CYP2D6 Testing for Breast Cancer Patients: Is There More to the Story?

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The promise of pharmacogenetics is personalization of therapy for individuals through refinement of the risk/benefit profile of pharmaceuticals based on inherited gene mutations. Classic examples of the impact of pharmacogenetics in clinical practice include variants in dihydropyrimidine dehydrogenase and treatment with fluorouracil.

The promise of pharmacogenetics is personalization of therapy for individuals through refinement of the risk/benefit profile of pharmaceuticals based on inherited gene mutations. Classic examples of the impact of pharmacogenetics in clinical practice include variants in dihydropyrimidine dehydrogenase and treatment with fluorouracil. However, its use in the routine management of women with breast cancer who are starting treatment with tamoxifen has been hampered by conflicting evidence regarding associations between cytochrome P450 (CYP) 2D6 single-gene polymorphisms (SNPs), tamoxifen metabolism, and breast cancer outcomes. In the current issue of ONCOLOGY, Kuderer and Peppercorn provide a comprehensive overview of this topic, with a particular focus on issues surrounding use of CYP2D6 genetic testing in routine clinical practice.[1] In general, we agree with the authors in their conclusion that routine testing for CYP2D6 for tamoxifen therapy is not yet justified by the available evidence.

CYP2D6 SNPs and Tamoxifen Efficacy

As discussed by Kuderer and Peppercorn, the metabolism of the relatively inactive prodrug tamoxifen to its highly active metabolite endoxifen is highly dependent on CYP2D6.[2] Endoxifen has equivalent potency to the other active metabolite, 4-hydroxytamoxifen, but is about 10-fold more abundant in serum from subjects with fully functional CYP2D6 enzyme. In contrast, endoxifen is present at much lower concentrations in patients with homozygous variant alleles of CYP2D6, or in those who take CYP2D6 inhibitors. Therefore, the hypothesis has been developed that patients with decreased CYP2D6 enzymatic activity, either due to inherited gene mutations or to concomitant use of inhibitory medications, may not obtain as much clinical benefit from tamoxifen because of their decreased ability to produce endoxifen.

The authors highlighted the published studies that have investigated associations between CYP2D6 SNPs and breast cancer outcomes in tamoxifen-treated patients. Most, but not all, have demonstrated an association between poor metabolizer CYP2D6 genotype and worse disease-free survival.[3-7] However, two studies from Wegman et al have demonstrated the opposite results.[8,9] All of these studies have limitations, however, including retrospective analysis, small sample size, limited number of analyzed SNPs, different doses and duration of tamoxifen therapy, and lack of information about concomitant medications and other potentially confounding factors. In addition, association between endoxifen concentration and breast cancer outcome has not yet been evaluated, since most previously conducted trials do not have serum samples available for analysis. Given the limitations noted above, additional data are still needed before the controversy regarding the impact of CYP2D6 variant alleles on breast cancer outcome in tamoxifen-treated patients is resolved.

Potential Reasons for Conflicting Results

There are a number of potential causes for these conflicting results:
(1) As mentioned above, one reason for the apparent association (or lack thereof) between CYP2D6 genotype and breast cancer outcomes in some studies may be the effect of concomitant medications that inhibit CYP2D6.[10] A tamoxifen-treated subject who concomitantly received CYP2D6-inhibiting medications may have the phenotype of a poor metabolizer, even though her genotype suggests she is an extensive metabolizer. Since most studies did not comprehensively collect concomitant
medications, this key confounder has been omitted from most analyses. (2) Subjects who are homozygous for inactive CYP2D6 alleles are still able to produce some endoxifen.[10,11] In addition, 4-hydroxytamoxifen is an active metabolite of tamoxifen, and its production is less dependent on CYP2D6. The amount of metabolite necessary for estrogen receptor saturation is unknown, and therefore even small amounts may be sufficient for activity. (3) Polymorphisms in a single drug-metabolizing enzyme may not be a good predictive marker for outcome. Multiple genes are known to be involved in tamoxifen metabolism and clearance, as well as in estrogen receptor signaling, yet the studies described above have focused almost exclusively on variants in a single gene. Therefore, the conflicting results could be due to the impact of inherited variants in other genes that lead to decreased efficacy of tamoxifen in subjects regardless of their CYP2D6 genotype. (4) None of the studies controlled for adherence to and discontinuation of therapy. A poor metabolizer who is persistent with tamoxifen treatment probably obtains more benefit than an extensive metabolizer who discontinues the drug after a few months. In addition, CYP2D6 genotype might influence rates of discontinuation.

**Risks of CYP2D6 Testing**

The authors do an excellent job of outlining the potential risks of routine CYP2D6 testing in this patient population. In postmenopausal women, multiple endocrine therapy options are available, so avoidance of tamoxifen therapy is possible for most poor metabolizers if one wants to avoid a therapy that may be ineffective. Of particular concern, however, is the issue of CYP2D6 testing in either postmenopausal women for whom an aromatase inhibitor is not an acceptable alternative to tamoxifen, or in premenopausal women. Ongoing studies in this patient cohort, such as the international Suppression of Ovarian Function Trial (SOFT; NCT00917969), are evaluating hormonal treatments other than tamoxifen, including ovarian suppression in combination with either aromatase inhibitors or tamoxifen. It therefore remains unknown if treatment of premenopausal breast cancer patients with estrogen depletion is effective, and if it is an appropriate alternative to tamoxifen monotherapy.

In addition, the clinical impact on breast cancer outcomes of concomitant medications that can modify CYP2D6 activity is unknown. In general, experts are recommending avoidance of medications known to be potent inhibitors of CYP2D6 if alternative therapies are available, under the assumption that the presence of CYP2D6 activity is beneficial. The Mayo Clinic is currently conducting a prospective study to gather more information about the impact of commonly used antidepressants that are believed to be intermediate or weak CYP2D6 inhibitors on serum concentrations of tamoxifen and its metabolites (NCT00667121). However, even if these data were available now, the required minimum serum endoxifen concentration for adequate breast cancer therapy is unknown, and therefore how these data should be applied in clinical practice remains unclear.

**Potential Benefits of CYP2D6 Testing**

As Kuderer and Peppercorn state, based on currently available data it remains unclear whether testing for CYP2D6 variants should be part of routine clinical care for women considering initiation of tamoxifen for breast cancer. However, given the number of medications in clinical use that are metabolized by CYP2D6, consideration could be given to routinely testing everyone for CYP2D6 gene mutations. For example, CYP2D6 poor metabolizers are intolerant of dextromethorphan and obtain minimal benefit from codeine. A recent publication noted that a patient treated with venlafaxine experienced toxicity and no clinical benefit from the medication, likely due to a lack of CYP2D6 enzyme activity.[12] Therefore, knowledge of one’s CYP2D6 genotype could be helpful when making routine medical decisions.

**Future Perspectives**

Overall, this is an excellent overview of the controversy surrounding routine clinical assessment of inherited variations in CYP2D6 for women with breast cancer who will be treated with endocrine therapy.[1] Since most of the previously conducted studies were performed on samples of convenience, they lacked key information about potential confounding factors, and had insufficient sample for analysis of other variants, other genes, and/or endoxifen concentrations. Therefore, these studies mostly offer level III evidence.[13] Data from additional prospective and prospective-retrospective studies, such as the large randomized prospective clinical trials of
tamoxifen vs aromatase inhibitors, are essential for solving the mystery of which inherited mutations in which genes impart the greatest, or least, benefit from tamoxifen therapy. In the future, it may be possible to test a panel of genes involved in drug metabolism and activity to determine whether a woman is more likely to benefit from a specific medication, such as tamoxifen or an aromatase inhibitor. At the present time, however, available data do not support routine testing of CYP2D6 in women starting endocrine therapy for breast cancer. Nevertheless, it appears that CYP2D6 gene testing itself is likely to become an important tool for the management of all people, given the large number of pharmaceuticals whose metabolism is affected by this key enzyme.

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**References:**

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