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# Genetic Study Divides Breast Cancer Into 4 Distinct Types

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In findings that are fundamentally reshaping the scientific understanding of **breast cancer**, researchers have identified four genetically distinct types of the **cancer**. And within those types, they found hallmark genetic changes that are driving many cancers.

These discoveries are expected to lead to new treatments with drugs already approved for cancers in other parts of the body and new ideas for more precise treatments aimed at genetic aberrations that now have no known treatment.

The study, published online on Sunday in the journal **Nature**, is the first comprehensive genetic analysis of breast cancer, which kills more than 35,000 women a year in the United States. The new paper, and several smaller recent studies, are electrifying the field.

“This is the road map for how we might cure breast cancer in the future,” said Dr. Matthew Ellis of Washington University, a researcher for the study.

Researchers and patient advocates caution that it will still take years to translate the new insights into transformative new treatments. Even within the four major types of breast cancer, individual **tumors** appear to be driven by their own sets of genetic changes. A wide variety of drugs will most likely need to be developed to tailor medicines to individual tumors.

“There are a lot of steps that turn basic science into clinically meaningful results,” said Karuna Jaggar, executive director of **Breast Cancer Action**, an advocacy group. “It is the ‘stay tuned’ story.”

The study is part of a large federal project, the **Cancer Genome Atlas**, to build maps of genetic changes in common cancers. Reports on similar studies of **lung** and **colon cancer** have been published recently. The breast cancer study was based on an analysis of tumors from 825 patients.

“There has never been a breast cancer genomics project on this scale,” said the atlas’s program director, Brad Ozenberger of the [National Institutes of Health](#).

The investigators identified at least 40 genetic alterations that might be attacked by drugs. Many of them are already being developed for other types of cancer that have the same mutations. “We now have a good view of what goes wrong in breast cancer,” said Joe Gray, a genetic expert at [Oregon Health & Science University](#), who was not involved in the study. “We haven’t had that before.”

The study focused on the most common types of breast cancer that are thought to arise in the milk duct. It concentrated on early breast cancers that had not yet spread to other parts of the body in order to find genetic changes that could be attacked, stopping a cancer before it metastasized.

The study’s biggest surprise involved a particularly deadly breast cancer whose [tumor](#) cells resemble basal cells of the skin and sweat glands, which are present in the deepest layer of the skin. These breast basal cells form a scaffolding for milk duct cells. Such cancers are often called triple negative but the study researchers call them basal-like.

Basal-like cancers are most frequent in younger women, in African-Americans and in women with breast cancer genes BRCA1 and BRCA2.

And, the researchers report, their genetic derangements make these cancers a much closer kin of ovarian cancers than of other breast cancers. Basal-like breast cancers also resemble squamous cell cancer of the lung.

“It’s incredible,” said Dr. James Ingle of the Mayo Clinic, one of the study’s 348 authors, of the [ovarian cancer](#) connection. “It raises the possibility that there may be a common cause.”

The study gives a biologic reason to try routine treatments for ovarian cancer — platinum drugs, for example — in basal-like breast cancer, the investigators said. And a common class of drug used in breast cancer, anthracyclines (adriamycin or epirubicin), might be dropped from the basal-like cancer treatment regimen because they do not increase help in ovarian cancer.

Anthracyclines, Dr. Ellis said, “are the drugs most breast cancer patients dread because they are associated with heart damage and leukemia.”

A new type of drug, PARP inhibitors, that seems to help squelch ovarian cancers, should also be tried in basal-like breast cancer, Dr. Ellis said.

Two other types of breast cancer, accounting for most cases of the disease, arise from the luminal cells that line milk ducts. These cancers have proteins on their surfaces that grab **estrogen**, fueling their growth. Just about everyone with estrogen-fueled cancer gets the same treatment. Some do well. Others do not.

The genetic analysis divided luminal cancers into two distinct subtypes. The luminal A subtype had good prognoses while luminal B did not, suggesting that perhaps patients with luminal A tumors might do well with just hormonal therapy to block estrogen from spurring their cancers while luminal B patients might do better with **chemotherapy** in addition to hormonal therapy.

In some cases, genetic aberrations were so strongly associated with one or the other luminal subtype that they appeared to be the actual cause of the cancer, said Dr. Charles Perou of the University of North Carolina, who is the lead author of the study. And he called that “a stunning finding.”

“We are really getting at the roots of these cancers,” he said.

After basal-like cancers, and luminal A and B cancers, the fourth type of breast cancer is what the researchers called HER2-enriched. Breast cancers often have extra copies of a gene, HER2, that drives their growth. A drug, Herceptin, can block the gene and has changed the prognosis for these patients from one of the worst in breast cancer to one of the best.

Yet although Herceptin is approved for every breast cancer patient whose tumor makes too much HER2, the new analysis finds that not all of these tumors are alike. The HER2-enriched should respond readily to Herceptin; the other type might not.

The only way to know is to do a clinical trial, and one is already being planned. Herceptin is expensive and can occasionally damage the heart. “We absolutely only want to give it to patients who can benefit,” Dr. Perou said.

For now, despite the tantalizing possibilities, patients will have to wait for clinical trials to see whether drugs that block the genetic aberrations can stop the cancers. And it could be a massive undertaking to get all the drug testing done. Because there are so many different ways a breast cancer cell can go awry, there may have to be dozens of drug studies, each focusing on a different genetic change.

One of Dr. Ellis’s patients, Elizabeth Stark, 48, has a basal-type breast cancer. She has gone through three rounds of chemotherapy, surgery and radiation over the past four years. Her

disease is stable now and Dr. Stark, a biochemist at Pfizer, says she knows it will take time for the explosion of genetic data to produce new treatments that might help her.

“In 10 years it will be different,” she said, adding emphatically, “I know I will be here in 10 years.”