Slight changes in 2 key genes appear to launch breast cancer development

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Researchers at Georgetown Lombard Comprehensive Cancer Center have been able to show, in mice, how just a little adjustment in the expression of two common genes can promote the kind of cellular changes that led to breast cancer. They say these tweaks likely mimic natural variation women have in expression of the two genes.

In the May 15 issue of *Cancer Research* published online today, the scientists say that a readout of these two genes - estrogen receptor alpha and p53 - in healthy women could provide an "interacting biomarker" that might predict future breast cancer risk.

"It was believed that both of these genes only act once breast cancer had developed - p53 mutations are found in many cancers, including breast cancer, and the majority of women with breast cancer have over-expression of this common estrogen receptor," says the study's lead investigator, Priscilla A. Furth, MD, a professor of oncology and medicine with Lombardi at Georgetown University Medical Center. "What wasn't known is that different levels of expression of these genes can help launch the cellular changes that lead to breast cancer.

"That suggests that testing women for their own variations in these genes might potentially give us a clue as to which women are at higher risk for development of breast cancer," Furth says.

The first author of the study is Edgar S. Díaz-Cruz, Ph.D., a fellow at Lombardi supported by a Susan G. Komen for the Cure Postdoctoral

Fellowship.

One focus of Furth's lab is to eventually develop a panel of tests that will accurately determine an individual woman's future risk of developing breast cancer so that counseling and monitoring can be tailored to each patient. To find the genes and proteins that carry such risk, she has developed unique mouse models in which she can manipulate various genetic factors to see how breast cancer risk changes over time.

In this study, Díaz-Cruz and Furth developed mice in which one copy of the p53 gene was silenced (mice, and humans, inherit two copies, one from each parent), and tested the effect on what is known as development of preneoplasia, or early breast cancer progression. The p53 gene, long called the "guardian of the genome," is known as a very powerful tumor suppressor because it regulates cell growth. Alterations to p53 are reported in 30-40 percent of human breast cancers, and this loss is linked to increased cancer aggressiveness, poor prognosis, and chemotherapy resistance.

The researchers also increased expression of the estrogen receptor by two-fold, an equivalent elevation sometimes seen in women. Almost 70 percent of women with breast cancer have estrogen receptor-positive breast cancer, meaning that the estrogen hormone is driving cell growth because it is binding to, in some cases, an over abundance of its receptors on the outside of breast cells.

Both mouse models showed significant precancerous changes in breast tissue.

They then compared those effects with changes seen in mice that had one p53 gene as well as twice as much estrogen receptor expression, and found substantially higher evidence of early stage breast cancer progression.

"Normal breast tissue functioning requires a balance of cell growth and cell death, and in this study we found that both deregulated estrogen receptor function and p53 expression independently, and in combination, altering this balance and transforming cells," Furth says.

Furth says that both tweaks in gene expression levels were relatively minor, and that she was sobered to find that they had such an effect on otherwise healthy breast tissue. "We increased ER expression, but in a way that could be found in normal variation among women," she says. "And the mice lost one of their two p53 genes, but loss of that single copy only decreases but does not eliminate expression.

"These are not the only two molecules that are responsible for breast cancer development, but they are important and they can potentially provide us with an early warning or even with prevention strategies," Furth says.

Provided by Georgetown University Medical Center