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New clues to breast cancer development in high-risk women

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Physicians who treat women with the breast cancer susceptibility gene BRCA1 often remove their patients' ovaries to eliminate the source of estrogen they believe fuels cancer growth. Yet they also know that anti-estrogen therapies don't work to treat breast or ovarian cancer that might develop. That paradox has led scientists to question exactly how, or if, estrogen is involved in cancer development and whether removal of ovaries makes sense.

Now, a team of researchers from Georgetown University's Lombardi Comprehensive Cancer Center have shed light on the mechanism that makes ovary removal protective against tumor development in this unique population. They discovered that estrogen is needed to start the cancer process, but then the BRCA1 mutations somehow render the new tumors unresponsive to estrogen, producing cancer that is more aggressive and difficult to treat.

In a study published electronically on July 23 in the journal *Oncogene*, Georgetown researchers found that mutations of the BRCA1 gene can cause the estrogen-signaling pathway to go awry after cancer starts to grow. The mutated gene somehow causes the tumor cells to stop expressing the estrogen receptor, a protein that sits on the surface of the cell and recognizes the presence of the hormone. This means that these cancers lose sensitivity to estrogen (and potent anti-estrogen therapies like Tamoxifen) after tumors begin to form.

To show that estrogen was involved in the initiation of the cancer, the

researchers overexpressed the estrogen receptor in a laboratory mouse model with a BRCA1 mutation and a p53 gene mutation (the two gene mutations usually coexist in human cancer). As predicted, they found that when exposed to estrogen, these mice developed cancerous tumors.

“Estrogen is definitely necessary for these tumors to develop, but somewhere along the tumor development pathway, the emerging tumors lose their sensitivity to estrogen,” said Priscilla Furth, MD, the study’s senior author and a professor of oncology at Georgetown. “The cells that develop into cancers frequently lose their ability to express the estrogen receptor and therefore are not sensitive to anti-estrogen therapies.”

Although the molecular mechanisms to explain this loss of sensitivity are not yet clear, the researchers believe that the BRCA1 mutation is causing the estrogen signaling pathway to malfunction, ultimately making these tumors harder to treat.

The findings also explain why the small proportion of women who have had an oophorectomy and still develop breast cancer frequently have tumors that are unresponsive to anti-estrogens like Tamoxifen, said Furth.

Both breast and ovarian cancers are often stimulated by estrogen, so oncologists counsel women who are over the age of 35 and know they carry a BRCA mutation to remove their ovaries—the body’s major source of estrogen—to reduce their chances of developing breast cancer and virtually eliminate risk of ovarian cancer, she explained.

Women with a BRCA1 mutation develop breast cancers that are most often unresponsive to hormones and anti-hormonal therapies like Tamoxifen, said Furth, but doctors continue to see reduced incidence of breast cancer among high-risk women who have undergone the oophorectomy procedure.

“The finding that estrogen is important in the development of BRCA1 mutant breast cancers is one of the strongest pieces of evidence to support removing the ovaries to reduce incidence of cancer in BRCA1 mutation carriers,” said co-author Eliot Rosen, MD, PhD, professor of oncology, biochemistry & cell and molecular biology, and radiation medicine at Georgetown.

The research also explains why oophorectomy appears to be more effective for younger women than older women, he said. “This study demonstrates that estrogen is important to the early development of cancer,” said Rosen. “Women who have lost BRCA1 function need estrogen to generate a tumor, so fewer years of estrogen exposure from the ovaries could be protective against the generation of new tumors.”

BRCA serves as a DNA repair molecule throughout the body, fixing cellular processes that have malfunctioned for some reason, said Furth. But once BRCA is damaged or mutated, these repair processes are slowed or stalled, which can set off a chain reaction resulting in cancer, as demonstrated in their laboratory model.

“The reason why BRCA mutations are so potent for causing breast cancer is because of the multiple actions it can cause,” said Furth. “Loss of BRCA function interferes with DNA repair and, as shown in this study, it appears to enhance to growth effects of estrogen.”

The team’s research might also reveal why pregnancy does not appear to be as protective against the development of breast cancer in this population as it does in women without genetic mutations. In non-inherited breast cancers, early pregnancy and multiple pregnancies appear to be protective against breast cancer development, explained Rosen.

“But for women who have inherited BRCA1 mutations, the situation is

the opposite—early and multiple pregnancies seems to accelerate the development of breast cancer," he said. "We can now speculate that the higher levels of estrogen and other hormones during pregnancy stimulate the early stages of cancer development."

The researchers intend to build upon their findings in future studies, investigating what is happening in the very early stages of cancer development and figuring out how tumor cells can become estrogen receptor negative. Furth and Peter Shields, MD, professor of oncology and medicine at Georgetown and the associate director for Cancer Control and Population Sciences at the Lombardi Comprehensive Cancer Center, recently received a two-year, $776,000 grant from the Department of Defense to study the role of another protein, transforming growth factor-beta (TGF-beta), believed to be involved in the development of BRCA1-deficient breast cancer.

Source: Georgetown University Medical Center