and expensive. However, certain populations have been characterised in which the same *BRCA*1 and 2 mutations are present in multiple families. These are usually associated with a common haplotype for flanking genetic markers, indicating that they result from an ancestral mutation. The most notable examples being the 185delAG *BRCA*1 and the 6174delT *BRCA*2 mutations, each of which are present in the Ashkenazi Jewish population at a frequency of greater than 1%. Screening for the common mutations is quick and relatively inexpensive. It is believed that other low penetrance genes may account for a greater proportion of breast cancer cases than those attributable to *BRCA*1 and 2. One such gene is *ATM*, which has a carrier frequency of about 1 in 200. It has been estimated that *ATM* carriers have a 4-fold increased risk of breast cancer, compared to non-carriers. It is therefore possible that 5% of all breast cancer cases are due to *ATM* susceptibility mutations.

287

Molecular and biologic markers of DCIS, ADH and IDC

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Purpose: Infiltrating ductal breast carcinomas (IDC) originate from presumed in situ precursor lesions. Recently, atypical ductal hyperplasia (ADH) was shown to derive from a monoclonal proliferation and can therefore be considered a neoplasic precursor lesion of IDC. Ductal carcinoma in situ (DCIS) might be an intermediate step in the transformation process between ADH and IDC or, alternatively, ADH might represent a direct precursor of some IDC.

Methods: The biological and molecular characterisation of the different lesions help answering this question.

Results: ADH are negative for c-erbB-2 overexpression, whereas 70% of DCIS (mainly the comedo type) and 30% of IDC are positive for overexpression of this oncogene. If DCIS were the precursor lesion of all IDC, this would imply a decrease in c-erbB-2 overexpression during transformation from DCIS to IDC, which is very unlikely considering the definitively established role of this oncogene in tumour progression. Thus, it is possible that a proportion of IDC, mainly those that are negative for c-erbB-2 overexpression, derive directly from ADH or from non-comedo type DCIS. This possibility is consistent with the observation that most of the pathobiologic parameters found in comedo type DCIS, such as high grade, necrosis, lymphoid infiltration, c-erbB-2 overexpression and p53 alteration, are also found in some but not all IDC, supporting the concept that two different in situ lesions give rise to two different IDC. Indeed, our multiple correspondence analysis of 700 primary IDC revealed an association between different DCIS-related characteristics, which when used together, delineate two subsets of IDC. These two subsets were found to differ with respect to age at diagnosis, prognosis, time to recurrence and response to therapy.

Conclusions: Together, these data suggest that IDC comprises two different diseases that can be identified based on pathobiologic characteristics and that derive from two different preinvasive precursor lesions.

288

Genetic alterations in ductal carcinoma in situ of the breast: Association with histologic type

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Purpose: Ductal carcinoma in situ (DCIS) of the breast is heterogeneous with respect to histologic and clinical characteristics. Recently, a histologic classification of DCIS has been proposed: poorly differentiated, intermediate and well differentiated DCIS (Holland et al., Sem. Diagn. Pathol. 11: 167–180 (1994)). We have characterized the profile of genetic alterations in DCIS in relation to histologic type.

Methods: 164 Cases of DCIS and 9 cases of lobular carcinoma in situ (LCIS) were collected. Immunohistochemical staining was done using various antibodies, DNA isolated from frozen material and from paraffin was analyzed for gene amplification and loss of heterozygosity (LOH).

Results: c-erbB-2/neu and cyclin D1 gene amplification and protein overexpression, p53 overexpression and LOH on chromosome 17 were associated with intermediate and poorly differentiated DCIS; LOH on chromosome 16 was associated with well differentiated DCIS. E-cadherin inactivation was found in all cases of LCIS, but never in DCIS.

Conclusion: Each of the different histologic types of DCIS is associated with specific genetic alterations.

289

The surgical management of screening detected and genetic breast cancer

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There are so far no prognostic markers to tell us that screening detected or genetic breast cancer should be treated widely different from lesions detected clinically. Thus the overriding principles for surgical treatment is the same in these clinical domains, namely radical excision of the primary tumour and adequate staging with due consideration of functional and cosmetic results.

However, there are some important qualifications. A quality assurance goal for mammography screening within EU is that the proportion of invasive cancer less than 15 mm in diameter should be at a minimum of 50% of the invasive cancers detected at screening. A large proportion of these cancers will have a low malignancy grade at the risk of finding axillary metastases at an axillary dissection will be small. Of malignant lesions overall detected in a screening program, 15–20% will be DCIS. In both these patient groups surgeons are confronted with the challenge to both ensure that small palpable or non-palpable lesions have been securely removed and avoid overtreatment both in terms of the amount of breast tissue resected and how the axilla is explored. The sentinel node biopsy technique for the axilla is a most welcome development.

For hereditary breast cancer the management of the contralateral breast presents a clinical dilemma. A search for indicators – such as e.g. the patient's family history, type of tumour and age at diagnosis – for choice of surgical management of the contralateral breast is important.

290

Update on ductal carcinoma in situ trials

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It is tough to carry out a clinical trial for the treatment of slow growing lesions which criteria constantly change and for which many aspects are still unknown. Therefore trials activated often more than ten years ago included all D.C.I.S, the classification was based on architectural pattern