Genetic variation of enzyme linked with outcomes for women receiving tamoxifen

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Among women with early stage breast cancer, genetic variation of a certain enzyme appears to be associated with clinical outcomes for women treated with tamoxifen, according to a study in the October 7 issue of *JAMA*.

"Tamoxifen has been the gold standard for the last 25 years for endocrine treatment of breast cancer. It is estimated that the lives of half a million women have been saved with adjuvant [supplemental] tamoxifen therapy," according to background information in the article. The growth inhibitory effect of tamoxifen is mediated by its metabolites, 4-hydroxytamoxifen and endoxifen.

The formation of active metabolites is brought about by the polymorphic cytochrome P450 2D6 (CYP2D6) enzyme. "Approximately 100 CYP2D6 genetic variants have been identified, which manifest in the population in 4 distinct phenotypes, extensive (normal activity), intermediate (reduced activity), poor (no activity), and ultrarapid (high activity) metabolism, and a gene-dose effect with respect to endoxifen plasma concentrations has been demonstrated. Thus, it can be speculated that genotype-related differences in the formation of active metabolites influence therapeutic response to tamoxifen."

Werner Schroth, D.Phil., of the Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany, and colleagues conducted a study to determine whether CYP2D6 variation is associated with clinical outcomes in women receiving tamoxifen as a supplemental

treatment. The study included 1,325 patients who had diagnoses of stage I through III breast cancer between 1986 and 2005 and who were mainly postmenopausal (95.4 percent). Last follow-up was in December 2008, and the median (midpoint) follow-up time was 6.3 years. DNA from tumor tissue or blood was genotyped for CYP2D6 variants associated with reduced or absent enzyme activity. Women were classified as having an extensive (n = 609), heterozygous extensive/intermediate (n = 637), or poor (n = 79) CYP2D6 metabolism.

The researchers found higher breast cancer event rates in patients with reduced or absent CYP2D6 function vs. extensive metabolism patients. "At 9 years of follow-up, the recurrence rates were 14.9 percent for extensive metabolizers, 20.9 percent for heterozygous extensive/intermediate metabolizers, and 29.0 percent for poor metabolizers, and all-cause mortality rates were 16.7 percent, 18.0 percent, and 22.8 percent, respectively," the authors write. Compared with extensive metabolizers, heterozygous extensive/intermediate metabolizers had a 40 percent increased risk of recurrence; poor metabolizers had nearly twice the risk.

"Compared with extensive metabolizers, those with decreased CYP2D6 activity (heterozygous extensive/intermediate and poor metabolism) had worse event-free survival and disease-free survival, but there was no significant difference in overall survival."

"Genotyping has the potential for identification of women who have the CYP2D6 poor metabolism phenotype and for whom the use of tamoxifen is associated with poor outcomes, thus indicating consideration of alternative forms of adjuvant endocrine therapy," the authors conclude.

More information: *JAMA*. 2009;302[13]:1429-1437.