# Breasts May Secrete Tumor Suppressor

Since the 1994 identification of the *BRCA1* gene and its link to breast and ovarian cancer, researchers have wondered how the gene normally prevents malignant cell growth. Now, investigators from the University of Washington in Seattle and Vanderbilt University School of Medicine in Nashville have shown that adding a working *BRCA1* to some cancer cells inhibits their proliferation and suppresses tumor growth.

This finding supports the idea that understanding *BRCA1* may lead to new cancer therapies. Adding to that hope is a more controversial result from the same researchers: They contend that BRCA1, the protein encoded by *BRCA1*, is secreted by breast cells and belongs to an obscure family of proteins called granins. If these observations are correct, *BRCA1*'s role may differ from that of other known tumor-suppressing genes, most of whose proteins act within the cell to control proliferation.

The surprising claim that BRCA1 is secreted raises the possibility that the protein stops cancerous cell growth by binding to molecules on the surfaces of breast and ovarian cells. If so, investigators might design cancer-fighting drugs that mimic BRCA1's ability to latch onto those surface molecules.

"If I were a pharmaceutical firm and heard about this, I would be really excited," says Vanderbilt's Roy A. Jensen, an author of the BRCA1 reports, which appear in the March NATURE GENETICS.

"It opens the door to what would appear a quite simple therapeutic measure," adds Simon A. Gayther of the Cancer Research Campaign in Cambridge, England.

In one series of experiments, led by Vanderbilt's Jeffrey T. Holt, researchers added functional copies of *BRCA1* to a variety of cancer cells growing in test tubes. The added genes slowed the growth of breast and ovarian cancer cells but had no effect on cells from other cancers or normal muscle.

Then the investigators added *BRCA1* to other cancerous breast cells and injected the cells into mice. Ordinarily, cancer cells of this type form large tumors that kill mice within 2 weeks, but such cancer cells with the added gene either developed slowly into small tumors or didn't generate tumors at all.

The investigators also inserted copies of *BRCA1* into breast cancer tumors growing in the abdomens of five mice. When they autopsied the mice, two of them no longer had discernible tumors.

"For people who already have tumors, *BRCA1* may be therapeutically useful. [In mice,] you can not only prevent tumors but make them regress," says Barbara Weber of the University of Pennsylvania Medical Center in Philadelphia.

In other experiments, led by Jensen, investigators found evidence that the BRCA1 protein is secreted. For example, they were able to deplete breast cells of BRCA1 by adding a compound that stimulates secretion.

Researchers then noted that BRCA1 contains an unusual string of 10 amino acids, known as the granin motif. In addition to secretion and the motif, granins share other characteristics with BRCA1, such as an unusual resistance to heat. "[Granins] get secreted and chopped into little bioactive peptides that do all sorts of stuff," says Jensen.

The granin model for BRCA1 appears to offer further evidence that the location of a mutation in the *BRCA1* gene determines the risk of ovarian cancer, a hotly debated suggestion (SN: 12/21/95, p. 374). The investigators found that families with mutations in *BRCA1* almost never had ovarian cancer if the mutation in the gene was to one particular side of the stretch of DNA encoding the granin motif.

The secreted nature of BRCA1 could also help explain the observation that pregnancy before age 20 mysteriously cuts a woman's risk of breast cancer in half. Studies by several research teams recently have revealed that BRCA1 production in mice rises dramatically during pregnancy and lactation.

Taken together, says Jensen, the findings suggest that there is a protective effect if women secrete more growth-inhibiting BRCA1 while their breasts are still maturing.

Other researchers, including a group at the University of Texas Health Science Center at San Antonio, have asserted that BRCA1 normally resides in the nucleus (SN: 11/18/95, p. 334). "We stand by our results. We're even more confident based on some recent data," says C. Kent Osborne of the San Antonio team.

"There are different groups getting different results, and it's not yet clear what the explanation for the discrepancy is," concludes Weber. —*J. Travis*

## U.N. body rules tamoxifen a carcinogen

Last week, a World Health Organization (WHO) research agency formally designated tamoxifen—a synthetic hormone and the most widely prescribed drug to prevent recurrence of breast cancer—as a human carcinogen. The compound joins the roughly 70 chemicals, about one-quarter of them pharmaceuticals, that have already received this dubious distinction from the United Nations agency.

Several major studies have reported a sharply elevated rate of endometrial cancer, a malignancy of the uterine lining, in breast cancer survivors taking tamoxifen (SN: 4/16/94, p. 247). However, WHO's International Agency for Research on Cancer (IARC) in Lyon, France, noted that its 17-member panel found neither animal evidence nor these human studies conclusive. Only by considering both did they conclude that tamoxifen causes cancer.

The world's foremost authority on what constitutes a human carcinogen, IARC does not challenge tamoxifen's ability to prolong substantially the survival of people who have had breast cancer. In fact, IARC notes that the drug remains "one of a small group of pharmaceuticals recognized by the WHO as an essential drug for the treatment of this disease."

In a prepared response to the IARC announcement, the National Cancer Institute in Bethesda, Md., said it had "reviewed the same data and [considered it] in the study designs and informed consent procedures in all tamoxifen clinical trials"—including its prevention trial involving healthy women.

That "consideration" by NCI probably won't satisfy many women recruited to the prevention trial, suggests Cindy Pearson of the National Women's Health Network, in Washington, D.C. In fact, she predicts that "some will drop out, because it doesn't make sense to use something that's listed as a carcinogen to try and prevent cancer."

California regulators, who have a legal obligation to identify carcinogens, stood poised last fall to add tamoxifen to the state's growing list—until lobbying by NCI and Zeneca Pharmaceuticals of Wilmington, Del., which manufactures the drug, prompted an unprecedented second review (SN: 10/7/95, p. 236). Though the new tamoxifen designation comes too late to affect those California deliberations, George Kostyrko, a state spokesman in Sacramento, notes that IARC's ruling "is consistent" with what a state-appointed committee of outside scientists concluded during the first review. —*J. Raloff*