the study were of such low quality that they were useless for detecting the very small cancers that would be the easiest to treat successfully. Contributing to this problem, says Logan-Young, was the Canadians' decision to use very low radiation doses because of worries that too-high doses might increase breast cancer development. In addition, Kopans and Feig contend that many more women who eventually proved to have advanced breast cancers were accidentally randomized into the mammogram group, thereby skewing the study results so that the death rate would appear higher in that group.

For their part, Miller and Baines are emphatic in their defense of the study's design and results. Miller says that the U.S. researchers saw only early mammograms and results that were not representative of the entire study. "They were looking at small samples from a large study," he notes. As the study progressed, he maintains, the quality of the mammograms improved, a reflection of the general trend toward better mammograms throughout Canada. Miller's defense of the study is supported by David Beatty, the executive director of Canada's National Cancer Institute, one of the study's major funding sources, who describes Miller as a "good investigator."

Grumbles about the study were largely confined to the radiology community—until April of last year. That's when NBSS researchers presented some preliminary findings at the Second International Cambridge Conference on Breast Cancer Screening in England. They reported that the breast cancer mortality rate among screened women aged 40-to-49 was 50% higher than among controls. This information found its way into the press—each camp blames the other for the leak—and women across the UK were soon greeted by the headline, "Women Who Have Breast Scanning Are More Likely to Die of Cancer," in the Sunday *Times* of London, a theme that was repeated in several other news stories.

New Clue Found to Oncogene's Role in Breast Cancer

While epidemiologists have been arguing over how effective mammography is in preventing breast cancer deaths (see accompanying story), more molecularly inclined researchers have been buzzing over a flurry of new results on an oncogene, called HER2, that appears to play a key role in the progression of some breast cancers. Several groups have recently reported results that should help explain how HER2 works, and these findings may point the way toward improved breast cancer therapies. The reason for the excitement is that about 5 years ago women whose tumors have an overactive HER2 gene were found to be more likely to relapse and die than women without the abnormality.

Researchers have known since 1984 that HER2 codes for a protein with all the characteristics of a growth factor receptor, but they've had trouble finding its ligand, the molecule that binds to the receptor and activates it. That's where the new work comes in, as researchers are at last getting their hands on the HER2 ligand. And that should help clear up some mysteries about the way HER2 activity affects cell growth and other responses, says molecular biologist Stuart Aaronson of the National Cancer Institute, whose own work includes HER2 studies. Until the ligand was identified, he points out, "we couldn't know whether it would turn up the receptor activity or whether it might in fact turn it down." And without that information, researchers don't know whether they should try to design anticancer therapies to block the ligand-receptor interaction or enhance it.

The immediate task, however, is to sort out competing claims concerning who identified the HER2 ligand. Indeed, the work is producing something of an embarrassment of riches, as at least four different groups claim to have found candidate ligands. Some, but not all, may be identical, and it will take some time to determine just how they are related to one another and what each one does. And, to complicate matters even further, there are signs that a priority dispute is brewing between two of the groups.

One group, led by William Holmes and Richard Vandlen of Genentech Inc. in south San Francisco, reports its results on page 1205 of this issue. These researchers found that a line of cultured human breast cancer cells secretes a family of proteins, which they named "heregulins," that not only bind to the HER2 receptor protein but also stimulate its biological activity. That follows hard on the heels of a report in *Cell* earlier this month in which Yosef Yarden and his colleagues at the Weizmann Institute of Science in Rehovot, Israel, along with co-workers at Amgen Inc., in Thousand Oaks, California, and Cell Analysis Systems in Illinois, describe the purification of a protein that binds the rat HER2 receptor. Both of these groups have cloned the genes for their HER2 ligand candidates, and the sequences reveal that the Yarden group's protein is the rat equivalent of heregulin.

But even though Genentech's Holmes says heregulin constitutes the "first identification and DNA sequence of a human ligand for HER2," it's not clear that this is the first sighting of that particular protein. Two years ago, Ruth Lupu and Marc Lippman of Georgetown University in Washington, D.C., found two proteins that are secreted by breast cancer cells and also bind to the HER2 receptor. Lupu, who has worked with the Genentech group, and in fact sent them the cancerous tumor cell line from which they isolated the heregulins, says, "I don't have any doubts that the proteins [derived by her group and the Genentech group] are the same or very similar." Holmes says that he cannot confirm that contention until the Georgetown group's DNA sequence is available for comparison with the Genentech sequence.

Many HER2 ligands. In addition, last year Mark Greene and colleagues at the University of Pennsylvania Medical School came up with still another HER2 ligand from the rat that differs from the other reported proteins, a situation that he says was to be anticipated. "There seems to be a number of these ligands floating around, and that's not uncommon." He suggests that the HER2 receptor may be analogous to that for epidermal growth factor, which is activated by several agents. That possibility is supported by recent work by Robert Bast's group at Duke University. They've shown that there may be at least three different ways of activating the HER2 receptor, only one of which seems to require the ligand provided him by the Georgetown group.

While Genentech's Holmes is quite confident that the heregulins will prove to be the primary activator of the HER2 receptor, the matter is far from settled. And equally confusing are the results the different groups obtained when they tested their ligands' effects on cells. When the Genentech group exposed cells to heregulins, they found that the cells divided and proliferated. In contrast, the rat version of the protein caused some cell types to do the opposite—they matured and stopped dividing. And the human ligand isolated by the Georgetown group did both, depending on the concentration used.

But as perplexing as the HER2 ligand situation is, it should not take long to settle the questions regarding the identities of the ligands and their role in the cell, says Dennis Slamon of the University of California School of Medicine in Los Angeles, who first noted that HER2 gene activity correlates with a poor prognosis. "Now that these molecules are available, there will be a flurry of activity. It will be fairly clear within 6-12 months," he says.

–Michelle Hoffman