

Clinical Implications of *CYP2D6* Genotyping in Tamoxifen Treatment for Breast Cancer

Vincent O. Dezentjé,^{1,2} Henk-Jan Guchelaar,² Johan W.R. Nortier,¹ Cornelis J.H. van de Velde,³ and Hans Gelderblom¹

Abstract In October 2006 the Food and Drug Administration recommended an update in the tamoxifen label to reflect the increased risk of recurrence in breast cancer patients who are cytochrome P450 2D6 (*CYP2D6*) poor metabolizers. This recommendation was based on only a few studies at that time. More clinical studies addressing the relation between the *CYP2D6* genotype and tamoxifen efficacy have been published since, mostly describing Caucasian populations in the adjuvant treatment setting. An updated analysis of the literature is presented. Furthermore, the possibility to implement *CYP2D6* genotyping in clinical practice is evaluated by analyzing the results of six studies on mainly Caucasian patients using adjuvant tamoxifen. Three studies were consistent with the FDA advice, but the three other studies showed contradictory results. Although some of the published criticism on the negative studies is justified, this does not imply that these results should be discarded. The reviewed literature is put in perspective acknowledging the limiting effect of Mendelian randomization on confounding and the limitations of the various study designs. The current accumulation of data showing worse clinical outcome in patients with decreased *CYP2D6* metabolism in other types of populations still indicates that the *CYP2D6* genotype may well become a clinically relevant predictive marker. The *CYP2D6* genotype might be one of the first predictors of therapeutic response in cancer care based on germline DNA creating the possibility to analyze blood instead of tumor.

Recently, the potential effect of cytochrome P450 (*CYP*) 2D6 (*CYP2D6*) genetic variants on clinical response to tamoxifen treatment in breast cancer patients has gained much interest. The need for a new predictive marker is expressed by the observation that about half of estrogen receptor-positive tumors in women with advanced breast cancer do not respond to tamoxifen therapy (1–3) and that the 15-year recurrence probability after 5 years of tamoxifen in early breast cancer is approximately one third in estrogen receptor-positive disease (4). Tamoxifen pharmacogenetics focuses on enzymes transforming the prodrug tamoxifen to 30 to 100 times more active metabolites (4-hydroxy tamoxifen and endoxifen). This creates the possibility to identify pharmacogenetic markers that can predict efficacy and may be used in clinical practice. The Food and Drug Administration recommended an update in the tamoxifen package insert in 2006 to reflect the increased risk of breast cancer recurrence in postmenopausal estrogen receptor-positive patients who are *CYP2D6* poor metabolizers. This recommendation, however, was based on only a few studies at that time. Whether and how to implement *CYP2D6*

genotyping in daily practice was not exemplified. More clinical studies addressing the relation between the *CYP2D6* genotype and tamoxifen efficacy have been published since.

In this review an updated analysis of the literature is presented. Most studies describe a Caucasian breast cancer population treated with adjuvant tamoxifen. An evidence-based clinical application of *CYP2D6* genotyping is therefore nearest at hand in this specific population. Will *CYP2D6* genotyping become common practice in breast cancer treatment despite all challenges a new test is confronted with (5, 6)? To answer this question we provide the rationale and a critical appraisal of all currently available clinical studies.

Rationale

Tamoxifen metabolism. Tamoxifen undergoes extensive metabolism and is considered a “prodrug.” Several metabolic enzymes are involved in primary and secondary biotransformation. *CYP3A4* and *CYP3A5* are the major enzymes responsible for *N*-demethylation, whereas 4-hydroxylation is predominantly mediated by *CYP2D6* (7–10). Figure 1 shows a simplified scheme of the tamoxifen metabolism including the major metabolites and enzymes, although the complete metabolism is more complicated (11). Primary metabolites are *N*-desmethyltamoxifen and 4-hydroxytamoxifen. The first is the most abundant tamoxifen metabolite in plasma (~90%; ref. 11); the latter, however, is 30- to 100-fold more potent with regard to antiestrogen activity compared with tamoxifen and *N*-desmethyltamoxifen. In 2003, another metabolite, 4-hydroxy-*N*-desmethyltamoxifen (endoxifen), was recognized

Authors' Affiliations: Departments of ¹Clinical Oncology, ²Clinical Pharmacy and Toxicology and ³Surgical Oncology, Leiden University Medical Center, Leiden, The Netherlands

Received 8/1/08; revised 9/19/08; accepted 9/22/08.

Note: Presented in part as an oral presentation at the EBCC 2008 annual meeting in Berlin.

Requests for reprints: Hans Gelderblom, Department of Clinical Oncology, Leiden University Medical Center, PO Box 9600, 2300 RC Leiden, The Netherlands. Phone: 31-0-71-526-3464; Fax: 31-0-71-5266760; E-mail: a.j.gelderblom@lumc.nl.

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doi:10.1158/1078-0432.CCR-08-2006

Translational Relevance

The basic research on the influence of the *CYP2D6* genotype on tamoxifen metabolism has shown to be of translational relevance as it has led to several studies relating clinical tamoxifen response in breast cancer with the *CYP2D6* genotype. The Food and Drug Administration even recommended an update on the tamoxifen package insert reflecting the increased risk of recurrence in patients who are poor metabolizers of *CYP2D6* based on this fundamental and clinical research. Along with the publication of more studies on this topic, we are moving closer to a clinical application of *CYP2D6* genotyping in breast cancer treatment. In this review article we will discuss the strengths and limitations of the present literature. Based on this analysis we will also outline what more evidence is useful for a future implementation of *CYP2D6* genotyping in clinical practice.

as an important active metabolite (12). This metabolite is mainly a result of the hydroxylation of *N*-desmethyltamoxifen by *CYP2D6*. A series of *in vitro* studies have shown that endoxifen has the same potency as 4-hydroxytamoxifen with regard to estrogen receptor- α and - β binding (13), suppression of estrogen receptor-dependent human breast cancer cell line proliferation (13, 14) and global estrogen receptor-responsive gene expression (15). Endoxifen is now considered the most active tamoxifen metabolite, because its plasma concentrations are 5- to 10-fold higher than of 4-hydroxytamoxifen (12, 16). The importance of endoxifen is supported by *in vitro* data only, as no study so far has associated endoxifen directly with clinical outcome. The concentration-effect relation of endoxifen is also unknown.

To increase solubility and facilitate excretion of the drug, metabolites undergo sulfation by sulfotransferases and glucuronidation by UDP-glucuronosyltransferases. Sulfotransferase 1A1 is considered the primary sulfotransferase responsible for the sulfation of 4-hydroxytamoxifen (17, 18) and endoxifen (19, 20). UDP-glucuronosyltransferase 2B15 (21) and other UDP-glucuronosyltransferases are involved in the glucuronidation of 4-hydroxytamoxifen and endoxifen (22).

CYP2D6 is the leading enzyme involved in endoxifen formation, although other CYP enzymes, sulfotransferase 1A1, and UDP-glucuronosyltransferases most likely influence the endoxifen plasma level as well. Certain genetic variants of *CYP2D6* and other contributing enzymes may lead to a lower and thus less effective endoxifen level.

***CYP2D6* genetic variants.** Some polymorphisms of *CYP2D6* produce a less active or inactive enzyme. Also, the whole *CYP2D6* gene can be deleted. Amplification of a functional allele may lead to higher enzymatic activity. Variant alleles (indicated by "*" followed by a number) have frequencies ranging up to 40% (Table 1) and may alter biotransformation of tamoxifen to its active metabolite and thus clinical response. Over 80 genetic variants of *CYP2D6* have been described.⁴

⁴ Home Page of the Human Cytochrome P450 (*CYP*) Allele Nomenclature Committee [updated 21 May 2008]. Available from: <http://www.cypalleles.ki.se>.

Information on ethnicity is crucial to understanding the impact of genetic *CYP2D6* variation in a population as allelic frequencies differ greatly among races (Table 1).

The *CYP2D6* phenotype (i.e. enzymatic activity) can be assessed by quantifying concentrations of an administered probe drug (e.g. debrisoquine) and its metabolite in serum or urine. According to the metabolic ratio (concentration unchanged drug/concentration drug metabolite), one can be classified as a poor metabolizer, intermediate metabolizer, extensive metabolizer, or ultrarapid metabolizer. The *CYP2D6* genotype is predictive for the phenotype (23), albeit both epigenetic factors and drug interaction can influence the translation to phenotype. MicroRNA and gene methylation regulate expression of CYPs and may be partially responsible for the interindividual variability in phenotype among the same genotypes (24, 25). Pharmaceuticals can inhibit *CYP2D6* activity (i.e. *CYP2D6* inhibitors) and may transform an extensive metabolizer predicted by genotype to a poor metabolizer phenotype (i.e. phenocopying; ref. 26). Whereas the homozygous carriers of inactive alleles (e.g. *4/*4) clearly reflect a poor metabolizer phenotype, uncertainty exists on how to classify the heterozygous carriers (e.g. *1/*4). Heterozygous carriers are classified either as intermediate metabolizers or extensive metabolizers (27).

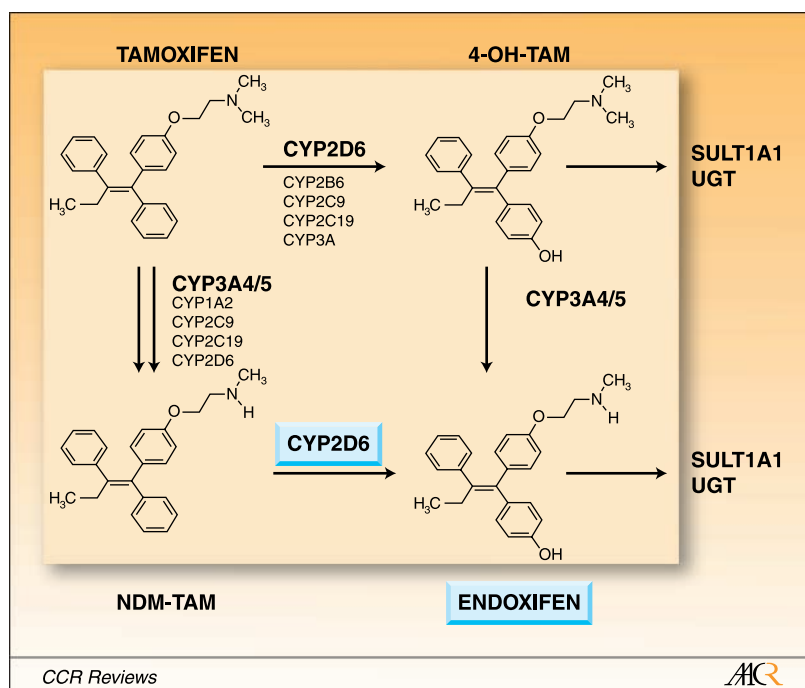
In Caucasian populations, poor metabolizers and intermediate metabolizers are observed in 5% to 10% and 10% to 15% respectively (28). Up to 25% of Caucasian patients with a decreased metabolism may suffer from undertreatment with tamoxifen assuming an effect of genotype on tamoxifen response. This may be most distinct in adjuvant treatment because in metastatic breast cancer nonresponsiveness may lead to relatively quick alteration of treatment strategy.

Effect on Recurrence in Caucasians

To assess the association of the *CYP2D6* genotype with clinical outcome in tamoxifen-treated breast cancer patients, a research on the literature was done. In April 2008 searches were conducted on Medline, Embase, Web of Science, scientific meeting proceedings, and a manual review of references from eligible publications was done. Six studies were evaluated involving a mainly Caucasian breast cancer population treated with adjuvant tamoxifen. Three studies were consistent with the hypothesis that *CYP2D6*-decreased metabolism results in a higher recurrence rate compared with extensive *CYP2D6* metabolism (hereafter referred to as "positive studies"). Nevertheless, two studies showed no association between the *CYP2D6* genotype and tamoxifen efficacy, and one study even showed results contradictory to the former hypothesis (hereafter referred to as "negative studies").

The study design and main results of the six studies are summarized in Tables 2 and 3. The results by Goetz (29), Schroth (30), and Gonzalez-Santiago (31) all show lower recurrence-free survival in poor metabolizers compared with extensive metabolizers. The results presented by Nowell (32) and by Wegman in her 2005 publication (33) fail to show any association, whereas in 2007 Wegman (34) shows an even better recurrence-free survival in poor metabolizers. All studies combined the heterozygous genotypes (e.g. *1/*4 or *1/*41) either with the poor metabolizers (e.g. *4/*4) or with the homozygous wild-type genotype (*1/*1). A total of 471

Fig. 1. Simplified scheme of the tamoxifen metabolism (main metabolic routes). 4-OH-TAM, 4-hydroxytamoxifen; CYP, cytochrome P450 isoenzyme; SULT1A1, sulfotransferase 1A1; UGT, UDP-glucuronosyltransferase; NDM-TAM, *N*-desmethyltamoxifen.



tamoxifen-using patients were genotyped and included in the Goetz, Schroth, and Gonzalez-Santiago studies, whereas 915 patients were studied in the Nowell and Wegman publications. All studies are retrospective follow-up studies investigating a trial population (29, 33), a hospital registry population (30–32), or a combination of trial and nontrial populations (34). In most studies only the most frequent absent-activity *4 allele is investigated whereas Schroth also included other common decreased or absent-activity alleles (*5, *10, and *41).

The strengths and limitations of all six studies will be outlined in this paper, although previously in editorials and reviews most criticism has focused on the limitations of the negative studies (35–37).

Possible Causes of Conflicting Results

Confounders/interaction. The populations studied by Wegman and Nowell are the most heterogeneous in comparison with the trial population investigated by Goetz which consisted of patients using 5 years of tamoxifen without additional chemotherapy. Tumor and patient characteristics are often better registered in study trials. In the final analysis the administration of chemotherapy in the Wegman and Nowell studies was not accounted for. Tumor grade and Her2 status were not adjusted for and different tamoxifen dosages (20 or 40 mg) and durations (2 and 5 years) were described. Nowell, Schroth, and Gonzalez-Santiago included both premenopausal and postmenopausal patients, whereas other investigators described postmenopausal patients only. Actually all studies, to some extent, did not account for certain prognostic tumor and/or patient characteristics. The Nowell and Wegman studies may suffer the most from unaccounted possible confounders. However, *CYP2D6* genetic variants are believed to be inherited independent of the inheritance of other genetic traits following Mendel's second law. Studies associating germline genetic

variants that proxy for a modifiable exposure of interest (e.g. endoxifen) to a certain outcome of interest can be considered as analogous to a randomized controlled trial because of what is called "Mendelian randomization" (38). This natural randomization may cause equal distribution of possible confounding factors among genotypes, assuming no association of the *CYP2D6* genotype itself with breast cancer risk or with confounding factors (30, 32, 39–43). Therefore, accounting less for possible confounders will not necessarily lead to a devaluation of the results.

An important factor influencing the possible effect of the *CYP2D6* genotype on tamoxifen response is the concomitant use of *CYP2D6* inhibitors. Selective serotonin reuptake inhibitors are important *CYP2D6*-inhibiting drugs that are frequently used (up to 30%; refs. 12, 19, 44) in breast cancer patients in case of depression or to treat hot flashes, a common side effect of tamoxifen (45). The selective serotonin reuptake inhibitor paroxetine strongly impairs *CYP2D6* activity causing a significant decrease in endoxifen levels especially in extensive metabolizers (12). Goetz found that moderate to severe hot flashes occur more often in extensive metabolizers than in poor metabolizers using tamoxifen (29) possibly causing more selective serotonin reuptake inhibitor use in extensive metabolizers. When *CYP2D6* inhibitors are commonly prescribed in a population especially for extensive metabolizers, the differences in endoxifen levels among the various kinds of metabolizers might be less prominent. Not adjusting for the interaction by comedication may then incorrectly lead to the conclusion that there is no association between the *CYP2D6* genotype and clinical outcome. Goetz used the same 2005 patient data added with medication history in a second publication and accounted for *CYP2D6* inhibitors (46). Also, Gonzalez-Santiago registered concomitant *CYP2D6*-inhibiting drug use. All other authors did not publish information about medication use and probably could not account for *CYP2D6* inhibitors.

Table 1. CYP2D6 allelic frequencies

Allele	Enzyme activity	Major genetic variant*	dbSNP ID †	Allelic frequencies (%)		
				Caucasian ‡ (23, 52–54)	Japan (55)	Tanzania (56)
*1	Normal	Wild-type		32.2-36.4	43	27.8
*2	Normal	2850C>T, 4180G>C	rs16947, rs1135840	28.5-32.4	12.3	40
*2×2	High	Duplication		1-1.3		
*3	Absent	2549delA	rs4986774	1-2		0
*4	Absent	1846G>A	rs3892097	17.2-20.7	0.2	0.9
*5	Absent	CYP2D6 deleted		2-6.9	4.5	6.3
*6	Absent	1707delT	rs5030655	0.9-1.3		0
*9	Reduced	2615_2617delAAG	rs5030656	1.8-2.7		
*10	Reduced	100C>T	rs1065852	1.5-2	38.1	3.8
*17	Reduced	1023C>T, 2850C>T	rs28371706, rs16947			17
*41	Reduced	2988G>A	rs28371725	8.4		

*The CYP2D6 gene is located at chromosome 22: q13.2.

† Reference ID from the NCBI Single Nucleotide Polymorphism database (dbSNP).

‡ European.

Comparison of different genotype groups. Most investigators only studied the most prevalent *4 inactive allele in Caucasians. The *4/*4 genotype represents a poor metabolizer phenotype. The heterozygous genotype is considered either an extensive metabolizer or an intermediate metabolizer phenotype, but probably reflects intermediate endoxifen levels dependent on the extent of functional allele expression. Interindividual variance in endoxifen concentrations is therefore expected to be high. Moreover, it is unclear whether the average endoxifen level in heterozygous patients will be enough to achieve a clinical response as no study has investigated the association between endoxifen levels and clinical outcome. Therefore, there is no justification in combining the heterozygous genotype either with the homozygous *1 or with the homozygous *4 genotype. Goetz combined the *1/*4 genotype with the *1/*1 genotype and compared this group with the *4/*4 genotype. However, other groups shared the heterozygous genotype with the *4/*4 genotype (Tables 1 and 2). Comparison of different genotype groups, probably because of statistical reasons, makes results difficult to compare and could cause misinterpretation.

Worse compliance in extensive metabolizers in nontrial populations. This hypothesis is based upon study results by Rae presented at the San Antonio Breast Cancer Symposium in 2007 (47). Rae showed that patients with a poor metabolizer

phenotype were more likely to adhere to tamoxifen (100% compliance) than were extensive metabolizers, among whom 14% stopped their tamoxifen treatment within one year because of tamoxifen-related side effects. This study was started to confirm the observation by Goetz that extensive metabolizers experienced more hot flashes compared with poor metabolizers, which may subsequently lead to less adherence. If this is true, the compliance of extensive metabolizers may be even worse in nontrial populations where there is less motivation to continue tamoxifen therapy. This may explain the conflicting results between the Goetz study and the Nowell and 2007 Wegman study. Nevertheless, other positive studies (30, 31) also involved nontrial populations. Validating this hypothesis in all six studies seems impossible, because information on compliance is unlikely available. A substantially higher recurrence rate in extensive metabolizers in nontrial populations could only give some support to this hypothesis.

Conclusion on conflicting study results. Despite clear limitations of the studies by Wegman and Nowell, not all criticism is justified. The limiting effect of Mendelian randomization on confounding and limitations of the study designs both of positive and negative studies complicate the drawing of firm conclusions from the present literature. Although some of the criticism on the negative studies is justified, this does not imply that the results should be discarded. To answer the

Table 2. "Positive" studies on mainly Caucasian breast cancer patients using adjuvant tamoxifen: higher recurrence in Poor Metabolizers

Author (population)	Study design	N	Results
Goetz et al. 2005 (29)	*4/*4 vs. 1/*1 + *1/*4	190	RFS HR, 1.86; P = 0.08
Goetz et al. 2007 (ref. 46; trial)			RFS HR, 1.74; P = 0.02 (+ CYP2D6 inhibitors)
Schroth et al. (ref. 30; non-trial)	Rest (*4,*5, *10, *41)* vs. *1/*1	197	EFS HR, 1.89; P = 0.02
Gonzalez-Santiago et al. (ref. 31; non-trial) †	*4/*4 + *1/*4 vs. *1/*1	84	RFS HR, 2.82; P = 0.05

Abbreviations: N, number of patients; RFS, recurrence-free survival; EFS, event-free survival; HR, adjusted hazard ratios.

*Rest group includes all heterozygous and homozygous variant genotypes.

† Abstract at 2007 ASCO Annual Meeting.

Table 3. "Negative" studies on mainly Caucasian breast cancer patients using adjuvant tamoxifen: lower recurrence in Poor Metabolizers

Author (population)	Study design	N	Results
Wegman et al. 2005 (ref. 33; trial)	*4/*4 + *1/*4 vs. 1/*1	76	DRFS HR, <1; nonsignificant
Wegman et al. 2007 (ref. 34; partly trial)	*4/*4 vs. *1/*4 or 1/*1	677	RFS HR, <1; <i>P</i> = 0.055
Nowell et al. (ref. 32; nontrial)	*4/*4 + *1/*4 vs. 1/*1	162	PFS HR, 0.67; <i>P</i> = 0.19

Abbreviations: DRFS, distant recurrence-free survival; PFS, progression-free survival.

question whether in Caucasian populations the *CYP2D6* genotype is a clinically relevant predictive marker for tamoxifen response, all studies should be taken into account.

Additional Study Results

In addition to the studies mentioned above, in which predominantly Caucasian patients were treated in the adjuvant setting, more studies involving different types of populations have been published (Table 4). In two publications an Asian population was analyzed using adjuvant tamoxifen (43, 48). In one publication Korean patients with metastatic breast cancer were studied (49). Bonanni used data from the Italian tamoxifen prevention trial to investigate whether the poor metabolizer phenotype was more common in breast cancer patients than in healthy controls all having used prophylactic tamoxifen (50). The Asian studies found statistically significantly worse clinical outcome (recurrence-free survival, disease-free survival, and time to progression) in the *10/*10 *CYP2D6* genotype, which represents a very frequent intermediate metabolizer phenotype in Asian populations (48%; ref. 43) whereas it is rare in Caucasians. The consistent large effect size in Asians may reflect a racial difference with Caucasians that is of great importance because tamoxifen is more frequently prescribed in Asia than aromatase inhibitors. Italian breast cancer patients more often harbored the *4/*4 (15%) genotype than women who did not develop breast cancer (1.5%) after being treated with prophylactic tamoxifen. All four studies are consistent with the studies by Goetz, Schroth, and Gonzalez-Santiago, although describing different populations.

Conclusion and Discussion

The *CYP2D6* genotype has great potential to become a useful predictive marker for tamoxifen response. Certain

characteristics are beneficial for a marker to become successful (5). Testing of this marker should be cost-effective as well as easy to apply in daily practice. Obviously, the evidence for the predictive value should be unequivocal and the association with clinical outcome should be clinically relevant.

Cost-effectiveness is best illustrated by Punglia who used a statistical model to predict survival of a subgroup of only extensive metabolizers using tamoxifen in the BIG-1-98 trial and compared this group with the other arm using adjuvant letrozole (51). Modelling suggested that among extensive metabolizers, 5-year disease-free survival with tamoxifen is similar or perhaps even superior to that with letrozole. As *CYP2D6* genotyping is not expensive and the costs of aromatase inhibitors are much higher than of tamoxifen, tailored therapy using the *CYP2D6* genotype as a predictive marker could be profitable. The hypothesis that patients with absent or decreased *CYP2D6* activity experience less tamoxifen effect is supported by three out of six retrospective studies involving mainly Caucasian breast cancer patients treated with adjuvant tamoxifen. However, three studies resulted in no or even a contradictory association. Despite the limitations of these studies, the results cannot be discarded. Furthermore, pooled analysis of eligible patients is needed to investigate any clinical relevance of effect on clinical outcome as all separate studies suffer from small sample size.

In conclusion, there are not enough solid data to justify implementation of individual *CYP2D6* genotyping in the adjuvant treatment of breast cancer in Western countries at this moment. Nevertheless, the accumulation of more literature describing other types of populations (Asian, metastatic breast cancer, and prophylactic tamoxifen) strengthens the hypothesis and stresses the need for more validation preferably in well-designed prospective studies. Pharmacogenetic analysis of material from participants in large completed trials comparing different adjuvant hormonal treatment strategies

Table 4. Other studies relating *CYP2D6* genotype to breast cancer risk

Author (population)	Study design	N	Results
Kiyotani et al. (ref. 48; Japanese; adjuvant)	*10/*10 vs. *1/*1	67	RFS HR, 10.04; <i>P</i> = 0.036
Xu et al. (ref. 43; Chinese adjuvant)	*10/*10 vs. *1/*10 + *1/*1	152	DFS HR, 4.7; <i>P</i> = 0.04
Lim et al. (ref. 49; Korean; metastatic breast cancer; partly prospective; <i>N</i> = 12)	*10/*10 vs. *1/*10 + *1/*1	21	TTP, 5.03 vs. 21.8 mo; <i>P</i> = 0.016
Bonanni et al. (ref. 50; Italian; prophylactic tamoxifen)	*4/*4 frequency*	85	15% vs. 1.5%; <i>P</i> = 0.04

Abbreviations: DFS, disease-free survival; TTP, time to progression.

*Breast cancer cases versus healthy controls who used prophylactic tamoxifen.

(e.g. ATAC and BIG-1-98) is especially suitable to obtain rapid results. Additional studies are needed to address some important issues. For example, although the *CYP2D6* genotype predicts endoxifen levels, explained variance of endoxifen levels by *CYP2D6* genotype is low ($R^2 = 0.23$; ref. 19), partly suggesting the involvement of other enzymes. Moreover, it is unclear whether endoxifen plasma concentration in turn predicts tamoxifen response. Investigating a direct relationship of endoxifen plasma concentration with clinical outcome is imperative. To achieve better understanding of variation in endoxifen level and its possible effect on tamoxifen response, all relevant variant alleles of *CYP2D6* and of other involved enzymes should be studied. Comparison of separate *CYP2D6* phenotypes instead of genotype combinations may avoid misinterpretation of results. If a gene-dose effect is assumed, the use of statistical tests accounting for such an effect is preferable. Different treatment strategies, guided by *CYP2D6* genotype, need to be explored in randomized trials if implementation in clinical practice is our goal. An alternative therapy for poor metabolizers and even intermediate metabolizers may be an aromatase inhibitor or an escalated tamoxifen dose to increase plasma endoxifen concentrations. At the Leiden University Medical Center, the Netherlands, a prospective study is ongoing associating *CYP2D6* phenotype determined by single nucleotide polymorphism array and endoxifen

plasma concentration with breast cancer recurrence and survival. The possibility of increasing the endoxifen plasma concentration by temporarily escalating tamoxifen dosage in poor metabolizers and intermediate metabolizers is also investigated.

Tamoxifen has long proven to be an effective drug with low toxicity. In adjuvant trials in postmenopausal women, only small survival benefits are shown with aromatase inhibitors. In the adjuvant setting among premenopausal patients and male breast cancer patients, tamoxifen is still the most important hormonal therapy. In our opinion, tamoxifen may remain an important adjuvant drug also in postmenopausal women, when patients who profit most from tamoxifen can be selected by *CYP2D6* genotype. *CYP2D6* genotyping and pharmacogenetics in general still hold great promise in individualizing hormonal therapy in breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Dr. J.G. van der Bom, epidemiologist at the Leiden University Medical Center for valuable discussions.

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