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**Immunohistochemical analysis of bilateral breast carcinomas: tendency to concordance of ER, PgR and erbB2/HER2 status**

E. Suspitsin[1], H. Giercksky[2], Y. Lazareva[1], D. Matsko[1], A.-L. Borresen-Dale[2], E. Imyanitov[1]. [1]*NN Petrov Institute of Oncology, Group Of Molecular Diagnostics, St. Petersburg, Russian Federation;* [2]*Norwegian Radium Hospital, Oslo, Norway*

**Background:** Bilateral breast cancer (biBC) is a common disease however its molecular features have not been systematically studied. Although being clonally independent, biBC tumor pairs do share essential host and environmental factors. Here we addressed the question whether this similarity of the natural history of the disease results in a concordance of selected immunohistochemical (IHC) characteristics of the bilateral neoplasms.
**Materials and methods:** Expression of estrogen receptor (ER), progesterone receptor (PgR) as well as erbB2/HER2 and p53 proteins was evaluated in 51 patients (102 tumors) using IHC staining of tissue arrays.
**Results:** Expression of ER, PgR, erbB2 and p53 was detected in 71%, 75%, 70%, and 31% of tumors, respectively. Based on the above frequencies, the expected concordance of the IHC status was calculated to be 58%, 62%, 59%, and 58% for ER, PgR, erbB2, and p53, respectively. Actual concordance tended to be higher than the expected one for ER (76%), PgR (78%), and erbB2 (71%) but not for p53 (59%). The difference between actual vs. expected concordance was especially prominent in synchronous biBC (ER: 83% vs. 56%; PgR: 87% vs. 56%; erbB2: 87% vs. 56%).
**Conclusions:** biBC demonstrate tendency to concordance of IHC status for ER, PgR, erbB2/HER2 but not p53. The concordance of expression profiles is particularly evident in the synchronous form of biBC.

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**Prognostic significance of IFN-gamma receptor (IFNGR1) in breast carcinomas**

Z. Madjd[1], A. Al-Attar[1], I. Spendlove[1], N. Watson[1], I. Ellis[2], L. Durrant[1]. [1]*University of Nottingham, Clinical Oncology, Nottingham, United Kingdom;* [2]*University of Nottingham, Dep. Histopathology, Nottingham, United Kingdom*

**Introduction:** IFN-γ and STAT-1 (Signal transducers and activators of transcription) knockout mice are more susceptible to both chemically induced and spontaneous tumours implicating this cytokine and its signalling in immune-surveillance. Tumours may therefore escape immune recognition by down regulation of the IFN-γ receptor or abnormal signal transduction. STAT-1 has a very short half life and can not be visualised by immunohistochemistry in normal tissues. However mutation or hyper-activation may increase its half life and allow detection in tumours.
**Material and methods:** Samples from 668 patients with primary operable breast cancer diagnosed between 1987 and 1992 (median follow-up of 86 months) were analyzed in tissue microarray format. Immunohistochemical analysis of expression of IFNGR1 and STAT1 was performed and the results correlated with different prognostic factors and patient outcome. All tumours expressed IFNGR1 but only 43% expressed STAT-1.
**Results:** Univariate analysis showed a positive relationship between intensity of expression of IFNGR1 and lymph node involvement ($p < 0.001$). In lymph node positive patients a significant association was noted between higher expression of STAT1 and increased tumour grade ($p = 0.039$), development of distal metastasis ($p = 0.012$) and vascular invasion ($p = 0.043$). Survival analysis demonstrated that patients with tumours with low expression of STAT1/IFNGR1 had an improved survival compared with those with high expression (log rank=0.045).
**Conclusion:** It is concluded that breast cancer patients with a STAT1(+)/IFNGR1(+) phenotype demonstrate poor survival times. Abnormal expression of STAT-1 may make tumours resistant to immune control by IFN-γ and thus develope a more aggressive phenotype.

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**Inactivation of the *BRCA1*-, *BRCA2*- and *p53*-genes in sporadic breast carcinomas**

M. Janatova, P. Pohlreich, J. Prokopcova, B. Matous. *First Faculty of Medicine, Charles University, Institute of Biochemistry and Exp. Oncology, Prague, Czech Republic*

**Background:** Breast cancer is the most frequently diagnosed malignancy affecting women in Europe. Mutations in the *BRCA1* and *BRCA2* genes, the two major susceptibility genes in hereditary breast cancer, are responsible for approximately 80–90% of all inherited breast tumors. However, the large majority of breast cancers belongs to a sporadic form. The role of the *BRCA1/2* genes in noninherited tumors is not exactly defined. The *p53* gene is the most frequently mutated gene in human cancers. In breast carcinomas, the *p53* gene is inactivated in about 20–30% of the tumors.
**Material and methods:** In this study, we analysed loss of heterozygosity (LOH) of the microsatellite markers intragenic or flanking to the *BRCA1, BRCA2* and *p53* genes in 40 unselected breast carcinomas. In the samples with allelic deletions, we screened for mutations in the respective the genes. The analysis included entire coding regions of the genes and was performed by protein truncation test (PTT) for the *BRCA1/2* and by sequencing for the *p53*. Automated sequencing of the appropriate genomic DNA fragments was used to confirm and characterize the mutations.
**Results:** LOH was identified in 8 of 38 (21%), 13 of 39 (33%) and 16 of 35 (46%) informative tumor samples in the *BRCA1, BRCA2* and *p53* genes, respectively. Allelic losses in *BRCA1* and *BRCA2* were linked to losses in *p53* in 100% and 77% of cases. On the other hand, losses in *p53* occurred often individually. We identified six somatic missense mutations in the *p53* gene, two somatic truncating mutations in the *BRCA1* gene and no mutation in the *BRCA2* gene.
**Conclusion:** Our results prove the role of the *p53* gene in the breast cancer development. Furthermore, inactivation of the *BRCA1/2* genes is involved in tumorigenesis of at least a minor subset of sporadic breast tumors and is often associated with inactivation of the *p53* gene. Somatic inactivation of *p53* thus seems to precede further alterations in the *BRCA1/2* genes.
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**E-cadherin and Snail expression in epithelial cells isolated from primary tumor and peritumoral tissue from breast cancer patients and their relation to epithelial circulating cells**

F.B.A. Makdissi[1], L.V.T.S. Machado[2], T.T. Benvenuti[3], E.C. Lyra[4], M.M. Netto[1], M.L.H. Katayama[2], C.A.B.T. Osório[5], L.C.S. Góes[4], M.M. Brentani[3], M.A.K. Folgueira[6]. [1]*Hospital do Câncer de São Paulo – A.C. Camargo, Mastologia, São Paulo, Brazil;* [2]*Faculdade de Medicina da Universidade de São Paulo, Biotecnologia, São Paulo, Brazil;* [3]*Faculdade de Medicina da Universidade de São Paulo, Departamento de Radiologia-Disciplina de Oncologia, São Paulo, Brazil;* [4]*Instituto Brasileiro de Controle do Câncer, Mastologia, São Paulo, Brazil;* [5]*Hospital do Câncer de São Paulo – A.C. Camargo, Anatomia Patológica, São Paulo, Brazil;* [6]*Faculdade de Medicina da Universidade de São Paulo, Departamento de Radiologia-Disciplina de Oncologia, São Paulo, Brazil*

**Background:** To invade, breast cancer cells reduce their intercellular cohesion, enhance their motility and proteolytic activity, and acquire mesenchimal cell characteristics, in a process similar to epithelial-mesenchimal transition, that takes place during embriogenesis. E-cadherin is the main molecule of cell-cell adhesion and defects on its fuction was described in carcinomas. E-cadherin expression is modulated by some transcriptional factors, among them, Snail, which may repress genes mainly expressed in epithelial tissues, as well as induce the expression of certain mesenchimal markers. Our aim was to study isolated epithelial cells, obtained from the tumor itself or its adjacent tissue, to determine whether variations in E-cadherin, Snail (related to the epithelial-mesenchimal transition) expression, between transformed and non-transformed cells, might occur. We have also evaluated whether the expression ot these genes might be correlated to the presence of epithelial circulating cells, as detected by the expression of cytokeratin 19.
**Patients and methods:** We have studied 48 samples from breast cancer patients, whose median age was 49 years (33–88 y). Most of them presented invasive ductal carcinoma (79.2%) and 52%, histopathologically involved lymph nodes. Early breast cancer (clinical stages I/II) was detected in 33 patients. Primary tumor and peritumoral samples, as well as peripheral blood, were collected and epithelial cells were isolated, by an immunomagnetic method. RNA was extracted from each individual sample and gene expression was evaluated by real-time PCR.
**Results:** No variations in the expression of E-cadherin and Snail were observed between cancerous and normal samples. Cytokeratin 19 (CK19) expression in mononuclear cells, obtained from peripheral blood, was positive in six and negative in 23 patients. No relation was observed between CK19 expression in the peripheral blood and lymph node involvement. However, there was a trend towards lower expression of E-cadherin, but not of Snail, in tumor specimens from patients presenting epithelial circulating cells.
**Conclusions:** In breast cancer, expression of E-cadherin and Snail, in epithelial cells obtained from tumor and peritumoral tissues seems similar. There was a trend towards a lower expression of E-cadherin in tumors from