Estrogen-mimicking compounds in foods may reduce effectiveness of breast cancer treatment

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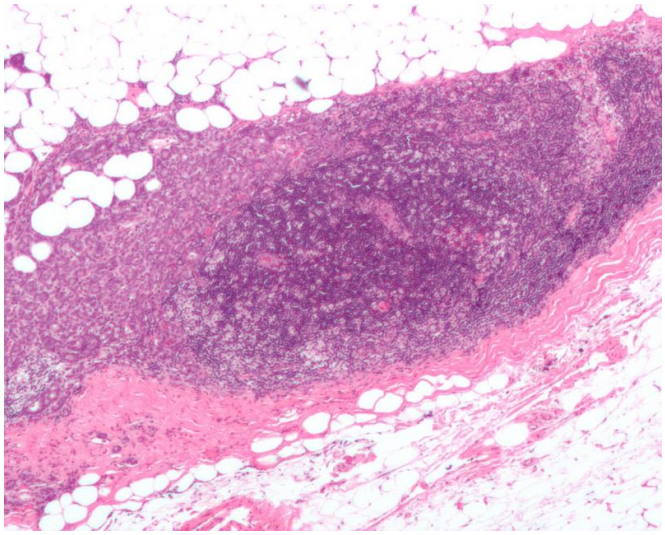

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Scientists from The Scripps Research Institute (TSRI) have discovered that two estrogen-mimicking compounds found in many foods appear to potently reverse the effects of palbociclib/letrozole, a popular drug combination for treating breast cancer.

The study, published today in the journal *Cell Chemical Biology*, suggests that exposure to chemical compounds called xenoestrogens may significantly reduce the effectiveness of anti-estrogen treatments for cancer.

"Breast cancer patients taking palbociclib/letrozole should consider limiting their exposure to foods that contain xenoestrogens," says Gary Siuzdak, PhD, the study's senior author and senior director of TSRI's Scripps Center for Metabolomics.

The palbociclib/letrozole combination therapy was approved by the U.S. Food and Drug Administration in 2015 after a clinical trial showed it doubled the progression-free survival time in postmenopausal women with estrogen receptor (ER) positive, metastatic breast cancer. Letrozole blocks the production of estrogen, thus reducing the growth-promoting stimulation of ERs on breast cancer cells. Palbociclib blocks a different signaling pathway to impede cell division. The combination is now one of the standard therapies for ER-positive breast cancers.

Siuzdak and colleagues, including first and lead author Benedikt Warth, PhD, then a visiting Erwin-Schrödinger Fellow in the Siuzdak Lab, used advanced metabolomics technology to analyze the effects of palbociclib/letrozole on breast cancer cells. Metabolomics studies detail cells' metabolomes—populations of metabolites, the small-molecule end products of cellular processes.

"By profiling cell metabolomes with and without drug treatment we can get very useful information, for example about the biological pathways perturbed by the drug," says Siuzdak, a professor of chemistry, molecular and computational biology.

Their analysis revealed that neither palbociclib alone nor letrozole alone had a strong effect on metabolites in an ER-positive breast cancer cell line. However, the combination had a strikingly large impact. "The combination had a much more pronounced effect on cell-growth-related metabolites, which is consistent with the clinical trial results," Warth says.

Cancer researchers are increasingly concerned that xenoestrogens in food and water may enhance the growth of estrogen-fueled cancers, and may also hamper the effectiveness of anti-estrogen

drugs such as letrozole. TSRI scientists therefore examined breast cancer cells treated with palbociclib/letrozole to see how their metabolite populations changed when they were also exposed to two common dietary xenoestrogens: zearalenone and genistein.

Zearalenone is produced by fungi that colonize maize, barley, wheat and other grains. It has been linked to birth defects and abnormal sexual development in pigs and other livestock, and is suspected of having caused an outbreak of early breast development among girls in Puerto Rico in the 1970s. Genistein is produced in certain plants including soybeans and is often highly concentrated in phytoestrogen-rich food supplements.

Even using very low doses, similar to typical dietary exposures, the researchers found that both model xenoestrogens largely reversed the metabolomic impact of the cancer drug combination. "This included many key metabolites," says Siuzdak.

Under the influence of either xenoestrogen, the breast cancer cells also resumed proliferating at a rate comparable to that seen in the absence of drug treatment.

"It's intriguing that even a low, background-level exposure to these xenoestrogens was enough to impact the effect of the therapy to this degree," says Warth, who is now an assistant professor at the University of Vienna's Department of Food Chemistry & Toxicology.

The results indicate that these dietary xenoestrogens do have the potential to affect cancer therapy outcomes—and genistein and zearalenone are just two of the many xenoestrogens commonly found in the human diet. "There's a high likelihood that other xenoestrogens would counteract the therapy in a similar way," Siuzdak says.

The impact of xenoestrogens on health and on hormonally-targeted therapies is nevertheless an understudied, underfunded area of research, the researchers emphasized.

"We generally know very little about the interactions of bioactive compounds we are exposed to through our food or the environment with drug treatments," Warth says. "So, in this field there are probably a lot of clinically relevant discoveries yet to be made."

"What I find intriguing is that metabolomics can be used to identify active metabolites that are therapeutically beneficial or, as in this case, exogenous fungal and plant metabolites that are detrimental," Siuzdak says. "Clearly, metabolites can have a significant impact in modulating therapeutics."

More information: "Metabolomics reveals that dietary xenoestrogens alter cellular metabolism induced by palbociclib/letrozole combination cancer therapy," *Cell Chemical Biology* (2018).

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