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No Additive Impact on Patient Survival of the Double Alteration of p53 and c-erbB-2 in Breast Carcinomas

Innovative therapies for cancer patients take into account the inhibition or repair of altered oncoproteins and tumor suppressor genes or their corresponding protein products. The c-erbB-2 oncogene and the p53 tumor suppressor gene play major roles in the aggressiveness of many carcinomas, especially breast carcinomas; thus, they represent good targets for gene therapy (1-4).

Alterations in c-erbB-2 and p53 gene expression, leading to cellular accumulation of functional and nonfunctional proteins, respectively, have been reported (5-7) to be predictors of poor prognosis in breast carcinoma patients. Other reports (8,9) have noted the frequent association of c-erbB-2 and p53 gene abnormalities in breast tumors.

Since both genes encode proteins that share the same signaling transduction pathway in cell cycling, we investigated whether alterations of these two proteins have a synergistic effect on tumor aggressiveness in 717 patients with primary breast carcinomas who have had long-term follow-up. Of these patients, 280 (39%) had stage I disease, 409 (57%) had stage II disease, and 28 (4%) had stage III disease. The 373 lymph node-positive case patients (52%) were treated after surgery with adjuvant combination chemotherapy (cyclophosphamide + methotrexate + fluorouracil).

Immunohistochemical analyses, performed with the avidin–biotin method and monoclonal antibodies against the p53 tumor suppressor protein (DO7) and the c-erbB-2 oncoprotein (CB11), revealed that 131 (18%) and 158 (22%) of the 717 patients were p53 positive and c-erbB-2 positive, respectively. A strong association (P = .00006) was observed between the elevated expression of both p53 and c-erbB-2 proteins in tumor tissues (relative to normal tissues). Analysis of patient survival as a function of the alteration of the two proteins (Fig. 1) revealed nearly superimposable estimates for patients with tumors with one or both genes altered, and these rates were significantly lower (P = .001) than those for patients with tumors found not to express elevated levels of either protein.

These data indicate that tumor aggressiveness associated with elevated expression of either protein is already at a maximum and is not increased by the alteration of a second protein involved in the same signal transduction pathway. The clinical implication of this finding is that correction of any abnormality in either the c-erbB-2 or the p53 gene is unlikely to be effective in reducing the aggressiveness of all tumors. Indeed, 47 (19%) of the 242 tumors that were found to be immunohistochemically positive for the p53 or c-erbB-2 protein were altered in both genes and would likely maintain the same aggressiveness even if the defect in one of the two genes and/or gene products is corrected by therapeutic intervention.

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References

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This study included 2569 case subjects aged 23-78 years (median age, 55 years) with incident (i.e., diagnosed within the year before interview), historically confirmed breast cancer. Control subjects included 2588 women aged 20-79 years (median age, 56 years) who resided in the same geographic areas as the case subjects and who were admitted to the same network of hospitals where case subjects had been admitted. The control subjects had been diagnosed with acute non-neoplastic, non-hormone-related diseases; 22% had traumatic conditions, 32% had non-traumatic orthopedic disorders, 16% had acute surgical conditions, and 30% had other miscellaneous illnesses, such as eye, ear, nose, throat, and dental disorders. In the overall dataset, there was a direct relationship with later age at first giving birth and menopause and an inverse relationship with parity (3). A total of 299 case subjects (11.6%) of a total of 2569 case subjects and 135 (5.2%) control subjects of a total of 2588 control subjects reported a family history of breast cancer; 383 (88.2%) of those reported a family history of breast cancer in first-degree relatives and 51 reported it in their grandmothers. These 434 subjects are considered here.

Table 1 shows the relationship between selected menstrual and reproductive factors and risk of breast cancer in women with a family history of the disease. Odds ratios and the corresponding 95% confidence intervals were computed from multiple logistic regression equations that included terms for age, center, education, and the variables of interest.

No clear association emerged between breast cancer risk in women with a family history of the disease and number of births and ages at menarche and at menopause. Among parous women, case subjects tended to report an older age at first giving birth, but the association was not statistically significant.

The lack of a clear association between reproductive and menstrual factors and risk of breast cancer observed in the Nurses' Health Study (4), as well as in this study and in another Italian case-control study (2), suggests that...