Tamoxifen resistance linked to high estrogen levels in utero

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An animal study suggests that resistance to tamoxifen therapy in some estrogen receptor positive breast cancers may originate from in utero exposure to endocrine disrupting chemicals. The study provides a new path forward in human research as about half of the breast cancers treated with this common cancer therapy do not respond well, say researchers at the Georgetown Lombardi Comprehensive Cancer Center, who led the multi-institutional research.

The study, published in the *Journal of the National Cancer Institute* (*JNCI*), identified four genes that are linked to tamoxifen resistance and poor prognosis of breast cancer, by comparing results obtained in a new animal model, in human breast cancer cells grown in culture, and in publically available datasets collected from thousands of estrogen receptor positive breast cancer patients treated with tamoxifen.

"Higher estrogen levels in utero have been known to increase risk of estrogen positive breast cancer in laboratory animals—and humans—but it wasn't known until this study that these elevated levels may also be responsible for tamoxifen resistance," says the study's co-lead author, Leena Hilakivi-Clarke, PhD, a professor of oncology at Georgetown Lombardi..

Researchers further demonstrated that changes in these genes were reversed by adding well-tolerated epigenetic modifying drugs, valproic acid and hydralazine, to tamoxifen therapy regimen. These drugs also prevented tamoxifen resistance and recurrence of breast cancer in the animal model.

"We have found that the same genes responsible for tamoxifen resistance in our animals are also turned off in human breast cancer cells that do not respond to the drug," she says "Because these genes were epigenetically silenced—meaning they were not irreversibly altered, just switched off—it was possible to turn them back on. It remains to be determined if these genes are markers of in utero estrogen exposure in breast cancer patients.

"Tamoxifen is an excellent agent to use to both prevent breast cancer in high-risk women, and to reduce cancer recurrence in women who develop tumors, so our goal is to ensure that patients who use this drug can respond to it," Hilakivi-Clarke says.

The animal model used is the same that was used over 40 years ago to discover that tamoxifen prevents breast cancer. It was used in this study for the first time to study factors that cause estrogen receptor positive breast cancer to recur during tamoxifen therapy.

The researchers conducted the study by using an endocrine disrupting chemical present at low levels in drinking water—ethinyl estradiol (EE2), an ingredient in birth control pills and hormone replacement therapy. "Everyone is exposed to some environmental estrogens, and many pregnant women naturally produce a lot of this hormone," Hilakivi-Clarke says. "The exposures may pose risks both in terms of breast cancer risk and tamoxifen resistance."

Provided by Georgetown University Medical Center