Background: Tamoxifen, a selective estrogen receptor modulator (SERM), is converted to 4-hydroxy-tamoxifen and other active metabolites by cytochrome P450 (CYP) enzymes. Selective serotonin reuptake inhibitors (SSRIs), which are often prescribed to alleviate tamoxifen-associated hot flashes, can inhibit CYPs. In a prospective clinical trial, we tested the effects of coadministration of tamoxifen and the SSRI paroxetine, an inhibitor of CYP2D6, on tamoxifen metabolism. Methods: Tamoxifen and its metabolites were measured in the plasma of 12 women of known CYP2D6 genotype with breast cancer who were taking adjuvant tamoxifen before and after 4 weeks of coadministered paroxetine. We assessed the inhibitory activity of pure tamoxifen metabolites in an estradiol-stimulated MCF7 cell proliferation assay. To determine which CYP isoforms were involved in the metabolism of tamoxifen to specific metabolites, we used CYP isoform–specific inhibitors. All statistical tests were two-sided. Results: We separated, purified, and identified the metabolite 4-hydroxy-N-desmethyl-tamoxifen, which we named endoxifen. Plasma concentrations of endoxifen statistically significantly decreased from a mean of 12.4 ng/mL before paroxetine coadministration to 5.5 ng/mL after paroxetine coadministration (difference = 6.9 ng/mL, 95% confidence interval [CI] = 2.7 to 11.2 ng/mL) (P = .004). Endoxifen concentrations decreased by 64% (95% CI = 39% to 89%) in women with a wild-type CYP2D6 genotype but only 24% (95% CI = 23% to 71%) in women with a variant CYP2D6 genotype (P = .03). Endoxifen and 4-hydroxy-tamoxifen inhibited estradiol-stimulated MCF7 cell proliferation with equal potency. In vitro, troleandomycin, an inhibitor of CYP3A4, inhibited the demethylation of tamoxifen to N-desmethyl-tamoxifen by 78% (95% CI = 65% to 91%), and quinidine, an inhibitor of CYP2D6, reduced the subsequent hydroxylation of N-desmethyl-tamoxifen to endoxifen by 79% (95% CI = 50% to 108%). Conclusions: Endoxifen is an active tamoxifen metabolite that is generated via CYP3A4-mediated N-demethylation and CYP2D6-mediated hydroxylation. Coadministration of paroxetine decreased the plasma concentration of endoxifen. Our data suggest that CYP2D6 genotype and drug interactions should be considered in women treated with tamoxifen. [J Natl Cancer Inst 2003;95:1758–64]

Tamoxifen is a highly effective endocrine treatment for breast cancer in the adjuvant and metastatic settings (1). Data from several large randomized clinical trials indicate that tamoxifen is also valuable in the prevention of breast cancer in women at high risk for the disease (2–5). However, not all women benefit from tamoxifen, and the side effect profiles vary considerably from patient to patient. Because tamoxifen is a prodrug that is metabolized to active metabolites, the most potent of which has been thought to be 4-hydroxy-tamoxifen (6), it is possible that changes in the concentration of active metabolites may contribute to interindividual differences in responses to the drug. Such differences may result from changes in the activity of specific metabolic routes induced by drug interactions or by genetic variants in cytochrome P450 enzymes that catalyze tamoxifen metabolism.

Although tamoxifen is generally well tolerated, up to 80% of women who take tamoxifen complain of hot flashes and up to 45% of women grade them as severe (2). Thus, the treatment of hot flashes is a common reason for co-prescription of tamoxifen with other drugs. Because exogenous estrogens are not commonly recommended for the treatment of hot flashes in women with breast cancer, other therapies have been sought (7). Several studies have recently demonstrated that the antidepressants of the selective serotonin reuptake inhibitor (SSRI) and the selective norepinephrine reuptake inhibitor (SNRI) classes are effective for the treatment of hot flashes. In separate prospective, randomized, placebo-controlled studies (8–10), the SNRI venlafaxine and the SSRIs fluoxetine and paroxetine were each associated with a 50%–65% reduction in the frequency and severity of hot flashes, whereas the placebo was associated with a 27%–38% reduction. Given these recent results, it is likely that the frequency of administering tamoxifen with the drugs of the SSRI and SNRI classes will increase.

Tamoxifen, venlafaxine, paroxetine, and fluoxetine are all metabolized by a shared pathway involving the cytochrome P450 enzyme family. In the liver, extensive N-demethylation...
and 4-hydroxylation of tamoxifen are catalyzed by cytochrome P450 enzymes. Within this family of enzymes, CYP2D6, CYP2C9, and CYP3A4 are thought to be primarily responsible for the metabolism of tamoxifen into its active metabolite 4-hydroxy-tamoxifen (11–13). However, the routes of metabolism to other potentially active metabolites such as 4-hydroxy-N-desmethyl tamoxifen have not been characterized (6).

Because venlafaxine, paroxetine, and fluoxetine are all metabolized by CYP2D6 and are potent inhibitors of this enzyme (14–20), we hypothesized that SNRIs and SSRIs might alter tamoxifen metabolism by disrupting the conversion of tamoxifen to 4-hydroxy-tamoxifen. To test this hypothesis, we conducted a prospective clinical trial to determine the effect of paroxetine on the pharmacokinetics of tamoxifen and its metabolites in women who were receiving adjuvant tamoxifen therapy for breast cancer. Herein, we report the identification and characterization of a previously unrecognized active metabolite of tamoxifen, 4-hydroxy-N-desmethyl tamoxifen, a metabolite that decreased upon paroxetine coadministration, and which we have named endoxifen.

**Subjects and Methods**

**Subjects**

Eligible women included those with a history of breast cancer who had no evidence of disease and who were receiving standard-dose tamoxifen as an adjuvant treatment. The women had to have been taking tamoxifen for at least 4 weeks before starting the study and had to have continued taking tamoxifen throughout the study period between June 1999 and July 2000. For entry into the study, women had to have troublesome hot flashes reported to their primary care physician for which treatment with a non-hormonal agent was appropriate.

Women were excluded from the study if they had been taking other, simultaneous treatments for hot flashes, such as clonidine or herbal supplements, for at least 1 month before enrolling in the study. Although women were permitted to take vitamin E while on the study, they were excluded if they were taking concomitant medications that are known to inhibit CYP2D6 activity, including amiodarone, haloperidol, indinavir, ritonavir, or quinidine, or if they were taking any SSRI other than paroxetine. Women were excluded from the study if they had received cytotoxic chemotherapy, hormonal therapy other than tamoxifen, or radiation therapy for at least 1 month before starting the study. Women were also excluded if they were pregnant or lactating, or had a known allergy or hypersensitivity to paroxetine hydrochloride.

**Trial Design**

Twelve eligible women were enrolled sequentially between June 1999 and July 2000. Each individual signed an informed consent form. The study was approved by the Georgetown University Medical Center Institutional Review Board. Baseline blood samples were obtained to determine the CYP2D6 genotype and the plasma concentrations of tamoxifen and its metabolites. No selection of patients by genotype was made, and no otherwise eligible patients were excluded on the basis of CYP2D6 genotype. Each woman was administered paroxetine for 4 weeks at a dose of 10 mg/day while continuing tamoxifen at a dose of 20 mg/day. Paroxetine and tamoxifen were both administered by mouth. After 4 weeks of co-prescription of paroxetine and tamoxifen, a second blood sample was collected to measure the plasma concentrations of tamoxifen and its metabolites.

**CYP2D6 Genotype**

A 5-mL blood sample was collected in a tube containing sodium heparin (standard clinical green-top tube) and stored on ice. Within 1 hour of collection, the sample was centrifuged (1600g for 10 minutes at room temperature), and the buffy coat cell layer was removed. The cells were stored at −20 °C until analysis. CYP2D6 genotype for the *1 (wild-type) or *4, *6, and *8 (variant) alleles was determined using endonuclease-specific mutation analysis, as described previously (20).

**Measurement of Plasma Tamoxifen and Metabolite Concentrations**

A 10-mL blood sample was collected in a tube containing sodium heparin (standard clinical green-top tube) and stored on ice. Within 1 hour of collection, the plasma was isolated. Tamoxifen and its metabolite concentrations in plasma were determined by using high-performance liquid chromatography with online photocyclization as previously described by Fried and Wainer (21), with minor modifications (22). In brief, this method allows for the rapid extraction and specific detection of tamoxifen and its metabolites on the basis of a technique originally described by Kikuta and Schmid (23) that used a mobile phase of 65% acetonitrile, 35% potassium phosphate (pH 3.0) and eluted the metabolites on a 4.6 × 250 mm 0.5-μm cyanonitrile column (23). This method has been modified to use a novel column-switching technique (21) that allows for high recovery and precise separation of the drug and metabolites. Consistent separation of tamoxifen, N-desmethyl-tamoxifen, 4-hydroxy-tamoxifen, endoxifen, and N-didesmethyl-tamoxifen was achieved using this method. We found that the limits of quantification were 0.5 ng/mL and 0.25 ng/mL for endoxifen and 4-hydroxy-tamoxifen, respectively. The inter- and intra-day coefficients of variation were less than 10% at the midpoint of the standard curves for each metabolite tested.

**Synthesis of Endoxifen**

Endoxifen was synthesized in our laboratory as described by Ogawa et al. (24), with the modification that 98% [Z]-4-hydroxy-tamoxifen (Sigma, St. Louis, MO) was demethylated to endoxifen. Briefly, 10 mL of anhydrous dioxane was added to 75 mg (180 μmol) of [Z]-4-hydroxy-tamoxifen in a 75-mL stainless steel sample cylinder, and 50 μL (582 μmol) of vinyl chloroformate was then added dropwise. The cylinder was sealed and heated for 5 hours at 135 °C to 145 °C to form a crude mixture. After cooling, the contents of the cylinder were transferred to a round-bottomed flask and evaporated to dryness. For acid-catalyzed removal of the vinyl oxy carbonyl group, 20 mL of a solution containing 5% hydrochloric acid in ethanol was added to the flask, and the solution was allowed to reflux for 30 minutes at 80 °C. The contents of the flask were allowed to cool and then were evaporated to dryness. Silica gel (60–200 mesh) column (25 × 160 mm) chromatography of this residue with chloroform–methanol–triethylamine (9 : 1 : 0.05 v/v/v) gave 20 mg of product that eluted as a single peak on the chromatographic system described above. Synthesized endoxifen was
subsequently stored at −80 °C at a concentration of 1 mM in 100% ethanol. The synthesized endoxifen peak consistently co-eluted with a peak that changed during paroxetine administration using the chromatographic method described here and that described by Fried and Wainer (21).

**Determination of Metabolite Anti-Proliferative Activity**

MCF7 breast cancer cells were obtained from the Tissue Culture Shared Resource at the Lombardi Cancer Center (Georgetown University, Washington, DC) and were routinely cultured in modified Improved Minimum Essential Medium supplemented with 10% fetal calf serum (Life Sciences, Gaithersburg, MD). Estrogen stimulates the growth of MCF7 cells *in vitro*. To determine whether tamoxifen and its metabolites could inhibit MCF7 cell growth, and to obtain reproducible data, it was necessary to deplete estrogen from the culture medium to make the cells completely dependent on the exogenous estradiol. When cell monolayers were approximately 70% confluent, the culture medium was replaced with an estrogen-depleted medium consisting of phenol red–free modified IMEM supplemented with 10% charcoal-stripped newborn calf serum (estrogen-free medium). To remove any residual estrogen, the monolayer was washed every hour for 5 hours with phenol red–free IMEM and cultured in fresh estrogen-free medium between washes. After the cells were cultured overnight, they were detached from the culture plate with phenol red–free trypsin and counted. Cells were plated into several 96-well plates at a concentration of 1000 cells per well in a total volume of 100 μL in estrogen-free medium. After allowing the cells to attach (approximately 5 hours), 100 μL of medium containing various concentrations of tamoxifen, endoxifen, or 4-hydroxy-tamoxifen, alone or in combination with estradiol (E2) or the vehicle control (ethanol), was added to each well to yield the appropriate concentrations of the various compounds and a final ethanol concentration of 0.1%. On each plate, four wells were treated with 0.2 mM estradiol and four with the vehicle alone (ethanol) as controls to show the baseline growth of the cells in the presence and absence of estradiol, respectively. Four wells per plate were used for each concentration of tamoxifen, endoxifen, or 4-hydroxy-tamoxifen. Several duplicate plates were prepared and, after the cells had grown for the specified times (4, 7, or 10 days), the media were removed and the cells stained with crystal violet (0.52% crystal violet in 25% methanol). The plates were washed with distilled water to remove excess stain and air dried before the bound stain was solubilized by the addition of 100 μL of 100 mM sodium citrate in 50% ethanol. Staining intensity, which is proportional to cell number, was then determined by measuring absorbance at 550 nm. The data are presented as the mean absorbance at 550 nm of replicate wells for each treatment condition and 95% confidence intervals. The experiment was repeated three times. Data from a representative experiment are shown.

**Tamoxifen Metabolism in Human Liver Microsomes**

Human liver microsomes were prepared as previously described (25–27). In brief, tamoxifen (5 μM) or N-desmethyl-tamoxifen (10 μM) substrates were incubated with or without specific inhibitors of individual cytochrome P450 isoforms. The isoform-specific inhibitors used, working concentrations, and the enzymes they specifically inhibit were sulfaphenazole (20 μM) to inhibit CYP2C9, omeprazole (10 μM) to inhibit CYP2C19, quinidine (1 μM) to inhibit CYP2D6, and ketoconazole (1 μM) and troleandomycin (50 μM) to inhibit CYP3A.

Incubations were carried out in human liver microsomes (0.5 mg/mL of protein) in the presence of a reduced nicotinamide adenine dinucleotide phosphate (NADPH)-generating system for 60 minutes at 37 °C, and the rates of formation of N-desmethyl-tamoxifen from tamoxifen and endoxifen from N-desmethyl-tamoxifen were monitored. The reactions were carried out under conditions and concentrations documented to allow the inhibitors to be isomser-specific. Rates of metabolite formation from the test conditions were compared with rates of metabolite formation from control conditions, in which the inhibitors were replaced with appropriate concentrations of ethanol, methanol, or dimethyl sulfoxide as vehicle. Each inhibitor was tested in three different preparations of human liver microsomes (HL2, HK23, and HG23), with the exception of omeprazole, which was tested in only two (HL2 and HK23). The rates of N-desmethyl-tamoxifen and endoxifen formation during incubation with the inhibitors are presented as percent control activity without the inhibitor (mean with 95% confidence intervals; n = 4 or 6 duplicate measurements).

**Statistical Analysis**

The differences between the plasma concentrations of tamoxifen and its metabolites at baseline and after 4 weeks of tamoxifen and paroxetine were compared using a two-way paired *t* test. A *P* value of .05 was considered to be statistically significant. Differences in metabolite concentrations that resulted from *in vitro* incubations with cytochrome P450 isoform–specific inhibitors were also tested using a two-way paired *t* test. In a retrospective power analysis using the coefficient of variance of the plasma concentration of endoxifen at baseline and an alpha of .05, we had 80% power to detect a 56% change in endoxifen plasma concentration using a two-tailed *t* test (Microsoft Excel data analysis toolpack; Microsoft, Redmond, WA).

**RESULTS**

Tamoxifen and metabolite concentrations in the plasma of patients on chronic tamoxifen therapy (baseline, Fig. 1, upper panel) and 4 weeks after coadministration of tamoxifen and paroxetine (Fig. 1, lower panel) were available from all 12 study participants. From a preliminary inspection of chromatograms from these patients, we observed notable decreases in the plasma concentration of a single metabolite in a number of samples (Fig. 1, peak X). We subsequently separated and purified this metabolite and determined that it had a molecular mass (373.5 d) consistent with that of 4-hydroxy-N-desmethyl-tamoxifen using liquid chromatography–mass spectrometry (data not shown). We have renamed this metabolite endoxifen. We then synthesized endoxifen, separated the E and Z enantiomers, and found that Z-endoxifen co-eluted with peak X (data not shown). Because tamoxifen is administered as the Z-isomer, the Z-form of the metabolite is the expected form in human plasma.

The average concentration of endoxifen in the plasma of patients in our study was 12.4 ng/mL before the administration of paroxetine and that of 4-hydroxy-tamoxifen was 1.1 ng/mL, a statistically significant difference (*P* < .001, using an unpaired *t* test). When the plasma concentrations of tamoxifen, N-desmethyl-tamoxifen, 4-hydroxy-tamoxifen, and en-
doxifen were compared before and after paroxetine treatment, the mean plasma concentration of endoxifen decreased by 56% (95% CI = 31% to 81%) (P = .02) (Fig. 2), but none of the other metabolites underwent statistically significant changes in concentration. Reduced levels of endoxifen were evident primarily in women who carried the wild-type genotype for CYP2D6. The concentration of endoxifen decreased by a mean of 64% (95% CI = 39% to 89%) in the seven women with a wild-type CYP2D6 genotype, and by 24% (95% CI = 23% to 71%) in the five women who carried a variant allele (P = .03, using an unpaired t test). Baseline plasma endoxifen concentrations before paroxetine treatment were lower in women who carried a variant CYP2D6 allele (*4, *6, or *8) (Fig. 2, dashed lines) than in those who carried the wild-type genotype (P = .002). Paroxetine had no statistically significant effect on endoxifen levels in women who carried a variant genotype.

Because little information is available regarding the properties of endoxifen as an estrogen receptor antagonist, we assessed whether endoxifen could negate the effect of estradiol in MCF7 cells, which are dependent on estrogen stimulation for their proliferation. Both endoxifen and 4-hydroxy-tamoxifen (100 nM) suppressed estradiol (200 pM)-stimulated MCF7 proliferation to control levels (Fig. 3, upper panel). As previously reported (6), tamoxifen also inhibited proliferation, though less effectively than either metabolite. A dose–response analysis revealed that endoxifen and 4-hydroxy-tamoxifen were equipotent in this system (P = .949 for the difference) (Fig. 3, lower panel).

We next conducted experiments using human liver microsomes to determine which cytochrome P450 isoforms are involved in the metabolism of tamoxifen to endoxifen. This approach allowed us to estimate human metabolism in vivo by using in vitro preparations from human liver. For these ex-
experiments, we studied the inhibition of cytochrome P450 isoforms already known to be involved in tamoxifen metabolism: the CYP2C9, CYP2C19, CYP3A, and CYP2D6 (11–13). Tamoxifen (5 μM) was incubated with different preparations of human liver microsomes under conditions in which inhibitors are specific for individual cytochrome P450 isoforms, and the formation of N-desmethyl-tamoxifen was assessed. Troleandomycin and ketoconazole were the most potent inhibitors of the formation of N-desmethyl-tamoxifen, reducing levels by a mean of 78% (95% CI = 65% to 91%) (Fig. 4), indicating that the primary catalyst of this N-demethylation reaction is CYP3A, consistent with data from other investigators (12). The relatively mild inhibition of tamoxifen N-demethylation by sulfaphenazole and omeprazole indicates lesser contributions of CYP2C9 and CYP2C19, respectively, to this reaction. When N-desmethyl-tamoxifen was incubated with the inhibitors under similar conditions, only quinidine inhibited the metabolism of N-desmethyl-tamoxifen to endoxifen, by a mean of 79% (95% CI = 50% to 108%) in the three liver preparations tested (Fig. 4). Quinidine had no effect on the metabolism of 4-hydroxy-tamoxifen to endoxifen (data not shown) or on the metabolism of tamoxifen to N-desmethyl-tamoxifen (Fig. 4).

DISCUSSION

We have identified an active metabolite of tamoxifen, 4-hydroxy-N-desmethyl-tamoxifen (endoxifen), that is present in higher concentrations than 4-hydroxy-tamoxifen in the blood...
of women on chronic adjuvant tamoxifen therapy. The average concentration of endoxifen in the plasma of patients in our study was 12.4 ng/mL before the administration of paroxetine, whereas that of 4-hydroxy-tamoxifen was 1.1 ng/mL ($P<.001$). Although previous investigators have identified 4-hydroxy-N-desmethyl-tamoxifen (endoxifen) as a tamoxifen metabolite that is present in humans, it has been widely believed for many years that the clinical activity of tamoxifen is largely mediated by 4-hydroxy-tamoxifen. Furthermore, many researchers who have studied the activity of tamoxifen in vitro have used the 4-hydroxy-tamoxifen metabolite exclusively. Our data emphasize that this approach may be overly simplistic and that future studies involving tamoxifen effects in vitro should consider the contributions of endoxifen and other metabolites whose concentration and potency may contribute to clinical effects.

We have shown in vitro that the primary route of metabolism to endoxifen is via CYP2D6 from N-desmethyl-tamoxifen. The metabolic route from tamoxifen to endoxifen and 4-hydroxy-tamoxifen suggested by our data is illustrated in Fig. 5. The in vitro data suggesting involvement of CYP2D6 in tamoxifen metabolism to endoxifen were confirmed by the clinical data. We demonstrated that paroxetine coadministration was associated with decreased plasma concentrations of endoxifen in women who carry the wild-type CYP2D6 allele and that the concentration of endoxifen during chronic tamoxifen treatment was lower in women who carry a variant CYP2D6 allele than in those who carry the homozygous wild-type genotype. Although women taking paroxetine had a statistically significantly reduced concentration of endoxifen, concentrations of tamoxifen, 4-hydroxy-tamoxifen, and N-desmethyl-tamoxifen did not change.

These preliminary data are consistent with an effect of the CYP2D6 genotype on the plasma concentration of endoxifen and raise the possibility that pharmacogenetic variation in CYP2D6 activity may influence therapeutic outcomes from tamoxifen treatment. In the Caucasian population, approximately 7% of patients would be expected to carry variant alleles of CYP2D6 that would result in deficient enzyme activity and therefore in substantially lower plasma endoxifen levels (28). Similarly, in patients who carry the wild-type CYP2D6 gene, concomitant treatment with medications that are known to inhibit the enzyme would likely reduce endoxifen levels. However, larger trials are required to evaluate the clinical implications of low circulating endoxifen concentrations and, until further data become available, the results of this small study should not alter treatment recommendations.

Our data indicate that the plasma concentrations of tamoxifen and N-desmethyl-tamoxifen are higher than those of 4-hydroxytamoxifen and endoxifen, and that, in women with wild-type CYP2D6, endoxifen concentrations are approximately 14-fold higher than those of 4-hydroxy-tamoxifen. Thus, endoxifen is likely to be at least as important as 4-hydroxy-tamoxifen in mediating tamoxifen activity in women with wild-type CYP2D6. Consequently, these preliminary findings may have clinical implications because endoxifen is as potent as 4-hydroxy-tamoxifen in suppressing growth of estrogen-dependent cultured human breast cancer cells. Further studies are ongoing to carefully characterize the activity and potency of endoxifen in breast cancer cell lines and in vivo tumor models. The relative ratio of endoxifen to other tamoxifen metabolites may also be important to the overall effect of tamoxifen on other parts of the body, such as the central nervous system, the cardiovascular system, the liver, and bone, although our study did not specifically address these tissue-specific effects.

We conclude that tamoxifen metabolism is vulnerable to drug interactions with SSRIs. The women in our clinical trial received paroxetine for tamoxifen-associated hot flashes. Although other medications are available for the treatment of hot flashes, SSRIs are among the most promising nonhormonal pharmacologic interventions (29). SSRIs also improve sleep, libido, and overall quality of life in women with hot flashes (7). More important, paroxetine and other SSRIs are often prescribed for other reasons, such as depression, anxiety, or social phobias, to patients who may be on tamoxifen. If endoxifen is an active metabolite of tamoxifen in vivo, then our study raises the possibility that administration of paroxetine and other SSRIs that interact with CYP2D6 may decrease the antiestrogenic activity of tamoxifen. However, given the increasingly important role of SSRI treatment of hot flashes and depression in breast cancer survivors, this hypothesis requires further clinical testing before definitive recommendations for or against concomitant tamoxifen and SSRI use should be made.

Our results do emphasize the potential importance of pharmacogenetic considerations in the assessment of the efficacy of tamoxifen. Further studies of the activity of endoxifen and larger prospective clinical trials that examine the associations of CYP2D6 genotype and other pharmacogenetic factors with validated clinical outcomes will be required to test the hypothesis that pharmacogenetic testing may be useful before tamoxifen treatment to determine who is best suited for tamoxifen treatment. Similarly, it is not yet clear that patients with low CYP2D6 activity and low endoxifen concentrations will experience less clinical benefit from tamoxifen; further research in this area is now merited. Because there are, as yet, few validated surrogates of clinical outcome in breast cancer, studies that examine the effects of endoxifen concentrations and germline

Fig. 5. The metabolic route from tamoxifen to endoxifen and other metabolites. Plasma concentrations of 4-hydroxy-tamoxifen are low relative to those of N-desmethyl-tamoxifen, indicating that the primary route for metabolism of the parent drug, tamoxifen, is via N-demethylation. Our data indicate that the primary route of metabolism from tamoxifen to endoxifen is first N-demethylation by cytochrome P450 3A to N-desmethyl-tamoxifen, followed by hydroxylation by cytochrome P450 2D6.
pharmacogenetic genotype on clinical outcome in relatively short-term trials, such as those in the neo-adjuvant and metastatic settings, will be important. In addition, the results of this study emphasize that prospective collection of DNA in future trials that use tamoxifen will be critical to any demonstration that a pharmacogenetic test can improve our ability to determine which patients may be vulnerable to harm and which patients may most benefit from tamoxifen treatment.

References

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Notes

Editor’s note: Dr. Stearns has served as a consultant to GlaxoSmithKline Pharmaceuticals, maker of paroxetine.

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