Breast cancer patients could benefit from controversial hormone

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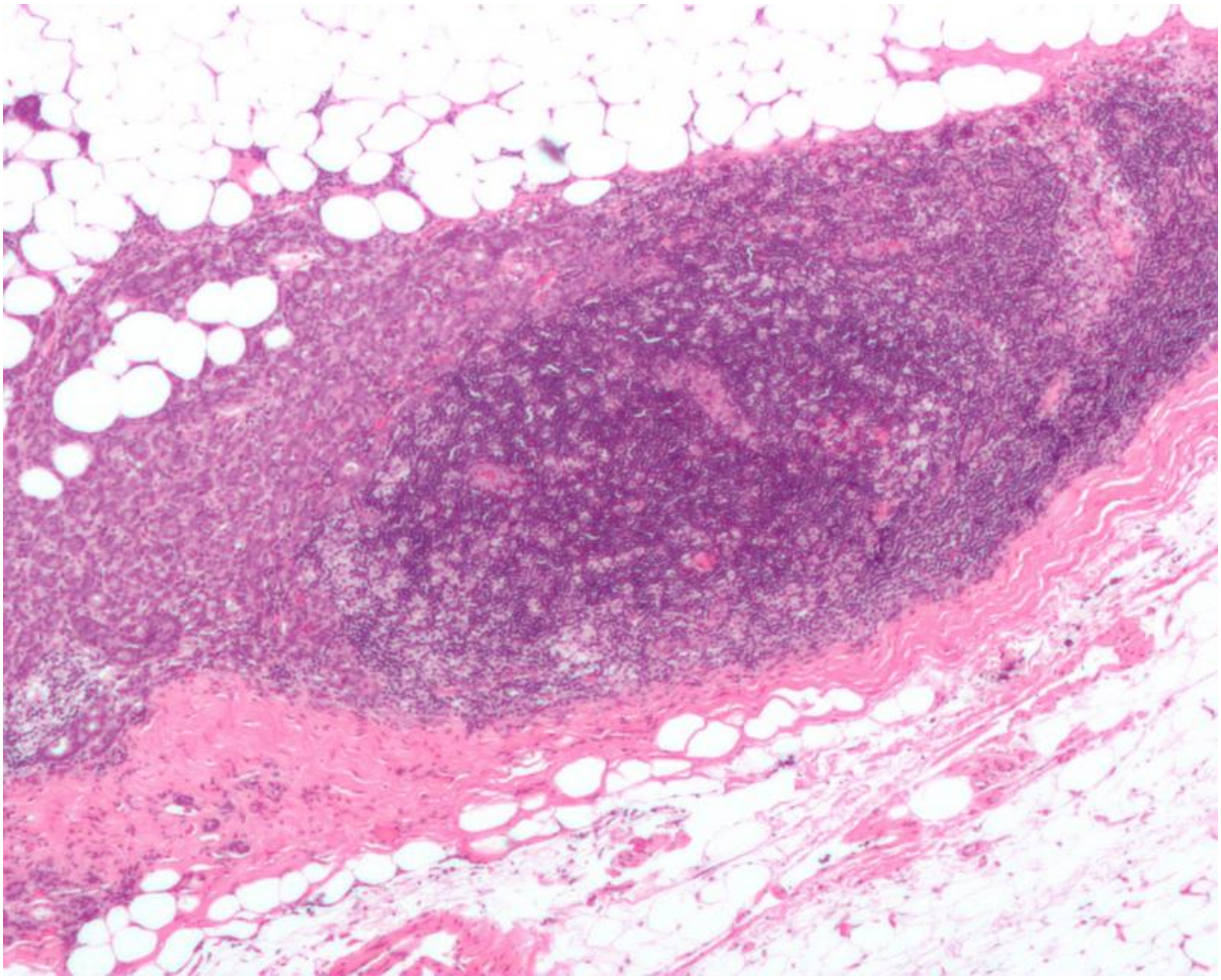

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

An international team of researchers involving the University of Adelaide is tackling the controversy over what some scientists consider to be a "harmful" hormone, arguing that it could be a game changer in the fight against recurring breast cancers that are resistant to standard treatments.

The controversy centres on the different effects in women of the naturally occurring sex steroid hormone progesterone compared with synthetic forms (i.e. progestins) designed to mimic its actions.

Some, but not all, progestins have been linked with increased breast cancer risk when used in menopausal hormone therapy, leading to concerns in the scientific community about the use of these drugs.

However, in a paper now published online ahead of print in the prestigious journal *Nature Reviews Cancer*, an international team – involving the University of Adelaide's Dame Roma Mitchell Cancer Research Laboratories (DRMCRL) and the Cancer Research UK (CRUK) Cambridge Institute – highlights that progesterone when used in menopausal hormone therapy does not increase breast cancer risk . Indeed, progesterone may have an important role to play in the safe and effective management of recurring breast cancer.

"Breast cancer arises because of abnormal hormone activity, with about 75% of these cancers being driven by the oestrogen receptor. Unfortunately, despite good initial responses in many women, drug resistance is common, usually leading to a recurrence and lethal spread of the disease," says Professor Wayne Tilley, Director of the Dame Roma Mitchell Cancer Research Laboratories at the University of Adelaide, and a lead author of the paper.

"Moreover, current hormonal treatments that target the oestrogen receptor in breast cancer, especially specific inhibitors that block

oestrogen production, can markedly impact quality of life, often leading women to stop taking the drugs or change their treatment."

Professor Tilley says the team's recent studies, including landmark research already published in Nature, suggest that a safe way of improving treatment – without having a deleterious effect on quality of life – does exist, through the use of natural progesterone and certain other progestins.

"There is a natural 'crosstalk' between oestrogen and progesterone receptors that we strongly believe can be exploited," he says.

"In particular, progesterone can reprogram oestrogen action in the breast in a way that results in oestrogen receptor action improving breast cancer outcomes. Because of this unique interaction of the two natural female sex hormones in the breast, we see great potential benefits in adding progesterone to existing drugs that target the oestrogen receptor, thereby helping to switch off the growth of cancer cells.

"This gives us a unique opportunity to develop a new hormonal treatment which, when used in conjunction with the current standard of care, would enhance and improve outcomes for many breast cancer patients.

"Unfortunately, there are some serious misconceptions about the role of progesterone in cancer biology that have so far prevented it from being widely used in the management of breast cancer. We hope to change that thinking," Professor Tilley says.

The team, which is highly regarded for its research into both breast and prostate cancer, believes this new paper will have a global impact on clinical, scientific and public opinion on the relative risks and benefits of using progesterone and certain progestins to treat women with breast cancer. "Ultimately, we hope this work will eventually result in saving

women's lives," Professor Tilley says.

The real proof will come from two new clinical trials being conducted by the international team, with patients being recruited for the studies in the UK early next year.

One trial in collaboration with a UK group at the University of Liverpool will test the potential benefit of combining progesterone treatment with the breast cancer drug Tamoxifen in premenopausal women with breast cancer.

A second trial involving postmenopausal women with breast cancer has been initiated by collaborators at the CRUK Cambridge Institute and will evaluate whether a particular progestin, Megace, provides added therapeutic benefit when combined with a current oestrogen receptor target treatment, compared to the target treatment alone.

"Resistance to current therapies that target the androgen receptor is the main cause of lethal prostate cancer. Researchers in the Dame Roma Mitchell Cancer Research Laboratories are developing and testing a new drug that is effective against the androgen receptor in preclinical models of treatment resistant prostate cancer. It is hoped that this new drug will inhibit the growth of tumours that currently kill approximately 3,300 men in Australia each year," he says.

More information: Jason S. Carroll et al. Deciphering the divergent roles of progestogens in breast cancer, *Nature Reviews Cancer* (2016). DOI: 10.1038/nrc.2016.116

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