Breast Cancer: Two Steps Closer to Understanding

Two papers in this issue of Science *throw light on the genetics of breast cancer—and might ultimately lead to early detection*

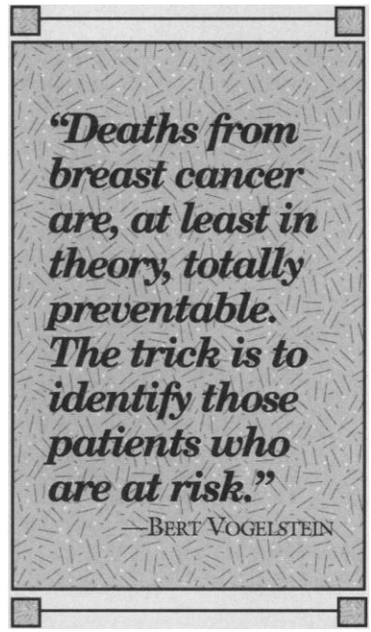
IN 1990, 150,000 WOMEN IN THE U.S. WILL receive a diagnosis of breast cancer; 44,000 will die of the disease. Those deaths are—in theory—"totally preventable," says Bert Vogelstein of Johns Hopkins. "The trick," he adds, "is to identify those patients who are at risk." Until recently that hope was a will-o'-the-wisp, but in recent weeks researchers have taken three long strides toward that goal by identifying genetic factors that may increase susceptibility to breast cancer. Last month, Stephen Friend's group at the Massachusetts General Hospital published evidence that inherited mutations in a tumor-suppressor gene called p53 are associated with the high rate of breast and other cancers in families with Li-Fraumeni syndrome.

Now, two papers in this issue of *Science* provide further insight into the genetics of breast cancer, seeming to confirm that the disease develops in a progression that includes a series of genetic events. On page 1684, a group led by Mary-Claire King of the University of California School of Public Health reports finding a genetic marker that may signal the presence of a breast cancer susceptibility gene. And on page 1715 Mark Skolnick and colleagues at the University of Utah Medical Center report that a benign condition known as proliferative breast disease (PBD) may be a precursor to breast cancer in genetically predisposed individuals. Both findings apply to individuals with inherited susceptibilities to breast cancer. But because the same genes may also be involved in "sporadic" (noninherited) breast cancers, the work holds out hope that in the future most women at risk could be identified early.

Inherited factors may be responsible for 5% to 10% of all cases of breast cancer, according to geneticist Neil Risch of Yale University School of Medicine. Risch's conclusion is based on an analysis of some 4800 cases of breast cancer that will be published in the *American Journal of Human Genetics* in February. A woman's risk of getting the disease depends on how many of her relatives have it and on the age at which they develop their disease: The younger the relatives were when their tumors developed, the greater the risk. Increased occurrence of cancer in both breasts or breast cancer in male family members (a very rare condition) are also considered signs of a herditary predisposition.

Those were the assumptions King and her colleagues took as a point of departure. They identified 23 families in which there were a total of 146 cases of breast cancer diagnosed early, in both breasts, or in male family members. Genetic analysis of the 329 people in those families showed that one region of chromosome 17, which is ordinarily very variable genetically, is quite similar among the family members—and is associated with the breast cancers.

King concludes that an as yet unidentified gene on chromosome 17 that is different from p53 causes an inherited susceptibility to early-onset breast cancer. Future work, King says, will be aimed at identifying the gene involved and trying to find out whether different genes are implicated in early- and late-onset forms of the disease. King adds that her confidence in the results was recently strengthened by the news that Gilbert Lenoir's group at the International Agency for Research on Cancer in Lyons, France, obtained similar results on chromosome 17 in a study of five families with breast and ovarian cancer (which are thought to share etiological factors).



Skolnick and his colleagues took a different tack. They tracked the incidence of PBD, a benign proliferation of epithelial cells at the ducts of the breasts, in women who had no cancer but whose relatives did. Such women had a dramatically higher incidence of PBD (35%) than did a group of controls (13%). Although such benign abnormalities have been identified as precursors for other cancers, it's the first time this has been done for breast cancer, and the work has several important implications. First, it appears to be another confirmation of the widely held hypothesis that several genetic events are needed for progression to cancer: in the case of breast cancer perhaps the first genetic "hit" is in a gene associated with PBD, and others in genes associated with tumor development.

It also suggests that some elements of the genetic predisposition to cancer—in the form of a gene that gives rise to PBD—may be somewhat more common than was previously thought. "We've extended the pathology to premalignant states," says Skolnick. Yet clinician John Ward, one of the authors of the paper, notes that a diagnosis of PBD alone does not mean a woman will get breast tumors. "The mere fact that we can detect the cell abnormalities does not mean these women are going to develop breast cancer," Ward says.

Partly for that reason, Skolnick and Ward are by no means recommending that all women be screened by their method. In any event, they sound a note of caution on whether their technique—aspiration of breast tissue through a fine needle—will become a clinically useful method for detecting women at risk. Although in their paper they say it might, in interviews both authors stressed that the research procedure may not be appropriate for use on healthy women.

Yale's Risch warns against reaching airtight conclusions on the basis of the Skolnick work. He notes that "one has to be very careful in using so-called precursors in a genetic analysis," partly because the correlation of a precursor with a disease does not demonstrate a simple genetic link between the two. It may be tempting, Risch says, to infer that the two conditions must have a similar etiology, but studies such as Skolnick's don't make clear what the connection might be. "Sometimes it can even obfuscate the issue," he says.

Vogelstein, however, suggests that in the long run the Skolnick and Ward findings could be useful, providing a clinical assay for women at risk. Likewise, he says, King's data may be a step toward identifying a genetic predisposition for breast cancer in much the same way that the gene for Huntington's disease can now be identified. And because spontaneous mutations in the same genes may also be linked to noninherited breast cancers, Vogelstein notes that these two papers could ultimately lead to better understanding—and early diagnosis—of the great majority of breast cancers.

■ KAREN WRIGHT