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Review article

Pharmacogenomics Implication of Tamoxifen in Breast Cancer Treatment: Clinical Relevance and Future Directions

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Abstract:

Tamoxifen is a cornerstone therapy for estrogen receptor-positive (ER+) breast cancer, improving survival and reducing recurrence. Its efficacy and toxicity, however, vary due to genetic polymorphisms influencing metabolism and transport. Key genes, such as CYP2D6, CYP3A4, and ATP-binding cassette transporters (ABCB1, ABCC2), are crucial in forming and distributing active metabolites like endoxifen. This review explores tamoxifen pharmacogenetics through an analysis of literature from PubMed, Scopus, Google Scholar, and PharmaGKB. Genetic variations like CYP2D6*10 in Asians and CYP2D6*17/29 in Africans impact therapeutic outcomes. Barriers to personalized tamoxifen therapy include inconsistent guidelines, limited access to genetic testing, and underrepresentation of ethnic groups in research.The findings highlight the need for multidisciplinary approaches integrating genetic, clinical, and environmental factors to optimize therapy. Large-scale, diverse, population-specific studies are essential to establish universal pharmacogenetic guidelines.

Keywords: Tamoxifen, Breast Cancer, Pharmacogenomics, CYP2D6, ABC transporter

Introduction

Genetic variations can influence the propensity for the initiating event, the progression to a clinical disease state, and the trajectory of the disease[1]. The implementation of precision medicine in various medical fields has seen a global increase in recent times. Precision medicine describes a treatment approach that considers a patient's genetics, behavior, environment, and lifestyle[2].

Individuals vary considerably in their clinical responses to administered drugs and their outcomes[3]. Such inter-individual dissimilarities frequently pose a challenge to the optimization of a dosage regimen because, according to estimations, most drugs are efficacious in only 25–60% of patients. Many patients don't fully respond to and benefit from the initial recommended drug treatment—even as many as 75% of patients who have cancer show no response to the first therapy. The response to the same drug and dose can also differ in various patients. The same dose may be ineffective in a group of patients due to a too-low drug concentration, while in another group it can lead to the occurrence of serious side effects or even be lethal [4][5].

Breast cancer [BC) is a disease characterized by different pathologies, biological characteristics, and clinical behaviors. It is the leading cancer among females worldwide with 641,000 cases reported in 1980 and 1,643,000 cases in 2010; the annual incidence increase between the two years was 3.1% [6]. In the year 2018, the World Health Organization (WHO) reported 626,679 deaths from BC[7]. while in 2023 it represented 24.2% of all cancers and 15% of deaths due to cancer among females[8]. The recent shift in its burden in the developing world is revealed by a high mortality rate and poorer overall survival. The highest standardized mortality rate worldwide according to WHO statistics, six regions were found in the East Mediterranean Office (EMRO) and Africa Regional Office (AFRO) with respectively 18.6% and 17.%. On the other hand breast cancer among males is still considered a rare condition, representing 1% of the total breast cancer patients in Europe compared to over 6% in Central African countries [9].

Ethnic background and population structure can affect the pharmacokinetic properties of drugs through differences in factors such as the prevalence of genetic polymorphisms involved in metabolism or transport pathways. Also, the effect of variables such as medical practices, use of concomitant medications, body habits, and diet on drug absorption and disposition predicts phenotypic drug response burdensome[10].

Treatment in oncology has made great progress over the past decade due to the recent revolution in medical interventions. Narrow therapeutic indices, variable overall response rates and clinical outcomes, and toxicities from chemotherapies are examples of the problems that arise from cancer treatment [11]. Although many patients have similar clinical presentations, they manifest quite different responses to the same treatment. Some of the therapeutic schemes appear to be ineffective in patients with cancer. On the other hand, this may lead to adverse drug reactions or might increase the likelihood of overtreatment. Optimizing treatment regimens for the individual patient will conceivably lead to better clinical outcomes[11]. Over recent years, owing to the advancement of medical genomics and proteomics we have improved our knowledge of personal differences in pharmacokinetics and pharmacodynamics based on genetic makeup. Pharmacogenomics is an important tool in personalized medicine. There is wide variability in the response of individuals to standard doses of drug therapy which can lead to therapeutic failures or adverse drug reactions[12]. Polymorphism in drug-metabolizing enzymes is of great importance for inter-individual differences in drug therapy[13].

Breast cancer treatment

Breast cancer treatment is a rapidly evolving field that incorporates various therapeutic approaches tailored to the type, stage, and molecular characteristics of the disease. Standard treatment modalities include surgery, radiation therapy, chemotherapy, hormone therapy, targeted therapy, and immunotherapy. Each of these treatments plays a crucial role in improving patient outcomes, either alone or in combination.

Hormone therapy, for instance, is primarily used in hormone receptor-positive breast cancers, which account for the majority of breast cancer cases. Medications like tamoxifen and aromatase inhibitors (e.g., anastrozole, letrozole, and exemestane)are designed to block estrogen's role in promoting cancer growth.

Breast cancer treatment has become increasingly individualized, integrating molecular and clinical data to guide therapy selection. The advent of targeted and immune-based therapies has significantly improved survival and quality of life for many patients, underscoring the importance of continued research and innovation in this field.

Nearly two-thirds of breast cancers are classified as estrogen receptor (ER)-positive, which is prognostic for improved survival outcomes and predicts responsiveness to endocrine manipulations. By binding to either ER-alpha or -beta, estrogen regulates a wide variety of cellular effects and physiological conditions including breast cancer cell proliferation. Though not always considered in this manner, endocrine therapies are indeed breast cancer-targeted therapies, as they treat cancer by blocking specific receptors, which prevents or inhibits tumor growth[14].

Tamoxifen remains a cornerstone in the treatment of estrogen receptor-positive (ER+) breast cancer, with its efficacy relying on its metabolism to active metabolites like endoxifen via cytochrome P450 enzymes, primarily CYP2D6. Genetic polymorphisms in CYP2D6 lead to interindividual differences in drug metabolism and therapeutic outcomes, highlighting the importance of pharmacogenetic profiling to optimize treatment. Other genes, such as CYP3A4, Sulfotransferase 1A1 (SULT1A1), and ABCB1, also influence tamoxifen's metabolism and transport, contributing to variability in its efficacy and toxicity. Although pharmacogenetics holds great promise, its integration into routine clinical practice still encounters numerous obstacles. These include the absence of universal guidelines for genetic testing, discrepancies in the evidence linking CYP2D6 polymorphisms to clinical outcomes, and variations in allele frequencies across ethnic groups. Additionally, the high cost and limited availability of pharmacogenetic testing in low-resource settings, coupled with ethical and logistical concerns, hinder its widespread adoption. Recent advances, including genome-wide association studies and multi-gene panels, are paving the way for a more comprehensive understanding of tamoxifen pharmacogenetics. However, further large-scale, population-specific studies and cost-effectiveness analyses are essential to address these challenges and enable the global implementation of personalized tamoxifen therapy[15][16].

Therefore, the objective of this review is to provide a comprehensive analysis of the pharmacogenetics of tamoxifen, focusing on the genetic variations that influence its metabolism, efficacy, and safety in breast cancer treatment. Summarizing current knowledge on the roles of key genes, it has an impact on tamoxifen therapy.

Methodology

In this review, a comprehensive search was conducted to gather relevant scientific literature on the pharmacogenetics of tamoxifen in breast cancer treatment. The databases used included PubMed, Google Scholar, Scopus, and PharmaGKB. These platforms were chosen for their extensive coverage of biomedical, pharmacological, and clinical studies, as well as their focus on genetic and pharmacogenomic data.

Tamoxifen

Tamoxifen, a selective estrogen receptor modulator (SERM), is widely used in the treatment and prevention of estrogen receptor-positive (ER+) breast cancer. Its efficacy lies in its ability to act as an estrogen antagonist in breast tissue, thereby inhibiting estrogen-dependent tumor growth. Clinically, tamoxifen reduces the risk of breast cancer recurrence by approximately 40-50% in premenopausal and postmenopausal women and decreases the risk of contralateral breast cancer by up to 47%. Additionally, it has been employed for breast cancer prevention in high-risk populations, showing a 38% reduction in incidence among such individuals over five years of therapy[17][18].

The pharmacodynamics of tamoxifen is characterized by its dual activity as an estrogen antagonist in breast tissue and a partial agonist in other tissues, such as the endometrium and bones. This duality explains some of its therapeutic benefits, such as preserving bone density, and its adverse effects, including an increased risk of endometrial cancer and thromboembolic events. Tamoxifen exerts its effects by binding to estrogen receptors (ER-alpha and ER-beta) and modulating the transcription of estrogen-responsiveness. Its active metabolites, particularly 4-hydroxytamoxifen and endoxifen, have a 100-fold greateraffinity for estrogen receptors compared to the parent drug, making them critical for its therapeutic efficacy [19][20].

Tamoxifen pharmacogenomics:

While tamoxifen has demonstrated its ability to enhance survival outcomes individual patient responses to the therapy can vary significantly. Genetic factors are key contributors to differences in tamoxifen, 's therapeutic impact, as they affect both its metabolism and effectiveness. The interindividual variability in tamoxifen response is largely driven by genetic differences in the enzymes responsible for its metabolism, particularly the CYP2D6 gene [24]. CYP2D6 is the enzyme responsible for converting tamoxifen into its active metabolite, endoxifen, which is key to the drug's anticancer effects.

Variations in the CYP2D6 gene, including polymorphisms such as CYP2D6 poor metabolizers, ultra-rapid metabolizers, and extensive metabolizers, have been shown to significantly influence the therapeutic outcomes of tamoxifen. Patients with reduced CYP2D6 activity, such as those with certain polymorphisms CYP2D6 4 allele), have lower levels of endoxifen, which may lead to diminished efficacy and a higher risk of cancer recurrence [25]. Moreover, ABCB1, a gene encoding for the P-glycoprotein efflux transporter, has also been implicated in tamoxifen pharmacogenetics. This transporter is involved in the intestinal absorption and distribution of tamoxifen and its metabolites. Variants in ABCB1 can influence the bioavailability of tamoxifen, thereby affecting its clinical efficacy [26]. The clinical implications of these genetic variations are significant. Personalized treatment strategies based on pharmacogenetic testing of CYP2D6 and other relevant genes may offer a way to optimize tamoxifen therapy. In clinical practice, patients identified as poor metabolizers could potentially benefit from alternative therapies or adjusted doses of tamoxifen to achieve adequate endoxifen levels [27]. However, there is still debate over the clinical implementation of routine pharmacogenetic testing for tamoxifen metabolism, with varying recommendations from different healthcare bodies. While some studies suggest that genetic testing may improve patient outcomes, other studies emphasize the need for further clinical trials to validate these findings [28]. Differences in tamoxifen response and toxicity among racial and ethnic groups are primarily linked to genetic diversity in metabolizing enzymes such as CYP2D6.. Moreover, variations in adherence, access to healthcare, and environmental factors contribute to observed disparities in outcomes across racial and ethnic groups. Understanding these differences is critical for optimizing tamoxifen therapy through personalized medicine approaches [29][30].

Tamoxifen Metabolism:

Tamoxifen is metabolized into its more active forms by various cytochrome P450 enzymes (e.g., CYP2D6, CYP3A4, CYP3A5, CYP2C9, and CYP2C19) to produce endoxifen; a metabolite of greater potency[31]. tamoxifen metabolism involves two parallel metabolic pathways that metabolize tamoxifen through different cytochrome P450 enzymes into N-desmethyl-tamoxifen and 4-hydroxy-tamoxifen. Then, a second transformation from N-desmethyl-tamoxifen and 4-hydroxy-tamoxifen into endoxifen occurs. Tamoxifen has a relatively low anti-estrogenic activity compared with these three active metabolites[32][30].In a genome-wide microarray analysis of tumors from women with ER-positive breast cancer treated with adjuvant tamoxifen, Ma ***et al*** discovered the HOXB13/IL-17BR gene ratio as an independent predictor of treatment outcome and demonstrated that ectopic expression of HOXB13 in a non transformed human mammary epithelial cell confers increased cell migration and invasion. HOXB13 expression in cells leads to reduced sensitivity to tamoxifen-induced apoptosis. Both genes are used as a prognostic marker and a biomarker predictive of tamoxifen benefit. [33][31][32][33]

The enzyme primarily responsible for the metabolic conversion of tamoxifen to endoxifen is CYP2D6, but other enzymes and transporters are also active in this metabolic pathway [34].

CYP2D6: The Key Enzyme in Tamoxifen Metabolism and Ethnic Variability

CYP2D6 is a polymorphic gene with more than 100 reported allelic variants, often due to single nucleotide polymorphisms (SNPs). Several CYP2D6 alleles have been associated with either increased or decreased enzyme activity. The following table summarizes the differences between various CYP2D6 variant alleles,their corresponding enzyme activity levels,and their prevalence across different population.

Table 1: Distribution of CYP2D6 Allelic Variants and Enzyme Activity Across Population

CYP2D6 Allele	Enzyme activity	Prevalence in different population
CYP2D6*1	Wild type (normal enzyme activity)	Common on all population
CYP2D6*3	Negligible enzyme activity	Rare ,mostly found in Europeans
CYP2D6*4	Negligible enzyme activity (poor metabolizer)	High in Europeans (20%),low in East Asians (1%-2%),(2-7%) in Africans
CYP2D6*5	No enzyme activity (gene deletion)	More common in Asians than in other population
CYP2D6*9	Decreased enzyme activity	Found in Europeans and some Africans
CYP2D6*10	Decreased enzyme activity (intermediate metabolizer)	High in Asians and pacific islanders, low in north central ,and south America
CYP2D6*17	Decreased enzyme activity (intermediate metabolizer)	Mostly found in black Africans (35% allele variation in these populations
CYP2D6*29	Reduced function allele	More prevalent in African Americans
CYP2D6*41	Active allele variation	Common in middle in Eastern population,associated with duplication/multiplication.

This genetic variabiability emphasizes the need for considering ethinic differences to optimize therapeutic outcomes [35][[36].

Secondary Enzymes in Tamoxifen Metabolism: The Role of CYP3A4, CYP2C9, and Others

While CYP2D6 is the most important enzyme in the metabolism of tamoxifen, secondary enzymes such as CYP2C9, CYP2C19, CYP3A4, and CYP2B6 also contribute to its overall metabolism. These enzymes, although secondary in nature, can still influence the formation of endoxifen, the active metabolite of tamoxifen, and there by affect its therapeutic efficacy. CYP2C9 and CYP2C19 have been shown to impact tamoxifen metabolism, with certain polymorphisms potentially altering drug effectiveness, especially in populations with specific genetic backgrounds [37]. However, CYP2D6 remains the primary enzyme responsible for the conversion of tamoxifen to its active form, and its polymorphisms have a more significant impact on tamoxifen's clinical outcomes compared to secondary enzymes. The variability in the effect of secondary enzymes such as CYP3A4 and CYP2B6 is generally less pronounced, and their influence is considered minor compared to CYP2D6, especially in certain ethnic populations [38].Understanding the role of secondary enzymes is important for personalized treatment strategies, but CYP2D6 remains the key determinant in tamoxifen metabolism and its subsequent clinical outcomes [39].

The effects of CYP polymorphisms have been extensively studied globally to evaluate their impact on tamoxifen efficacy and pharmacokinetics. These polymorphisms significantly affect drug metabolism, leading to variability in therapeutic outcomes and side effects among patients from different populations. The following table highlights the key studies conducted globally, and summarizes the differences in gene polymorphism across various populations, emphasizing the need for pharmacogenetic-guided therapy.

Table 2: Comparison of Studies on Genes Affecting Tamoxifen Metabolism

No.	Genes	design	n	Population	Key Findings	Note	Year (Reference No)
1	CYP2D6	cohort study	766	Korean	The clinical utility of CYP2D6 polymorphism in predicting tamoxifen outcomes is still unclear	CYP2D6*10 is the most common variant allele, and CYP2D6*4 has a rare incidence in this study similar to previous studies in the Asian population	**2011[41]**
2	CYP2D6	cohort study	608	White Northern European e	Identified genetic variants in CYP2D6 and other genes(TCF20, WBP2NL)strongly associated with endoxifen concentration and clinical outcomes such as relapse-free survival	Results highlight the importance of non-CYP2D6 genes in tamoxifen metabolism and efficacy	**2024[20]**
3	CYP2D6, CYP2C9, CYP2C8, CYP2C19 ,CYP3A4	Retrospective secondary analysis	302	United States population, the majority of them caucasian	The variability in endoxifen concentration is not solely dependent on the CYP2D6 genotype Other enzymes, such as CYP2C9, May also influence endoxifen concentration, along with factors like weight and season. However, CYP2D6 has the most significant impact on endoxifen concentration, even so, its effect is not exclusive.	The finding emphasizes the need for integrating genetic and clinical factors into personalized tamoxifen dosing strategies	**2017[42]**
4	CYP2D6 *4 , CYP2D6 *10 , CYP3A5 *3 and CYP2C19*2	case-control study	110 case ,100 control	Indian	CYP2D6 polymorphism (*4and*10) significantly impacts metabolism and is associated with breast cancer risk, CYP3A5*3 polymorphism has no significant effect, CYP2C19*2 polymorphism moderately affects tamoxifen metabolism		**2017[43]**
5	CYP2D6, CYP3A4, CYP3A5, CYP2C9, CYP2C19,CYP2B6	Observation study	229	Black south African	among Black African patients with breast cancer CYP2D6 polymorphisms, the variants CYP2D6*17 and CYP2D6*29 were mostly found and associated with a significant reduction of tamoxifen metabolism. - No significant effect of polymorphisms in CYP3A4, CYP3A5, CYP2C9,CYP2C19, and CYP2B6 on tamoxifen metabolism.	The study highlights the need for further controlled research on dose adjustments for individuals with certain genetic variants	**2023[44]**

					- Minimal risk of drug-drug interactions with efavirenz-based antiretroviral therapy. - Dose escalation for patients with reduced-function CYP2D6 alleles may improve outcomes.		
6	CYP2D6 and HOXB13 /IL17BR	Cohort study	160	United state population	combination of inherited (CYP2D6) and tumor (HOXB13/IL17BR) genetic variation influences the risk of breast cancer recurrence and death. Patients with both risk factors decreased CYP2D6 metabolism(presence of one or two CYP2D6 *4 alleles) and high HOXB13/IL17BR genes ratio, had significantly shorter disease-free survival and tamoxifen resistance.		**2008[45]**
7	CYP2D6	Multicenter prospective study	119	African American patients	The study demonstrated that increasing the tamoxifen dose from 20mg to 40mg per day significantly improved endoxifen levels in patients with intermediate or poor metabolizer genotypes, this supports the use of personalized dosing based on genotype.	The study highlights that African American patients had a higher prevalence of reduced function CYP2D6 alleles particularly *10,*17 suggesting that African American may benefit from higher tamoxifen doses.	**2011 [46]**
8	CCYP2D6,CYP3A5,CYP2C9,CYP2C19	Prospective cohort study	165	Asian	This study confirmed that polymorphism in CYP2D6(*5,*10) is the most prevalent allelic variant in Asians and is significantly associated with lower endoxifen levels, indicating their impact on tamoxifen metabolism and therapeutic efficacy.	Polymorphism inCYP3A4, CYP2C9, and CYP2C19 did not significantly affect tamoxifen metabolism	**2011[47]**
9	CYP2D6	Randomized clinical trial	4861	global	- No significant association was found between CYP2D6 phenotypes and breast cancer-free intervals(BCFI), indicating no impact on tamoxifen's efficacy in preventing recurrence. - PM and IM phenotypes showed increased risk of tamoxifen-induced hot flushes	- The study concluded that CYP2D6 genotyping does not justify withholding tamoxifen or switching to aromatase inhibitors. - The presence or absence of hot flushes should not guide decisions on tamoxifen treatment. This finding is in contrast to the hypothesis that lower endoxifen levels are manifest by fewer or less severe tamoxifen-induced hot flushes	**2012[48]**
10	CYP2D6 (*4, *5, *10, *41),	Cohort study	486	European descent,	CYP2D6 impaired metabolism (*4, *5, *10, *41) is associated with worse outcomes (e.g., shorter relapse-free time).		**2007[49]**

	CYP2C19 (*2, *3, *17), CYPA5,CYPB6,CYP2C9				- CYP2C19 *17 associated with better outcomes (e.g., reduced risk of recurrence). - No significant associations for other genes like CYP3A5, CYP2B6, CYP2C9.		
11	CYP2D6 (CYP2D6*10, CYP2D6*4, CYP2D6*5)	case-control study	39	Thai	- CYP2D6*10 homozygous variant (T/T) was associated with shorter disease-free survival (DFS). - CYP2D6*4 and CYP2D6*5 were rare or not detected in this population. - CYP2D6*10 allele is highly prevalent in Asian populations, affecting tamoxifen metabolism and efficacy		**2012[50]**
12	CYP2D6	Retrospective observational study	24	Sinhalese patients from Sri Lanka. | |	The CYP2D6*41 allele combination (2988G>A, -1584C, and 2850C>T SNPs) showed a significant association with fatty liver (P=0.029). Postmenopausal women were more likely to experience adverse effects (e.g., hot flashes, ALTelevation) compared to premenopausal women (P=0.041).	No significant correlation was found between CYP2D6 polymorphisms and breast cancer recurrence Intermediate metabolizers (IM) with reduced CYP2D6 activity had lower endoxifen levels, which may increase the risk of fatty liver Patients with fatty liver had significantly lower tamoxifen metabolite levels due to reduced CYP2D6 activity	**2017[51]**
13	CYP2D6, CYP2C19, UGT2B15, ABCG2	Cohort study	5959	Danish women	There is weak evidence that phase 1 metabolism may influence recurrence. No significant impact from individual genetic variants was observed The findings support current guidelines recommending against genotype-guided prescribing of tamoxifen	Phase 1 metabolism has slight clinical importance for tamoxifen response, but analyzing specific genetic variants has no clinical utility No significant risk of recurrence was observed in carriers of the CYP2D6 variant	**2020[52]**

14	CYP2D6	Cross-sectional observational study	40	Zimbabwean	The study identified high frequencies of CYP2D6*17 (15%) and CYP2D6*29 (18%), which are unique to African populations and associated with reduced enzyme activity, These genetic variants significantly impacted the plasma levels of endoxifen. 55% of patients had endoxifen concentrations below the therapeutic threshold (5.97 ng/mL), which could lead to reduced tamoxifen efficacy, This means that some of these patients may not fully benefit from this dose and may end up experiencing recurrence	The study emphasizes the need for dose adjustments for intermediate metabolizers or alternative therapies, such as aromatase inhibitors, to improve clinical outcomes Based on self-reported adherence, 76.6% of patients were adherent. However, biochemical assessments showed that only 67.5% were high adherers.	**2023[53]**
15	CYP2D6	prospective multicenter study	667	Netherlands and Belgium	No significant association was found between endoxifen concentrations or CYP2D6 genotypes and relapse-free survival. - The threshold of 5.9 ng/mL for endoxifen concentration, as identified in this study was found to be below the optimal therapeutic level required for tamoxifen to achieve its full anticancer effect. This suboptimal threshold may have contributed to the lack of significant impact on clinical outcomes, such as relapse-free survival	No additional toxicity was reported from increased endoxifen concentrations due to dose escalation; however, the study did not directly test adverse effects	**2019[54]**
16	CYP2D6	Cross-sectional analytical study	71	Mexican mestizo women	Hot flashes (57.75%), arthralgia (45.07%), headache (43.66%), and cramps (39.44%) were the most frequent side effects. - No significant association between CYP2D6 genotypes or phenotypes and tamoxifen side effects. - Chemotherapy before tamoxifen treatment and contraceptive use during reproductive age were significant predictors of side effects. Contraceptive use during reproductive age in the present results was identified as a protective factor against HF development.	A high prevalence of side effects was reported (90.14% of participants experienced at least one). Severe side effects were rare (e.g., 4.23% for hot flashes). Two alleles, CYP2D6*34 (13.2%) and CYP2D6*39 (14.7%), were identified at unusually high frequencies compared to other populations.	**2019[55]**

17	CYP2D6, ABCC2, ABCB1, ABCG2	Retrospective study	282	Japanese women	- CYP2D6 polymorphisms significantly reduce recurrence-free survival and plasma levels of active tamoxifen metabolites (e.g., endoxifen). - ABCC2 rs3740065 SNP is linked to shorter recurrence-free survival, likely affecting local drug exposure at tumor sites. - Combined risk alleles (CYP2D6 + ABCC2) dramatically worsen outcomes (e.g., 45.25-fold increased risk with 4 risk alleles).	CYP2D6 variants are significantly associated with lower endoxifen and 4-hydroxytamoxifen plasma levels. - No significant plasma concentration differences by ABCC2 genotypes	**[56]**
18	CYP2D6 (*4 and *6 alleles) - CYP3A5 (*3 allele)	Retrospective pharmacogenetic analysis	256	Predominantly white	CYP2D6*4/*4 genotype associated with worse relapse-free time and disease-free survival indicating a higher risk of relapse, but no significant difference in overall survival and hot flashes. Women with CYP2D6*4/*4 reported fewer hot flashes.	CYP3A5*3 polymorphism showed no association with clinical outcomes or hot flashes severity.	**2005[24]**
19	CYP2D6 and CYP3A4	Retrospective analysis of the CYPTAM study data (2008-2010).	668	Netherlands and Belgium	- Older patients had higher concentrations of tamoxifen and endoxifen. - Age and genetic polymorphisms explained variability but did not impact survival outcomes.	- CYP2D6 poor metabolizers had lower endoxifen levels. - No evidence to support tamoxifen dose adjustments based on age or therapeutic drug monitoring (TDM).	**2023[57]**
20	CYP2D6, CYP2C19 ,CYP3A4	Prospective observational multi-center trial	297	Belgium and Switzerland	No significant relationship between endoxifen levels and tamoxifen efficacy (progression-free survival) Endoxifen monitoring and tamoxifen activity score are not clinically valuable for guiding tamoxifen treatment.		2018[58]

Tamoxifen Transporter:

Tamoxifen efficacy depends on both metabolic activations, producing potent metabolites such as endoxifen, and intracellular transport mechanisms. Membrane transporters, particularly efflux and uptake transporters, are integral in modulating tamoxifen and its metabolites' intracellular and systemic concentrations, thereby affecting therapeutic outcomes and adverse effects[56]. Key efflux transporters implicated in tamoxifen pharmacokinetics include ABCB1 (P-glycoprotein), ABCC2 (MRP2), and ABCG2(BCRP)transporters. These transporters actively expel drugs and metabolites from cells, limiting intracellular accumulation and potentially influencing therapeutic efficacy. Conversely, uptake transporters such as SLCO1B1 and SLCO2B1 mediate drug entry into cells, playing an equally critical role[59]. The human ABC genes superfamilyincludes 48 functional transporters categorized intoseven subfamilies. Importantly, research over the past decade has implicated a multitude of genetic variations in ABC transporter genes in differences in response and toxicity of breast cancer treatment, of which ABCB1 (encoding MDR1 also known as P-gp), ABCC1 (encodingMRP1) and ABCG2 (encoding BCRP) are most extensively studied[60]. Genetic polymorphisms in transporter genes, particularly ABCB1, ABCC2, and ABCG2, have been linked to significant interindividual variability in tamoxifen pharmacokinetics, treatment response, and toxicity profiles. For instance, specific single nucleotide polymorphisms (SNPs) in the ABCB1 gene have been associated with altered tamoxifen disposition and treatment outcomes. Similarly, ABCC2 gene variations may impact tamoxifen metabolite clearance and tissue distribution, influencing drug efficacy and resistance. Emerging evidence also highlights the role of ABCG2 transporters, particularly in modulating the intracellular transport of tamoxifen metabolites, though their precise contribution requires further investigation [61].

In contrast to the drug-metabolizing enzymes, studies on the potential impact of ABC transporters and breast cancer outcomes remain scarce [62]. The predominant polymorphisms (SNPs) in ATP-binding cassette (ABC) transporters vary significantly across different populations. For ABCB1 (MDR1), the rs2032582 (A893S/T) polymorphism shows that the reference allele G is predominant globally (55%), while the T allele is highly prevalent in Asian populations (41.4%) but much rarer in Europeans and Africans. Similarly, rs1045642 (C3435T), a silent polymorphism, is common worldwide, with a frequency of 50–55% in both Europeans and Asians. In ABCC1 (MRP1), rs45511401 (G671V) is notable for its prevalence in Europeans (5.6%) but is extremely rare in Asians (<0.1%). For ABCG2 (BCRP), the rs2231142 (Q141K) variant is particularly frequent in Asians (35%), less so in Europeans (~12%), and rarer in Africans; this SNP reduces transporter activity and has clinical relevance in conditions like hyperuricemia. These population-based differences emphasize the critical role of ethnic variability in understanding the pharmacogenetics of ABC transporters, particularly in predicting drug resistance, toxicity, and therapeutic outcomes in diverse patient groups [59]. The comprehensive review published in 2020provides an in-depth evaluation of the effect of variants in ATP-binding cassette (ABC) transporters on breast cancer treatment and concludes that the role of ATP-binding cassette (ABC) transporters in tamoxifen therapy for breast cancer is limited. Specifically, ABCB1 variants such as rs1045642 (I1145I) have shown inconsistent associations with tamoxifen efficacy and toxicity. While tamoxifen metabolites, including endoxifen and 4-hydroxytamoxifen, are substrates of ABCB1, the evidence remains inconclusive regarding their impact on clinical outcomes. Furthermore, an intronic variant in ABCC2 (rs3740065) has been linked to reduced recurrence-free survival in patients receiving tamoxifen monotherapy; however, this finding lacks strong replication and mechanistic support. Overall, the influence of ABC transporter variants on tamoxifen efficacy is minimal and not yet clinically actionable. [61]. This section reviews the updated role of transporter polymorphisms in tamoxifen pharmacokinetics and pharmacodynamics, supported by a comparative analysis of global studies on their clinical implications.

Table 3:**The Impact Of ABC Transporters Polymorphism On Tamoxifen Outcomes In Breast Cancer Patients Across Different Populations**

NO	Genes	design	n	Population	Key Findings	Note	Year (Reference No)
1	ABCB1 ABCC2	Retrospective cohort study	73	Thai	Polymorphisms of ABCC2(-24CC): Associated with increased risk of distant metastasis and shorter DFS. - polymorphisms in (ABCC2-24CC3435CT/TT + ABCB1 Increased risk of distant metastasis and bone metastasis	The study suggests the pharmacogenetic testing utility	2016[62]
2	ABCC2	Retrospectiv e study	282	Japanese	ABCC2 rs3740065 SNP is linked to shorter recurrence-free survival, likely affecting local drug exposure at tumor sites. - Combined risk alleles (CYP2D6 + ABCC2) dramatically worsen outcomes (e.g., 45.25-fold increased risk with 4 risk alleles).	The study highlights the importance of genetic testing to predict response to tamoxifen therapy	2010[63]
3	ABCB1	Observational study	81	Ethiopian	The ABCB1 c.4036A>G variant has a moderate impact on tamoxifen metabolites, particularly endoxifen, and enhances the predictive ability of CYP2D6 for interindividual variability	ABCB1 c.3435C>T Variant: - No significant association was found with tamoxifen or its metabolite levels. The study highlights the need for therapeutic drug monitoring (TDM) and genotype-based tamoxifen dosing in Ethiopian populations.	2019 [64]
4	ABCB1	Retrospective cohort study	258	European populations	ABCB1 polymorphism rs1045642:statistically significant effect on Time to event in premenopausal patients only, associated with the development of gynecological and vasomotor adverse events. In contrast, the rs2032582 polymorphism did not show a clear effect on clinical outcomes, although there was a trend toward longer time to event in variant allele carriers, particularly in postmenopausal patients.		2017[65]

Critical Analysis of Genetic Variants and Their Impact on Tamoxifen Efficacy: Contradictions and Challenges in Current Literature:

While several studies have explored the impact of CYP2D6 polymorphisms on tamoxifen metabolism, their findings present conflicting conclusions, highlighting the need for a more nuanced understanding of genetic influences on treatment outcomes. For instance, the 2011 cohort study in Korea reported that the CYP2D610 allele was the most common variant in the Asian population and significantly affected tamoxifen metabolism[40] .However, a more recent cohort study in Denmark found minimal impact from CYP2D6 genotyping on breast cancer-free intervals (BCFI), suggesting that genetic variants in CYP2D6 have limited clinical utility in predicting tamoxifen efficacy[51]. This discrepancy raises questions about the overall relevance of CYP2D6 genotyping in clinical practice, as some studies, such as the 2017 retrospective secondary analysis in the United States, emphasized the importance of integrating other genetic variants, such as those in CYP2C9, in determining tamoxifen metabolism [37]. Furthermore, the 2023 study in Black South African patients noted that variants like CYP2D617 and *29 were linked to reduced enzyme activity, underscoring the necessity of considering population-specific genetic variations when assessing genotyping strategies[38]. Despite these findings, studies such as the 2012 randomized clinical trial did not establish a significant association between CYP2D6 phenotypes and recurrence-free survival, suggesting that CYP2D6 alone may not be sufficient to guide treatment decisions [47]. The lack of consistent evidence on the clinical impact of CYP2D6 genotyping calls for further research to better understand the complexities of tamoxifen metabolism and the potential roles of other genetic factors, as indicated in the 2017 cohort study in Asia, which found that polymorphisms in other genes, such as CYP3A4 and CYP2C19, also contribute to variability in tamoxifen response [46]. These discrepancies underscore the challenges in establishing universal guidelines for CYP2D6 genotyping in tamoxifen therapy and suggest that personalized treatment approaches should consider a broader range of genetic markers.

Divergence in global guide lines on tamoxifen and the need for pharmacogenetic testing

Despite its effectiveness, variability in patient response has led to the consideration of pharmacogenetic testing, particularly CYP2D6 genotyping, to optimize treatment outcomes. However, global clinical guidelines differ significantly in their recommendations regarding the duration of Tamoxifen therapy and the necessity of pharmacogenetic testing. The following table summarizes the comparison between different global guidelines on the use of Tamoxifen, highlighting variations in treatment duration, and the necessity of pharmacogenetic testing.

Clinical implications of tamoxifen pharmacogenomics findings

The clinical implications of pharmacogenomics in tamoxifen therapy have been the subject of much research, particularly due to the variability in clinical response observed in breast cancer patients[27]. Tamoxifen, a cornerstone in the treatment of estrogen receptor-positive breast cancer, has shown considerable effectiveness over the past four decades[68]. However, predicting the efficacy of tamoxifen remains a significant challenge, and this variability can be largely attributed to genetic factors influencing its metabolism.. Early studies suggested that genotyping for CYP2D6 polymorphisms could help predict tamoxifen response, as poor metabolizers were expected to experience suboptimal levels of endoxifen, thereby reducing therapeutic effectiveness[69][70]. While this approach initially seemed promising, it has become evident that CYP2D6 genotyping alone cannot fully account for the variability in tamoxifen efficacy. This is because CYP2D6 polymorphisms explain only a portion of the variability in endoxifen levels, and other genetic and non-genetic factors also contribute to the drug's effectiveness[69].

Another approach that has been explored is therapeutic drug monitoring (TDM) of endoxifen concentrations. The concept of individualized dosing based on measured endoxifen levels is attractive, as it offers the potential to optimize treatment by ensuring patients achieve therapeutic concentrations. However, despite its theoretical appeal, the lack of consensus on what constitutes a "therapeutic"

Table 4: Comparison of Global Clinical Guidelines for Tamoxifen Use

Organization	Target Population	Duration	Genetic Testing (CYP2D6)	Main Challenges	Special Considerations	References
NCCN (National Comprehensive Cancer Network)	ER+/PR+ breast cancer (pre/post-menopause)	5-10 years	Optional	High cost, lack of insurance coverage in some countries	Avoid during pregnancy, monitor thrombosis risks	[66]
ASCO (American Society of Clinical Oncology]	Early-stage breast cancer (ER+/PR+)	5+ years	Not routinely recommended	Insufficient clinical evidence, difficulty interpreting test results	Assess thrombosis risks	[67]
ESMO (European Society for Medical Oncology)	ER+/PR+ breast cancer (pre-menopause)	5-10 years	Neutral	Limited evidence on long-term survival benefits, complexity in daily clinical practice	Monitor fatty liver and uterine effects	[67]

endoxifen concentration has hindered the widespread adoption of TDM[71]. In addition, while endoxifen is considered the most active metabolite, other metabolites, such as 4-hydroxy-tamoxifen, also contribute to tamoxifen's anti-estrogenic effects. This adds further complexity to using serum endoxifen levels as the sole predictor of treatment success[72].

The role of non-genetic factors in tamoxifen metabolism should not be underestimated. Variables such as age, body mass index, comorbidities, and concurrent medications can all influence tamoxifen pharmacokinetics and pharmacodynamics[[72]]. Therefore, pharmacogenetic models that solely focus on genetic determinants, like CYP2D6, may be insufficient for predicting tamoxifen response. A more comprehensive approach, integrating both genetic factors (such as the roles of other enzymes like CYP3A4, CYP2C9, and CYP1A2) and non-genetic factors, could provide a more accurate prediction of treatment outcomes. Such models would need to consider the individual patient's genetic makeup, lifestyle, and clinical context to optimize tamoxifen therapy[70][41].

Furthermore, there is growing interest in the potential of new tamoxifen-related compounds, such as z-endoxifen hydrochloride, especially in the metastatic setting. While this alternative may hold promise, more research is needed to determine its clinical utility compared to traditional tamoxifen[75]. Despite the challenges in personalizing tamoxifen therapy, these ongoing studies highlight the evolving landscape of pharmacogenetic research in oncology, aiming to refine treatment strategies and ultimately improve patient outcomes. Therefore, while the use of pharmacogenetics to predict tamoxifen efficacy is still in its developmental stages, it is clear that a multifaceted approach, combining genetic, clinical, and environmental factors, holds the key to more individualized and effective breast cancer treatment.

Conclusion

The pharmacogenomics of tamoxifen in breast cancer treatment emphasizes the crucial role of genetic variability in determining therapeutic outcomes. As a cornerstone therapy for estrogen receptor-positive (ER+) breast cancer, tamoxifen's efficacy and toxicity are significantly influenced by polymorphisms in genes responsible for its metabolism and transport. CYP2D6 is the key enzyme, with variants such as *10 in Asian populations and *17/*29 in African populations significantly altering endoxifen levels and clinical outcomes. However, the impact is not limited to

CYP2D6 alone, as secondary enzymes like CYP3A4, CYP2C9, and CYP2C19, along with transporters such as ABCB1 and ABCC2, contribute to the complexity of tamoxifen's pharmacokinetics. Therefore, a comprehensive understanding of its metabolic pathway is essential.Ethnic disparities in allele frequencies and metabolic phenotypes highlight the need for population-specific pharmacogenetic guidelines. However, current barriers, such as inconsistent clinical recommendations, limited access to genetic testing, and underrepresentation of certain ethnic groups in research, hinder the implementation of pharmacogenomic insights into personalized care. To overcome these challenges, large-scale, multiethnic studies are essential to develop universally applicable yet adaptable guidelines, along with cost-effective strategies to expand genetic testing in resource-limited settings.Future research should focus on integrating multi-omics approaches (genomic, transcriptomic, proteomic) to explore gene-environment interactions and epigenetic factors influencing tamoxifen response. Collaboration between clinicians, pharmacologists, and policymakers is crucial to advancing precision medicine and ensuring equitable access to personalized therapies. By bridging the gap between pharmacogenetic research and clinical practice, personalized tamoxifen regimens can optimize survival outcomes, reduce adverse effects, and address global disparities in breast cancer care. Ultimately, the promise of precision medicine lies in its ability to translate genetic insights into actionable strategies, empowering ER+ breast cancer patients to achieve the full therapeutic potential of tamoxifen.

Conflict of interest

The authors declare no conflict of interest.

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