

Tamoxifen Metabolism and Its Effect on Endocrine Treatment of Breast Cancer

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Abstract: Tamoxifen is the most common endocrine therapy administered worldwide to women with hormone receptor-positive metastatic breast cancer or as adjuvant therapy for early stages of the disease. Tamoxifen may also be prescribed to women with ductal carcinoma in situ or to decrease the risk of breast cancer in women at high risk of developing the disease. While the use of aromatase inhibitors is increasing in the postmenopausal treatment setting, tamoxifen remains the drug of choice for premenopausal women. Several factors may contribute to reduced benefit from tamoxifen. It has been increasingly recognized in recent years that pharmacogenetics may play a role in tamoxifen's metabolism, efficacy, and safety. Cytochrome P450 (CYP) 2D6 encodes for a liver enzyme that is responsible for the conversion of tamoxifen into its active metabolite, endoxifen. Variant alleles in *CYP2D6* or the use of medications that inhibit the enzyme clearly influence tamoxifen's metabolism into endoxifen. In addition, several retrospective studies suggest that variants in *CYP2D6* may influence long term outcomes. In this review, we will summarize recent data that examined associations between *CYP2D6* activity and effects on tamoxifen's metabolism and efficacy.

Introduction

Despite a considerable decline in breast cancer incidence and death, the disease will account for an estimated 40,000 deaths in 2008 among women in the United States.¹ Tumors from approximately 75% of women with newly diagnosed breast cancer will express steroid hormone receptors² and these women will likely be recommended endocrine therapy to reduce the risk of recurrence and death. Different endocrine approaches are currently available, including selective estrogen receptor modulators (SERM; eg, tamoxifen), selective estrogen receptor down-regulators (SERD; fulvestrant in postmenopausal women), and aromatase inhibitors (AI; including the third generation inhibitors anastrozole, exemestane, and letrozole) in postmenopausal women, or ovarian function suppression (by surgery, luteinizing hormone-releasing hormone [LH-RH] agonists, or radiation) in premenopausal women.

Keywords

Breast cancer, endocrine treatment, pharmacogenetics, tamoxifen metabolism, CYP2D6

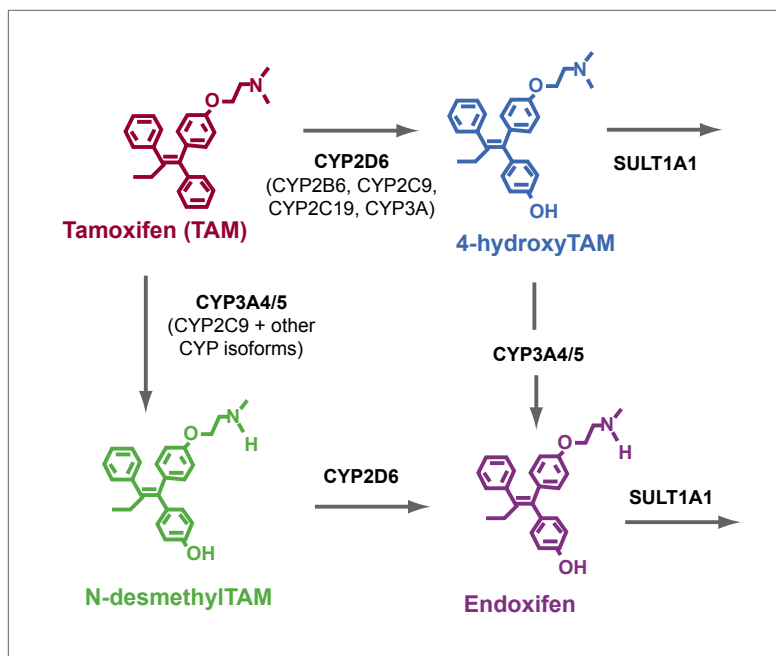


Figure 1. Tamoxifen and main metabolites.

Note: Cytochrome P450 (CYP)3A4/5 is the major isoform responsible for the formation of N-desmethyltamoxifen. The generation of 4-hydroxytamoxifen and endoxifen are predominantly catalyzed by CYP2D6.

Courtesy of Jin et al. *J Natl Cancer Inst.* 2005;97:30-39.

How to apply these various treatment possibilities in order to maximize therapeutic index is controversial. Tamoxifen remains the standard of care in premenopausal women. Most postmenopausal women will be recommended 5 years of an AI or 2–3 years of tamoxifen followed by an AI for a total of 5 years. Five years of tamoxifen with or without 5 additional years of an AI is also appropriate for postmenopausal women. Currently, it is not known whether one of these AI-containing regimens is superior, and the choice is primarily based on preferences of women and their physicians. Decisions are usually made based on estimates of recurrence, efficacy, and potential treatment-related adverse events.³

Tamoxifen has been the gold standard for the treatment of breast cancer for over 3 decades, leading to countless clinical data regarding treatment efficacy, secondary benefits, and adverse events. The 2005 report by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), also designated the Oxford Overview, revealed that, in women with estrogen receptor (ER)-rich tumors, adjuvant tamoxifen reduces breast cancer recurrences by 40% and the annual breast cancer death rate by 31% irrespective of the use of chemotherapy, age, and progesterone receptor (PR) status.⁴ These data have also been confirmed in patients younger than 40 years in a meta-analysis of 4 different trials of the European Organization for Research and Treatment of Cancer (EORTC).⁵ Whether tamoxifen alone or tamoxifen in combination with ovarian suppression is the optimal choice of endocrine treatment for premenopausal women is under investigation, as is the optimal duration and sequence of tamoxifen and AIs in postmenopausal women.

Unfortunately, a considerable number of patients will suffer a recurrence despite optimal endocrine therapy. Several mechanisms may contribute to endocrine resistance, including other tumor characteristics and balance of co-activators and co-suppressors. Emerging data further suggest that host factors such as pharmacogenetics may play a role in this process. In particular, tamoxifen's metabolism, and perhaps efficacy, is greatly influenced by variants in candidate genes and will be discussed in this review.

Metabolism of Tamoxifen

Drug metabolism and elimination are important predictors of drug safety and efficacy. More than one enzyme may be responsible for the metabolism of a single drug. A drug's activity may therefore be influenced by genetic variants and drug interactions that may lead to an enzyme with reduced or no activity.

Tamoxifen has a fairly weak affinity to its target, the ER, and at the same time is metabolized to several compounds; some are strong anti-estrogens with high affinity to the ER, whereas others exhibit estrogen-like activity⁶ (Figure 1). The most important metabolites of tamoxifen include 4-hydroxy tamoxifen (4-OH-tamoxifen)⁷ and 4-hydroxy-N-desmethyl tamoxifen (endoxifen).^{8,9} Both metabolites^{7,10} have a much stronger affinity to the ER compared to tamoxifen.^{9,11} Endoxifen is prevalent at a 6- to 12-fold higher concentration compared with 4-OH-tamoxifen in women on chronic tamoxifen therapy.¹² Further, endoxifen is associated with equivalent anti-estrogenic potency to 4-OH-tamoxifen, measured as

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the effect on mRNA expression of the PR.¹¹ Therefore, it has been speculated that endoxifen is the most important metabolite required for tamoxifen's action.

The main route of tamoxifen's metabolism is demethylation and hydroxylation. N-methylation is predominantly performed by cytochrome (CYP) P450 isoenzymes *CYP3A4* and *CYP3A5*. In contrast to 4-OH-tamoxifen and endoxifen, N-desmethyl tamoxifen is less effective in its ability to bind to the ER and to subsequently suppress the estrogen-dependent cell growth and gene expression.¹² However, N-desmethyl tamoxifen may be transformed to endoxifen via 4 hydroxylation which is nearly exclusively accomplished via *CYP2D6*.¹³ *CYP2D6*, first described in 1979,¹⁴ represents less than 2% of the total CYP450, but is thought to account for 25% of the metabolism of commonly used drugs, such as antidepressants. In contrast, the formation of 4-OH-tamoxifen represents a minor route of tamoxifen's metabolism to endoxifen and is accomplished by various CYP450 enzymes.¹³ Thus, the main route for metabolizing tamoxifen to its highly potent metabolite, endoxifen, is mostly dependent on the function of one enzyme, *CYP2D6*, which has therefore been extensively explored.

In addition, 4-OH-tamoxifen and endoxifen are thought to exist in equilibrium of *cis* and *trans* isoforms, which differ in their ability to act either as an agonist or an antagonist towards the ER. 4-OH-tamoxifen isoforms may be different in patients with an acquired resistance to endocrine therapy as compared to those without a resistance.¹⁵ The final steps in the metabolism of tamoxifen are sulfate conjugation and glucuronidation, yielding to an increase of solubility in order to facilitate the excretion of the drug. The sulphotransferase isoform 1A1 (*SULT1A1*) and UDP-glucuronosyltransferase isoform 2B15 (*UGT2B15*) are likely responsible for the formation of *cis* and *trans* 4-OH-tamoxifen, and may thus have a role in acquired tamoxifen resistance as well.¹⁶

Candidate Gene Variants and Their Role In Tamoxifen Metabolism

Specific variants of genes that encode for important enzymes may alter the pharmacokinetics of drugs.¹⁷ For *CYP2D6*, over 100 allelic variants have been described varying according to race and ethnicity.¹⁸ These alleles may lead to an enzyme that is active, or that may have reduced or no activity. Several definitions have been used to describe *CYP2D6* activity. Individuals homozygous for wild-type alleles are designated extensive metabolizers (EM).¹⁹ Multiple copies of *CYP2D6* alleles are thought to be associated with a high enzyme activity and such individuals are considered ultra-rapid metabolizers (UM).²⁰

Those with 1 or 2 variant alleles with reduced or null activity are designated intermediate (IM) and poor metabolizers (PM), respectively.

The wild-type *CYP2D6* allele is designated *CYP2D6*1*. The allelic variants due to single nucleotide polymorphisms (SNPs) may influence the metabolic activity of an enzyme. *CYP2D6*4* is the most common null allele in Caucasians, and 5–10% of Caucasians are thought to be PMs. While *CYP2D6*4* is the most common nonfunctional allele in Caucasian PMs, in the Asian population, the *CYP2D6*10* mutation is more frequent and associated with a reduced metabolic activity. Across the Black African and the African American population, the *CYP2D6*17*, also associated with a reduced metabolic activity, occurs with a frequency of 24% and 22%, respectively.^{21,22}

Interaction of Various CYP2D6 Genotypes and the Level of Tamoxifen and Its Metabolites

The relationship between endoxifen plasma concentrations and the *CYP2D6* genotype was initially examined in a study of 12 women on chronic adjuvant tamoxifen who were co-prescribed paroxetine,¹² a selective serotonin reuptake inhibitor (SSRI), used to treat hot flashes, and a potent *CYP2D6* inhibitor. Women with *CYP2D6* variants had a low baseline concentration of endoxifen compared to women with 2 wild-type alleles. The co-administration of tamoxifen and paroxetine was associated with a significant reduction in endoxifen concentrations by 64% for patients with a wild-type *CYP2D6* and by 24% for those with a variant of *CYP2D6*. These results suggested that the genotype of *CYP2D6* and drug interaction should be considered when prescribing tamoxifen. In a larger trial that included 80 tamoxifen-treated patients, the strong relation of endoxifen concentrations and the presence of 4 *CYP2D6* nonfunctional alleles was verified.⁶ Moreover, after correction for *CYP2D6* status, a considerable variability concerning the endoxifen level remained, leading to a further and more sophisticated analysis of 33 *CYP2D6* alleles in 158 patients, confirming the association between enzyme activity and endoxifen concentration.¹³ In addition, a ratio of endoxifen and N-desmethyl tamoxifen is significantly different between patients with 2 reduced activity *CYP2D6* alleles compared to those with 1 functional allele and those with 2 or more functional alleles. Together, the studies have demonstrated that tamoxifen's metabolism is greatly influenced by *CYP2D6* activity, determined by the number of normal alleles, whether the inhibitor is co-administered, and the strength of the inhibitor.

CYP2D6 Genotype and Clinical Outcome

Recent studies have attempted to correlate CYP2D6 activity and outcomes of women with steroid receptor-positive breast cancer treated with tamoxifen (Table 1). In the first analysis, investigators used archival tumor blocks of patients who participated in an adjuvant trial comparing 5 years of tamoxifen alone or with the addition of 1 year of fluoxymesterone conducted by the North Central Cancer Treatment Group (NCCTG) between 1991 and 1995.^{23,24} In the multivariate analysis, disease-free survival (DFS) was significantly worse in patients with the *CYP2D6**4/*4 alleles.¹⁷ Differences in overall survival (OS) were not observed among the genotype groups, which may be due to a small sample size. Importantly, not all *CYP2D6* alleles that may lead to an intermediate metabolizer status were studied and the effect of *CYP2D6**4 on the outcome of women not treated with tamoxifen was not evaluated. In a further analysis, the same investigators reviewed medical records to ascertain whether CYP2D6 inhibitors were co-prescribed with tamoxifen.²⁵ Extensive, intermediate, and poor metabolizers were defined according to the presence of the *CYP2D6**4 allele and the co-administration of a CYP2D6 inhibitor. In the multivariate analysis, patients with a reduced metabolism (65/181) had a shorter time to recurrence and a worse relapse-free survival compared to EMs.

Other investigations have also suggested that reduced activity in CYP2D6 is associated with a worse outcome. In a retrospective nonrandomized cohort of 206 women receiving adjuvant tamoxifen, investigators analyzed genetic variants of 5 different CYP isoenzymes. Those treated with tamoxifen who were carriers of a variant *CYP2D6* allele experienced more recurrences and had shorter relapse-free survival rates as well as worse event-free survival rates compared to patients with normal alleles²⁶ (Table 1).

In a prospective study from Korea, *CYP2D6* was examined in 202 patients treated with tamoxifen, of whom 12 had metastatic breast cancer (MBC).²⁷ The authors evaluated the presence of *CYP2D6**5 and *CYP2D6**10 alleles and correlated their presence with tamoxifen biotransformation and pharmacokinetics.^{22,28} Interestingly, the women with metastatic disease were more likely to carry *CYP2D6**10 (57.1%) compared to the women in the adjuvant treatment group (24.3%). Patients with *CYP2D6**10/*10 had a statistically significantly lower concentration of endoxifen and 4-OH-tamoxifen ($P < .0001$) compared to patients who were either heterozygous for *CYP2D6**10 or who had wild-type alleles. In the second part of the study, investigators assessed the relation between the genotype and tamoxifen efficacy in 21 patients (12

patients with MBC of the above described group and 9 additional patients who were enrolled with MBC). A statistically significant association was reported for the *CYP2D6**10/*10 patients, with a shorter time to progression compared to the *CYP2D6**10 heterozygous patients. In a more recent report of 67 Japanese women treated with adjuvant tamoxifen, those with the *CYP2D6**10/*10 genotype had a statistically higher incidence of recurrence as compared to those with the *CYP2D6**1/*1 genotype ($P = .0057$).²⁹

There were, however, other investigators who reported opposite results. A Swedish group evaluated the influence of different *CYP2D6* and *SULT1A1* genotypes on the effect of tamoxifen therapy in 2 different studies. Tumor blocks of patients treated earlier with tamoxifen were analyzed for genetic variants of *CYP2D6* and *SULT1A1*.³⁰ The investigators reported that carriers of a *CYP2D6**4 allele, those homozygous for *SULT1A1**1/*1, and patients with the combination of *CYP2D6**4 and *SULT1A1**1/*1 had a lower risk of recurrence when treated with tamoxifen. A further study published by the same group examined, in addition to *CYP2D6* and *SULT1A1*, different *CYP3A5* and *UGT2B15* alleles.³¹ In the total population, DFS was significantly improved in *CYP2D6**4 carriers than in those with 1 or 2 *CYP2D6**1 alleles ($P = .05$ and $P = .04$, respectively). In the groups randomized to 5 years of tamoxifen, *CYP3A5**3/*3 carriers had improved recurrence-free survival. A relationship was not observed between the duration of tamoxifen treatment and the genotypes of *CYP2D6*, *SULT1A1*, and *UGT2B15*. The results may be difficult to interpret due to differences in adjuvant chemotherapy administration, length of endocrine therapy, dose of tamoxifen, ER testing, and lack of specific inclusion criteria.³²

The functional polymorphisms of *CYP2D6* and other genes important in tamoxifen biotransformation were evaluated in another retrospective study of women treated with adjuvant tamoxifen.³³ A statistically significant difference was not found between *CYP2D6**4/*4 and overall survival. However, a faster elimination of the active metabolite of tamoxifen, caused by genetic variants of the phase II enzymes *SULT1A1* or *UGT2B15*, was associated with an increase in the risk of recurrence and worse survival. The effect was more pronounced in patients with a genetic variant in both *SULT1A1* and *UGT2B15*,³³ suggesting that genetic variants in the conjugating enzymes may also play a role in the efficacy of tamoxifen.

Since 5-year therapy with an AI is associated with a small benefit compared to 5 years of tamoxifen, the influence of CYP2D6 activity on tamoxifen's metabolism and efficacy raised provocative questions concerning the true advantage of AIs in women with normal CYP2D6 activity. Investigators have constructed a Markov model

Table 1. Genetic Variation of CYP2D6 and Other Enzymes Involved in Tamoxifen Metabolism

Author and Year	Number of Patients	Patient and Study Characteristics	Genotypes	Main Results
Goetz ²⁴ 2005	256	Retrospective study of postmenopausal HR+ women, received Tam 20 mg/day x 5 ys in a prospective study	CYP2D6*4 CYP2D6*6 CYP3A5*3	CYP2D6*4/*4 vs other: RFS (HR 1.85; <i>P</i> =.176) DFS (HR 1.86, <i>P</i> =.089) CYP2D6*4/*4 no hot flashes
Goetz ²⁵ 2007	190	Retrospective study of postmenopausal HR+ women, received Tam 20 mg/day x 5 ys in a prospective study	CYP2D6*4 Concomitant inhibitors	PM vs other: TTR (HR, 1.91; <i>P</i> =.034) RFS (HR, 1.74; <i>P</i> =0017)
Schroth ²⁶ 2007	486	Retrospective study, pre- and postmenopausal women, 206 Tam (100% HR+) 280 CT or no therapy (53.8% HR+)	CYP2D6*4,*10,*41 CYP2C19*2,*3,*17 CYP2B6 CYP2C9*2,*3 CYP3A5*3	Tam-treated PM vs other RFS (HR, 2.24; <i>P</i> =.02) EFSR (HR, 1.89; <i>P</i> =.02)
Novell ³³ 2005	337	Retrospective study of pre- and postmenopausal women 160 Tam, 177 no Tam	CYP2D6*4 SULT1A1*1,*2 UGT2B15*1,*2	CYP2D6*4 vs other DFS (HR, 0.67; <i>P</i> not significant) OS (HR, 0.79; <i>P</i> not significant)
Kiyotani ²⁹ 2008	67	Retrospective study of pre-and postmenopausal women Tam 20 mg/day x 5 ys	CYP2D6*10	CYP2D6*10/*10 vs *1/*1 RFS (HR, 10.94; <i>P</i> =.036)
Wegman ³⁰ 2005	226	Retrospective study of postmenopausal women Tam 40 mg/day x 2 ys	CYP2D6*4 SULT1A1*1,*2	CYP2D6*4 carrier Lower risk of recurrence RR, 0.28; <i>P</i> =.0089 SULT1A1*1/*1 Lower risk of recurrence RR, 0.48, <i>P</i> =.0074 CYP2D6*4 and/or SULT1A1*1/*1 Lower risk of distant recurrence RR, 0.38; <i>P</i> =.0041
Wegman ³¹ 2007	238	Retrospective study of peri- and postmenopausal women randomized to Tam 40 mg/day 2 or 5 ys (until 1994) or 20 mg/day (since 1994)	CYP2D6*4 SULT1A1*1*2 CYP3A5*3 UGT2B15*1,*2	CYP2D6*4/*4 vs *1/*1 or CYP2D6*1: improved DFS (<i>P</i> =.05 and <i>P</i> =.04) CYP3A5*3/*3 improved RFS (HR, 0.20; <i>P</i> =.002)
Lim ²⁷ 2007	211	Prospective pre- and postmenopausal women includes 21 with metastatic breast cancer 190 adjuvant Tam 20 mg/day	CYP2D6*5,*10	CYP2D6*10/*10 lower concentration of Tam metabolites (<i>P</i> <.0001) More often found among nonresponders 100% vs 50% (<i>P</i> =.0186) Median TTP 5 vs 21.8 ms, (<i>P</i> =.0032)

(Table continued on following page)

Table 1. (Continued) Genetic Variation of CYP2D6 and Other Enzymes Involved in Tamoxifen Metabolism

Author and Year	Number of Patients	Patient and study Characteristics	Genotypes	Main Results
Bonanni ³⁵ 2006	46	Retrospective study of women enrolled in a prospective chemoprevention study Tam 20 mg/day x 5 ys vs placebo x 5 ys	CYP2D6*4	Frequency of breast cancer for CYP2D6*4/*4 carrier (8.7% vs 0.7% in other) Hot flashes independent of CYP2D6*4/*4
Bonanni ³⁶ 2007	47	Retrospective study of women enrolled in a prospective chemoprevention study Tam 20 mg/day x 5 ys vs placebo x 5 ys	32 CYP2D6 alleles, classifying to PM, IM, EM UM	Increased risk of PM vs other to develop breast cancer, ($P=.035$)

CT=chemotherapy, DFS=disease-free survival, EFS=event-free survival, EFSR=EFS after relapse, EM=extensive metabolizer, HR+=hormone receptor positive, HR=hazard ratio, IM=intermediate metabolizer, ms=month, OS=overall survival, PM=poor metabolizer, RFS=relapse-free survival, RR=recurrence risk, Tam=tamoxifen, TTP=time to progression, TTR=time to response; UM=ultrarapid metabolizer, ys=years

based on the annual recurrence risk, as described in the Breast International Group (BIG) 1-98 trial that compared 5 years of tamoxifen to 5 years of letrozole and the association between CYP2D6 status and disease recurrence, reported by NCCTG investigators.³⁴ Indeed, the modeling suggested that patients with CYP2D6*1/*1 have similar outcomes to AI-treated women. Although these results suggest that women with normal CYP2D6 activity benefit equally from tamoxifen or an AI, prospective studies and economic analyses are required.

Finally, the role of CYP2D6 was examined in women receiving tamoxifen in the preventive setting. Bonanni and colleagues correlated the CYP2D6*4/*4 genotype and incidence of breast cancer in women randomized to 5 years of tamoxifen or placebo in the Italian chemoprevention trial.³⁵ Interestingly, the frequency of the CYP2D6*4/*4 genotype was higher in the group of women who developed breast cancer as compared to the healthy controls (Table 1). Updated data concerning the number of participants and additional polymorphisms were recently presented³⁶ and further supported the hypothesis that women with certain CYP2D6 variants may endure reduced benefit from tamoxifen compared to women with functional alleles.

Candidate Gene Associations and Tamoxifen-Associated Adverse Events and Secondary Benefits

Tamoxifen is associated with rare serious side effects and more common and bothersome symptoms such as

hot flashes. Since endoxifen is a potent anti-estrogen, it was hypothesized that women with CYP2D6 variants may be less likely to report hot flashes.²⁴ In the NCCTG investigation, patients with the CYP2D6*4/*4 genotype did not report moderate to severe hot flashes when compared to women who were heterozygous or homozygous for the CYP2D6*1 allele (0% vs 20%; one-sided $P=.06$). Other investigators hypothesized that there may be an association between hot flashes, recurrence-free survival, and tamoxifen metabolism.³⁷ Using the control group of the Women's Healthy Eating and Living (WHEL) trial, 864 patients who were treated with tamoxifen were included in the report. Hot flashes were reported by 78% of women. Women who reported hot flashes during treatment were less likely to suffer a breast cancer recurrence compared to women who did not report the side effect (12.9% vs 21% respectively; $P=.01$). The Hazard ratio (HR) of recurrence was 0.50 for women reporting hot flashes and the hot flashes were more predictive for outcome than age, grade, hormone receptor status, and stage, thus suggesting a relation between side effects and the efficacy of treatment. However, it is important to note that baseline information regarding hot flashes was not available in all study participants. In contrast to the WHEL and NCCTG reports, the 3 women with the CYP2D6*4/*4 genotype who developed breast cancer while treated with tamoxifen in the Italian chemoprevention study reported hot flashes.³⁵

Investigators from the Consortium On Breast Cancer Pharmacogenomics (COBRA) evaluated the association of tamoxifen-induced hot flashes with ER

polymorphisms in a prospective observational study in 3 academic centers. The 298 women recruited to the trial were monitored during their first year of tamoxifen treatment via validated hot flash diaries at baseline and following 1, 4, 8, and 12 months of treatment. The study suggested that different variant alleles of ER alpha and beta (*ESR1* and *ESR2* respectively) influenced the likelihood of women to experience hot flashes.³⁸ The investigators of the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial have recently reported that patients who experienced hot flashes had a 3.6% absolute lower recurrence rate compared to those without the side effect (HR, 0.74; $P < .001$).³⁹ Overall, the data suggest that there may be a correlation between hot flashes and efficacy of endocrine breast cancer treatment. However, while these data are very intriguing, it is premature to utilize them for clinical decision making.

Despite the tremendous benefits of adjuvant tamoxifen, several studies report that up to 55% of patients discontinue their prescribed medication over the course of 5 years.⁴⁰ COBRA investigators have suggested in a preliminary report that CYP2D6 activity may influence adherence to tamoxifen.⁴¹ The investigators reviewed data collected in a prospective observational trial which randomized patients with ER-positive early stage breast cancer, ductal carcinoma in situ, or those at high risk for breast cancer to examine the relation of genetic polymorphisms of candidate genes and the response to tamoxifen treatment.¹³ Of the 280 patients with a genotype analysis, 10% discontinued treatment due to tamoxifen-induced side effects after 4 months of therapy. Almost half of these patients (44.8%) had at least one *CYP2D6*1* allele. Whereas none of the poor metabolizers dropped out of the trial, a strong association was found between intermediate and extensive metabolizers and discontinuation of tamoxifen at 4 months. These preliminary results suggest that patients who benefit most from treatment, based on their ability to metabolize the drug, may also be most likely to stop their tamoxifen treatment.

Finally, variants in tamoxifen's target and metabolizing enzymes may also influence the likelihood of secondary benefits, such as improvement in lipid profile and bone density. In the COBRA trial, lipid profile was evaluated at baseline and during the first year of tamoxifen therapy in 176 women. Overall, tamoxifen was associated with a significant reduction in low-density lipoprotein (LDL) cholesterol and an increase in triglycerides. When stratified by ESR genotype, postmenopausal women with the *ESR1-XbaI* and *ESR2-02* genotypes predicted tamoxifen-induced changes in total cholesterol ($P = .03$;

GG vs GA/AA) and triglycerides ($P = .01$; gene-dose effect, respectively).⁴² In premenopausal women, the *ESR1-XbaI* genotypes were associated with tamoxifen-induced changes in triglycerides ($P = .002$; gene-dose effect) and high-density lipoprotein ($P = .004$; gene-dose effect). Baseline and change in lumbar spine and total hip bone mineral density were correlated with *ESR* genotypes in the 297 women enrolled in the COBRA study, and results presented in a preliminary manner suggested overall little correlation.⁴³

Conclusion

A large amount of data concerning the metabolism of tamoxifen has been recently reported. Although key tamoxifen metabolites were identified a number of years ago, only recently has their role in predicting outcome of tamoxifen-treated women been described. The metabolism of tamoxifen is clearly complex and involves a number of different enzymes. The function of these enzymes is determined by host factors, which are determined by genotypes or concomitant medication use resulting in varying expression and function. Only few findings have been published to date to describe the association of variant alleles in candidate genes and the outcome of tamoxifen treatment. The pharmacogenetic determinants affecting tamoxifen's side effects, adherence, and secondary benefits require further validation. The results of prospective trials and retrospective examination of existing study populations are highly warranted to allow for deeper insights into the genetic influence on efficacy and safety of tamoxifen and other endocrine treatments in breast cancer.

AIs are recommended instead of or following 2–5 years of tamoxifen in postmenopausal women, whereas tamoxifen is the drug of choice in premenopausal women. At this time, it may be reasonable to consider *CYP2D6* genotyping for women who are candidates for tamoxifen monotherapy but for whom other standard treatments are available.

To date, fewer data have been published elucidating the role of genetic polymorphisms for the safety and efficacy of AIs and LHRH-agonists. The benefits and adverse effects of tamoxifen for women with hormone-receptor positive breast cancer are well established. However, the likelihood of benefit or toxicity may vary considerably for an individual based on her genetic makeup. It is hoped that studies conducted to date, combined with prospective evaluations, will lead to a future of individualized therapy based both on the cancer and host genetics.

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