Studies show that CYP2D6 genotype does not predict tamoxifen benefit

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Two studies published March 6 in the *Journal of the National Cancer Institute* provide insights about the CYP2D6 genotype in postmenopausal breast cancer patients and represent a major step forward in understanding the usefulness of CYP2D6 testing for deciding whether or not a patient should receive adjuvant tamoxifen for treatment of early-stage breast cancer. Both studies found that CYP2D6 genotypes that were indicative of reduced activity of enzymes that metabolize tamoxifen did not predict clinical responsiveness to adjuvant tamoxifen therapy among postmenopausal women with early-stage breast cancer. One study also found that CYP2D6 genotypes of reduced enzyme activity were not linked with fewer tamoxifen-induced hot flushes in patients.

Adjuvant tamoxifen therapy decreases the risk of recurrence and mortality in women with hormone receptor-positive early-stage breast cancer. But tamoxifen is known to have a weak affinity for the estrogen receptor, and undergoes extensive metabolism by the CYP2D6 enzyme to form more potent active metabolites including 4-hydroxytamoxifen and endoxifen. As a result, pharmacogenetic testing of CYP2D6 polymorphisms to identify patients with reduced tamoxifen metabolism phenotypes has been recommended, as testing may predict a poorer response to tamoxifen therapy, to help with treatment decision-making. And studies have proposed that metabolic conversion of tamoxifen to endoxifen by CYP2D6 is essential for a patient to benefit from tamoxifen therapy, leading to a trend of CYP2D6 genotyping among patients.

In order to determine the association between CYP2D6 polymorphisms and breast cancer recurrence, Meredith M. Regan, ScD, IBCSG Statistical Center, in the Department of Biostatistics and Computational Biology at the Dana-Farber Cancer Institute in Boston and Brian Leyland-Jones, MD, Emory University School of Medicine in Atlanta and colleagues, obtained tumor tissues from postmenopausal breast cancer patients who participated in the Breast International Group (BIG) 1-98 trial between March 1998-May 2003 and received adjuvant tamoxifen and/or letrozole. They isolated DNA from these tissues, performed CYP2D6 genotyping, and based on the genotype combinations, categorized the CYP2D6 metabolism phenotypes as poor, immediate, and extensive metabolizers.

The researchers found that CYP2D6 phenotypes of reduced enzyme activity were not associated with worse disease control, but were associated with increased tamoxifen-induced hot flushes, contrary to the prevalent hypothesis. Hot flushes are a commonly-reported side effect from tamoxifen, and it has been suggested that women who do not experience hot flushes may not be getting the full benefit of the drug because their body does not metabolize it adequately (i.e. poor and intermediate metabolizers). They write, "Our results indicate that CYP2D6 metabolism phenotype is not the correct surrogate for predicting symptoms and outcome of tamoxifen-treated post-menopausal women….The relationship of tamoxifen metabolism with symptoms and disease control is not adequately understood."

In a second study, James M. Rae, Ph.D., of the Division of Hematology/Oncology at the University of Michigan Comprehensive Cancer Center and colleagues, examined postmenopausal, hormone receptor-positive early-stage breast cancer patients from the UK population of the Arimidex Tamoxifen, Alone or in Combination (ATAC) clinical trial who received tamoxifen or anastrazole and were genotyped for CYP2D6 variants. UGT2B7 was also genotyped due to its

known gene product which inactivates endoxifen. Patients were assigned a CYP2D6 activity score based on the genotype, and classified as poor, intermediate, and extensive metabolizer phenotypes.

The researchers found that the CYP2D6 genotype showed no association with disease recurrence rates, and phenotypes indicating reduced CYP2D6 enzyme activity were not found to be connected with worse disease outcomes. The researchers also reference the results found in the BIG 1-98 trial, saying that, "Taken together, these represent a high level of evidence demonstrating that CYP2D6 genotyping should not be recommended for such patients and that there is no need to avoid CYP2D6 inhibitors in postmenopausal patients taking tamoxifen."

In an accompanying editorial, Catherine M. Kelly of the department of medical oncology at the Mater Misericordiae University Hospital in Dublin, and Kathleen I. Pritchard, of the department of medical oncology at the Odette Cancer Centre at Sunnybrook Health Sciences Centre in Toronto, note that, "Over the last 9 years, a great industry of CYP2D6 measurement has arisen." Furthermore, the FDA's Clinical Pharmacology Subcommittee has suggested that the tamoxifen label include information about the increased risk of breast cancer recurrence in CYP2D6 poor metabolizers taking tamoxifen. The editorialists question this suggestion. "Validation of predictive biomarkers is a complicated process," they write, adding, "For example CYP2D6 metabolism status would have little impact on tamoxifen benefit if the breast cancer was already de novo resistant to endocrine therapy, or the patient had a very low risk of recurrence and surgery alone was sufficient."

The editorialists also advocate "large confirmatory studies….for decisions regarding the use of therapeutic agents," and "data from randomized clinical trials for clinical demonstration of associations between biomarkers and disease outcomes."