Ability to metabolize tamoxifen affects breast cancer outcomes, study confirms

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For nearly a decade, breast cancer researchers studying the hormone therapy tamoxifen have been divided as to whether genetic differences in a liver enzyme affect the drug's effectiveness and the likelihood breast cancer will recur. A new study by researchers from the Mayo Clinic Cancer Center and the Austrian Breast and Colorectal Cancer Study Group provides evidence that genetic differences in the enzyme CYP2D6 play a key role in how well tamoxifen works.

"Our findings confirm that, in early breast cancer treated with tamoxifen, genetic alterations in CYP2D6 lead to a higher likelihood of recurrence and death," says Mayo Clinic oncologist Matthew Goetz, M.D., lead author of the study in the journal Clinical Cancer Research.

In the clinical trial, Dr. Goetz and his colleagues studied the rates of cancer recurrence and death in two groups: postmenopausal women with primary estrogen receptor-positive breast cancer who received tamoxifen for five years and those who received tamoxifen for two years followed by the aromatase inhibitor anastrozole for three years. Anastrozole is a breast cancer drug whose metabolism does not require the CYP2D6 enzyme.

The study showed that women who were born with genetic alterations of CYP2D6 that abolish the enzyme's critical metabolizing activity and who took tamoxifen for five years had recurrence of breast cancer, or died at a rate 2.5 times higher than women with normal CYP2D6 enzyme activity. Women with intermediate levels of the CYP2D6 enzyme had

rates of recurrence or death 1.7 times higher than women with normal CYP2D6 activity. Importantly, Dr. Goetz notes, that genetic alterations in CYP2D6 did not affect the likelihood of recurrence or death in women who switched to anastrozole after two years of tamoxifen.

"Switching from tamoxifen to an aromatase inhibitor may be one reason for the discrepant studies surrounding CYP2D6 and tamoxifen—as information about whether a patient took an aromatase inhibitor after tamoxifen was not available in most of the prior studies," says senior author James Ingle, M.D., of Mayo Clinic, an expert on hormone therapies for breast cancer.

A blood test can determine whether a woman has alterations in CYP2D6 and predict how efficiently her body will convert tamoxifen to endoxifen. Approximately 5 to 7 percent of European and North American populations are considered poor metabolizers of tamoxifen.

"The results of this successful high-level international research collaboration are an important step forward in our quest to individualize breast cancer treatment and provide tailored care to women with breast cancer," says Michael Gnant, M.D., professor of surgery at the Medical University of Vienna and president of the Austrian study group.

So what should a woman do if she is unable to effectively metabolize tamoxifen into its most active form? Dr. Goetz believes that the current recommendation of switching from tamoxifen to an aromatase inhibitor is likely to result in the greatest benefit in women with decreased CYP2D6 metabolism. For CYP2D6 poor metabolizers, avoiding tamoxifen altogether and starting out with an aromatase inhibitor may be the best approach, he says.

Dr. Goetz's group is working with the National Cancer Institute to develop endoxifen as an alternative to tamoxifen. If women can be given

endoxifen, the active part of tamoxifen, it won't matter how tamoxifen gets metabolized, he says.

Provided by Mayo Clinic