New approach found to tackle breast cancer hormone therapy resistance

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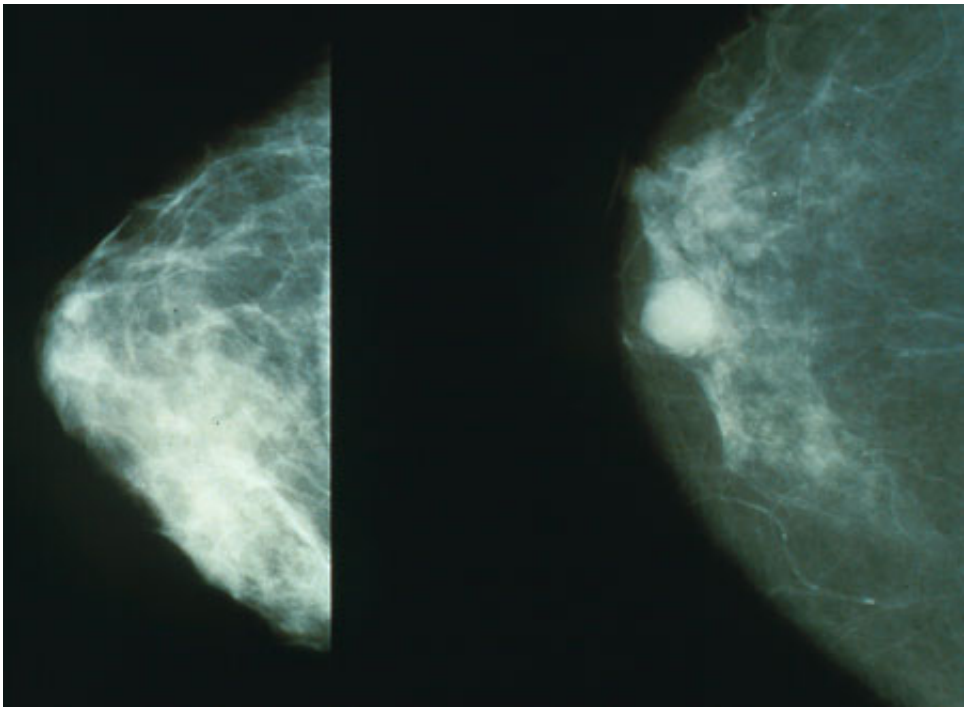

Mammograms showing a normal breast (left) and a breast with cancer (right). Credit: Public Domain

University of Manchester researchers funded by Breast Cancer Now have discovered a new explanation as to why women with oestrogen receptor positive (ER+) breast cancer develop resistance to hormone treatment, and a potential new approach to overcome the problem.

Around 80% of breast cancers are ER+ and are treated with anti-

oestrogen therapies such as tamoxifen and aromatase inhibitors. But around one in five of these cases recur within 10 years, and nearly all advanced cases develop resistance, which is why it's so important that we continue to learn more about how the disease finds ways to survive in some patients and not others.

The study team, based at The University of Manchester's Institute of Cancer Sciences, found that while short-term treatment with anti-oestrogen drugs decreased tumour growth, it increased the activity of breast cancer stem cells. They found that these stem cells were driven by a signal called NOTCH4. Their results from patient-derived breast cancers in mice and cells grown in the laboratory indicated that it was the presence of NOTCH4 that enabled the cancer stem cells to avoid anti-oestrogen treatment. In patient tumours, having high levels of NOTCH4 before treatment was linked to breast cancer spread and worse survival outcomes.

This suggested that resistance to anti-oestrogen treatment could be overcome by targeting the cancer stem cells with a NOTCH inhibitor, using the cells' reliance on NOTCH4 as their Achilles heel.

Study team leader Dr Rob Clarke, from the Breast Cancer Now Research Unit at The University of Manchester's Institute of Cancer Sciences said: "When treating with both tamoxifen and a NOTCH inhibitor, tamoxifen decreased the tumour growth while the NOTCH inhibitor decreased the numbers of breast cancer stem cells that could form new tumours, compared to treating with tamoxifen alone.

"This showed us that combining standard hormonal therapies with a NOTCH pathway inhibitor, or other drugs targeting breast cancer stem cells, could improve treatment of ER+ breast cancer patients by preventing relapse due to therapy resistance."

Importantly, testing for high levels of NOTCH4, or another molecule called ALDH1, could predict whose breast cancer is likely to be resistant to anti-oestrogen drugs and which patients could benefit most from combined treatment with anti-oestrogen therapies and a NOTCH inhibitor.

Katie Goates, Senior Research Communications Officer at Breast Cancer Now, said: "This is an exciting new explanation as to why women become resistant to tamoxifen and how we could predict and prevent this by testing for, and blocking, NOTCH4 in breast cancer stem cells.

"Validating these findings will take time but general inhibitors of the NOTCH pathway are already being tested in breast cancer clinical trials. The development of resistance to cancer therapies is a huge challenge in the clinic which is why it's vitally important that we continue to find ways to counteract it, taking us closer towards our ambitious goal of stopping women dying from this devastating disease by 2050."

The research was published in *Cell Reports*.

Provided by University of Manchester