

Homing in on inherited breast cancer genes

The intense competition to find a flawed gene responsible for a familial form of breast cancer reached its zenith last week when a scientific team announced it had bagged this sought-after quarry. At the same time, another group reported homing in on the location of a second such gene.

Researchers hailed the findings as a crucial step toward early diagnosis of breast cancer, which this year alone will kill an estimated 46,000 women and 300 men in the United States.

"This is a very exciting day," said Francis S. Collins, director of the National Center for Human Genome Research at the National Institutes of Health in Bethesda, Md. NIH Director Harold E. Varmus called the new findings "extremely important."

This particular gene chase began with Mary-Claire King of the University of California, Berkeley. King was the first

BRCA1 plays no role in most breast cancer

The vast majority of breast cancers do not involve an inherited susceptibility. Breast cells divide repeatedly during a lifetime. Oncologists know that each time a cell divides, it runs the risk of developing a mutation. If it does, the resulting tumor is known as a sporadic tumor, a malignancy that arises from damage inflicted during the life of a cell.

Researchers have long suspected that BRCA1 causes some sporadic breast cancers as well as the inherited form of the disease. Now, Roger Wiseman of NIH's National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, N.C., and his colleagues have found evidence that seems to dash that theory. Their findings will appear in the Oct. 7 *SCIENCE*.

The team studied 32 breast and 12 ovarian tumors obtained from women not known to have a family history of such cancer. When they zoomed in on the BRCA1 region, they found mutations in just four tumors.

However, the evidence showed that those mutations had been inherited at birth. Sure enough, when the team restudied those families, they found that two of the four women had a close relative who had had breast or ovarian cancer.

"We were quite surprised," says J. Carl Barrett, a molecular biologist at NIEHS. The findings suggest that BRCA1 does not play a significant role in the development of sporadic breast cancers, he says. — *K.A. Fackelmann*

scientist to postulate that some women are born with a vulnerability to early breast cancer, sometimes developing the disease in their twenties. In 1990, she and her colleagues identified a region on chromosome 17 as the home of this gene, which is called BRCA1.

That report kicked off a gene hunt involving scores of scientists. Mark H. Skolnick of the University of Utah Medical Center in Salt Lake City and 44 colleagues at five institutions in the United States and Canada have now emerged as the winners of this particular race.

Skolnick's team studied eight families with a history of breast and sometimes ovarian cancer. The researchers found the defective BRCA1 gene in four of the eight families and described several distinct mutations at different locations along the gene. Their report will appear in the Oct. 7 *SCIENCE*.

Humans aren't the only species with this gene. The research team found the same gene in the cells of rats, rabbits, sheep, pigs, and monkeys, which suggests that BRCA1 plays an important role in the regulation of mammalian cells, comments Louise C. Strong, a geneticist at the University of Texas M.D. Anderson Cancer Center in Houston.

Some scientists believe BRCA1 acts as a tumor-suppressor gene — one that provides the blueprint for a protein that acts as a brake on cellular growth. In this scenario, women who inherit one mutant and one normal BRCA1 would remain cancerfree as long as the healthy gene directs the production of the cellular brake. However, if an environmental toxin or some other agent damaged the normal gene, the cell would lose that protein.

The result: A wildly proliferating cell that can generate a malignant tumor.

The flawed gene puts women at extraordinarily high risk of developing breast cancer. They're also at risk of ovarian cancer.

In a related paper, this one scheduled for publication in the Sept. 30 *SCIENCE*, Michael R. Stratton of the Institute of Cancer Research in Sutton, England, and his colleagues describe another major advance in the story of familial breast cancer.

Just as King had narrowed the search for BRCA1 to an area along chromosome 17, Stratton's team described another breast cancer hot spot, this one located on chromosome 13. They believe this region contains a second breast cancer gene, one designated BRCA2.

Stratton led an international team of 31 scientists from nine institutions in North America and Europe. The team began its gene hunt with 15 families who had cases of breast cancer that couldn't be explained by a defect in BRCA1.

The search pinpointed a region on the long arm of chromosome 13. Stratton says several candidate genes reside in that area. Scientists will now begin the competition to isolate and sequence BRCA2.

This gene, interestingly enough, appears to be tied to familial breast cancer but not to ovarian cancer. And unlike mutations in BRCA1, mutations in BRCA2 seem to put men at risk of breast cancer. Although male breast cancer is rare — physicians will diagnose only about 1,000 cases in the United States this year — this gene may prove an important factor in determining why some men develop this lethal disease, Stratton says.

The news regarding BRCA1 and BRCA2 applies directly to a unique group of people, those with several close relatives who developed breast or ovarian cancer, often at an early age. To date, no definitive way exists to tell if a woman has inherited her family's curse. Yet the identification of BRCA1 means that scientists can proceed to develop a blood test that picks out mutations in this gene, Skolnick says. He believes the task will take about 2 years.

Scientists hope that someday, women at risk of familial breast cancer will have available a simple test that identifies mutations in BRCA1, BRCA2, and any other genes that turn out to play a role in this form of the disease.

Women who do have such mutations could then pursue an aggressive strategy of breast self-examination and mammography screening to find a tumor when it's still curable, Stratton says.

There is no surefire way to prevent breast cancer. Thus, some women with a positive test result may opt for a mastectomy before they even develop the disease. Such surgery may seem drastic, but women with a flawed BRCA1 or BRCA2 run an approximately 85 percent risk of developing breast cancer at some point in their lifetime.

For breast cancer patients, the huzzahs are mixed with worry.

"I am concerned that a test will be developed and distributed widely before we know if it is effective," says Fran Visco, president of the National Breast Cancer Coalition, a Washington, D.C., advocacy group. Visco points out that a blood test could spur insurers to deny coverage to those who test positive for such mutations.

It will take years for scientists to answer basic questions about BRCA1 and BRCA2. How do such genes work in the healthy cell? What goes wrong in a malignant cell?

The answers to such questions will bring scientists closer to their ultimate goal. As Stratton puts it: "Learning about the structure and function of such genes will hopefully allow us to develop new strategies for the prevention — and cure — of breast cancer."

— *K.A. Fackelmann*