Biomarkers in Breast Cancer

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New findings offer advances in diagnosis and therapy

Based on global data collected from 2005 to 2007, 12% (one in eight) of women born today will be diagnosed with breast cancer (BC) at some point in their lives. In 2007, it was estimated that 2.6 million women in the US had a history of BC – a figure that included individuals with active BC, as well as those who had been cured of the disease. (Source: US National Cancer Institute).

Based on five-year relative survival figures, global data collected from 1999 to 2006 showed that 98% of women diagnosed with localised BC are alive five years after diagnosis, compared to 83.6% in the case of BC with regional lymph node involvement, and 23.4% for distant metastatic BC (Source: US National Cancer Institute). This means that 2 in 100 patients diagnosed with localised BC will die within five years, whereas this number increases to 77 out of 100 for metastatic disease.

More effective drug treatments are required for BC, and these statistics, notably those on survival rates, underline the need for better diagnosis. Today, early diagnosis remains a key priority, to enable treatments to start as soon as possible.

BC may be discovered by self-examination. However, routine mammograms (breast x-ray) may identity changes the individual is not aware of, and which require further investigation. Other tests used to detect or investigate BC include MRI, ultrasound, full-field digital mammogram, ductograms, ductal lavage, nipple discharge and nipple aspirate analysis.

Histochemical tests are also important in the diagnosis of BC – a field that is seeing substantial development and growth. Today, histochemical tests are used to investigate the presence of cell receptors, including oestrogen (ER), progesterone (PR) and Human Epidermal growth factor Receptor 2 (HER2). Patients found to be oestrogen receptor positive (ER+) may be treated with anti-oestrogens, and HER2+ positive patients may be prescribed the therapeutic antibody trastuzumab (Herceptin®), that targets the HER2 receptor. BC cells that do not show any of these three receptors are described as triple negative, which is associated with a poorer prognosis. Individuals with a family history of BC may also be offered genetic tests to investigate whether or not they may be at increased risk of developing the disease (e.g. BRCA1 or BRCA2 mutations).

ER, PR and HER2 are well known examples of biomarkers used in the diagnosis of BC and, in these cases, commonly influence subsequent treatments. The American Society of Clinical Oncology (ASCO) has produced recommendations on the use of nine BC biomarkers, namely: CA15-3, CA27.29, carcinoembryonic antigen, oestrogen receptor, progesterone receptor, human epidermal growth factor receptor 2 (HER-2), urokinase plasminogen activator, plasminogen activator inhibitor 1 and some multi-parameter gene expression assays.

These 2007 ASCO recommendations are based on defined clinical circumstances. For example, HER2 tests are recommended to be used on all primary invasive breast tumours to establish whether the patient will benefit from trastuzumab. Overexpression of HER2 is also believed to identify patients who benefit from

anthracycline-based adjuvant therapy. In the case of uPA/PAI-1, tests can be carried out to determine the prognosis of patients with newly diagnosed node negative BC. Low levels of both uPA and PAI-1 indicate a low risk of recurrence, especially in hormone receptor–positive women who receive adjuvant endocrine therapy. Patients with high levels of uPA and PAI-1 show significant benefit from cyclophosphamide, methotrexate and fluorouracil 5FU (CMF).

However, a recent report by John Bates of Biopharm Reports (http://www.biopharmreports.com/Report_description.asp?startingPoint=0&interval=10&id=3231&s=&ss=&i=&search=ks&key identifies more than 190 BC biomarkers, from studies largely published in the last five years. While many of these findings are based on small early studies and will require more expansive investigations, they offer significant hope of new and much-needed advances in the tests that can be used in the diagnosis of BC. These findings may also advance the range of end-points that can be used in clinical trials, as well as giving new insights and opportunities in drug discovery.

More importantly, new biomarkers are required in the treatment of patients, notably in guiding the most effective use of today's BC drugs and in better defining patient groups, as therapeutic developments move ever-closer to more-personalised therapies.

Today, the very small number of officially recognised BC biomarkers reflects several factors, not least the complexity of reliably and unambiguously linking specific molecules (or parameters) or combinations to specific clinical (patient) circumstances. All cancers are highly diverse, genetically and phenotypically, and do not readily offer up unambiguous indicators upon which fixed clinical recommendations can be based. Nevertheless, there is urgent need to make the maximum use of existing findings on breast cancer biomarkers, to more rapidly translate these advances into better diagnostics and the most effective treatments. Today, biomarkers are driving these developments.

The recent report by Biopharm Reports classifies the list of 190 candidate biomarkers according to their potential utility in early detection, metastasis, in directing therapy, response to therapy, prognosis and predisposition. Developments in this area are also offering greater scope for minimally invasive methods, such as blood or urine tests, as distinct from invasive tissue biopsies. For further information, contact John Bates of Biopharm Reports (http://www.biopharmreports.com/Report_description.asp?startingPoint=0&interval=10&id=3231&s=&ss=&i=&search=ks&key