

HER2 Expression in Breast Cancer: Correlation with Endocrine Function and Psychological Status in Operable and Metastatic Breast Cancer

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Abstract. *Background: Node involvement, negative estrogen receptor (ER) and HER2 expression are the main negative prognostic factors for breast cancer. Prolactin (PRL) is involved in the control of breast cancer growth and differentiation. Surgery-induced hyperprolactinemia seems to be a positive prognostic factor for operable breast cancer, whereas high PRL levels may predict a poor prognosis in women with metastatic breast cancer. In this study, we evaluated the relation between HER2 expression and PRL blood concentrations in women with metastatic breast cancer women and those with operable breast cancer patients prior to before and 7 days after surgery. Patients and Methods: The study included 50 women with breast cancer, 22 of whom had metastatic disease. HER 2 expression and serum levels of PRL were evaluated by fluorescence in situ hybridization (FISH) method and immunoradiometric assay (IRMA) method, respectively. Results: HER2 expression occurred in 11/28 operable cases and in 8/22 metastatic cases. The percentage of surgery-induced hyperprolactinemia was significantly higher in HER2-negative patients than in those with its expression. Moreover, HER2-positive metastatic cases showed significantly higher mean serum PRL levels than in the negative group. Conclusion: These preliminary results show that metastatic cancer-related hyperprolactinemia and lack of surgery-induced hyperprolactinemia are statistically more frequent in HER2-positive patients, thus suggesting a link between PRL endogenous secretion and HER2 expression in breast cancer.*

The expression of the HER2 antigen as a tumor histological feature appears to be associated with a higher biological malignancy in breast cancer (1, 2) and is believed to represent one of the main negative prognostic variables within the biological and genetic tumor characteristics of breast cancer (3). However, gene and oncogene expression would not only depend on the genetic profile of normal and neoplastic cells, since it is physiologically under immunoneuroendocrine control via cytokines released from activated immune cells and hormones (4). Hence the degree of tumor malignancy may also be modulated by cytokines, hormones and neurohormones by regulation of the expression of both oncogenes and cell surface receptors for tumor growth factor, namely epidermal growth factor receptor (EGFR) (5). In particular, the hypophyseal hormone prolactin (PRL) appeared to stimulate HER2 expression by breast cancer cells (6). It is also known that PRL may be a tumor growth factor for breast cancer (7, 8). PRL could thus stimulate breast cancer cell proliferation by inducing HER2 expression (9), which appears to predict a poor prognosis (1, 2). The *in vitro* stimulatory effect of PRL on breast cancer cell proliferation has also been confirmed *in vivo* because abnormally high blood levels of PRL are associated with less efficacy of treatments and a lower survival time in women with metastatic breast cancer (10, 11). At present, however, the relationship between metastatic breast cancer-related hyperprolactinemia and HER2 expression remains to be established. In the same way, the evidence of high PRL blood concentrations before surgical treatment predicts a poor prognosis in operable breast cancer cases (12). In contrast, the occurrence of postoperative hyperprolactinemia in such cases seems to be associated with a better prognosis (13, 14), despite the potential stimulatory action of PRL on breast cancer cells (7, 8). This apparently controversial evidence may be explained by interpreting the lack of postoperative hyperprolactinemia as the expression of an alteration in the neuroendocrine control of

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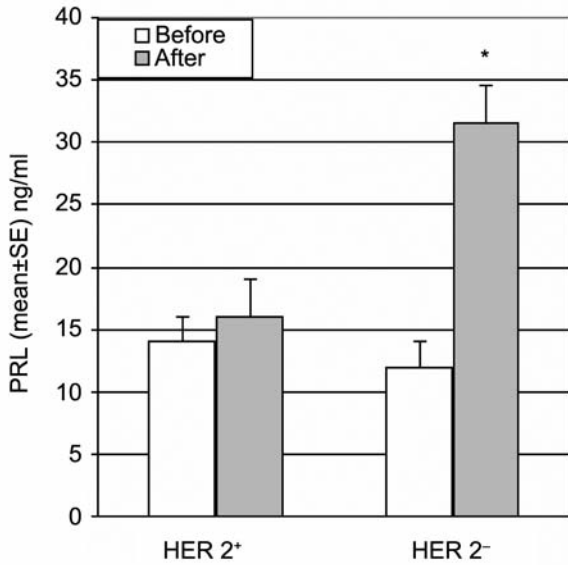


Figure 1. Mean serum levels of PRL before and after surgery in HER2-negative and -positive cases of operable breast cancer (* $p < 0.01$ vs. HER2+).

mammary cell proliferation, since the physiological response to mammary manipulation has to consist of increased PRL secretion (15). In addition, we must consider that PRL induces and influences maternal psychological behaviour (16). Hence, the neuroendocrine alteration responsible for the lack of PRL response to breast surgical manipulation could simply reflect the existence of an altered maternal psychological profile, which is at least in part influenced by PRL itself. On these bases, a study was performed in an attempt to establish which relationship may exist among HER2 expression, PRL secretion and psychological status in breast cancer patients with locally limited or metastatic disease.

Patients and Methods

The study included 50 cases of consecutive breast cancer, 28 of whom had locally limited disease, whereas the remaining 22 patients showed distant organ metastasis. PRL secretion was evaluated for venous blood samples collected in the morning after an overnight fast. No patient was under treatment with drugs stimulating PRL secretion from at least 15 days prior to the study, including opioids, corticosteroids and anti-dopaminergic agents. Patients with metastases were investigated before the onset of chemotherapy, while those surgically treated were investigated before surgery and at day 7 of the postoperative period. HER2 expression was assessed by a fluorescence *in situ* hybridization (FISH) (1-3) method (Kreatech Diagnostics, Amsterdam, the Netherlands) which was considered positive by in presence of gene amplification, as expressed by HER2/CEN14 ratio.

Serum levels of PRL were measured with commercially available kits, based on an immunoradiometric (IRMA) method.

Normal values of PRL obtained in our laboratory for women (95% confidence limits) were less than 25 ng/ml. The psychological investigation of maternal behaviour was assessed by the Rorschach

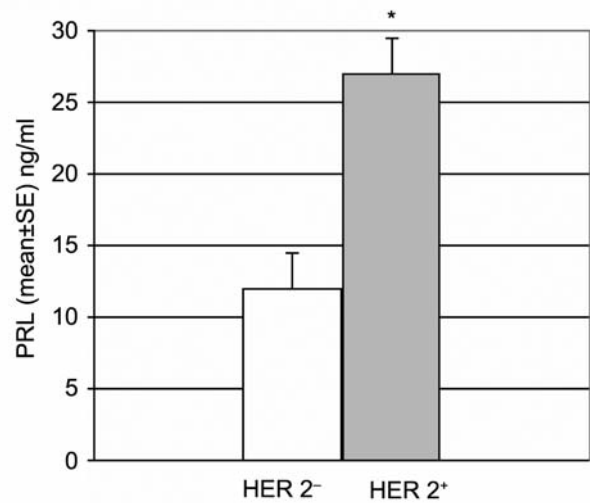


Figure 2. PRL mean serum levels in HER2-negative and -positive metastatic breast cancer women (* $p < 0.025$ vs. HER2-).

test, as reported in the literature (17). Data were statistically analyzed by Student's *t*-test and the chi-square test, as appropriate.

Results

A positive expression of HER2 was found in 19/50 (38%) patients. HER2 was expressed in 11/28 operable cases and in 8/22 metastatic patients. Breast surgery was followed by postoperative hyperprolactinemia in 13/28 operable cases. Moreover, the percentage of surgery-induced hyperprolactinemia observed in HER2-negative patients was statistically significantly higher than that found in the HER2-positive ones (10/17 vs. 3/11, $p < 0.05$). Figure 1 illustrates PRL mean serum levels observed before and after surgery in patients with negative and those with positive HER2 expression. No significant difference was seen in mean preoperative PRL values between patients with positive or negative HER2 expression, whereas the mean postoperative PRL concentrations observed in HER2-negative patients were statistically significantly higher than those found in the HER2-positive ones ($p < 0.01$). Moreover, high presurgical PRL levels occurred only in 2/28 operable cases, who were both positive for HER2 expression. The mean PRL concentration in metastatic cases in relation to HER2 expression are illustrated in Figure 2. The mean PRL value was significantly higher in HER2-positive cases of metastasis than in the HER2-negative ones ($p < 0.025$). In more detail, abnormally high concentrations of PRL were seen in 5/8 HER2-positive patients with metastasis and in only 3/14 HER2-negative patients. This difference was statistically significant ($p < 0.01$). As far as the response to the Rorschach test is concerned, normal maternal psychological profile was maintained in 31/50 (62%) patients. The proportion of

patients with normal maternal behaviour observed in the HER2-positive group was significantly lower than that found in HER2-negative patients (7/19 vs. 24/31), $p < 0.005$. The difference was also statistically significant in relation to both groups of patients with and those without metastasis (with: 3/8 vs. 10/14, $p < 0.05$; without: 5/11 vs. 13/17, $p < 0.02$).

Discussion

According to our own previous clinical studies and those of other authors (10-14), women with metastatic breast cancer may often present abnormally high blood concentrations of PRL. In contrast, hyperprolactinemia prior to surgery seems to be extremely rare in operable breast cancer cases, whereas breast surgery is followed by a postoperative hyperprolactinemia in about half of all patients. Moreover, this study shows that metastatic disease-related hyperprolactinemia is significantly more frequent in HER2-positive patients and this finding would appear to confirm previous *in vivo* experimental studies, which already demonstrated that PRL may stimulate HER2 expression (6). On the contrary, in operable breast cancer, HER2 expression occurred more frequently in patients with no surgery-induced PRL increase, which must be considered as a consequence of a neuroendocrine alteration in the control of PRL secretion, since mammary stimulation promotes PRL release under physiological conditions (15). Therefore, an altered neuroendocrine control of PRL secretion might also result in stimulation of HER2 expression by breast cancer cells. Finally, the results of this study, by showing a significantly higher frequency of psychological alterations of maternal behavior in breast cancer patients expressing HER2 antigen and presenting an altered PRL secretion, would suggest the existence of a connection between an anomalous maternal psychological profile and the altered secretion of PRL, which has been proven to influence maternal behaviour (16). In conclusion, this study, by demonstrating that HER2 positivity in breast cancer patients is associated with alterations of both PRL secretion and maternal behavior, suggests that HER2 expression, which may have a negative prognosis (1-3), would not only depend on tumor genetic properties (18, 19, 20) but, at least in part, could be influenced by the neuroendocrine and psychological conditions of women with breast cancer themselves.

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