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Higher estrogen production in the breast could confer greater cancer risk than thought

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Could some women who naturally produce excess aromatase in their breasts have an increased risk of developing breast cancer? Results of a new animal study suggests that may be the case, say researchers at Georgetown Lombardi Comprehensive Cancer Center, a part of Georgetown University Medical Center.

In the issue of August 15 Cancer Research, the investigators say their mice study shows that overproduction of aromatase, which converts testosterone into estrogen, in breast tissue is even more important in pushing breast cancer development than excess production of the estrogen receptor that the hormone uses to activate mammary cells. In addition, the researchers found that aromatase over-expressing mice also expressed more estrogen receptors on the breast cells.

While current breast cancer therapies target both of those processes — inhibition of aromatase and inactivation of the estrogen receptor — the researchers say this study suggests that aromatase inhibitors may prove to be a more potent choice for cancer prevention in postmenopausal women. Tamoxifen and other drugs that block the estrogen receptor have long been used to prevent breast cancer and deter recurrence, while aromatase inhibitors are only now being studied as a protectant.

"We know that estrogen is the fuel that most breast tumors use to grow, and this study shows us that making more estrogen in the breast, right next to cells that can use the hormone as fuel, appears to be a key trigger of early breast cancer," says the study's senior investigator, Priscilla

Furth, M.D., professor of oncology and medicine at Georgetown Lombardi.

The study also reached another important conclusion, says Edgar Díaz-Cruz, Ph.D., a postdoctoral researcher working in the Furth laboratory and first author of the study.

"This study appears to help inform a longstanding controversy about whether it is systemic estrogen or estrogen produced in the breast that is the primary risk factor for breast cancer," he says. "With our animal models, we've demonstrated that local production of estrogen in mammary tissue is potent enough to spur development of breast cancer, and does not require estrogen from the ovaries or produced from fat tissue, as had been hypothesized."

Their study set out to achieve two goals: to look at whether production of estrogen or production of estrogen receptors in the breast was more potent in breast cancer development, and to find more answers to the controversy alluded to by Díaz-Cruz.

To address these issues, the researchers developed the first "conditional" mouse model of aromatase production in mammary tissue. That means they inserted a gene into mice that expresses human aromatase in the animal's mammary tissue — a gene the researchers can turn on or off.

They compared this new mouse model to one they had developed several years ago —a conditional mouse model in which a gene that produces estrogen receptors (ER) could also be turned on and off.

While they study found that both mouse models experienced the earliest stages of tumor formation, known as preneoplasia, the aromatase over-expressing mice model exhibited both increased preneoplasia and outright development of cancer. These mice also expressed proteins that

are tightly linked to cancer, Furth says.

The researchers also found, to their surprise, that aromatase over-expressing mice expressed more estrogen receptors than did the ER-conditional mice. "Increased aromatase produced both more estrogen and the receptors that the hormone needs to enter breast cells," says Díaz-Cruz. "This is obviously a greater risk for development of breast cancer than just over-expression of estrogen receptors."

"In our conditional mice, aromatase provides a double whammy – more estrogen and more estrogen receptors," Furth notes.

These mice also over-expressed progesterone receptors, downstream targets of estrogen receptors that can be cancer-promoting in some settings, as shown in this study in the context of aromatase over-expression.

Furth notes that the amount of aromatase and estrogen receptors produced in these mice is high, but not higher than would be expressed in a woman with breast cancer. "These were not super large amounts. Comparable levels can be measured in women."

Finally, they tested the effect of local versus systemic estrogen on development of preneoplasia. The researchers made three comparisons: between mice in which the ER was over-expressed; mice that had excess estrogen due to aromatase; and mice that were given more estrogen systemically. "If we give extra systemic estrogen, we don't see any increased risk of breast cancer, but the risk increases with extra expression of ER, and is higher still with local production of aromatase," says Díaz-Cruz. "That suggests that estrogen production in the breast is an important risk factor for development of breast cancer."

What these results suggest for women is that if females vary in the

amount of aromatase they naturally produce, as some studies suggest, then women with higher aromatase levels may be more susceptible to breast cancer, Furth says.

"Some day we may have a test available that can determine individual aromatase levels in postmenopausal women so that a preventive aromatase inhibitor can be prescribed to women at higher risk for breast cancer," she says.

Provided by Georgetown University Medical Center

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