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## Relationship of p53, uPA, pS2, EGF-R, and c-ERBB2, with response to systemic treatment in recurrent breast cancer patients

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**Purpose:** Based on our and other people's work, several cell biological parameters appeared recently to be associated with response to systemic therapy, but have not been compared by multivariate analysis.

**Methods:** Of 368 patients, 287 patients received first-line treatment with tamoxifen, and 81 received CMF or FAC as first-line treatment for recurrent disease. The membrane levels of EGF-R and c-erbB2, and cytosolic levels of p53, uPA and pS2, of primary breast tumors were determined by quantitative immunoassays (EGF-R, c-erbB2: Oncogene Science; p53: Sangtec Medical; uPA: American Diagnostica; pS2: Cis bio international).

**Results:** In logistic regression analysis for response to first-line tamoxifen therapy, of the modern parameters studied, high levels of c-erbB2 (16% of pts) or EGFR (78% of pts) showed the worst response to treatment, with respective odds ratio's of 0.22 ($p < 0.001$) and 0.44 ($p < 0.01$). In multivariate analysis for response to tamoxifen and for the length of progression-free survival, corrected for all relevant clinical and biological factors, c-erbB2 was the only significant biological parameter, together with ER. The odds ratio for response was 0.29 ($p = 0.001$), the relative progression and death rates were 2.28 ($p < 0.0001$) and 1.84 ($p = 0.001$) resp. None of parameters studied showed a significant association in analyses for response and survival on first-line chemotherapy.

**Conclusion:** The membrane c-erbB2 level is the most potent (and also) independent predictor of response on tamoxifen therapy in recurrent breast cancer in addition to ER. *(supported by the Dutch Cancer Society, Grant DDHK 96-1234).*

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## Immunohistochemically detected lymph node micrometastases (N1A-IHC) in breast cancer (BC)

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**Purpose:** Whereas lymph node involvement is one of the most powerful prognostic factors in BC, the prognostic value of N1a-IHC in conventionally node negative BC patients (pts.) is controversial.

**Methods:** 3,616 axillary lymph nodes of 202 pts. with pT1-2N0M0 BC were examined for micrometastases using a monoclonal pancytokeratine antibody. In addition to histological findings, ER, PR, S-Phase, ploidy, EGF-R, p53, Ki-67, HER-2/neu, Cathepsin D and pS2 were determined. The mean follow-up time was 52 ± 19 months.

**Results:** Micrometastases were detected in 76 of 3,616 (2.1%) lymph nodes resulting in a conversion of conventional N0 to N1a-IHC in 10.4% (21/202) pts. Compared with N0-IHC, these patients had a prognostic disadvantage for distant metastases-free survival ($p = 0.003$) and overall survival ($p = 0.006$). By multivariate analysis tumor size, severe loss of differentiation and vessel invasion were confirmed as independent prognostic factors in N0 pts..

**Conclusion:** N1a-IHC in axillary lymph nodes are of prognostic importance. However, they do not represent independent prognostic factors in N0 pts. and are not helpful in treatment decisions.

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## Changes in expression of the adhesion molecule CD66a in different stages of human breast carcinogenesis

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**Purpose:** CD66a is the human homologue of the well-defined cell adhesion molecule (Cell-CAM) of the rat. It was our aim to characterise for the first time the distribution of CD66a in human breast epithelia at different stages of malignant transformation.

**Methods:** The expression of CD66a was studied in 31 benign lesions, 15 in situ carcinomas and 100 invasive carcinomas of the mammary gland. Formalin-fixed, paraffin-embedded specimens and a monoclonal antibody (MAb4D1/C2) specific for CD66a were used for immunohistochemistry.

**Results:** CD66a was expressed at the apical sites of normal epithelial cells and in myoepithelia, but changed gradually from low to high grade in situ carcinomas into a uniform membranous staining. Apical staining was observed in only 11 out of 77 CD66a positive invasive carcinomas, while 23 cases showed no expression at all. A correlation was found between the apical CD66a staining and high differentiated carcinomas ($p = 0.03$) or tumour types like tubular and papillary carcinomas ($p = 0.0002$).

**Conclusion:** The uniform membranous expression of CD66a might be due to a loss or reduction of the interaction of the adhesion molecule with its binding molecules. Our findings indicate that not the loss of CD66a expression alone, but the change in expression patterns characterise an important event in breast cancer carcinogenesis.

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## Cytological grading of breast carcinoma

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**Purpose:** Fine needle aspiration cytology (FNAC) is widely used in the diagnosis of breast carcinoma. The aim of this study was to devise a system for grading breast carcinoma based on cytological features alone. Such a system would be helpful in the selection of patients for appropriate therapy.

**Methods:** Diagnostic FNAC smears taken from 100 patients with breast carcinoma were studied. There were usually at least to two slides from each patient. The cytological preparation were studied without knowledge of the subsequent grade and type of the tumors. The features assessed were the nuclear diameter (compared with adjacent white blood cells), nuclear pleomorphism, the presence of easily visible nucleoli, mitoses, the degree of cell clustering and necrosis. Each of the features studied was scored separately and compared to the histological grade of the tumors following excision.

**Results:** Significant associations between worsening cytological features and increasing histological grade were found with nuclear diameter, nuclear pleomorphism, mitoses and presence of nucleoli. Discriminant analysis confirmed these findings, showing that a combination of the scores for these four parameters gave the best correlation with histological grade. The sensitivity of this method of classification was 83.6% and the specificity 85.8%.

**Conclusion:** This simple system of grading breast carcinoma is possible from FNAC smear specimens which correlates with histological grade. With the current trend toward less aggressive diagnostic methods definitive treatment may be carried out without prior biopsy and histological examination.

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## Amplification of ERBB-2 (HER-2/NEU) oncogene as a potential prognostic marker for breast but not ovarian cancer in Russian group of patients

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**Purpose:** Amplification of ERBB-2 (HER-2/NEU) oncogene is widely accepted to be a frequent event (25–30%) and an indicator of unfavourable outcome for breast and ovarian cancer patients. Nonetheless some reports failed to confirm such phenomena due to unknown reasons. The purpose was to evaluate possible benefits from this test for North-Western Russia.

**Methods:** ERBB-2 copy number was determined by Southern-blot.

**Results:** In our study ERBB-2 oncogene was often amplified in breast carcinomas (BC) (36 of 142 (25%)), but not in ovarian malignancies (1 of 36 (3%)). There was a lack of association between ERBB-2 copy number and tumour size, lymph node involvement stage of disease, age of onset, estrogen and progesterone receptor level and family history in BC cohort. ERBB-2 extradosage was shown to have a prognostic importance in the group of 32 BC patients with sufficient follow-up (more than 40 months): 6 of 7 amplification-positive, but only 2 of 25 amplification-negative women relapsed ($P < 0.00005$).

**Conclusions:** Thus the data of the same research team are in agreement with the high occurrence of ERBB-2 activation in breast tumours, but contradict to similar reports on ovarian carcinomas. Therefore the peculiarities of the groups tested rather than technical variations in the gene copy num-