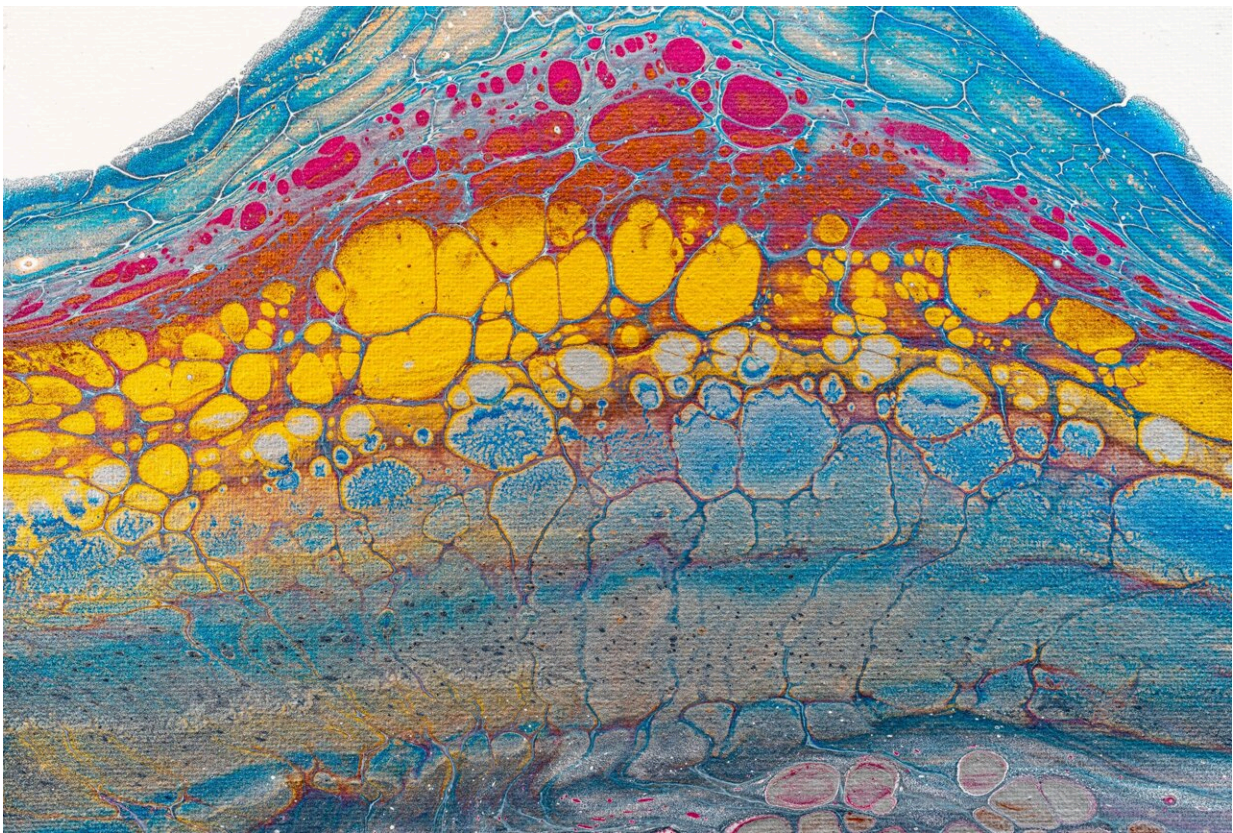


Study in mice suggests that expression of estrogen-related gene can impact post-menopausal breast cancer risk

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In a study using a first-of-its kind mouse model of aging that mimics breast cancer development in estrogen receptor-positive post-

menopausal women, investigators at Georgetown Lombardi Comprehensive Cancer Center and colleagues have determined that over-expression, or switching on of the *Esr1* gene, could lead to elevated risk of developing estrogen receptor-positive breast cancer in older women.

In a second study from the same research lab, investigators found that in the specially bred mice given anti-hormonal drugs (e.g., tamoxifen and letrozole) similar to those currently used by women to lower their [breast cancer risk](#), the elevated risk of developing [breast cancer](#) due to over-expression of *Esr1* could be lowered or reversed.

The findings appeared simultaneously December 1, 2022, in the *American Journal of Pathology*.

"In the clinic, we currently use tests for over-expression of particular patterns of genes to predict the probability of whether a woman's breast cancer could become metastatic," says Priscilla Furth, M.D., professor of oncology and medicine at Georgetown Lombardi and corresponding author of both studies. "If validated in [human studies](#), detection of over-expression of *Esr1*-related genes could be a new signature to add to current prognostic tools that would help post-menopausal women at risk for [estrogen](#) receptor-positive breast cancer decide what their best risk reduction strategy might be."

Most women start menopause in their late 40s or early 50s, with a risk of increased new cases of breast cancer peaking around 70 years of age. A substantial proportion of these breast cancers are fed by over-expression of the *Esr1* gene, resulting in higher expression of related estrogen pathway genes that help spur breast cancer development.

During human menopause, when overall estrogen levels typically decline, the breast tissue of some women can show an increase in expression levels of the estrogen receptor or even increased levels of

local estrogen production. To model this in mice, the investigators followed the mice as they aged through their natural reproductive cycle and decreased circulating estrogen levels. They then looked to see what factors were involved in resulting cancers by comparing outcomes in mice that were designed to overexpress one of two different genes: *Esr1*, which would model the increase in estrogen receptor levels, or *CYP19A1*, a gene that models the increase in local estrogen production. They found that *Esr1* over-expression resulted in more breast cancers than *CYP19A1* overexpression and was accompanied by high activation of estrogen pathway genes.

In the second study, they gave the mice estrogen-suppressive drugs, such as tamoxifen and letrozole, as a [preventive measure](#) to see if the drugs could resolve abnormal activation of estrogen pathway genes, which indeed turned out to be the case.

The investigators were guided in their study by the use of the PAM50 (Prediction Analysis of Microarray 50) [prognostic tool](#). The tool reads a sample of the tumor and determines expression levels for a group of 50 genes. The scientists found that many genes related to proliferation of breast cancer cells in the PAM50 tool were significantly expressed only in *Esr1* mice and this correlated with development of the same type of estrogen receptor-positive breast cancers that develop in humans, thereby giving them new evidence of which other genes might be implicated in inducing breast cancer in post-menopausal women. In current clinical practice, the results of the PAM50 test have helped predict the chance of metastasis for some ER-positive, HER2-negative breast cancers.

"One of the more important challenges in translating our findings from mice to people is the collection of [breast cancer](#) cells for testing with PAM50 or other prognostic tools," says Furth. "Removing breast tissue, even with a fine needle, is still invasive and perhaps unavoidable.

However, we have developed a method in my lab that requires collecting just a few [tumor cells](#) from a small tissue sample, as our process expands and grows the cells many-fold so that we can have adequate cancer cell numbers to run through prognostic tools like PAM50."

The scientists are hoping other researchers, including commercial prognostic tool developers, take note of this research advance and incorporate risk factors associated with some of the [genes](#) linked to *Esr1* in their tools, potentially enabling women to better avoid over-treatment or make more precise treatment choices.

More information: *Esr1* but Not CYP19A1 Overexpression in Mammary Epithelial Cells during Reproductive Senescence Induces Pregnancy-Like Proliferative Mammary Disease Responsive to Anti-Hormonals, *American Journal of Pathology* (2022).

Overexpression of Estrogen Receptor α in Mammary Glands of Aging Mice Is Associated with a Proliferative Risk Signature and Generation of Estrogen Receptor α -Positive Mammary Adenocarcinomas, *American Journal of Pathology* (2022).

Provided by Georgetown University Medical Center

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