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BIOCHEMICAL AND BIOLOGICAL MARKERS OF BREAST CANCER PROGRESSION

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Introduction

The behaviuor of breast cancer may change during the natural history of the disease, and the tumour heterogeneity allows many factors to influence this[1]. Although numerous predictive and prognostic markers have been described, with the exception of lymph-node status no widely accepted markers for metastasis or progression are available. The Nottingham prognostic index, a product of primary cancer size, grade and node status, continues to have a higher predictive value than any isolated tumour markers, and the addition of more objective measures such as S-phase may help[2]. Variation between laboratories makes the value of many biochemical markers (even CEA and CA 15-3) unclear, but biological markers, including recial, geographical, diet and lifestyle factors are likely to have a role in predicting progression and future interventions.

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Pathology

Apoptosis

Apoptosis, or programmed cell death, is likely to exert a strong influence on tumour progression. Identification of apoptotic cells relies largely in detection of DNA breakdown apoptotic changes. In a study of apoptosis by DNA strand breaks in fine-needle aspiration biopsies including 11 breast cancers [3], apoptosis was found to be more common in tumour cells than in normal cells of the same organ, but follow-up studies are needed.

Proliferation

The best single marker (or panel of markers) for cell kinetics has not yet been established. Gasparini et al.[4] comparing S-phase fraction (SPF), Ki67 and proliferating cell nuclear antigen (PCNA, using PC10 antibody), found the S-phase fraction determined by flow cytometry to be the strongest cell-kinetics marker for overall and disease-free survival. Positive PCNA staining was associated with a significantly worse overall survival [5].

Angiogenesis

In several cancers, quantification of new vessel growth appears to be a useful independent prognostic factor. However, for breast cancers the value is still uncertain. The value of detecting new vessels and the best antibodies for this remain unclear[6].

Tumour bed biopsy and margins

Objective information on the behaviour of cancers, in addition to lymph-node histology, may be obtained from the breast at the time of initial surgery by examination of the cavity wall or tumour bed after tumour excision for residual cancer.

After 3.5 years, 85% of women with negative biopsies were alive, compared to 62% of those with positive biopsies. When evaluating this together with nodal status, a group identified as positive for both risk factors was found to have 35.5% disease-free survival, compared to 95.7% for those with neither risk factor (P<0.01) [7].

S-phase

The S-phase fraction (SPF) provides a useful, if crude, independent estimate of the percentage of sells that are undergoing active cell division, and a high S-phase fraction is generally associated with progression[8]. It probably provides a more objective score than unclear grade, which does require some experience.

Sentinel lymph-node biopsy

The sentinel node is identified by injecting dye or radioactive tracer into or around the cancer, as the first node draining a primary invasive cancer. 'Skip' metastases are occasionally noted, in which the sentinel node is negative.

Veronesi et al. found that the sentinel node predicted axillary node status accurately in 97.5% (156 of 160) of patients, and in 38% of cases it was the only positive node[9].

Biochemical markers of tissue and serum

Carcinoembryonic antigen (CEA)

Carcinoembryonic antigen (CEA) continues its long run in monitoring serum levels. It is commonly used in tandem with CA 15-3 for follow-up aimed at detection of relapse[10].

Tissue polypeptide-specific antigen (TPS)

Tissue polypeptide-specific antigen (TPS) is considered to be particularly suitable for monitoring the response to treatment because of its more specific assessment of proliferation activity[11].

TPS appears to work best in combination with TPA and CEA or CA15-3.

Urokinase-type plasminogen activator (u-PA) and its inhibitor PAI-1

u-PA mediates proteolysis by breaking down the extra cellular matrix, and the proteolytic activity is controlled by plasminogen activator minhibitor type 1 (PAI-1). High levels of both compounds have been associated with poor prognosis, and the prognostic value may increase with time to a value of nearly node status [12].

Thymidine kinase (TK)

Thymidine kinase (TK) is a key regulatory enzyme of DNA synthesis. The levels measured in tumour extracts probably reflect tumour activity, but may be of a particular sub-group. Roman[13] in a study of 290 patients with breast cancer, found that high levels were associated with reduced survival in pre/ perimenopausal patients.

Serum levels detected systemic recurrence before clinical diagnosis, with an average lead time of 2 months.

Cathepsin D

Cathapsin D is an acidic lysosomal protease that is expressed in all cells.

The expression of cathepsin D in breast cancers may be related to tumour grade. Several reports have suggested that cathepsin D levels may be predictive of higher recurrence and lower survival, and show a significant correlation with node status. The association between high cathepsin D levels and poor survival appears to be particularly marked in node-negative breast cancer patients [14].

YKL-40

YKL-40 is a recently described glycoprotein related to chitinase. Serum levels of YKL-40 may be an interesting marker for extent of disease and survival in patients after recurrence of breast cancer[15].

Epidermal growth factor receptor (EGFR)

Expression of the epidermal growth factor receptor (EFGR) may be associated with oestrogen receptor (OR)-negative tumours and with increased metastasis.

Gasparini et al. suggested that EGFR might be a significant indicator of recurrence ($p<0.01$ and odds ratio 2.82) but not of death, when combined with S-phase fraction data [16].

pS2

pS2 protein is a polypeptide rich in cysteine, from the pS2 gene, also referred to as BCE1, pNR-2 or Md2, which may predict clinical responsiveness to hormone therapy. The expression is induced by oestrogens and Motomura et al. Reported that pS2 expression in cancer cells was inhibited in patients who were taking tamoxifen[17].

Heat-shock protein 27KD (HSP27), p29 or p24

Heat-shock protein 27KD (HSP27), p29 or p24, may have different roles at different stages of tumour progression. Love and King[18] follow up study of 361 patients suggested that high HSP27 levels were associated with a short disease-free interval in node-negative patients.

Heat-shock protein 70KD (HSP 70)

Heat-shock protein 70KD (HSP 70) is thought to be involved with protein products of the c-myc oncogene and p53 tumour suppressor gene. High levels of expression of HSP70 in node-negative cancers were associated with shorter disease-free survival by uni- and multivariant analysis in 345 tumours ($p=0.006$) [19].

Prostate-specific antigen (PSA)

PSA reported to be present in 30% of breast cancers and may be associated with OR-negative and / or node negative cancers and used for diagnosis of breast cancer for monitoring patients in remission[20].

Ring-shaped particles (RSP)

In a study of 120 breast cancers with a median follow-up of 8.7 years, Justice et al. reported that their commercial serum assay for RSP had greater sensitivity and specificity than CEA or CA 15-3 for the presence of active breast cancer[21].

P53 gene and gene product

P53 (sometimes known as TP53) is possibly the most widely evaluated anti-oncogene or tumour suppresser gene. Its value remains unclear, although a study of 998 patients indicates its value as an independent predictor of reduced survival[22].

Autoantibodies to p53

Autoantibodies to p53 have been detected in the sera of patients with a variety of cancers. The sera of 48 of 182 newly diagnosed breast cancer patients (26%) contained autoantibodies to p53, and their presence correlated with high grade ($P=0.0012$)[23].

Mucins, mucin-related markers and other carbohydrates

MUC1 gene product

It represents a major mucin group which is expressed in many secretory epithelial cells, but particularly in breast tissue. MUC1 to 6 have been described[24].

MUC2

MUC2 protein, which is present in 19% of invasive breast cancers, has been associated with shortened disease-free survival [25].

MCA

A related mucin-like carcinoma-associated antigen, MCA, was identified by monoclonal antibodies on breast cancer cell lines. It is raised in progressive disease, and may be of value in identifying patients with liver or bone metastases.

CA 15-3 (OR DF3)

CA 15-3 (sometimes known as DF3) antigen appears to indicate tumour mass and may be raised in the sera of up to 80% of patient with metastatic breast cancer.

Several assays are available, as it has been considered to be the most useful single or combination marker for metastatic breast cancer[26].

ST-439

This is another related mucin carcinoma-associated antigen. Positive tumours have a better prognosis than negative ones ($P<0.01$). Serum levels for detection of recurrence showed a greater sensitivity than CEA or CA 15-3, but a lower specificity [27].

Genes and gene products

Bcl-2 OR BCL2

In a study of 283 node-negative cancers which were followed for 6 years, Bcl-2-positive staining was associated with small, OR-positive, slowly proliferating and p53-negative tumours [28].

C-ERBB-2 (HER2/NEU GENE)

This is more frequently positive in ductal carcinoma in situ (DCIS) than in invasive cancers, although in DCIS there is a close association between c-erbB-2 protein expression and high-nuclear-grade, comedo types, so it may predict future invasiveness[29].

Biological and lifestyle markers

Comorbidity or presence of concurrent disease

Comorbidity here refers to the presence of other non-malignant disease in patients with breast cancer. Satariano and Ragland, in a longitudinal study of 936 women with breast cancer, found that comorbidity was a strong independent predictor of 3-year survival[30].

Familial and hereditary factors

Breast cancers in young women tend to show associations with a family history of breast cancers and to appear histologically more aggressive. However, as described below, the overall and recurrence-free survival periods may be longer in this group, and it has been suggested that increased awareness in these families might lead to earlier detection.

In a Japanese study of 4481 primary breast cancer patients[31], those with a family history (n=394, or 8.8%) had a longer survival over 15 years compared to those without such a history (72% vs. 60%; $P<0.01$).

Diet

Intake of beta-carotene (and vitamin C) was observed to be associated with prolonged survival by Ingram[32]. Fish consumption may be associated with lower breast cancer mortality [33].

Several studies have linked vegetable

consumption to a reduced risk of dying from cancers.

Race

The higher mortality observed in black compared to white patients with breast cancer may be more closely related to lifestyle.

The increasing incidence and age-adjusted mortality rate in Japan [34] may suggest a previously less aggressive type of cancer in the Japanese population.

Socio-economic factor

Numerous studies have shown shorter survival times for many diseases in lower compared to higher socio-economic status groups and in black compared to white breast cancer patients. This has been attributed to delay in diagnosis and later stage at presentation. However, after controlling for these prognostic variables, there increasingly seems to be a real association with some factors(s) in lower socio-economic status and perhaps in cancers of black patients. In a study of 1392 breast cancer patients followed for 5 to 16 years[35], lower socio-economic status (SES) was significantly related to overall survival, after controlling for stage, age, race or / and other prognostic factors.

Psychoscoial factors

Ramires et al. suggested a prognostic association between severe life stressors and recurrence of breast cancer in 50 women who had developed their first recurrence of breast cancer in remission (cases and controls were matched for physical, pathological and sociodemographic variables [36].

Patient support by family

In a study of 1011 patients [37], those women who reported receiving little emotional support from close friends and relatives had a higher death rate during a 5-year follow-up period.

Smoking

An intriguing association was reported by Calle et al. between current smoking and increased risk of death in a 6-year follow-up of a cohort of 604412 women with 880 breast cancer deaths[38]. It may be linked to comorbidity, but this increase was not seen in former smokers.

Gender of offspring

Janerich[39] in a study of 2155 parous women with invasive breast cancer in Utah, USA, found that the median survival among women diagnosed under the age of 45 years was 171 months if the first child was female, but only 66 months if the first child was male. This trend disappeared among women who were aged over 45 years at the time of diagnosis.

Time of observation as a factor

An Italian study suggests that long-term relapse (more than 8 years after surgery) is particularly associated with or positive cancer[40]. Yoshimoto investigated 11 pathological factors in 462 patients, and found that the influence of nodal involvement and nuclear grade on risk of relapse decreased with time, but that it increased with time for fat infiltration, another odd feature being a possible influence by tumour-infiltrating lymphocytes after 2 years post-operatively.

Conclusion

Finally, even a large study can produce odd markers. In a report of a study of nearly 33000 breast cancer patients by Sankila et al. [41], the adjusted relative excess risk of death was highest among those diagnosed in July and August and lowest for those diagnosed in March and November (the difference between the lowest and highest risk being 18%). The authors consider that this observation may be related more to behaviour and health services than to the stars!

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