

Reviews

Molecular genetics of solid tumours: translating research into clinical practice. What we could do now: breast cancer

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Abstract

Breast cancer is a common solid malignancy in women. Over the past decade, much progress has been made in understanding the biology of breast cancer. The use of molecular and immunohistochemical techniques is providing insights that will allow us to tailor the management of patients with breast cancer. In this review, progress in the understanding of lobular carcinoma in situ and atypical ductal hyperplasia, the use of the molecular marker CerbB2, and information gained from the morphological analysis of tumours arising in patients with BRCA1 and BRCA2 mutations is discussed.

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There is compelling evidence that breast cancers arise in a multistep fashion through a series of intermediate “hyperplastic” and neoplastic lesions, each of which has a greater chance of becoming malignant than the one that preceded it.¹ The reliable recognition of these stages is of great value in learning more about the pathogenesis and possible aetiology of human breast cancer, and in identifying women who are at increased risk of developing the disease.

The introduction of mammographic screening has led to increased detection of premalignant lesions, in particular ductal carcinoma in situ (DCIS).^{2,3} The classification of intraductal proliferations is controversial and pathologists encounter difficulties in subclassifying DCIS, differentiating it from atypical ductal hyperplasia (ADH), and distinguishing lobular carcinoma in situ (LCIS) from the solid variant of low nuclear grade DCIS. However, in situ carcinomas and atypical hyperplasias are not the only abnormalities thought to be precancerous, and some commonly encountered benign lesions also appear to be associated with increased cancer risk. There can be considerable difficulty in determining whether a particular lesion is premalignant and the

degree of risk with which it is associated. Furthermore, it may not be possible to distinguish those that are genuine precursors from those that are merely associated with cancer and consequently markers or indicators of risk.

Lobular carcinoma in situ (LCIS)

LCIS was described in 1941 by Foote and Stewart,⁴ although it had been recognised as a precancerous lesion some years before.⁵ Most cases of LCIS are diagnosed between the ages of 40 and 50 years, a decade earlier than DCIS. LCIS is not generally palpable and there are usually no mammographic abnormalities.⁶ Hence, it is usually an incidental finding in biopsies done for an unrelated benign or malignant condition. It is often multifocal and bilateral. More than 50% of the patients with LCIS have further disease in the ipsilateral breast and approximately a third of patients will have LCIS in the contralateral breast.^{7–9} Although Page *et al* reported that approximately two thirds of women will develop invasive carcinoma within 15 years of follow up,¹⁰ other studies suggest a lower risk (20%), and most cancers do not appear until 15–20 years later.^{11,12} Interestingly, only half the invasive cancers are lobular in type, the rest being invasive ductal carcinoma. Unlike DCIS, the risk of invasive carcinoma after LCIS is bilateral.^{10,13}

These features have raised questions about the biological nature of LCIS. Although originally described as an “in situ carcinoma”, with the implication that it was an invasive cancer in the making, the view has now changed to a “risk indicator”. Since the original description by Foote and Stewart,⁴ the trend has swung from mastectomy to follow up, follow up with regular mammography, and even “no action”.^{13–15}

Although it is recognised that a proportion of women with LCIS will go on to develop invasive carcinoma, at present, there are no clinical or morphological features that allow identification of the women at risk. This has created a problem for surgeons and oncologists managing patients who have a diagnosis of carcinoma in situ but in whom the lesion has uncertain significance.

Although LCIS has been documented as an entity for nearly 50 years, molecular data are

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limited. E-cadherin, an epithelial cell–cell adhesion molecule, is often found in DCIS and invasive ductal carcinoma, but is rarely seen in LCIS or invasive lobular carcinoma.^{16,17} Lakhani *et al* reported that loss of heterozygosity (LOH) involving chromosomal loci at high frequency in invasive carcinoma can also be detected in LCIS.¹⁸ The frequency in their study ranged from 8% on chromosome 17p to 50% on 17q. LOH on chromosome 16q, the site of the E-cadherin gene was approximately 30%. LOH was identified in LCIS with and without invasive carcinoma. This confirmed the neoplastic nature of LCIS and suggested that LCIS was probably a direct precursor of invasive cancer. Further support for this hypothesis has come from Nayar *et al*,¹⁹ who showed LOH in 50% of LCIS associated with invasive carcinoma at markers on chromosome 11q13.

The most direct evidence for a precursor role of LCIS comes from mutational analysis of the E-cadherin gene. Berx *et al* found that 27 of 48 invasive lobular carcinomas had mutations in the E-cadherin gene, whereas none of 50 breast cancers of other types had alterations.^{20,21} The same group subsequently demonstrated that truncating mutations identified in invasive lobular carcinoma were also present in the adjacent LCIS, providing strong evidence that LCIS is a precursor lesion.²²

There can be little doubt now that LCIS is a precursor of invasive cancer. Unfortunately, the data still do not allow us to stratify patients into meaningful groups for management. We still have no way of identifying the one in five women who need regular follow up or treatment for LCIS. The hope is that newer technologies, such as transcription profiling,²³ will help us to achieve that aim.

Atypical ductal hyperplasia (ADH)

ADH is a proliferation that exhibits some but not all the morphological features of DCIS and hence, by definition, shares histological features with carcinoma. Follow up studies have confirmed the precancerous nature of ADH. Page and his colleagues conducted a series of important prospective studies in the 1980s. In one of these,²⁴ they indicated that the relative risk of developing carcinoma in a woman with proliferative disease was 1.9 and this rose to 5.3 if the proliferation showed evidence of atypia. This risk was doubled in the presence of a positive family history of breast cancer. Subsequently, Tavassoli and Norris,²⁵ McDivitt *et al*,²⁶ and London and colleagues²⁷ have confirmed the increased risk associated with atypical hyperplasia, although the size of the risk has varied between studies.

However, ADH is a controversial entity, which poses considerable difficulties in diagnostic pathology. To solve this problem, Page and Rogers²⁸ laid down clear guidelines for diagnosis and a subsequent study by Schnitt *et al*,²⁹ in which the Page and Rogers criteria were used, showed an improvement, with complete agreement in 58% of cases. Other studies, including those associated with the UK National and European Commission Quality

Assurance Schemes (EQA), have revealed lower levels of agreement even among experienced breast pathologists.^{30–32}

Lakhani *et al* demonstrated that LOH identified at loci on 16q and 17p in *in situ* and invasive cancer is also present in ADH with a similar frequency.³³ This indicates that ADH is a neoplastic proliferation and is likely to be part of the spectrum of *in situ* ductal neoplasia. There is support for this view in the literature from several other studies.^{34–36} O'Connell *et al* studied 51 cases of ADH at 15 polymorphic microsatellite loci and found LOH for at least one marker in 42% of the cases.³⁶ The studies suggest that there is little difference between ADH and DCIS within the limits of current molecular investigations. The failure of EQA schemes to demonstrate reasonable agreement for this category, together with molecular data, which show pronounced overlap between ADH, and DCIS raise serious doubts about the validity of this diagnostic category. If future experiments do show that ADH is distinct from DCIS, more robust diagnostic criteria will have to be developed for use in clinical practice.

CerbB2 oncogene and Herceptin

The protooncogene *CerbB2* (*Her2/Neu*) encodes a transmembrane protein, which has homology with epidermal growth factor receptor. *CerbB2* is amplified in approximately 20% of invasive cancers and has received interest because of its association with lymph node metastases, short relapse time, poor survival, and decreased response to endocrine and chemotherapy.^{37–39} *CerbB2* amplification is almost always associated with an increase in mRNA and protein expression. In contrast to invasive cancer, the *CerbB2* protein has been identified in a high proportion (60–80%) of DCIS of high nuclear grade, comedo-type, but is not common in the low nuclear grade forms. Allred *et al* found that the expression of this protein is higher in invasive carcinomas associated with DCIS than in those without DCIS.⁴⁰ It is very rarely expressed in LCIS.^{41–43} This gene product has not been identified in benign proliferative disease or ADH.⁴⁴ This oncogene represents an excellent example of the translation of basic science to clinical practice. *CerbB2* status predicts response to antioestrogen and cytotoxic chemotherapy. *CerbB2* has attracted attention because of the availability of the humanised monoclonal antibody Herceptin for the treatment of breast cancer. Initial clinical trials suggest that it will have a useful role in the management of a proportion of breast cancers.⁴⁵

Familial breast cancer

A small proportion of breast cancers result from a heritable predisposition. Two predisposition genes, *BRCA1* and *BRCA2* have been cloned. The morphological features of tumours from patients with *BRCA1* and *BRCA2* mutations differ from each other and from sporadic breast cancers.^{46,47} Both are higher grade compared with sporadic cases. An excess of medullary/atypical medullary carcinoma has

been reported in patients with BRCA1 mutations.⁴⁸⁻⁴⁶ BRCA1 associated tumours are more likely than sporadic cancers to be steroid hormone receptor (oestrogen receptor (ER) and progesterone receptor (PR)) negative, CerbB2 negative, and to have mutations in the p53 gene.⁴⁹⁻⁵⁰ In contrast, BRCA2 tumours are not different from sporadic cancers in their ER, PR, or p53 status. The data derived from these studies, combining morphology and clinical data, have implications for clinical practice.

Grade is an independent prognostic indicator and is inversely related to outcome.⁵¹ The higher grade of BRCA1 associated tumours should have a worse prognosis than non-BRCA1 mutation carriers. Paradoxically, there are data within the literature suggesting that familial cancer in general, and medullary carcinomas in particular, have a better prognosis than ordinary ductal carcinomas, no special type.⁴⁸⁻⁵²⁻⁵⁵ A recent study suggests that the disease free interval and survival is not different from patients with sporadic breast cancers.⁵⁶ In contrast, Foulkes *et al* have shown that the worse prognosis predicted by the higher grade is indeed correct.⁵⁷ Data on prognosis in patients with BRCA2 mutations are scanty but preliminary reports suggest a similar prognosis to sporadic cancers.⁵⁸⁻⁵⁹

The use of breast cancer screening mammography in familial cancer is a controversial issue. It is likely to be replaced by ultrasound or magnetic resonance imaging. Whichever method is used, the pathology data (high grade, with a very high mitotic count and high proliferative index) suggests that the screening interval will have to be smaller than the present three years if interval cancers are to be avoided. The role of BRCA1 as part of a DNA repair complex also raises questions about radiation exposure, although at present there is no convincing evidence that the amount of radiation received by the patient during the mammographic screening is important.

Finally, morphology might have a role in genetic counselling of patients. It has been estimated that patients who develop breast cancers between the age of 25 and 29 years, and who do not have an obvious history of breast cancer in the family, have a risk of approximately 6-7% for carrying mutations in the BRCA1 gene.⁶⁰ On the assumption that the odds ratio from the analysis of the morphological features is independent of age, a patient under 30 years who has a high grade tumour (grade II or III) and who is also ER negative (D Easton 2000, personal communication) would have a risk of approximately 40-45% of harbouring a mutation in BRCA1. In the absence of these features the risk would be 3-4%. Hence, the use of morphological and molecular features in addition to the clinical data may enhance the counselling of patients who are likely to harbour mutations in this gene.

- 1 Lakhani SR. The transition from hyperplasia to invasive carcinoma of the breast. *J Pathol* 1999;187:272-8.
- 2 Evans AJ, Pinder S, Ellis IO, *et al*. Screening-detected and symptomatic ductal carcinoma in situ: mammographic features with pathologic correlation. *Radiology* 1994;191:237-40.

- 3 Molloy M, Azarow K, Garcia VF, *et al*. Enhanced detection of preinvasive breast cancer: combined role of mammography and needle localization biopsy. *J Surg Oncol* 1989;40:152-4.
- 4 Foote FW, Stewart FW. Lobular carcinoma in situ. *Am J Pathol* 1941;49:1-5.
- 5 Broder A. Carcinoma in situ contrasted with benign penetrating epithelium. *JAMA* 1932;99:1670-4.
- 6 Sonnenfeld M, Frenna T, Weidner N, *et al*. Lobular carcinoma in situ: mammographic-pathologic correlation of results of needle-directed biopsy. *Radiology* 1991;181:363-7.
- 7 Urban J. Bilaterality of cancer of the breast: biopsy of the opposite breast. *Cancer* 1967;20:1867-70.
- 8 Rosen PP, Senie R, Schottenfeld D, *et al*. Noninvasive breast carcinoma: frequency of unsuspected invasion and implications for treatment. *Ann Surg* 1979;189:377-82.
- 9 Rosen PP, Braun DW, Jr, Lyngholm B, *et al*. Lobular carcinoma in situ of the breast: preliminary results of treatment by ipsilateral mastectomy and contralateral breast biopsy. *Cancer* 1981;47:813-19.
- 10 Page DL, Kidd TE, Jr, Dupont WD, *et al*. Lobular neoplasia of the breast: higher risk for subsequent invasive cancer predicted by more extensive disease. *Hum Pathol* 1991;22:1232-9.
- 11 Rosen PP, Kosloff C, Lieberman PH, *et al*. Lobular carcinoma in situ of the breast. Detailed analysis of 99 patients with average follow-up of 24 years. *Am J Surg Pathol* 1978;2:225-51.
- 12 Nielsen M, Jensen J, Andersen J. Precancerous and cancerous breast lesions during lifetime and at autopsy. A study of 83 women. *Cancer* 1984;54:612-15.
- 13 Wheeler JE, Enterline HT, Roseman JM, *et al*. Lobular carcinoma in situ of the breast. Long-term follow-up. *Cancer* 1974;34:554-63.
- 14 Wheeler JE, Enterline HT. Lobular carcinoma of the breast in situ and infiltrating. *Pathol Annu* 1976;11:161-88.
- 15 Haagensen CD, Lane N, Lattes R, *et al*. Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. *Cancer* 1978;42:737-69.
- 16 Moll R, Mitze M, Frixen UH, *et al*. Differential loss of E-cadherin expression in infiltrating ductal and lobular breast carcinomas. *Am J Pathol* 1993;143:1731-42.
- 17 Rasbridge SA, Gillett CE, Sampson SA, *et al*. Epithelial (E-) and placental (P-) cadherin cell adhesion molecule expression in breast carcinoma. *J Pathol* 1993;169:245-50.
- 18 Lakhani S, Collins N, Sloane J, *et al*. Loss of heterozygosity in lobular carcinoma in situ of the breast. *J Clin Pathol: Mol Pathol* 1995;48:M74-8.
- 19 Nayar R, Zhuang Z, Merino MJ, *et al*. Loss of heterozygosity on chromosome 11q13 in lobular lesions of the breast using tissue microdissection and polymerase chain reaction. *Hum Pathol* 1997;28:277-82.
- 20 Bex G, Cleton-Jansen AM, Nollet F, *et al*. E-cadherin is a tumour/invasion suppressor gene mutated in human lobular breast cancers. *EMBO J* 1995;14:6107-15.
- 21 Bex G, Cleton-Jansen AM, Strumane K, *et al*. E-cadherin is inactivated in a majority of invasive human lobular breast cancers by truncation mutations throughout its extracellular domain. *Oncogene* 1996;13:1919-25.
- 22 Vos CB, Cleton-Jansen AM, Bex G, *et al*. E-cadherin inactivation in lobular carcinoma in situ of the breast: an early event in tumorigenesis. *Br J Cancer* 1997;76:1131-3.
- 23 Perou CM, Sorlie T, Eisen MB, *et al*. Molecular portraits of human breast tumours [in process citation]. *Nature* 2000;406:747-52.
- 24 Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985;312:146-51.
- 25 Tavassoli FA, Norris HJ. A comparison of the results of long-term follow-up for atypical intraductal hyperplasia and intraductal hyperplasia of the breast. *Cancer* 1990;65:518-29.
- 26 McDivitt RW, Stevens JA, Lee NC, *et al*. Histologic types of benign breast disease and the risk for breast cancer. The cancer and steroid hormone study group. *Cancer* 1992;69:1408-14.
- 27 London SJ, Connolly JL, Schnitt SJ, *et al*. A prospective study of benign breast disease and the risk of breast cancer [published erratum appears in *JAMA* 1992;267:1780]. *JAMA* 1992;267:941-4.
- 28 Page DL, Rogers LW. Combined histologic and cytologic criteria for the diagnosis of mammary atypical ductal hyperplasia. *Hum Pathol* 1992;23:1095-7.
- 29 Schnitt SJ, Connolly JL, Tavassoli FA, *et al*. Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria [see comments]. *Am J Surg Pathol* 1992;16:1133-43.
- 30 Sloane JP, Ellman R, Anderson TJ, *et al*. Consistency of histopathological reporting of breast lesions detected by screening: findings of the UK National External Quality Assessment (EQA) Scheme. *Eur J Cancer* 1994;30A:1414-19.
- 31 Sloane JP, Amendoeira I, Apostolikas N, *et al*. Consistency achieved by 23 European pathologists from 12 countries in diagnosing breast disease and reporting prognostic features of carcinomas. European Commission working group on breast screening pathology. *Virchows Arch* 1999;434:3-10.
- 32 Elston CW, Sloane JP, Amendoeira I, *et al*. Causes of inconsistency in diagnosing and classifying intraductal proliferations of the breast. *Eur J Cancer* 2000;36:1769-72.
- 33 Lakhani SR, Collins N, Stratton MR, *et al*. Atypical ductal hyperplasia of the breast: clonal proliferation with loss of

- heterozygosity on chromosomes 16q and 17p. *J Clin Pathol* 1995;48:611-15.
- 34 O'Connell P, Pekkel V, Fuqua S, *et al.* Molecular genetic studies of early breast cancer evolution. *Breast Cancer Res Treat* 1994;32:5-12.
 - 35 Chuaqui RF, Zhuang Z, Emmert-Buck MR, *et al.* Analysis of loss of heterozygosity on chromosome 11q13 in atypical ductal hyperplasia and in situ carcinoma of the breast. *Am J Pathol* 1997;150:297-303.
 - 36 O'Connell P, Pekkel V, Fuqua SA, *et al.* Analysis of loss of heterozygosity in 399 premalignant breast lesions at 15 genetic loci. *J Natl Cancer Inst* 1998;90:697-703.
 - 37 Berger MS, Locher GW, Saurer S, *et al.* Correlation of c-erbB-2 gene amplification and protein expression in human breast carcinoma with nodal status and nuclear grading. *Cancer Res* 1988;48:1238-43.
 - 38 Slamon DJ, Clark GM, Wong SG, *et al.* Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177-82.
 - 39 Varley JM, Swallow JE, Brammar WJ, *et al.* Alterations to either c-erbB-2(neu) or c-myc proto-oncogenes in breast carcinomas correlate with poor short-term prognosis. *Oncogene* 1987;1:423-30.
 - 40 Allred DC, Clark GM, Molina R, *et al.* Overexpression of HER-2/neu and its relationship with other prognostic factors change during the progression of in situ to invasive breast cancer. *Hum Pathol* 1992;23:974-9.
 - 41 Gusterson BA, Machin LG, Gullick WJ, *et al.* Immunohistochemical distribution of c-erbB-2 in infiltrating and in situ breast cancer. *Int J Cancer* 1988;42:842-5.
 - 42 Poller DN, Galea M, Pearson D, *et al.* Nuclear and flow cytometric characteristics associated with overexpression of the c-erbB-2 oncoprotein in breast carcinoma. *Breast Cancer Res Treat* 1991;20:3-10.
 - 43 Ramachandra S, Machin L, Ashley S, *et al.* Immunohistochemical distribution of c-erbB-2 in in situ breast carcinoma—a detailed morphological analysis. *J Pathol* 1990;161:7-14.
 - 44 Gusterson BA, Machin LG, Gullick WJ, *et al.* c-erbB-2 expression in benign and malignant breast disease. *Br J Cancer* 1988;58:453-7.
 - 45 Pegram MD, Lipton A, Hayes DF, *et al.* Phase II study of receptor-enhanced chemosensitivity using recombinant humanized anti-p185HER2/neu monoclonal antibody plus cisplatin in patients with HER2/neu-overexpressing metastatic breast cancer refractory to chemotherapy treatment. *J Clin Oncol* 1998;16:2659-71.
 - 46 Lakhani S, Easton D, Stratton MR. Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases. Breast cancer linkage consortium. *Lancet* 1997;349:1505-10.
 - 47 Lakhani SR, Jacquemier J, Sloane JP, *et al.* Multifactorial analysis of differences between sporadic breast cancers and cancers involving BRCA1 and BRCA2 mutations. *J Natl Cancer Inst* 1998;90:1138-45.
 - 48 Marcus JN, Watson P, Page DL, *et al.* Hereditary breast cancer: pathobiology, prognosis, and BRCA1 and BRCA2 gene linkage [see comments]. *Cancer* 1996;77:697-709.
 - 49 Crook T, Crossland S, Crompton MR, *et al.* p53 mutations in Brca1-associated familial breast cancer [letter]. *Lancet* 1997;350:638-9.
 - 50 Osin P, Crook T, Powles T, *et al.* Hormone status of in-situ cancer in BRCA1 and BRCA2 mutation carriers [letter]. *Lancet* 1998;351:1487.
 - 51 Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. *Histopathology* 1991;19:403-10.
 - 52 Porter DE, Cohen BB, Wallace MR, *et al.* Breast cancer incidence, penetrance and survival in probable carriers of BRCA1 gene mutation in families linked to BRCA1 on chromosome 17q12-21. *Br J Surg* 1994;81:1512-15.
 - 53 Eisinger F, Stoppa-Lyonnet D, Longy M, *et al.* Germ line mutation at BRCA1 affects the histoprostic grade in hereditary breast cancer. *Cancer Res* 1996;56:471-4.
 - 54 Eisinger F, Jacquemier J, Charpin C, *et al.* Mutations at BRCA1: the medullary breast carcinoma revisited. *Cancer Res* 1998;58:1588-92.
 - 55 Eisinger F, Nagues C, Birnbaum D, *et al.* Low frequency of lymph-node metastasis in BRCA1-associated breast cancer [letter]. *Lancet* 1998;351:1633-4.
 - 56 Verhoog LC, Brekelmans CT, Seynaeve C, *et al.* Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1 [in process citation]. *Lancet* 1998;351:316-21.
 - 57 Foulkes WD, Wong N, Rozen F, *et al.* Survival of patients with breast cancer and BRCA1 mutations [letter]. *Lancet* 1998;351:1359-60.
 - 58 Gaffney DK, Brohet RM, Lewis CM, *et al.* Response to radiation therapy and prognosis in breast cancer patients with BRCA1 and BRCA2 mutations. *Radiother Oncol* 1998;47:129-36.
 - 59 Robson M, Rajan P, Rosen PP, *et al.* BRCA-associated breast cancer: absence of a characteristic immunophenotype. *Cancer Res* 1998;58:1839-42.
 - 60 Ford D, Easton DF, Peto J. Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. *Am J Hum Genet* 1995;57:1457-62.



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