Chapter 14

Pharmacogenomics of Endocrine Therapy in Breast Cancer

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Abstract

The treatment of breast cancer with selective estrogen receptor modulators such as tamoxifen and with aromatase inhibitors represents a major advance in cancer chemotherapy. However, there are large variations among patients in both the therapeutic efficacy and side effects of these drugs. Pharmacogenomics is the study of the role of inheritance in this variation and genetic variation in tamoxifen response represents one of the most striking examples of the potential clinical importance of pharmacogenomics. Tamoxifen requires "metabolic activation" catalyzed by cytochrome P450 2D6 (CYP2D6) to form hydroxylated metabolites—4-hydroxytamoxifen and endoxifen (N-desmethyl-4-hydroxytamoxifen)—both of which are much more potent than is the parent drug. However, *CYP2D6* is genetically polymorphic. Approximately 5-8% of Caucasian subjects are CYP2D6 "poor metabolizers" on a genetic basis and, as a result, are relatively unable to catalyze tamoxifen hydroxylation. These same subjects appear to have poorer outcomes when treated with tamoxifen than do CYP2D6 "extensive metabolizers". These data led the US Food and Drug Administration (FDA) to hold public hearings in 2006 on the inclusion of this pharmacogenomic information in tamoxifen labeling. However, a series of important questions still remains to be addressed with regard to tamoxifen pharmacogenomics. There have also been preliminary attempts to study the pharmacogenomics of aromatase inhibitors, including the application of a genotype-to-phenotype research strategy designed to explore the nature and extent of common DNA sequence variation in the *CYP19* gene that encodes aromatase. Those results—together with our current level of understanding of tamoxifen pharmacogenomics—will be reviewed in this chapter and both will be placed within the context of the overall development of pharmacogenomics.

Introduction

Pharmacogenomics is the study of the role of inheritance in individual differences in drug response.[1] The therapy of breast cancer with selective estrogen receptor modulators (SERMs) such as tamoxifen and with aromatase inhibitors represents a major advance in the drug therapy of cancer.[2] That advance is part of a "therapeutic revolution" which occurred during the latter half of the twentieth and continues into the twenty-first century.[3] The convergence of that revolution with the dramatic advances that occurred at the same time in human genomics[4,5] makes it possible to apply the techniques of modern genomic science in an attempt to understand the contribution of inheritance to variation in drug response phenotypes. That variation can range from adverse drug reactions at one end of the spectrum to lack of the desired therapeutic effect at the other. Pharmacogenomics is a major component of efforts to "individualize" medicine and one of the

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most striking examples of the potential of pharmacogenomics to influence clinical practice involves the use of tamoxifen to treat breast cancer.

Pharmacogenomic effects are often classified as those that alter factors which influence the concentration of drug reaching its target, so-called "pharmacokinetic (PK)" factors and those that involve the drug target itself, "pharmacodynamic (PD)" factors.[1] When a drug such as tamoxifen is administered to a patient, it must be absorbed, distributed to its site of action, interact with its target(s), undergo metabolism and, finally, be excreted.[6] Absorption, distribution, metabolism and excretion can all influence "PK"—the concentration of drug or, in the case of tamoxifen, the concentrations of active metabolites of the drug, that finally reach the target. Genetic variation can also occur in the drug target itself or in signaling cascades downstream from the target, in this case involving "PD" factors. Historically, pharmacogenomic studies began with the observation of variation in phenotype, for example, the occurrence of an adverse drug reaction and then moved from clinical phenotype to biochemical cause, e.g., inherited lack of a drug-metabolizing enzyme and, ultimately, to the genome, in a "phenotype-to-genotype" progression. However, in today's post-genomic world, application of a genotype-to-phenotype research strategy is also possible. In the subsequent discussion of the endocrine therapy of breast cancer, both approaches will be illustrated.

The therapy of breast cancer patients with tamoxifen, as mentioned previously, represents a striking example of the potential clinical importance of pharmacogenomics—and the development of our knowledge of tamoxifen pharmacogenomics will be outlined subsequently. Studies have also been initiated of the pharmacogenomics of aromatase inhibitors, although they are not as well developed as is tamoxifen pharmacogenomics. Some of those latter studies began with an attempt to define common variation in the sequence of the aromatase gene (*CYP19*), the gene that encodes the target for aromatase inhibitors. In subsequent paragraphs, the observations and insights that resulted in our present understanding of tamoxifen pharmacogenomics will be described, followed by a brief overview of initial efforts to study the pharmacogenomics of aromatase inhibitors. Finally, both of these efforts involving the endocrine therapy of breast cancer will be considered within the context of the development of pharmacogenomics as a discipline, developments that promise to soon make it possible to query the entire human genome in order to better individualize drug therapy.

Tamoxifen Pharmacogenomics

Tamoxifen therapy of breast cancer patients represents one of the most striking and clinically relevant examples of the application of pharmacogenomics in an attempt to "personalize" pharmacologic therapy. It also illustrates the way in which knowledge of drug metabolism, a topic often regarded by students and practitioners alike as arcane or even "boring", provided important, clinically relevant insights. Although tamoxifen is itself a SERM, it is also a "pro-drug" that can be metabolized to form 4-hydroxy and N-desmethyl-4-hydroxy metabolites that are much more potent than is the parent compound (Fig. 1).[7] During the past decade, a series of events converged that resulted in the hypothesis that genetic variation in the CYP2D6-catalyzed hydroxylation of tamoxifen might represent a major factor responsible for individual variation in clinical response to that drug. Those events included a great deal of work which indicated that the selective serotonin reuptake inhibitors (SSRIs) used to treat depression were also effective in treating "hot flashes" induced by tamoxifen therapy;[8-10] the realization that many of those agents were—like tamoxifen—metabolized by CYP2D6; the characterization of a novel active metabolite of tamoxifen (endoxifen),[11-13] and clinical epidemiologic data in support of the hypothesis that CYP2D6 genotype was associated with tamoxifen efficacy.[14-16] In the text that follows, each of these topics will be addressed in turn—and presently unanswered questions with regard to tamoxifen pharmacogenomics will also summarized.

Hot flashes are a common side effect of tamoxifen therapy, occurring in 50-70% of patients treated with this drug, but it is obviously not possible to treat this side effect in breast cancer patients with exogenous estrogens.[17] Therefore, when anecdotal reports appeared that hot flashes might

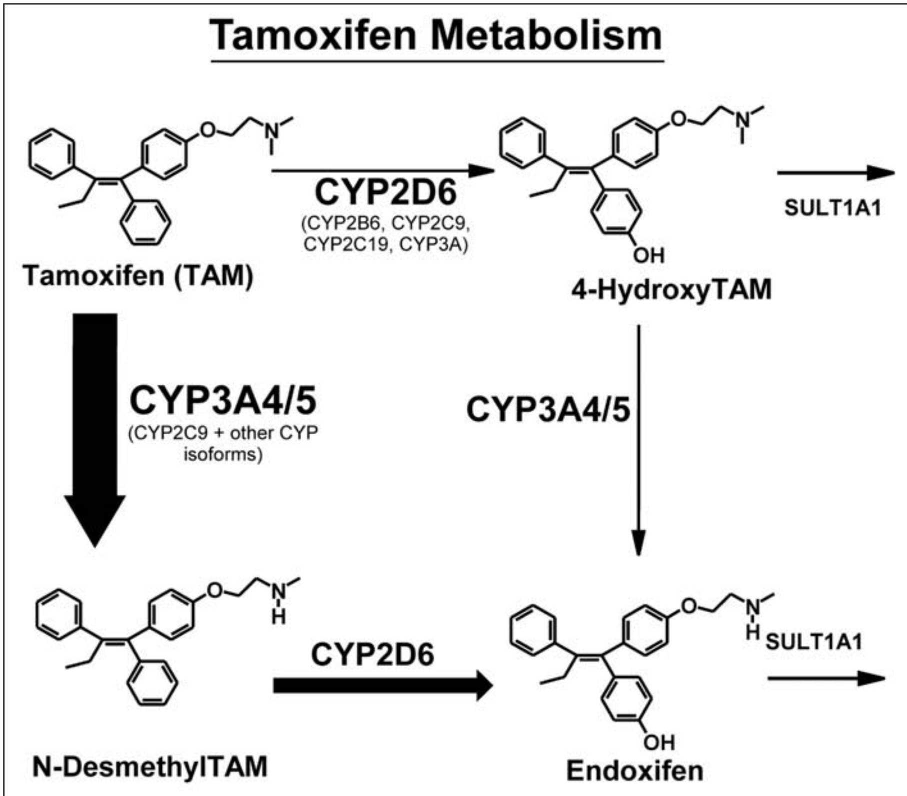

Figure 1. Tamoxifen (TAM) metabolism. Cytochrome P450 (CYP)3A4/5 catalyzes the formation of N-desmethyltamoxifen, while the generation of 4-hydroxytamoxifen and endoxifen are catalyzed predominantly by CYP2D6.[46] It has also been suggested that SULT1A1 may play a role in endoxifen clearance. The relative importance of each reaction is indicated by the size of the arrows (modified from Jin Y, Desta Z, Stearns V et al. J Natl Cancer Inst 2005; 97(1):30-39).[22]

respond to treatment with the SSRI drugs used to treat depression, those reports were followed by a series of clinical trials in which specific SSRIs were used to treat hot flashes. Included among the drugs studied in that fashion were venlafaxine, fluoxetine and paroxetine.[8-10] For example, 81 women were randomized to 20 mg of fluoxetine or placebo in one study and the "hot flash score" decreased by 50% in the fluoxetine arm versus 36% in the placebo arm.[9] In a similar study of 191 women treated with venlafaxine, hot flash scores were reduced 27% in the placebo arm and 61% in the 150 mg of venlafaxine arm.[8] It was a study of this type using paroxetine that led to the recognition of a potent active metabolite of tamoxifen and focused attention squarely on CYP2D6 and its pharmacogenomic variation as a potentially important factor in variation in response to tamoxifen therapy among patients with breast cancer.[7,10]

At that time, it was believed that the most therapeutically relevant tamoxifen metabolite was 4-hydroxytamoxifen—which was approximately 100 times as potent as the parent drug in its effect on the estrogen receptor.[18,19] Two studies published by Stearns and coworkers in 2003 were designed to test the hypothesis that paroxetine might be useful in the treatment of hot flashes in patients treated with tamoxifen.[7,10] The approach taken in those studies utilized a "drug metabolism perspective", with the use of HPLC assays of tamoxifen and its metabolites based, in

part, on the hypothesis the SSRIs might compete for and inhibit CYP2D6-catalyzed tamoxifen hydroxylation. Those investigators observed a metabolite that resulted from both 4-hydroxylation and N-demethylation—a metabolite that they named "endoxifen".[7] As shown in Figure 1, the formation of 4-hydroxytamoxifen and endoxifen is catalyzed predominantly by CYP2D6, while the N-demethylation step is catalyzed by CYP3A4/5. These were important observations because CYP2D6 is one of the most genetically polymorphic and one of the most intensively studied drug-metabolizing enzymes in all of pharmacogenomics.[20]

The gene encoding CYP2D6 includes functionally significant single nucleotide polymorphisms (SNPs); but the gene can also be deleted and it can undergo amplification, with up to 13 active copies.[20] Prior to the cloning and characterization of the *CYP2D6* gene, its genetic variation was explored by the use of "pro-drugs" such as the antihypertensive agent debrisoquine. In those studies, debrisoquine would be administered to a group of subjects and its CYP2D6-catalyzed 4-hydroxylation was monitored by assaying urinary 4-hydroxydebrisiquine and expressing the results as a "metabolic ratio", in which the parent drug concentration was divided by the concentration of the metabolite. Figure 2 shows debrisoquine "metabolic ratios" for 1,011 subjects studied at the Karolinska Institute.[21] At the far-right of the frequency distribution histogram the metabolic ratios for "poor metabolizers" (PMs)—subjects who either have inactive enzyme or the deletion of the *CYP2D6* gene—are shown, with a group of "extensive" metabolizers (EMs) in the center and, at the far-left, are data for ultra-rapid metabolizers (UMs)—some of whom have multiple

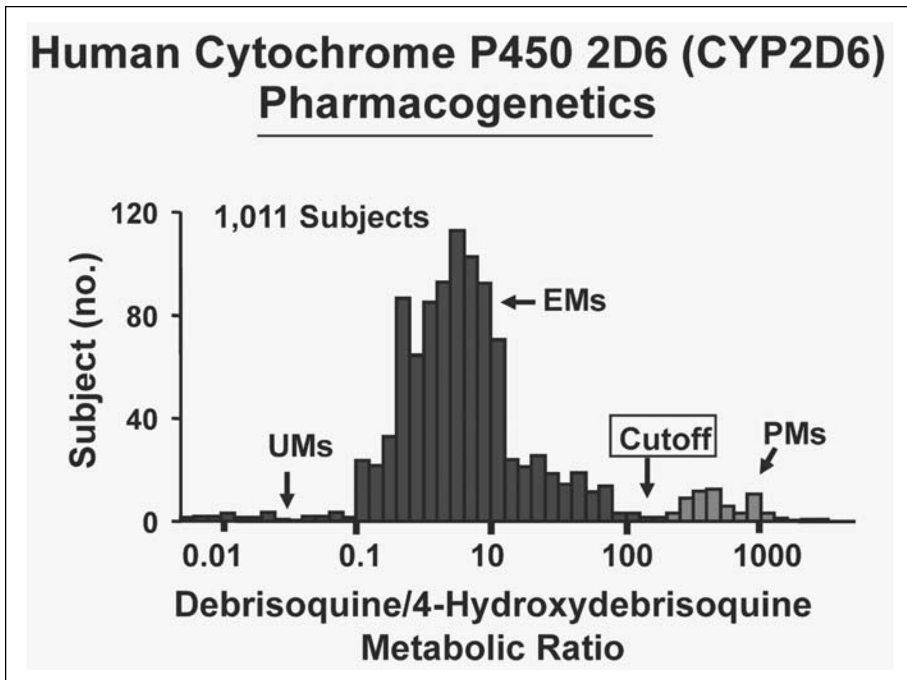

Figure 2. CYP2D6 pharmacogenetics. The figure shows the ratio of urinary debrisoquine to its metabolite, 4-hydroxydebrisoquine, in 1011 Swedish subjects. The formation of 4-hydroxydebrisoquine is catalyzed by CYP2D6. "PM" is "poor metabolizer"; "EM" is "extensive metabolizer"; and "UM" is "ultrarapid metabolizer". "Cutoff" is the demarcation between PMs and EMs (Reprinted by permission from Macmillan Publishers Ltd: Bertilsson L, Lou YQ, Du YL et al. Clin Pharmacol Ther 1992; 51:388-397.)

copies of the CYP2D6 gene. The next question addressed for tamoxifen was whether endoxifen was an active metabolite and whether its formation could be inhibited by other CYP2D6 substrates such as the SSRIs.

Stearns et al not only detected significant concentrations of endoxifen in the blood of patients treated with tamoxifen,[7] but this same group of investigators also showed that circulating endoxifen concentrations were reduced by paroxetine treatment.[7,22] Later studies demonstrated that plasma endoxifen concentrations were decreased by the administration of other SSRIs (Fig. 3)—in direct proportion to their metabolism by CYP2D6, i.e., these drugs could inhibit the formation of active metabolites of tamoxifen.[23] It was also demonstrated that endoxifen was an active metabolite that inhibited estradiol-stimulated MCF-7 cell proliferation.[7] Subsequent expression array studies showed that endoxifen had effects on global expression patterns in MCF-7 cells that were similar to those of 4-hydroxytamoxifen.[13] In addition, endoxifen concentrations in women treated with tamoxifen were approximately an order of magnitude higher than were 4-hydroxytamoxifen concentrations—indicating that endoxifen and not the 4-hydroxylated compound, might be the major active metabolite.[7,23] However, the formation of both 4-hydroxytamoxifen and endoxifen required CYP2D6. That fact raised a critical question with regard to the therapeutic efficacy of tamoxifen in the 5-8% of the Caucasian population who are relatively unable to catalyze the reaction required to form these active metabolites.[20] That question was addressed in a study of 94 patients on tamoxifen therapy who were genotyped for common variant CYP2D6 alleles. Those genotype-phenotype correlation data are depicted graphically in Figure 4 which shows the relationship between *CYP2D6* genotype and circulating endoxifen concentrations.[23] Patients without *CYP2D6* genes capable of encoding active enzyme has decreased endoxifen levels. The next

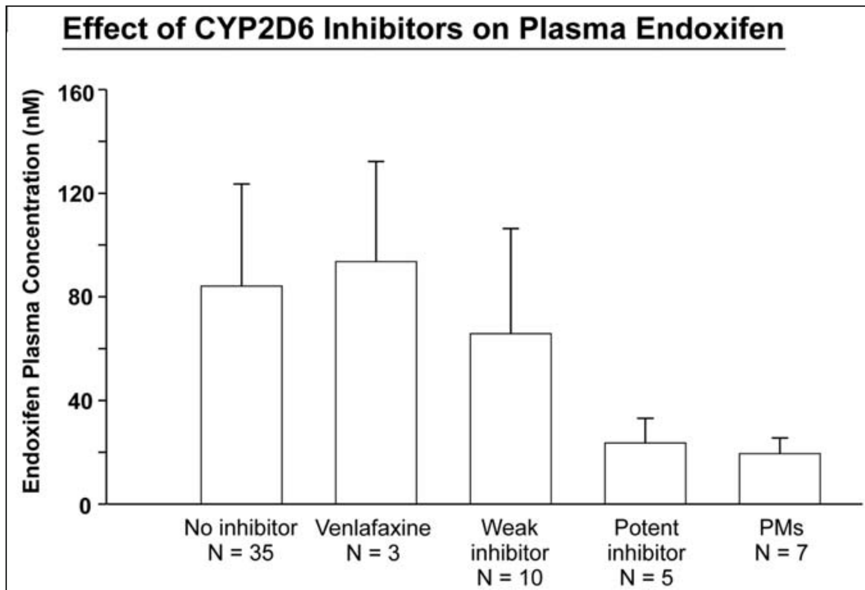

Figure 3. Effect of drugs that are CYP2D6 inhibitors on plasma endoxifen concentrations after 4 months of tamoxifen (20 mg/d). Bars represent mean ± SD. From left to right, the groups are composed of CYP2D6 EM/EMs who were taking neither CYP2D6 inhibitors nor venlafaxine, EM/EMs who were receiving venlafaxine, EM/EMs who were treated with drugs that are CYP2D6 inhibitors, EM/EMs who were receiving "potent" CYP2D6 inhibitors and PM/PMs who were not taking any CYP2D6 inhibitors (Reprinted by permission from Macmillan Publishers Ltd: Borges S, Desta Z, Li L et al. Clin Pharmacol Ther 2006; 80(1):61-74.)

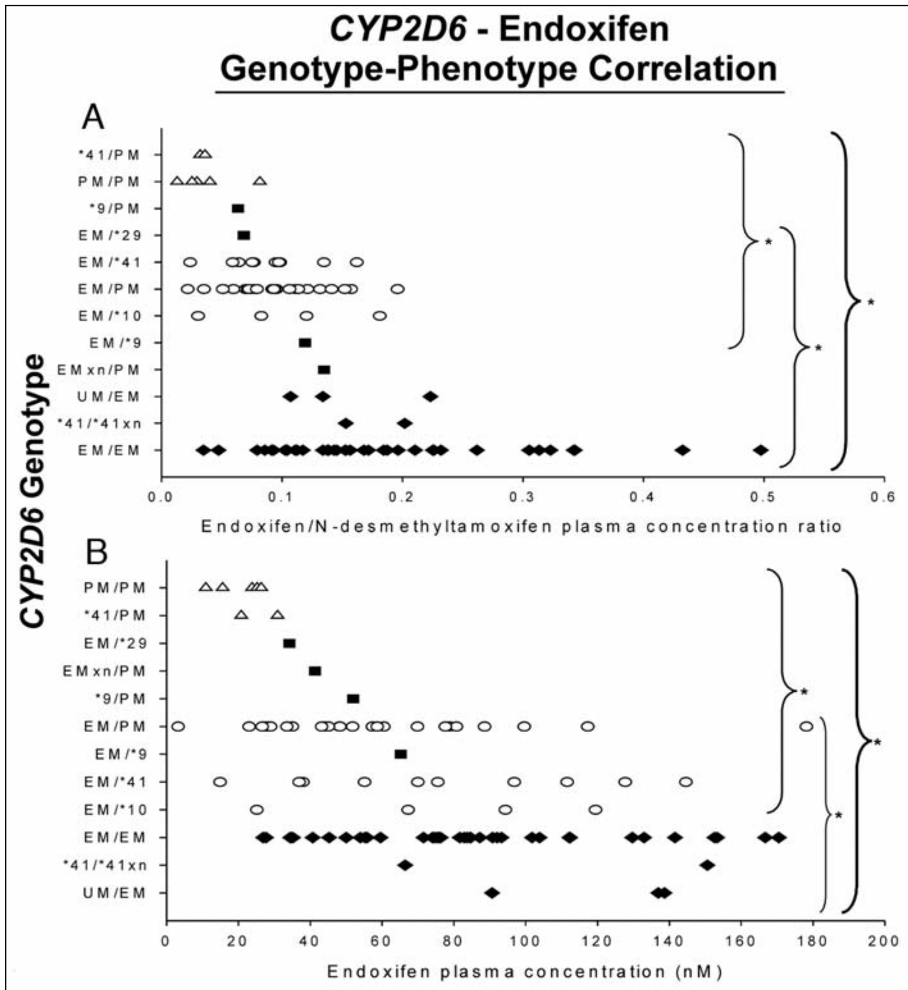

Figure 4. *CYP2D6*-endoxifen genotype-phenotype correlation. (A) Association of *CYP2D6* genotype with endoxifen/N-desmethyltamoxifen ratio in 94 breast cancer patients after 4 months of tamoxifen treatment (20 mg/d) without concomitant CYP2D6 inhibitors. Genotype groups are ranked on the basis of their mean values, from lowest (top) to highest (bottom). Genotypes represented by only one patient were excluded from group comparisons. Triangles indicate patients without any fully functional *CYP2D6* allele (mean, 0.04 ± 0.02), circles indicate patients carrying only one fully functional *CYP2D6* allele (mean, 0.09 ± 0.04), diamonds indicate patients with two or more copies of any functional or dysfunctional *CYP2D6* allele (mean, 0.18 ± 0.09) and squares indicate patients excluded from the group comparisons. * = $P < .001$. (B) Association of *CYP2D6* genotype with endoxifen concentration in the same breast cancer patients pictured in (A). Triangles indicate patients without any fully functional *CYP2D6* allele (mean, 21.9 ± 6.8 nmol/L), circles indicate patients with only one fully functional *CYP2D6* allele (mean, 64.2 ± 38.2 nmol/L), diamonds indicate patients with two or more copies of any functional or dysfunctional *CYP2D6* allele (mean, 88.6 ± 39.6 nmol/L) and squares indicate patients excluded from the group comparisons. * = $P < .05$ (Reprinted by permission from Macmillan Publishers Ltd: Borges S, Desta Z, Li L et al. Clin Pharmacol Ther 2006; 80(1):61-74.)

question to be addressed was whether there might be a relationship between CYP2D6 genotype and clinically relevant endpoints such as disease-free survival after the treatment of breast cancer with tamoxifen.

It would have taken years to complete prospective trials to test the hypothesis that tamoxifen response in patients with breast cancer might be influenced by *CYP2D6* genotype. Fortunately, paraffin block breast cancer tissue from which DNA could be extracted was available from previous tamoxifen clinical trials—many of which were initiated in the mid- or late-1980s. As a result, a series of retrospective studies was performed using that type of material. The results of the first of those studies, a study based on an NCI North Central Cancer Treatment Group (NCCTG) trial initiated in the 1980s, showed that patients with the most common "loss of function" *CYP2D6* allele, *CYP2D6*4*, had less favorable outcomes than did patients with the "wild type" genotype (Fig. 5).[14] Those results were confirmed by data for a small group of patients included in the Italian Tamoxifen Trial.[15] A recent follow-up study of these same NCCTG patients indicated that women who were treated with drugs that could compete for CYP2D6-catalyzed metabolism, drugs such as fluoxetine, also had a higher frequency of disease recurrence.[16] These reports stimulated a flurry of editorial comment,[24-27] review articles[28-30] and, in October 2006—US Food and Drug Administration (FDA) public hearings on the possible inclusion of CYP2D6 pharmacogenomic data in tamoxifen labeling.[25]

After those public hearings, the Clinical Pharmacology Subcommittee of the FDA Advisory Committee for Pharmaceutical Science recommended that tamoxifen labeling should inform prescribers that patients who are CYP2D6 "poor metabolizers" have an increased risk for disease recurrence.[25] They also recommended that the label should warn that certain antidepressants can inhibit a patient's ability to metabolize tamoxifen to form active metabolites.[25] It should be noted that these original positive studies were retrospective and that their results remain the subject of controversy. That is true because two retrospective studies published by a Swedish group reported not only that *CYP2D6*4* was not a risk factor for breast cancer recurrence, but that this genotype was actually protective—although the results were not statistically significant.[31,32] In addition, a retrospective study from the United States failed to observe a relationship between *CYP2D6* genotype and clinical outcome in breast cancer patients treated with tamoxifen.[33] However, a very recent study from Germany that genotyped additional *CYP2D6* alleles which are associated with decreased enzyme function confirmed and extended the original observations that genotypes with lower CYP2D6 enzyme activity are associated with poorer clinical outcomes in breast cancer patients treated with tamoxifen.[34]

In summary, tamoxifen illustrates the potential clinical importance of pharmacogenomics—as well as the challenges involved in "translating" this type of biomedical research into the clinic. It also raises a series of important questions. First, all of the present clinical data for tamoxifen pharmacogenomics were obtained (for obvious practical reasons) from retrospective studies, so this area of research cries out for a carefully designed prospective study. Second, all of the clinical data available thus far were obtained from Caucasian subjects and there are many examples of ethnic variation in pharmacogenomic response,[1] so studies in additional ethnic groups will be required. Not surprisingly, there have already been publications in which the ethical aspects of genomic testing for *CYP2D6* have been examined,[35] and this entire discussion needs to be placed within a context in which the development of aromatase inhibitors presents a practical alternative to tamoxifen therapy—at least in postmenopausal women. That is, have these pharmacogenomic results appeared too late in the "life span" of tamoxifen to be of any practical value or clinical relevance?[26] No matter what the answers to these questions might be, the tamoxifen "story" serves to demonstrate both the potential clinical importance of pharmacogenomics and the many challenges that we face if this aspect of personalized medicine is to move to the bedside—for even a single gene. It also brings us to the topic of aromatase inhibitors. What is known with regard to possible pharmacogenomic variation in clinical response to this class of drugs?

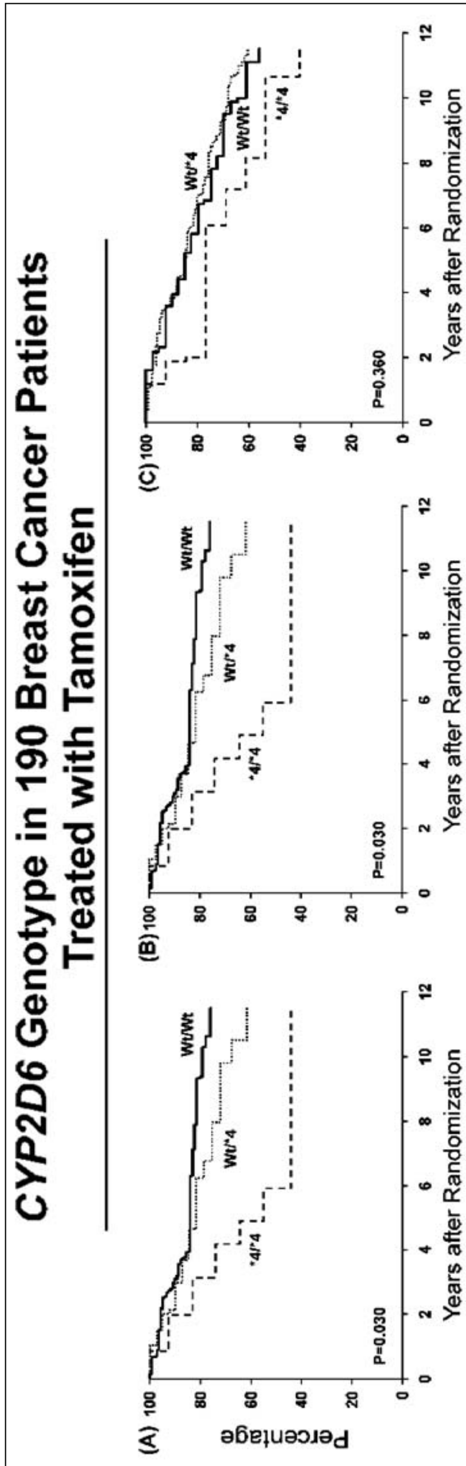

Figure 5. Kaplan-Meier curves for 190 women with breast cancer who were treated with tamoxifen and were genotyped for *CYP2D6*4*. Wt = wild type. (A) Relapse-free time, (B) disease-free survival and (C) overall survival for patients with the *CYP2D6* genotypes indicated (modified from Goetz MP, Rae JM, Suman VJ et al. J Clin Oncol 2005; 23(36):9312-9318.)

Aromatase Inhibitor Pharmacogenomics

The third generation aromatase inhibitors are much newer drugs than is tamoxifen.[36,37] Therefore, less is known with regard to the possible influence of inheritance on the pharmacokinetics or pharmacodynamics of letrozole, anastrozole and exemestane than is known with regard to tamoxifen. Although aromatase inhibitors, like tamoxifen, undergo biotransformation catalyzed by a variety of cytochromes P450,[36] there is currently no information with regard to the possibility that inherited variation in their metabolism or transport, i.e., their pharmacokinetics, might result in clinically relevant variation in their clinical effect. As in the case for tamoxifen, the question of greatest importance is whether inherited variation might influence outcomes relevant to the treatment of breast cancer (e.g., disease-free survival) and that type of study would require years to complete. In addition, these drugs are very potent and are used to treat postmenopausal women who already have very low circulating estrogen levels. Therefore, although there are data which indicate that individual differences in drug effect (inhibition of estrogen biosynthesis) occurs, no comprehensive studies of the effect of inheritance on the ability of third generation aromatase inhibitors to alter hormone levels have been published. However, as a step toward studies of the possible effects of inheritance on aromatase inhibitor "pharmacodynamics", resequencing of the

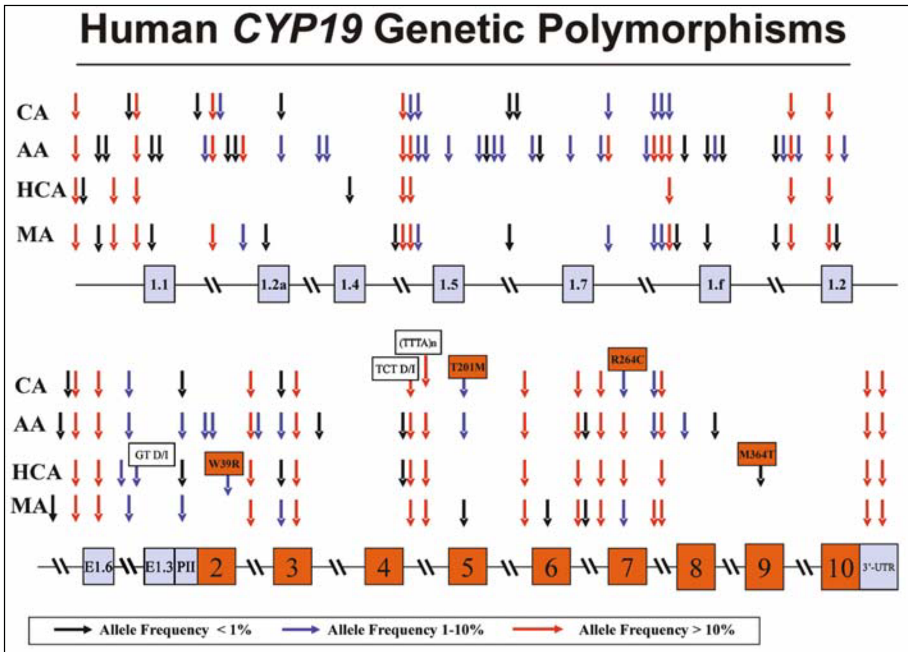

Figure 6. Human *CYP19* genetic polymorphisms. The figure shows a schematic representation of the *CYP19* gene structure, with arrows indicating the locations of polymorphisms in 60 DNA samples each from African-American (AA), Caucasian-American (CA), Han Chinese-American (HCA) and Mexican-American (MA) subjects. Orange rectangles represent the open reading frame and light blue rectangles represent untranslated regions. Red arrows represent minor allele frequencies (MAFs) greater than 10%; dark blue arrows frequencies from 1 to 10% and black arrows polymorphisms with MAFs of less than 1%. "I/D" indicates an insertion/deletion event. The GT and TTC I/D polymorphisms and the variable number of tandem repeat (TTTA)n polymorphism, as well as amino acids changes resulting from nonsynonymous cSNPs, are also indicated (modified from Ma CX, Adjei AA, Salavaggione OE et al. Cancer Res 2005; 65(23):11071-11082.)

gene encoding the target for these drugs, CYP19, aromatase, has been performed.[38] Specifically, *CYP19* was resequenced using 60 DNA samples (120 alleles) each from African-American, Caucasian-American, Han Chinese-American and Mexican-American subjects (Fig. 6). A total of 88 genetic polymorphisms, including four nonsynonymous coding single nucleotide polymorphisms (SNPs) that altered the encoded amino acid sequence, were identified.[38]

These *CYP19* gene resequencing studies were intended as a first step toward a determination of whether genetic variation in the target for these drugs might influence response to treatment with aromatase inhibitors. There is already a precedent for thinking that that type of effect can occur. That precedent involves the oral anticoagulant warfarin, a widely prescribed but potentially dangerous drug with a narrow therapeutic index, i.e., the difference between the therapeutic and toxic dose is small. Inherited variation in the gene encoding the target for warfarin and other coumarin-based anticoagulants, vitamin K oxidoreductase C1 (*VKORC1*), has been shown to have a striking effect on the dose of this drug required to achieve a target INR (the international normalized ratio, the universally used measure of the anticoagulant effect of this class of drugs).[39] Up to now, genetic polymorphisms in the aromatase gene, *CYP19*, have been genotyped predominantly to test their possible association with risk for diseases such as breast cancer, but they have not been studied systematically for a possible association with variation in response to treatment with aromatase inhibitors. The example provided by pharmacogenomic studies of tamoxifen and warfarin, among others, will undoubtedly serve as a "roadmap" for similar studies designed to test the hypothesis that individual variation in the sequence or structure of genes encoding proteins involved in the metabolism or transport of aromatase inhibitors—or in the gene encoding the target for these drugs—might contribute to variation in aromatase inhibitor response. The drug response phenotypes that might display individual variation include not only measures of drug efficacy, but also adverse drug reactions, in the case of aromatase inhibitors osteoporosis or musculoskeletal symptoms.[36,37]

Conclusions and Future Directions

Tamoxifen provides a striking example of the potential clinical relevance of pharmacogenomics. Although significant questions remain to be addressed with regard to tamoxifen pharmacogenomics and although the clinical application of genotyping for *CYP2D6* prior to the initiation of tamoxifen therapy remains controversial, there is a growing consensus, supported by a US FDA review panel, that genotyping might contribute to therapeutic decisions with regard to the adjuvant therapy of breast cancer. There is also a clear consensus that the treatment of patients on tamoxifen with drugs that are inhibitors of CYP2D6 should be discouraged.[25]

Tamoxifen is one of only four drugs for which the FDA has held public hearings with regard to the possible inclusion of pharmacogenomic information in labeling (see http://www.fda.gov). The first hearings involved thiopurine drugs such as 6-mercaptopurine and genetic variation in the thiopurine S-methyltransferase (*TPMT*) gene. *TPMT* polymorphisms are associated with life-threatening myelosuppression after exposure to "standard" doses of these drugs.[40] The second hearings involved another cytotoxic antineoplastic agent, irinotecan. The active metabolite of this anticancer drug is metabolized by glucuronidation catalyzed by UGT1A1 and the *UGT1A1*28* variant allele that is associated with Gilbert's syndrome results in decreased irinotecan metabolism and increased toxicity, particularly diarrhea and myelosuppression.[41] The third example selected for public hearings was warfarin and genetic variation in both the warfarin-metabolizing enzyme CYP2C9 and the drug target, VKORC1. In the case of warfarin, the focus was on preventing both drug toxicity, hemorrhage and lack of the desired therapeutic effect. The fact that the FDA included tamoxifen among this highly select group of drugs is telling. It is also important to note that three of these four examples of the potential clinical relevance of pharmacogenomics involve drugs used in the treatment of cancer and all three involve polymorphisms in germline DNA. It is necessary to emphasize that fact because a bias exists in some quarters that the only genetic variation of importance in the treatment of cancer is variation involving somatic DNA in the tumor. Obviously, the tumor genome is important but, as demonstrated by this list, so is germline DNA,

at least with regard to variation in drug response. It should also be emphasized that tamoxifen is the only member of this group for which the focus was squarely on genetic variation in efficacy rather than risk for toxicity, although pharmacogenomics might also provide insight into the possible contribution of inheritance to risk for the occurrence of serious tamoxifen side effects including thromboembolism or risk for endometrial cancer. Finally, the fact that the warfarin example involves two genes, *CYP2C9* on the pharmacokinetic (PK) side and *VKORC1* involving pharmacodynamics (PD), is a hint of possible future directions for pharmacogenomic studies of drugs used to treat breast cancer.

Pharmacogenomics, as a discipline, is rapidly moving beyond studies of single genes like *CYP2D6* to focus on entire pathways, pathways that include both PK and PD, as well as to genome-wide association studies. When genome-wide association studies have been applied to complex phenotypes such as risk for diseases like diabetes[42-44] and breast cancer,[45] multiple genes that could not have been anticipated are found to be associated with individual variation in disease risk. A similar approach is currently being applied to drug response phenotypes and is certain to be applied to complex therapeutic situations such as the endocrine therapy of breast cancer. Within that context, the "story" of tamoxifen and CYP2D6 represents only a first step toward truly individualized endocrine therapy of this important neoplastic disease.

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