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Late-breaking breast cancer research: from genomics to new drugs

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Full text

Do you find that despite your best intentions, you never feel completely up-to-date with the latest research publications in your field? Journals pile up on your desk, and only when you try searching do you suddenly get depressed and realise just how much has been published within the last few months. While journal clubs, review articles and the scope of the Internet all help, nothing quite gives you a comprehensive overview. With scores of journals that might publish on subjects of scientific relevance to breast cancer, how can you be truly up-to-date?

Paper Reports is an innovative new service that aims to highlight recent publications of relevance to breast cancer, providing short reports on the most important and interesting new articles. These reports are immediately published on our website, often before you would have the chance to read the paper itself. Our team currently consists of 11 scientists and clinicians who are all active in areas of breast cancer research. Between them they review the contents of over 40 journals, ranging from *Nature Genetics*, *Molecular and Cellular Biology* and *Oncogene* to *Carcinogenesis*, *Journal of Clinical Oncology*, and *Cancer Research*. We group the reports into 11 topics (outlined in italics below) which cover etiology, molecular and cellular biology, model systems and targeted therapeutic interventions.

In our first 4 months we have published 39 reports on our website which are of relevance or importance to those involved in breast cancer research. These are listed below, and 10 key reports are printed in full. In this issue alone we can see reports of important advances ranging from our understanding of the function of the BRCA1 and BRCA2 proteins to a clinical report of a novel selective estrogen receptor modulator which may prevent breast cancer. In *cellular models*, Hahn *et al* determined the minimum number of genetic events for cellular transformation *in vitro*. They demonstrated that clear co-operation is required between genes, often in a specific order, which may be of fundamental importance in tumorigenesis. Technological advances in molecular genetics have been reported, including the potential use of single nucleotide polymorphisms to provide a whole-genome scan for common breast cancer (Kruglyak *et al*), and cDNA microarrays to identify relevant gene expression patterns in breast tumors (Perou *et al*).

In the area of *pathogenesis and cellular biology*, Russo *et al* have described the relationship between steroid hormone receptor expression and cell proliferation in the normal mammary gland epithelium. They observed that the expression of both estrogen receptor (ER) and progesterone receptor occurs in separate subpopulations of cells from those that are proliferating, and that this relates to the structural differentiation of the mammary gland. These findings are of relevance both to our understanding of the hormonal control of the normal mammary gland, and possibly to the origin of ER-positive or -negative invasive carcinomas. Shoker *et al* extended these findings by their study of ER expression and

distribution in various pre-malignant lesions of the breast, while experimental findings by Sternlicht *et al* described the role of matrix metalloproteinases in mouse mammary carcinogenesis.

Several papers on the topic of *pathogenesis and molecular biology* have addressed the emerging function of the BRCA1 and BRCA2 proteins. Lee *et al* examined embryonic fibroblasts from mice homozygous for *Brca2* which expressed a truncated protein and had a severe proliferative defect. Retroviral transduction with mutant p53 rescued the growth arrest in these cells, confirming the potential interplay between the genes encoding these proteins in mitotic checkpoints. Zhong *et al* reported an association between BRCA1 and the hRad50-hMre11-p95 complex which senses DNA damage, raising the possibility that hereditary breast cancers may have differential sensitivity to both irradiation and chemotherapy. The interaction of BRCA1 with ER signaling is described by Fan *et al*, who suggest that wild-type BRCA1 suppresses ER-dependent gene transcription. In the topic of animal models, Davies *et al* used transgenic rats which overexpressed either c-erbB-2 or transforming growth factor-alpha under the control of the mouse mammary tumor virus long terminal repeat (MMTV-LTR), thus creating a defined genetic background on which to study the development of spontaneous mammary tumors.

From a clinical viewpoint in the topic of *pathology*, there were three key papers relating to pre-invasive ductal carcinoma *in situ* (DCIS). Fisher *et al* reported the findings of the NSABP-B24 trial, which showed that tamoxifen given in addition to lumpectomy and irradiation significantly reduced further breast cancer events, especially the incidence of ipsilateral invasive cancer. In relation to the significance of the margin of excision for DCIS lesions, Silverstein *et al* studied 469 cases and suggested the margin widths necessary to achieve local control in the presence or absence of further adjuvant radiotherapy. Finally, Fisher *et al* reported on the 8-year follow-up of the pathological data from the NSABP-B17 trial, with the most significant predictor of disease recurrence being the presence of comedo necrosis.

In *epidemiology*, Mansi *et al* described the long-term follow up of women identified as having micrometastatic bone marrow metastases, and showed that this knowledge was not as important as the traditional assessment of tumor size, nodal status and the presence of vascular invasion. In *screening*, The UK Trial of Early Detection of Breast Cancer reported their results after 16 years of follow up. They demonstrated a 35% reduction in mortality in women aged 45-49 using biennial screening together with clinical examination. These results contribute to the debate on the lower age-limit at which screening should commence, together with the most cost-effective interval and reliance on mammography alone.

Finally, in relation to novel therapeutic interventions for breast cancer, the last few months have seen the publication of several landmark papers. On the back of last year's data with tamoxifen in the *prevention* of breast cancer, Cummings *et al* reported that the selective ER modulator (SERM) raloxifene significantly reduced the incidence of early breast cancer in the MORE study of 7705 post-menopausal women with osteoporosis. The relative risk reduction of 0.35 represents an impressive effect in this population considered to have a normal risk for breast cancer. In *experimental therapies*, Cobleigh *et al*'s report on the role of HER-2 monoclonal antibody therapy in advanced breast cancer is significant in providing the first convincing clinical 'proof of concept' for a novel targeted anticancer strategy. Other promising strategies include Pandha *et al*'s report of genetic pro-drug activation in erbB-2-overexpressing breast cancer, and Chen *et al*'s report of a pre-clinical model of liposome-plasmid complexes encoding angiostatin and endostatin, both of which inhibited tumor growth.

As outlined above, the promise of recent advances in molecular biology does at last seem to be bridging the gap from bench to bedside in breast cancer research. We hope that, by bringing key papers to your attention on a regular basis, you too will feel more familiar with these developments.