Progress in Predicting Breast Cancer Relapses

New tests based on gene abnormalities may provide a better means of predicting which breast cancer patients will have relapses and thus need drug therapy

THE UNDERSTANDING GLEANED over the past several years of the gene changes that underlie cancer development is beginning to lead to new strategies for predicting the prognosis of breast cancer patients. Researchers have identified specific gene abnormalities that appear to be correlated with an increased risk of the cancer reoccurring after the primary tumor is removed surgically. If further clinical investigations bear out the promising preliminary results, the outcome could be more accurate tests for determining breast cancer prognoses.

The need for such tests is great. This year, 130,000 women in the United States will be diagnosed with breast cancer. There is currently no sure way of telling which of them will experience a recurrence of the cancer and should thus receive preventive treatment with chemotherapeutic drugs.

In the past, the decision to give a woman chemotherapy was usually based on a finding that the cancer had already spread to her underarm lymph nodes at the time the original tumor was removed. Women with negative nodes did not generally receive chemotherapy. But lymph node status is an imperfect indicator of breast cancer prognosis. Although about 70% of the women whose nodes show no signs of cancer metastasis will remain free of the disease for at least 5 years without further treatment, the other 30% will have a recurrence.

In fact, in May of this year the National Cancer Institute (NCI) recommended that women with negative nodes be given drug or hormonal therapy after all. The decision was based on as yet unpublished studies showing that such treatments could lower the breast cancer recurrence rate in the women.

Nevertheless, the drugs used for cancer chemotherapy have unpleasant or dangerous side effects. The best approach would be to devise more accurate ways of identifying women who will experience metastasis so that the others could be spared the chemotherapy.

That is what the new work, some of which was described at a science writers' seminar at the National Institutes of Health on 23 June in Bethesda, Maryland, aims to do. Robert Callahan of NCI described his group's identification of two separate genetic abnormalities in breast cancer cells that may be associated with a poor prognosis. The work was done in collaboration with Rosette Lidereau of the Centre Rene Huguenin in St. Cloud, France, and Iqbal Ali, also of NCI.

One of the abnormalities the researchers identified is an amplification of the *int-2* oncogene. The protein encoded by the *int-2* gene presumably acts positively to foster the development of malignant tumors, possibly stimulating cell division and the blood vessel formation needed for the growth of solid tumors.

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A growing body of evidence suggests that loss of tumor-suppressing genes can also contribute to tumor growth and malignancy. The second genetic alteration that the Callahan group has linked to poor breast cancer prognosis, a deletion of a region of chromosome 11, may involve the loss of such a suppressor gene. In any event, a study of some 150 breast cancer patients at the Centre Rene Huguenin has shown that cancer reoccurred more frequently in women whose tumor cells had one or the other of the two abnormalities than in women whose tumor cells did not have either.

Patricia Steeg and her colleagues at NCI have recently identified a gene, which they call NM23 that appears to suppress the metastatic potential of cancer cells. A pilot study of 25 breast cancer patients suggests that lack of expression of this candidate suppressor gene may be associated with a poor prognosis. Expression of the gene was low in the primary tumors of all of the 16 women with four or more positive nodes. It was high in the tumors of six of the nine women with three or fewer positive nodes, but low in the other three.

"One of these three has developed a metastasis," Steeg says, "which in 3 years is pretty quick." Some of the women with four or more positive nodes have also developed metastases, although none of the women with high NM23 expression in their tumors has.

The function of the NM23 gene is unknown. Determination of its nucleotide sequence did not reveal any similarities to other genes. Steeg is currently mapping the chromosomal location of the gene. It would be interesting if it turned out to be located in the deleted region on chromosome 11 that was identified by the Callahan group.

The gene abnormalities mentioned here are not the only ones that have been linked to a poor breast cancer prognosis. Last year, for example, Dennis Slamon of the University of California School of Medicine in Los Angeles, Gary Clark of the University of Texas Health Science Center in San Antonio, and their colleagues reported that amplification of the oncogene variously known as HER-2, *neu*, and *erb*B-2 is associated with a rapid relapse and decreased survival time for breast cancer patients (*Science*, 9 January 1987, p. 160).

Callahan now says that he and his colleagues have failed to confirm this finding in the French patients they are studying. Slamon and Clark, meanwhile, maintain that their original results have not only held up, but have been strengthened by an additional year and a half of following the patients. (A fuller discussion of Callahan's position on this issue, with a reply from Slamon and Clark, can be found in the "Technical Comments" on pages 1795 to 1798 of the 24 June issue of *Science*.)

The reason for the discrepancy is currently unclear. One possible problem is the mixed composition of breast tumors. Cancer cells may constitute only 50% of the tumors. Consequently, abnormalities in the tumor cell DNA may be masked by the presence of large amounts of normal DNA. Another problem is the relatively small number of patients studied to date. "There really hasn't been a large enough number of tumors looked at to make a definitive judgment on *erb*B or even on *int*-2," Callahan says. In particular, he cites the need for a large multicenter study in which all the participating clinicians use the same standardized methods for analyzing the candidate predictor genes or their products in breast cancer cells and for assessing the conditions of the patients. ■ JEAN L. MARX