

Tamoxifen and CYP2D6

A Controversy in Pharmacogenetics

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BOOK CHAPTER:

Tamoxifen and CYP2D6: a controversy in pharmacogenetics

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ABSTRACT

Tamoxifen reduces the rate of breast cancer recurrence by about one-half. It is converted to more active metabolites by enzymes encoded by polymorphic genes, including cytochrome P450 2D6 (CYP2D6), and transported by ATP-binding cassette (ABC) transporters. Genetic polymorphisms that confer reduced CYP2D6 activity or concurrent use of CYP2D6 inhibiting drugs may reduce the clinical efficacy of tamoxifen. The issue of the clinical utility of CYP2D6 genotype testing is subject to considerable and ongoing academic and clinical controversy. In this chapter, we outline tamoxifen's clinical pharmacology and give an overview of the research to date on the association between CYP2D6 inhibition and tamoxifen effectiveness. Based on the evidence to date, the impact of drug-induced and/or gene-induced inhibition of CYP2D6 activity is likely to be null or small, or at most moderate in subjects carrying two reduced function alleles. Future research should examine the effect of polymorphisms in genes encoding enzymes in tamoxifen's complete metabolic pathway, should comprehensively evaluate other biomarkers that affect tamoxifen effectiveness, such as the transport enzymes, and focus on subgroups of patients, such as premenopausal breast cancer patients, for whom tamoxifen is the only guideline approved endocrine therapy.

Keywords: Breast cancer, tamoxifen, pharmacogenetics, breast cancer recurrence, cytochrome P450 2D6, polymorphism, selective serotonin reuptake inhibitor, ATP-binding cassette transporter, Hardy-Weinberg Equilibrium

Abbreviations

ABC: Adenosine tyrosine phosphate binding cassette
AI: aromatase inhibitor
ATAC: Arimidex, Tamoxifen, Allone or in Combination
ATP: adenosine-tyrosine phosphate
BCRP: breast cancer resistance protein
BIG 1-98: Breast International Group 1-98
CYP: cytochrome P450
CYPTAM: cytochrome p450 tamoxifen
DNA: deoxyribonucleotide acid
EM: extensive metabolizer
ER α : estrogen receptor α
ER β : estrogen receptor β
FFPE: formalin-fixed paraffin-embedded
Hardy-Weinberg Equilibrium: HWE
IM: intermediate metabolizer
LOH: loss of heterozygosity
MDR1: multidrug resistance 1
MRP: multidrug resistance protein
P-glycoprotein: Pgp
PM: poor metabolizer
SERM: selective serotonin reuptake modulator
SNP: single nucleotide polymorphism
SSNRI: Selective norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TEAM: tamoxifen exemestane adjuvant multinational
UGT: UDP-glucuronosyltransferase
UM: ultrarapid metabolizer

Introduction

Tamoxifen is a selective estrogen receptor modulator (SERM). For almost 40 years, it has been used in routine clinical practice to target the growth of hormone-responsive breast tumors.(Jordan, 2008) Tamoxifen competes with estrogen for binding to the estrogen receptor α (ER α). Tamoxifen is the only endocrine therapy recommended for premenopausal women with breast tumors that express ER α .(NCCN practice guidelines in oncology, breast cancer - v.2.2014. invasive breast cancer, adjuvant endocrine therapy.2014; Jordan et al., 2011) Tamoxifen is an important alternate or sequential treatment to AIs among postmenopausal breast cancer patients whose tumors express ER α , depending on their risk of treatment-induced side-effects.(NCCN practice guidelines in oncology, breast cancer - v.2.2011. invasive breast cancer, adjuvant endocrine therapy.2010)

Five years of adjuvant tamoxifen therapy reduces the risk of breast cancer recurrence by almost one-half;(Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. swedish breast cancer cooperative group.1996; Early Breast Cancer Trialists' Collaborative Group (EBCTCG) et al., 2011; Early Breast Cancer Trialists,Collaborative Group, 2005) with further long-term survival benefit evident after ten years of tamoxifen treatment.(Davies et al., 2013; Gray et al., 2008) Despite the effectiveness of tamoxifen, patients with identical prognostic factors at diagnosis can vary substantially in their disease clinical course and treatment response. Some patients develop recurrent breast cancer resistant to tamoxifen, and eventually die of their disease.

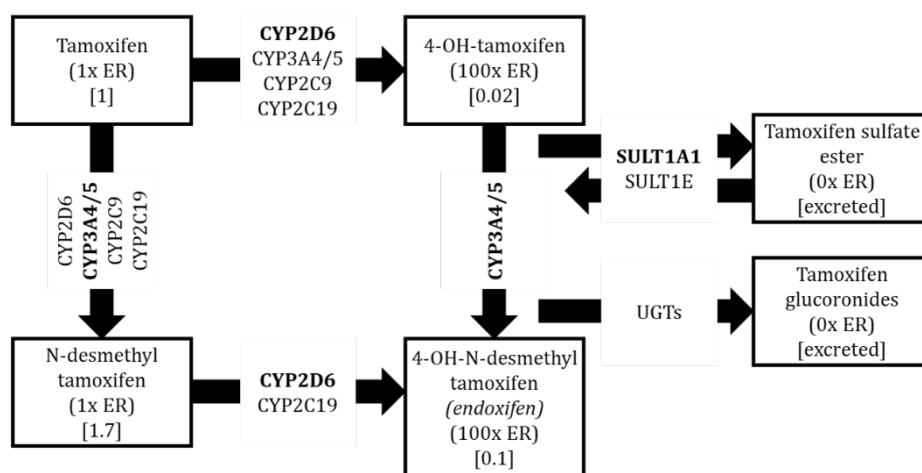
Intensive international research has investigated mechanisms of resistance to endocrine therapy. However, biomarkers of resistance, beyond ER α , remain elusive. A major challenge to the clinical course of breast cancer and outcomes of the disease is to improve the understanding of mechanisms of endocrine therapy resistance, particularly identifying

biomarkers that determine response to tamoxifen treatment, thereby enabling the development of more specific targeted therapies.

Tamoxifen metabolism

A series of cytochrome P450 (CYP) enzymes catalyze the conversion of tamoxifen to its more active derivatives—4-hydroxy-tamoxifen, N-desmethyltamoxifen, and 4-hydroxy-N-desmethyltamoxifen, also called endoxifen (*Figure 1: metabolic path*). (Jordan, Collins, Rowsby, & Prestwich, 1977; Lien, Solheim, Kvinnsland, & Ueland, 1988; Stearns et al., 2003) Each metabolite has its own specific binding affinity for ER α . The tamoxifen metabolites with the highest binding affinities for the ER α are hydroxylated at tamoxifen's four-carbon. The UDP-glucuronosyltransferase enzymes (UGTs, primarily UGT1A8, UGT1A10, UGT2B7 and UGT2B15), (Ahern et

Figure 1: Tamoxifen metabolic pathway



al., 2011; Lazarus, Blevins-Primeau, Zheng, & Sun, 2009) and sulfotransferase enzymes (primarily SULT1A1) (Gjerde et al., 2008) catalyze the

conversion of the tamoxifen metabolites into excretable forms. All enzymes in tamoxifen's metabolic pathway are encoded by polymorphic genes each with distinctive characteristics of allele frequencies and functional significance. Thus, individual differences in tamoxifen metabolism may contribute to variation in the serum metabolite concentration, which may in turn impact tamoxifen effectiveness.

Tamoxifen transport

Tamoxifen is transported by members of the ATP-binding cassette (ABC) transporters—ABCB1 (P-glycoprotein or P-gp/MDR1), ABCC1 (breast cancer resistance protein or BRCP), and ABCC2 (multidrug resistance associated protein 2 or MRP2). ABC transporters are normally expressed at the luminal side of enterocytes, on brain capillary endothelial cells, in the bile canaliculi, and in the proximal tubules of the kidney in germ-line cells. The ABC transporters transport a wide variety of toxins, nutrients, environmental carcinogens, and drugs out of the cells. Given their role in drug efflux, ABC transporters are often overexpressed in cancer cells, where they may mediate drug resistance, and potentially promote cancer cell survival. (Amiri-Kordestani, Basseville, Kurdziel, Fojo, & Bates, 2012; International Transporter Consortium et al., 2010; Lai et al., 2012; Leslie, Deeley, & Cole, 2005; Reed & Parissenti, 2011) The primary ER-binding metabolites of tamoxifen—endoxifen and 4-hydroxytamoxifen — also bind ABCB1. These metabolites are substrates of the ABCB1 transporter. (Iusuf et al., 2011; Teft, Mansell, & Kim, 2011)

Similar to CYP enzymes, polymorphic genes encode the ABC transporters. Polymorphisms that increase the expression of the transporters, enhance drug efflux, and in theory, may reduce the effectiveness of cancer-directed therapy. Yet, the association of genetic polymorphisms in the ABC transporters with tamoxifen effectiveness is poorly understood, as we discuss further below.

Taken together, tamoxifen metabolism and transport is complex and involves multiple enzymes and transporters, all encoded by highly polymorphic genes. Despite this, the majority of studies to date have investigated the association of one enzyme, CYP2D6, and tamoxifen effectiveness. In this chapter, we outline the research to date on the association of CYP2D6 inhibition and tamoxifen effectiveness in breast cancer patients. We highlight some controversies including studies where genotyping results have deviated from Hardy-

Weinburg Equilibrium (HWE) and the potential for loss of heterozygosity (LOH) at the CYP2D6 locus, which may result in genotype misclassification. We evaluate studies where researchers have taken a more complete approach to investigating gene-induced tamoxifen inhibition, namely by comprehensively genotyping enzymes and transporters in the tamoxifen pathway. We also highlight areas that require further investigation including the need for studies specifically focused on pre-menopausal women, for whom other endocrine therapies, such as aromatase inhibitors (AIs) are contraindicated. (NCCN practice guidelines in oncology, breast cancer - v.2.2014. invasive breast cancer, adjuvant endocrine therapy.2014; Jordan et al., 2011) Finally, we highlight the need for research on other biomarkers, which may impact tamoxifen effectiveness.

CYP2D6 & tamoxifen metabolism

Tamoxifen is sometimes referred to as a prodrug, which implies that it is biologically inactive in its administered form. (Goetz, Kamal, & Ames, 2008) However, as administered, tamoxifen has a weak affinity toward the ER, so the term prodrug is not entirely accurate. A number of CYP enzymes convert tamoxifen to its metabolites in complex parallel and serial pathways. Although the metabolites are present at substantially lower concentrations than the administered drug, they have a higher affinity toward the ER. CYP2D6 metabolises tamoxifen to endoxifen, the most abundant of the high-affinity 4-hydroxylated metabolites. Endoxifen is found at substantially lower concentrations than tamoxifen but has 100-fold higher affinity toward the ER α . (M. D. Johnson et al., 2004; Lim, Desta, Flockhart, & Skaar, 2005) It is therefore considered the key tamoxifen metabolite and is likely the most biologically active and important molecule among tamoxifen and its myriad of primary and secondary metabolites. Low serum concentrations of endoxifen, but not the other tamoxifen

metabolites, have been correlated with an increased risk of recurrent or new primary breast cancer. (Madlensky et al., 2011; Saladores et al., 2015) Endoxifen is therefore considered the key metabolite in modulating the estrogen receptor pathway. (Madlensky et al., 2011)

The CYP2D6 gene is highly polymorphic. CYP2D6 has over 100 distinct variants, and frequent gene duplications and deletions (<http://www.cypalleles.ki.se/cyp2d6.htm>). Several CYP2D6 variants can reduce or eliminate enzymatic activity. (Hu et al., 2016) This genetic variability results in considerable phenotypical variation in CYP2D6 activity between patients. Thus, theoretically, the effectiveness of tamoxifen may be related to an individual's CYP2D6 activity. With the notable exception of a complete gene deletion (as in the case of *CYP2D6*5*), or the inheritance of two alleles associated with a complete loss-of-function (most importantly the *CYP2D6*4* allele), substantial controversy surrounds the assignment of functional phenotype according to *CYP2D6* genotype. (J. K. Hicks, Swen, & Gaedigk, 2014) Based on *CYP2D6* genotype combinations, patients can be classified in four categories. Poor metabolizers (PM) are those with no or minimal enzymatic activity due to two inactive alleles. Intermediate metabolizers (IM) have reduced activity owing to two decreased activity alleles or one active and one inactive allele. Extensive metabolizers (EM) have normal enzymatic activity due to no variants or only one decreased activity allele. Ultrarapid metabolizers (UM) have greater than normal enzymatic activity either due to gene duplication or no inactive variants. (Zanger, Raimundo, & Eichelbaum, 2004) Metabolic activity correlates with steady-state endoxifen levels. (M. D. Johnson et al., 2004; Lien et al., 1988) Accordingly, poor metabolizers appear to have the lowest plasma endoxifen levels. (Helland et al., 2017; Madlensky et al., 2011) Extensive metabolizers have slightly higher Z-endoxifen concentrations than intermediate metabolizers. (Madlensky et al., 2011)

Some research suggests that the total concentration of tamoxifen and its metabolites is sufficiently high so as to overwhelm and inhibit estrogen binding to the estrogen receptor, irrespective of an individual's CYP2D6 genotype and phenotype. (Lash, Lien, Sorensen, & Hamilton-Dutoit, 2009) This may be especially relevant in premenopausal women as they have higher estrogen concentrations compared with their postmenopausal counterparts. (Burger, Hale, Dennerstein, & Robertson, 2008; Fan et al., 2009; Freour, Barriere, & Masson, 2017) Accordingly, reduction in tamoxifen metabolite concentrations could potentially reduce the competition with estrogen for binding to ER α . (D. P. Cronin-Fenton, Dankier, & Lash, 2013)

Studies on drug-induced inhibition of tamoxifen metabolism

Tamoxifen induces mild to moderate adverse effects, including hot flashes and vasomotor symptoms, but more rare and more severe adverse reactions including depression, venous thromboembolism, and endometrial cancer have also been reported. (Baum et al., 2002; Biglia et al., 2005; Deitcher & Gomes, 2004; Demissie, Silliman, & Lash, 2001; Fisher et al., 2005; Henry et al., 2009; Swerdlow & Jones, 2005) About one-quarter of women who use tamoxifen are co-prescribed selective serotonin reuptake inhibitors (SSRIs) to alleviate symptoms of depression and / or to treat the vasomotor side effects associated with tamoxifen therapy. SSRIs inhibit CYP2D6 to varying degrees. (Borges et al., 2006; Jin et al., 2005) Concurrent use of SSRIs and tamoxifen can therefore result in competitive or direct inhibition of tamoxifen metabolism. The net effect is a reduced plasma concentration of the tamoxifen metabolite, endoxifen. (Jin et al., 2005; Stearns et al., 2003) Substantial reductions in endoxifen plasma concentrations — comparable to those observed in homozygous carriers of the *CYP2D6*4* variant allele — have been observed in patients

using strong CYP2D6 inhibitors (i.e., paroxetine or sertraline) concurrent to tamoxifen, but not among those using the weaker CYP2D6 inhibitors citalopram or venlafaxine. (Jin et al., 2005) Concerns have therefore been raised regarding the safety of using these drugs concomitant to tamoxifen treatment. (D. Cronin-Fenton, Lash, & Sorensen, 2010; Sideras et al., 2010)

Paroxetine and fluoxetine are the most potent and effective CYP2D6-inhibiting SSRIs. Research suggests that concomitant use of these drugs converts phenotypically extensive or intermediate CYP2D6 metabolizers into poor metabolizers—phenotypically equivalent to subjects carrying two non-functional *CYP2D6* alleles. In contrast, other SSRIs, citalopram, escitalopram, sertraline, and fluvoxamine, are weak inhibitors of CYP2D6. Women who use paroxetine or fluoxetine concurrent to tamoxifen have lower serum endoxifen concentrations. Intermediate plasma endoxifen concentrations have been observed in women using the weaker CYP2D6 inhibitors, sertraline and citalopram, concurrent to tamoxifen, and little to no impact on endoxifen concentrations associated with concurrent use of the selective serotonin norepinephrine reuptake inhibitor (SSNRI) venlafaxine—a weak CYP2D6 inhibitor. (Borges et al., 2006; Borges et al., 2010; Jin et al., 2005; Stearns et al., 2003)

The clinical epidemiology studies investigating the association of concurrent use of SSRIs and tamoxifen with breast cancer recurrence have heterogeneous findings. We have previously conducted a quantitative and qualitative review outlining the association of drug-induced inhibition of tamoxifen metabolism with breast cancer recurrence and mortality. (D. P. Cronin-Fenton et al., 2013) From a total of eight studies of weak CYP2D6 inhibitor drugs, a random effects meta-analytic model suggested little evidence of an association between concurrent use of weak CYP2D6 inhibitors and breast cancer recurrence/survival among tamoxifen-treated women (effect estimate = 1.05, 95%CI=0.91, 1.22). Likewise, our meta-

analysis suggested little evidence of an increased risk of breast cancer recurrence/survival among tamoxifen-treated women who concurrently used strong CYP2D6 inhibitors (effect estimate = 1.03, 95%CI=0.86, 1.23).

Since the publication of the meta-analysis in 2014, a further four studies (Chubak et al., 2016; Donneyong et al., 2016; Haque et al., 2015; Valachis et al., 2016) investigated the impact of CYP2D6 inhibitor drugs on breast cancer recurrence/survival. However, similar to the preceding studies, the conclusions of these studies are somewhat ambiguous.

In a cohort study based on electronic pharmacy records in the US, Chubak and colleagues observed an increased rate of breast cancer recurrence among women who used paroxetine concurrent to their tamoxifen.(Chubak et al., 2016) In contrast, they found little evidence of an increased recurrence rate associated with use of fluoxetine—a SSRI with CYP2D6 potency equivalent to that of paroxetine. However, the study may be prone to information bias as information on breast cancer recurrence was obtained by medical record review. Also in a US-based cohort of 16,887 survivors of non-metastatic breast cancer,(Haque et al., 2015) Haque and coworkers investigated the association of concurrent use of strong or weak CYP2D6 inhibitors with the risk of new breast cancer—defined as breast cancer recurrence, metastases, or contralateral breast cancer. In a median follow-up of six years, they observed little evidence of an increased rate of new breast cancers among concurrent users of tamoxifen and any SSRIs. The null findings remained robust irrespective of the strength of the CYP2D6 inhibiting drug, or the use of other non-SSRI anti-depressants. A Swedish nested case-control study by Valachis et al.,(Valachis et al., 2016) also concluded no excess risk of breast-cancer specific mortality associated with concurrent use of SSRIs and tamoxifen. This null finding was evident even among users of strong CYP2D6-inhibiting SSRIs. In an overlapping cohort study, Valachis et al observed lower adherence to endocrine therapy among patients who used SSRIs either before or after breast cancer,

except among those patients who had more than 50% concurrent periods of use of SSRI use and endocrine therapy. Non-adherence to endocrine therapy correlated with poorer survival.

Finally, Donneyong et al used data from five US databases to investigate the association of potent CYP2D6 inhibitors (paroxetine and fluoxetine) with mortality in breast cancer patients. (Donneyong et al., 2016) They stratified SSRI exposure by their CYP2D6 inhibiting potential: patients who used an effective CYP2D6 inhibiting SSRI concurrent to tamoxifen (i.e., paroxetine and fluoxetine), and those who used a moderate or poor CYP2D6 inhibitor (citalopram, escitalopram, fluvoxamine, and sertraline) concurrent to tamoxifen. Their study included two cohorts—6,067 patients who initiated SSRI use during tamoxifen treatment, and 8,465 patients who were prevalent SSRI users at the time they initiated tamoxifen treatment. Median follow-up time was 2.2 (interquartile range 0.9-4.5) and 2.0 (0.8-3.9) years, respectively. They incorporated propensity scores estimating the probability of exposure to potent versus non-potent SSRIs, to account for potential confounding. Overall, they observed no evidence of an association of potent SSRI use with outcomes in tamoxifen-treated patients. However, an analysis stratified at age 50—as a proxy for menopausal status—suggested higher mortality associated with effective CYP2D6 inhibiting SSRI use concurrent to tamoxifen among women aged less than 50 at the time of their breast cancer diagnosis.

Limitations of the pharmacoepidemiological drug-drug interaction studies

The pharmacoepidemiology studies have several limitations, which are relevant when investigating the tamoxifen-SSRI interaction using pharmacoepidemiology techniques. An editorial of the Donneyong paper highlighted some of these limitations. (Juurlink, 2016) The potential interaction between tamoxifen and SSRIs is not a short-term effect, but may take

years to manifest an impact on breast cancer recurrence or mortality. Several papers had relatively short follow-up.(Donneyong et al., 2016) Others including a general outcome of mortality, rather than a cancer-specific endpoint, such as recurrence. In addition, other issues including a lack of data on adherence to treatment, the challenge of incorporating information on switching from one SSRI to another, and failure to detect a dose-response effect. Furthermore, few studies have considered the combination of gene-induced and drug-induced inhibition of tamoxifen metabolism, which may be most important to tamoxifen effectiveness. Taken together, these drug-drug interaction studies highlight a need for a greater understanding of the impact of concurrent use of CYP2D6-inhibiting drugs on tamoxifen metabolism using an endpoint of recurrence rather than mortality.

Studies on pharmacogenetically reduced tamoxifen metabolism

The association of CYP2D6 genotype and tamoxifen effectiveness is one of the most researched and disputed pharmacogenetic controversies.(D. P. Cronin-Fenton et al., 2013) Myriad studies conducted in observational settings, clinical series, or nested within clinical trials, have investigated the putative association between *CYP2D6* genotype and tamoxifen effectiveness.⁵²⁻⁷⁵ In our afore-mentioned meta-analysis,(D. P. Cronin-Fenton et al., 2013) we also comprehensively reviewed the studies of CYP2D6 genotype variants and associations to outcomes in breast cancer patients among studies published through March 2013. The findings from the published studies were highly discordant, with effect estimates ranging from a 50% decrease in the risk of recurrence or mortality, to a 12-fold increase in the risk of breast cancer recurrence or mortality among carriers of variant *CYP2D6*. Based on the evidence, we concluded that the impact of genetically reduced CYP2D6 activity on

tamoxifen effectiveness was likely null or small, or at best moderate among carriers of two reduced function alleles.

Studies were very heterogeneous with respect to design, study population, specific CYP2D6 allele coverage, genotyping methodology and DNA source material. As outlined in our meta-analysis, the published research had substantial limitations. These include small sample size yielding imprecise estimates, and retrospective data collection increasing a potential for information bias. Several studies incorrectly classified exposed person-time yielding immortal person-time bias. (Kiyotani et al., 2010; Lash et al., 2008; Xu et al., 2008) The *CYP2D6*4* variant is most common among Caucasians and this allele confers true null-activity, i.e. homozygotes have no CYP2D6 activity. The **10* allele which occurs frequently among Asians however, confers reduced enzyme activity. Clinical data on enzyme activity (phenotype) in subjects carrying two **10* alleles clearly suggest clinically meaningful enzymatic activity. While inferring phenotype and in vivo enzyme activity from IM genotypes has not met absolute scientific consensus, such is also in accordance with the phenotype classification suggested by Hicks et al (B. M. Hicks, Murray, Powe, Hughes, & Cardwell, 2013) and Gaedigk (Gaedigk, 2013). Despite this, the highest effect estimates were observed in Asian populations evaluating the **10* variant — counterintuitive to the underlying biologic rationale. (D. P. Cronin-Fenton et al., 2013) In addition, it seems plausible that overall tamoxifen effectiveness would depend on the activity of all the enzymes in the entire pathway, and their interaction, rather than on polymorphisms in a single gene. A widespread limitation of the research to date is a failure to comprehensively genotype the complete tamoxifen metabolic pathway. Taken together, we were unable to detect a consistent anomaly, which could explain the discrepant findings.

For the afore-mentioned meta-analysis, we used PubMed to retrieve articles on “tamoxifen” and “CYP2D6”, and searched the reference lists of the retrieved papers, including those that had cited those previously published. Since the publication of our meta-analysis, using the same search criteria through November 2017 (D. P. Cronin-Fenton et al., 2013), over 20 additional published studies have investigated the impact of *CYP2D6* genetic polymorphisms on breast cancer prognosis. (Argalacsova, Slanar, Bakhouché, & Pertuzelka, 2017; Chamnanphon et al., 2013; De Almeida Melo et al., 2016; Dezentje et al., 2013; Dezentje et al., 2015; Goetz et al., 2017; Hertz et al., 2017; Johansson et al., 2016; Lei et al., 2016; Marcatth et al., 2017; Markkula, Hjertberg, Rose, Ingvar, & Jernstrom, 2014; Martins, Vidal, Souza, Brusaca, & Brito, 2014; Mwinyi et al., 2014; Powers et al., 2016; Sanchez Spitman et al., 2017; Sanchez-Spitman et al., 2017; Sensorn et al., 2013; Zhang et al., 2015) Most suggest little evidence of an association of the *CYP2D6* *4 or *10 variant with recurrence and mortality in tamoxifen-treated breast cancer patients. Here, we provide some highlight some of these studies.

Several of the more recently published studies were restricted to considering one variant or a limited number of variants in a single gene. De Almeida Melo et al (2016) reported no correlation of *CYP2D6**4, *10 or *17 with breast cancer prognosis among 40 ER+ non-metastatic patients, and 40 metastatic patients. (De Almeida Melo et al., 2016) Martins et al also showed no correlation of *CYP2D6* (*3, *4, *10) with recurrence/mortality in a cohort of 58 patients, 47% of whom were premenopausal at the time of breast cancer diagnosis. (Martins et al., 2014) Yazdi et al., genotyped the *CYP2D6**4 variant and used this to predict phenotype. (Yazdi et al., 2015) In a study of 101 patients followed for a minimum of three years, they observed a decreased risk of recurrence among *CYP2D6* EM patients with HER2+ tumors. However, for all three studies, sample size was quite small consequently yielding imprecise estimates and questionable statistical power.

Comprehensive genotyping:

Up to recently, the only study to comprehensively genotype the enzymes relevant to the tamoxifen metabolic pathway was conducted in the cancer prevention setting. Borges et al evaluated polymorphisms in the genes encoding the entire tamoxifen metabolic path among women at high risk of breast cancer. (Borges et al., 2010) Overall, the study failed to observe a strong association of single *CYP2D6* variants and breast cancer incidence. *CYP2D6* was identified as a key node in the metabolic path, interacting with several variant alleles in other tamoxifen-metabolizing genes.

More recently, studies conducted in the treatment setting have increasingly integrated more comprehensive genotyping — recognizing that tamoxifen effectiveness is likely to hinge on multiple variants in several genes, rather than on single SNPs. A population-based cohort study by Hertz et al genotyped six *CYP2D6* variants and copy number variants among 500 tamoxifen-treated patients and 500 ER+ patients who did not undergo systemic therapy. (Hertz et al., 2017) The design of the study is commendable, and somewhat similar to a previously published case-control study design. (Lash et al., 2011) The tamoxifen-treated cohort aimed to address the utility of *CYP2D6* as a *predictor* of tamoxifen effectiveness (*i.e., a determinant of response to tamoxifen treatment*). On the other hand, the ER+ non-tamoxifen-treated cohort aimed to elucidate the utility of *CYP2D6* as a *prognostic* indicator (*i.e., a determinant of breast cancer prognosis in the absence of tamoxifen treatment*). The Hertz study showed no correlation between *CYP2D6* polymorphisms and recurrence risk in tamoxifen-treated patients in univariate analyses. Adjusted analyses suggested an increased risk of recurrence among patients with increased, rather than the hypothesized decreased, *CYP2D6* activity. Furthermore, among the non-treated ER+ patients, higher *CYP2D6*

activity correlated with prolonged recurrence-free survival. These conflicting findings does not align well to the suggested biologic rationale, and preclude any inference of a true association of *CYP2D6* genotype with outcomes in breast cancer patients.

A study by Markkula et al also took a more comprehensive approach to genotyping, examining the association of *CYP2D6* genotypes (*3, *4, *6, *10, *41) with second breast events (recurrence, contralateral breast cancer, or death) among 634 patients, 333 of whom had ER+ tumors and received tamoxifen therapy. (Markkula et al., 2014) Blood samples drawn at the time of breast cancer diagnosis were used as a source of DNA for genotyping. In a median follow-up of 4.9 years, they also concluded that there was no evidence of an association between *CYP2D6* genotype and second breast events.

Several studies have studied prediction of *CYP2D6* functional status from genotype combinations. (Dezentje et al., 2013; Hertz et al., 2017; Johansson et al., 2016; Karle et al., 2013; Marcath et al., 2017; Sanchez Spitman et al., 2017) A study by Marcath et al, including 302 tamoxifen-treated patients predicted phenotype based on genotypes of 19 enzymes and transporters and correlated these with endoxifen concentration. (Marcath et al., 2017) *CYP2C9* was the only gene that appeared to correlate with endoxifen concentrations. In contrast, Sanchez Spitman studied the combined impact of *CYP2D6* genotypes, *CYP3A4**22 and *CYP3A5**3 on tamoxifen metabolite concentrations in the sera of 667 women enrolled in the CYPTAM study. (Sanchez Spitman et al., 2017) They found little evidence of a meaningful role of the studied *CYP3A4* variant alleles. Highest tamoxifen metabolite concentrations were observed among carriers of the *CYP3A4**22 variant. However, the effect was small and deemed unlikely of clinical relevance.

Johansson et al pooled data from four randomized breast cancer prevention trials, including 367 patients followed for a median of 11 years. (Johansson et al., 2016) They

genotyped 13 SNPs in the *CYP2D6* gene and used these to predict functional metabolizer status. They observed lower recurrence rates in rapid metabolizers compared with slow metabolizers. They also observed higher endoxifen and 4-hydroxytamoxifen levels associated with decreased insulin-like growth factor I — making an important inference that other biomarkers may also impact tamoxifen effectiveness.

We have not focused on the association of the pharmacogenetics of tamoxifen and survival in metastatic patients. However, three recent studies suggest a correlation of *CYP2D6* mutations with decreased progression-free survival in patients with advanced breast cancer. (De Almeida Melo et al., 2016; Goetz et al., 2017; Karle et al., 2013) However, the studies included fewer than 100 patients, thus estimates were imprecise. In addition, the clinical significance of investigating the association of *CYP2D6* polymorphisms and prognosis in *metastatic* breast cancer patients remains unclear, as these patients are likely to have treatment-refractory disease.

Use of tumor-infiltrated DNA for genotyping

Source DNA for the study of the pharmacogenetics of tamoxifen remains a divisive issue. (Goetz et al., 2014; Pharoah, Abraham, & Caldas, 2012; Stanton, 2012) From a practical standpoint, formalin-fixed and paraffin-embedded (FFPE) tissue represent an important resource in most settings, but careful considerations on the quality of the extracted DNA should be made. (Wheeler, Maitland, Dolan, Cox, & Ratain, 2013)

A major controversy particularly pertinent to *CYP2D6* polymorphisms and tamoxifen effectiveness is the validity of using DNA derived from tumor tissue rather than genomic DNA. Two studies nested within two prospective clinical trials — Breast International Group

(BIG 1-98) and the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial — genotyped seven and eight CYP2D6 variant alleles, respectively.(Rae et al., 2012; Regan et al., 2012) Although the results of both studies were highly anticipated, neither study reported a positive association between reduced CYP2D6 function and breast cancer recurrence. However, the validity of the genotyping in both studies has been questioned as the *CYP2D6* allele frequencies departed substantially from Hardy-Weinberg equilibrium (HWE). Deviations from HWE can occur due to sampling error, nonrandom mating, or population admixture due to the inclusion of multiethnic genotype frequencies. The latter may be particularly relevant to the BIG 1-98 and ATAC trials, which were included patients from multiple countries.(Deng, 2001) Deviations from HWE may imply genotyping error.

In addition, BIG 1-98 and the ATAC trial studies used DNA derived from formalin-fixed paraffin embedded (FFPE) tumor tissue, which some believe may lead to important genotyping error.(Goetz et al., 2014; Pharoah et al., 2012; Stanton, 2012) Use of tumor-derived DNA may lead to germline genotype misclassification from loss of heterozygosity (LOH) at the *CYP2D6* locus (chromosome 22q13). Approximately 40% of ER+ breast tumors show a LOH near the *CYP2D6* locus.(Ellsworth et al., 2003; Goetz et al., 2014; Hirano et al., 2001; J. A. Johnson, Hamadeh, & Langae, 2015; Sheng et al., 1996) LOH can arise from chromosomal instability in tumor tissue leading to loss of an allele in the tumor DNA, and incorrect genotype assignment. Genotyping tumor-derived DNA can therefore inflate the proportion of homozygotes, and underestimate the proportion of heterozygotes in the germline DNA. However, except for microdissected tumor tissue, DNA extracted from tumor-infiltrated tissue is likely to contain germline information from surrounding stromal and immune cells. As tamoxifen is primarily metabolized in the liver, it is the germline genotype, and not the

tumor genotype, that potentially determines the impact of *CYP2D6* polymorphisms on tamoxifen effectiveness.

Several concordance studies have compared *CYP2D6* genotype in DNA derived from tumors with that from blood or adjacent marginal or non-malignant tissue. (Ahern et al., 2010; Goetz et al., 2005; Rae et al., 2003; Rae et al., 2013; Schneider et al., 2006; Thompson et al., 2011; Xie et al., 2006) These validation studies report near perfect concordance, with the exception of a study by Goetz et al., (Goetz et al., 2005) that observed LOH at the *CYP2D6* locus and 20% genotyping misclassification between the FFPE tumor and non-tumor tissue. Goetz et al concluded that tumor-derived DNA was not representative of germline DNA at the *CYP2D6* locus. The reasons underlying the discordance in the Goetz study versus the concordance observed in the previously published studies are unclear. In accordance with suggestions made by Berry, (D. Berry, 2013; D. A. Berry, 2014) we investigated the extent of potential misclassification by conducting a quantitative bias analysis on the 31 studies that investigated the impact of *CYP2D6* genotype and breast cancer outcomes. We observed little evidence of bias by discordant genotype, and no variation to the overall effect estimates, with or without bias adjustment. (Ahern et al., 2017) This is a landmark finding and suggests that studies using archived FFPE tumor tissue as a source of DNA are valid for genotyping the *CYP2D6* locus.

To date, one study that investigated *CYP2D6* and breast cancer outcomes incorporated a sensitivity analysis to assess the potential impact of LOH due to the use of FFPE tumor-derived DNA. (Dezentje et al., 2013) The study was nested within the tamoxifen exemestane adjuvant multinational (TEAM) trial and genotyped five *CYP2D6* (*CYP2D6* *3, *4, *6, *14, *41) alleles in 731 tamoxifen-treated patients. *CYP2D6* genotype and functional phenotype was correlated with disease-free survival (time from tamoxifen randomization to tamoxifen

discontinuation). Three microsatellite markers adjacent to the *CYP2D6* locus were assessed for potential LOH, resulting in the exclusion of 14 (2-3%) patients due to suspected LOH. Although overall genotype frequencies deviated from HWE, the frequencies were consistent with others reported in the literature. Notably, *CYP2D6* genotype did not correlate with disease-free survival, irrespective of the inclusion or exclusion of patients with potential LOH.

Perspectives

Several critically important yet sparsely researched issues require consideration to substantiate a better understanding of the interaction between *CYP2D6* genotypes and tamoxifen efficacy.

1. Comprehensive genotyping:

CYP2D6 is, while arguably the most important, just one enzyme in an intricate metabolic pathway of parallel and serial enzymatic conversions of tamoxifen and its metabolites. Further understanding of the contribution and impact of all polymorphic genes in tamoxifen's metabolic path is therefore urgently needed. Up to recently, the statistical models required to evaluate complex gene-gene interactions had not been well-developed. (Baurley, Conti, Gauderman, & Thomas, 2010) However, Bayesian pathway modeling offers an approach to better understand and identify the interaction of multiple metabolites with different affinities for ER α . Incorporating empirical Bayes shrinkage methods could reduce the potential for false positive interactions due to multiple comparisons. Methods such as the Algorithm for Learning Pathway Structure, which incorporates Bayesian

analysis, can provide an estimate of the effect of the tamoxifen metabolic pathway on breast cancer recurrence.

2. Genetically reduced CYP2D6 activity may have greatest impact on tamoxifen effectiveness in premenopausal breast cancer patients

Tamoxifen is the sole guideline-recommended endocrine treatment for premenopausal women. Despite this, studies to date have for the most part included postmenopausal women or, included a low prevalence of premenopausal patients. As premenopausal women account for about one-third of all breast cancer patients, and more than half of them have tumors that express the ER α , (Saladores et al., 2015; Sherman, Chapler, Crickard, & Wycoff, 1979) it is essential to fully evaluate the impact of gene-induced and drug-induced inhibition on tamoxifen effectiveness.

The tamoxifen metabolites — 4-hydroxy-tamoxifen and 4-hydroxy-N-desmethyl-tamoxifen — have approximately the same affinity for ER α as the naturally occurring estrogen, estradiol. Premenopausal women have over 10-fold higher serum estradiol levels compared with their postmenopausal counterparts. As tamoxifen treatment can further increase estradiol concentration, (Sherman et al., 1979) premenopausal women may require a higher tamoxifen dose to counter their inherently higher estradiol levels. Impaired tamoxifen metabolism by either genetic polymorphism or CYP-inhibition from concomitant drugs may therefore have the greatest impact on recurrence risk in premenopausal women, where the full production of tamoxifen metabolites is necessary to compete with the abundant estrogen.

A study by Saladores et al focused exclusively on tamoxifen metabolism, metabolite concentrations, and disease-free survival in premenopausal women. (Saladores et al., 2015)

They combined three cohorts including multiple ethnicities. In a median follow-up of 5.5 years, they observed lower endoxifen concentrations among women with low CYP2D6 activity scores, and poorer disease-free survival. When we stratified our meta-analytic models (D. P. Cronin-Fenton et al., 2013) by menopausal status (<20% versus over 20% of premenopausal women), we observed an increased risk of recurrence in studies that had a higher proportion of premenopausal women. We observed summary hazard ratios of 1.25 (95%CI=0.91, 1.71) in nine studies of predominantly post-menopausal women (0% to 9% premenopausal, median 0%), and of 1.54 (95%CI=1.09, 2.18) in sixteen studies with at least 20% premenopausal women (20% to 80% premenopausal, median 43%).(D. P. Cronin-Fenton et al., 2013) These findings strongly suggest that clinically meaningful effects resulting from CYP2D6 genotype and phenotype status on tamoxifen effectiveness may be limited to premenopausal women. Thus, studies of the significance of CYP2D6 pharmacogenetics and inhibition by concomitant administration of other drugs in this particular insufficiently studied population demands attention and clarification.

3. Tamoxifen transport

Few studies have investigated how interindividual differences in tamoxifen transport may influence tamoxifen effectiveness. Highly polymorphic genes also encode the ABC-transporters. Yet in contrast to the drug metabolizing enzymes, studies on the potential impact of ABC transporters and breast cancer outcomes remain scarce. Expression of ABCB1 in breast tumors correlates with clinical outcome in breast cancer patients, regardless of the receipt of adjuvant chemotherapy.(Sukasem et al., 2012) In a study of 105 breast cancer patients, where about two-thirds of patients received tamoxifen, higher expression of ABCB1 was associated with higher grade, lymph node involvement, and shorter survival.(Xu et al., 2008) In contrast, a study of 516 breast cancers (nested in a clinical intervention study of

1099 patients randomized to either tamoxifen/goserelin or cyclophosphamide/methotrexate/fluorouracil chemotherapy), tumor cell expression of ABCB1 correlated with poorer relapse-free and overall survival, except among tamoxifen-treated patients. (Teh et al., 2012) However, the impact of tamoxifen in the study was difficult to determine given its co-administration with goserelin.

Genetic variation in ABC transporters may influence outcomes in breast cancer patients. Kiyotani *et al* examined 52 different genomic tag-SNP variants of ABC transporters among 282 postmenopausal breast cancer patients undergoing tamoxifen monotherapy. (Kiyotani et al., 2008; Kiyotani et al., 2010) Carriers of the *ABCC2* variant allele (rs3740065) had ten-fold higher rates of recurrence, estimates were imprecise and were prone to immortal person-time bias. (Kiyotani et al., 2010; Lash et al., 2008; Lash & Cole, 2009) A study of 30 Thai patients suggested that ABCB1 may impact recurrence rates, (Sensorn et al., 2013) while a US-based study of 116 patients suggested that impaired ABCB1 combined with intermediate metabolism of CYP2D6 correlated with lower endoxifen concentrations. (Powers et al., 2016) In contrast, a study by Teh *et al.* of 95 breast cancer patients treated with tamoxifen found no association between two genetic polymorphisms in *ABCB1* and breast cancer recurrence. (Teh et al., 2012) However, when they examined the combined effect of polymorphisms in *ABCB1* and *CYP2D6*, they found an increased risk of breast cancer recurrence. Finally, a study of 196 patients by Teft et al reported no association of functional polymorphisms in ABCB1 and ABCG2 (BCRP) with endoxifen levels. (Teft et al., 2011) A universal limitation of the studies that investigated the association of the pharmacogenetics of ABC transporters with tamoxifen effectiveness is small sample size, and imprecise estimates. Clinical data are few, are prone to bias, and are inconsistent regarding the possible impact on breast cancer outcomes. Transporter expression and

genomic variants in transporter encoding genes require detailed analysis for their role in tamoxifen effectiveness.

4. *Other biomarkers may impact tamoxifen effectiveness*

To be effective, tamoxifen and its metabolites must compete with estrogen to overwhelm the estrogen receptor. Yet all clinical epidemiology studies of tamoxifen inhibition have considered one side of this competition — namely the profile of tamoxifen metabolites. No studies have investigated the impact of estrogen production and the expression levels of estrogen receptors (ER α and ER β) on tamoxifen effectiveness.

5. *Tamoxifen analogues*

Several studies have assessed the efficacy of other SERMs – raloxifene,(A. U. Buzdar, Marcus, Holmes, Hug, & Hortobagyi, 1988; Gradishar et al., 2000)(A. Buzdar et al., 2006) droloxifene,(A. Buzdar et al., 2002) arzoxifene,(Deshmane, Krishnamurthy, Melemed, Peterson, & Buzdar, 2007) toremifene(Hayes et al., 1995; International Breast Cancer Study Group et al., 2004) – but all failed to improve upon the effectiveness of tamoxifen. Based on the evidence that tamoxifen may not have equivocal efficacy in all patients, Z-endoxifen was developed. Orally administered Z-endoxifen potently inhibits tumor growth *in vitro*, and displays substantial bioavailability in mouse models. A recent phase I clinical trial assessed the efficacy of Z-endoxifen and prognosis in 38 endocrine-refractory metastatic breast cancer patients.(Goetz et al., 2017) The trial aimed to determine the toxicity profile of Z-endoxifen, maximum tolerated dose, and the potential clinical effectiveness. Findings suggest minimal toxicity and substantial antitumor activity in women with endocrine-refractory disease. A follow-on phase II trial is ongoing, comparing endoxifen (80mg/day) with tamoxifen (20mg/day) in women who have progressed during aromatase inhibitor therapy. It may take

several years for the clinical utility of Z-endoxifen to be fully assessed and for this molecule to receive regulatory approval.

Conclusion

Despite almost 50 studies, the clinical significance of the pharmacogenetics to tamoxifen effectiveness remains controversial and incompletely understood. Nonetheless, based on the current evidence, we believe regulatory bodies are appropriately recommending against routine *CYP2D6* genotype testing for patients assigned to tamoxifen therapy. The current evidence does not suggest that SSRI inhibition of *CYP2D6* reduces the effectiveness of tamoxifen.

The pharmacogenomics of tamoxifen therapy requires further clarification using a comprehensive approach to assessment of the involved metabolic pathways and special attention to premenopausal women with breast cancer.

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