Differences in Breast Cancer Risk Factors to neu (c-erbB-2) Protein Overexpression of the Breast Tumor

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Abstract

To investigate whether overexpression of the neu protein in breast tumors differentiates risk factor patterns for breast cancer, neu protein overexpression was determined in 296 breast carcinomas of patients participating in an ongoing population-based case-control study. Risk factor information on these patients and 737 controls was obtained during home interviews. Most breast cancer risk factors showed similar associations with neu-positive and neu-negative tumors, but remarkable differences were found for breast-feeding and age at first full-term pregnancy. In contrast to the slightly protective effect of breast-feeding in the neu-negative group, the risk of neu-positive breast cancer was 4.2-fold increased in women who ever breast-fed. Increasing age at first full-term pregnancy was positively associated with both neu-positive and neu-negative breast cancer, but the association was about 2 times stronger for neu-positive tumors. We conclude that neu oncoprotein overexpression of the breast tumor seems to be associated with a distinct risk factor pattern.

Introduction

Although many risk factors for breast cancer have been recognized, their associations with the disease are generally weak. It has been estimated that presently known risk factors explain only about 25% of breast cancer cases (1). Therefore, it is important to examine whether there are pathologically distinct types of breast cancer that bear a stronger relationship to specific risk factors. Previous studies that classified breast cancer according to breast cancer morphology or estrogen receptor status showed only minor differences between these breast tumor subtypes with regard to risk factor associations (2, 3).

Since oncoproteins have been shown to play a role in breast cancer pathogenesis (4), we hypothesized that the overexpression of oncoproteins might be associated with specific risk factors for breast cancer. Of all oncoproteins found amplified in breast tumors, neu oncoprotein amplification has been shown to be most frequently present, i.e., in 10–20% of all breast tumors (5). The neu oncogene, also known as HER-2 or c-erbB-2, encodes a protein that shows extensive homology to the receptor for the epidermal growth factor, indicating that the neu protein is a membrane-bound receptor (6). Thus far, a ligand for neu has not been identified. neu oncoprotein overexpression is supposed to be an early step in the development of a distinct histological type of breast carcinoma (7).

In our study we determined risk factors for the development of neu-positive versus neu-negative tumors separately. By examining the differences between both tumor groups with regard to risk factor associations, we expected to gain more insight into the etiological pathways of breast cancer development. We report, for the first time, that neu overexpression is positively associated with both breast-feeding and age at first full-term pregnancy.

Subjects and Methods

The association between neu protein overexpression and breast cancer risk factors was examined in an ongoing population-based case-control study of women ages 20–54 years, conducted in four areas of the Netherlands. Breast cancer patients were diagnosed between October 1, 1986, and July 1, 1989. Using an immunoperoxidase staining technique with monoclonal antibody 38S (7), neu overexpression was determined from paraffin-embedded formalin-fixed tissue sections of 296 of the cases. These 296 cases were selected because their tissue slides could be easily obtained from the larger pathological laboratories in the Netherlands. Membrane staining of tumor cells was scored as positive; all slides were reviewed by two of us (H. F. T., J. L. P.). Information on risk factors was obtained during home interviews and included parity, number of pregnancies, age at FFTP, age at menarche, breast-feeding, history of benign breast disease, and family history of breast cancer. Population controls (n = 737) drawn from the municipal registers were included in the analysis as a control group; overexpression of the neu protein based on gene amplification has thus far not been demonstrated in nontumorous breast tissue. Unconditional logistic regression analysis, allowing for the effects of multiple potential confounding factors, was used to estimate relative risks for neu+ and neu− breast cancer separately (8). For confounder selection the forward selection procedure was applied. Polychotomous logistic regression (with modeling of neu+ case, neu− case, or control status as classification variables) allowed us to directly compare associations of risk factors with both tumor types (9).

Results

The tumors of 53 of 296 patients (17.9%) were found to be neu-positive. Although all factors under study proved to be risk factors for breast cancer in our study population, the majority of them were not stronger related to neu+ than to neu− tumors. However, remarkable differences between both groups were found for associations with breast-feeding and age at FFTP (Table 1).

Women who ever breast-fed had a 4.2-fold increased risk of neu+ breast cancer as compared to women who never breast-fed. In contrast, a slightly protective effect of breast-feeding was found in the neu− group. The difference between both groups in this association was statistically significant (P = 0.021). The risk of neu+ breast cancer did not appear to increase with longer duration of lactation. In addition, no meaningful difference was found between both tumor groups with regard to the interval between first breast-feeding and diagnosis or regarding the interval between last breast-feeding and diagnosis...
of breast cancer. In each category of age at FFTP the relative risk of developing neu+ breast cancer was higher than that of neu− breast cancer. Here the difference between both groups in this association was not statistically significant, perhaps due to the relatively small numbers in the subgroups of neu+ patients.

**Discussion**

Our most striking finding is the positive association between breast-feeding and neu+ breast cancer, which is in sharp contrast to the protective effect of breast-feeding that is found in several epidemiological studies (10-12) and also in our neu− group (consisting of 82.1% of the patients). Present insight in molecular biology cannot explain our findings. It has recently been shown that the neu protein does not inhibit the lactogenic hormone-induced differentiation of mammary epithelial cells (13). This is in contrast to the findings with regard to the epidermal growth factor receptor, to which the neu protein is structurally quite similar.

Lactogenic hormones may play a role earlier in tumorigenesis by influencing neu overexpression or even neu amplification. For the c-myc oncogene, also found in breast tumors, an increase in the level of mRNA was reported after prolactin stimulation (14). Alternatively, breast-feeding might be associated with oncogenic activation of the precursor cell to neu-positive carcinomas.

The lack of a duration-response relationship for breast-feeding might point to a rapid, complete response of neu to hormone stimulation, as also described for c-myc (14). The increasing risk of neu+ tumors with increasing age at FFTP might be caused by an interaction between hormones and DNA of the older, undifferentiated breast cells. It is even possible that age at FFTP is not a crucial risk factor but age at first breast-feeding is, due to the effect of prolactin on the older breast tissue. In our study the effect of breast-feeding seemed to be similar in all age at FFTP categories, but the numbers in the subgroups were too small to draw a firm conclusion about the absence of interaction between these variables. We are currently investigating this issue in a larger population.

Our study demonstrates that in searching for breast cancer risk factors, it is important to discriminate between different subtypes of tumors. Oncogenes appear to be promising tumor markers in this respect and should be used more frequently in future molecular epidemiological research.

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