Cancer Chemotherapy and Pharmacology (2019) 83:71–79
https://doi.org/10.1007/s00280-018-3703-8

ORIGINAL ARTICLE

Effects of *CYP2D6*10* polymorphism on tamoxifen pharmacokinetics in patients with breast cancer in Asia: a meta-analysis

Yu Bai[1] · Hai-wei Wu[1] · Yan-hua Zhang[1]

Received: 28 May 2018 / Accepted: 10 October 2018 / Published online: 24 October 2018

Abstract

Purpose Insufficient serum metabolite concentrations of tamoxifen can compromise treatment efficacy in patients with breast cancer. The purpose of this meta-analysis was to explore correlations between cytochrome P450 (CYP) 2D6*10 gene polymorphisms and serum concentrations of tamoxifen and its active metabolites in patients with breast cancer in Asia.

Methods The study included a systematic literature search for cohort studies published before March 2018 in English databases (PubMed, Embase, Cochrane Library, and Web of Science) and Chinese databases (Chinese National Knowledge Infrastructure and Wan Fang database). The meta-analysis was performed using RevMan 5.3 software. Pooled means and standard deviations were calculated with 95% confidence intervals. Publication bias and sensitivity analyses were also performed using STATA 14.0.

Results In total, 7 studies and 552 patients were included in the meta-analysis. Serum concentrations of endoxifen were significantly different in each *CYP2D6*10* genotype group ($p < 0.05$). The CC genotype was associated with higher concentrations of 4-OH-TAM than the CT/TT genotype ($p < 0.05$). However, there were no statistically significant between-group differences in serum concentrations of TAM ($p > 0.05$). Publication bias and sensitivity analyses confirmed that the meta-analysis results were stable and reliable.

Conclusions *CYP2D6*10* polymorphisms influence the pharmacokinetics of tamoxifen in patients with breast cancer in Asia.

Keywords Breast cancer · *CYP2D6*10* · Pharmacokinetics · Polymorphism · Tamoxifen

Introduction

Breast cancer (BC) is the most common malignant tumor and has a higher mortality rate among women than among men [1]. Adjuvant endocrine therapies such as the selective estrogen receptor modulators tamoxifen (TAM) and toremifene as well as third-generation aromatase inhibitors including anastrozole, letrozole, and exemestane can decrease the risk of tumor recurrence and mortality in women with early-stage estrogen receptor (ER)-positive BC; 5-year treatment reduces this risk by one-third in the first 10 years after diagnosis [2, 3].

TAM is a competitive inhibitor for estrogen binding on cancerous ER-positive cells that require estrogen stimulation for growth [4]. TAM itself is a prodrug with poor affinity for the ER that requires biological activation by the cytochrome P450 (CYP) system in the liver [4]. It is mainly metabolized via demethylation by CYP3A4/5 to *N*-desmethyltamoxifen (NDM). A smaller proportion of TAM is converted to 4-hydroxytamoxifen (4-OH-TAM), which has 30–100-fold higher affinity for ERs than the parent molecule [5–7]. Subsequently, NDM and 4-OH-TAM are biotransformed to 4-hydroxy-*N*-desmethyltamoxifen (endoxifen) by CYP2D6 and CYP3A4, respectively [4, 5]. Endoxifen has 100-fold higher binding affinity to ERs than TAM [5, 7–9]. Moreover,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00280-018-3703-8) contains supplementary material, which is available to authorized users.

✉ Yan-hua Zhang
zyh8812@163.com

Yu Bai
baiyu901122@163.com

Hai-wei Wu
hyway_wu@126.com

[1] Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Pharmacy, Peking University Cancer Hospital and Institute, No.52, Fu Cheng Road, Hai Dian District, Beijing 100142, People's Republic of China

patients with endoxifen serum levels below a threshold of 5.97 ng/mL (16 nM) have an increased risk of BC recurrence after treatment [10, 11].

CYP2D6 is a key enzyme for TAM metabolism [4]. Germline genetic polymorphism of the *CYP2D6* gene can alter enzyme activity, resulting in individual differences in the efficacy of TAM treatment [12]. To date, more than 100 allelic variants of the *CYP2D6* gene have been reported [13]. These alleles are divided into three functional groups: those associated with normal enzymatic function, decreased function, and no function. This classification is implemented by assigning each allele an activity value ranging from 0 to 1. For example, 0 indicates a no-function allele, 0.5 indicates a decreased-function allele, and 1 indicates a normal-function allele [13]. The activity score (AS) of CYP2D6 in a given patient is calculated based on the allele combination and translated into a phenotype as follows: a poor metabolizer (PM) is defined as an AS of 0, an intermediate metabolizer (IM) as an AS of 0.5 or 1, a normal metabolizer (NM) as an AS from 1 to 2, and an ultrarapid metabolizer (UM) as an AS of > 2.0 [13].

Ethnicity is a major biological factor predicting *CYP2D6* germline genetic polymorphism; for example, approximately 50% of the Asian population has the *CYP2D6*10* (c.100C>T, rs1065852) polymorphism, whereas it is less common in Caucasian subjects with a prevalence of only about 3% [14–16]. The *CYP2D6*10* polymorphism is most commonly associated with a severe decrease in enzyme activity and decreased circulating concentrations of active TAM metabolites [17, 18]. *CYP2D6*10* genotypes are classified as CC, CT, and TT with enzyme AS values of 2.0, 1.5, and 1.0, respectively. According to the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2D6 and TAM Therapy [13], patients with the TT genotype (AS, 1.0) should receive alternative hormonal therapy or an increased dose of TAM designed to achieve adequate serum concentrations. However, the exact effects of individual *CYP2D6* gene polymorphisms on circulating concentrations of TAM and its active metabolites in patients with BC are unknown.

In the present study, we performed a meta-analysis to identify the correlations between *CYP2D6*10* gene polymorphisms and concentrations of TAM and its metabolites in an Asian population with BC.

Materials and methods

Literature search

We performed a comprehensive search of English databases (Pubmed, Embase, Cochrane Library, and Web of Science) and Chinese databases (Chinese National Knowledge Infrastructure and Wan Fang database) for articles published prior to March 2018. Our search strategy used the following terms: "*CYP2D6*" and "polymorphism" and "tamoxifen" and "breast cancer". We also manually inspected literature references from included studies for additional relevant papers. We only retrieved studies published in English and Chinese, and the search was thus prone to some language bias.

Inclusion and exclusion criteria

Eligible studies met the following criteria: (1) a target population of female Asian patients with BC; (2) clinical trials exploring the effect of *CYP2D6*10* polymorphisms on TAM pharmacokinetics; (3) patients were treated with adjuvant TAM (20 mg/day) for a minimum period of 1 month; (4) studies that measured serum concentrations of TAM or its metabolites including 4-OH-TAM and endoxifen; (5) studies including > 30 patients with BC; (6) a patient genotype distribution conforming to Hardy–Weinberg equilibrium (HWE); and (7) a Newcastle–Ottawa Scale (NOS) score > 5 points, indicating high quality of the study.

The exclusion criteria were as follows: (1) papers written in a language other than English or Chinese; (2) review articles, abstracts, or meeting reports; (3) non-clinical studies; (4) studies not evaluating the relationship between *CYP2D6*10* and TAM metabolism; (5) non-Asian or primarily Caucasian studies; and (6) a patient genotype distribution not conforming to HWE.

Data extraction and quality assessment

Two investigators (Yu Bai and Hai-wei Wu) independently screened titles and abstracts to select potentially eligible literature. All potentially eligible publications were evaluated using the eligibility criteria applied to the full text. Data extraction was also completed by two independent investigators; data of interest included the first author's name, year of publication, study population, sample size, genotype and concentration detection methods, and serum concentrations of TAM and its metabolites. Finally, two researchers crosschecked the extracted data. Any disagreements were resolved by discussion.

Statistical analysis

HWE was evaluated in each study population using the χ^2 test, with the threshold for HWE defined as $p > 0.05$. Heterogeneity across studies was also evaluated using the χ^2 test based on the Q test and I^2 metric [19]; studies were determined to be homogenous when $p > 0.1$ and $I^2 < 50\%$, and were analyzed using a fixed effects model. When $p < 0.1$ and $I^2 > 50\%$, studies were determined to be heterogeneous and a random effects model was used. Means and standard

deviations (SDs) of the concentrations of TAM and its metabolites were obtained from original articles; if the study only provided graphical data, GetData Graph Digitizer 2.25 (http://www.getdata-graph-digitizer.com) was used to compute numerical values in figures. For values reported as the median and range, the mean and SD were calculated using a previously reported formula [20]. The meta-analysis was performed using Review Manager 5.3 (Cochrane Community Software, London, UK) and the pooled mean and SD were demonstrated graphically using forest plots. Begg's funnel plot and Egger's test were used to examine publication bias in STATA 14.0 (StataCorp LLC, College Station, TX, USA) [21]. A sensitivity analysis was performed by sequential omission of each study to evaluate the stability of our results.

Results

Characteristics of included studies

The initial search identified 1129 studies including 1096 English articles and 33 Chinese articles. We deleted 344 repetitive articles and ultimately selected 23 articles for full text review. Of 10 such articles reviewed for possible inclusion, three [22–24] were excluded because the population genotype distributions did not conform to HWE. Finally, seven studies [18, 25–30] and 552 patients with BC were included in the meta-analysis. The screening process is summarized in Fig. 1 and basic information about the included studies is shown in Table 1.

*CYP2D6*10* polymorphisms and TAM concentration

A total of six studies including 350 patients with BC examined the relationship between *CYP2D6*10* polymorphisms and TAM serum concentration. Data for the CC vs. TT genotype comparison were heterogeneous ($I^2 = 55.00\%$, $p = 0.05$); therefore, a random effects model was used for meta-analysis. All other groups were analyzed with fixed effects models. The meta-analysis revealed no significant differences in TAM concentration between the CC and CT genotype groups [mean difference (MD) = 4.65; 95% confidence interval (CI) = (− 14.85, 24.14), $p = 0.64$], CC and TT genotype groups [MD − 12.81, 95% CI (− 49.87, 24.25), $p = 0.50$], or CT and TT genotype groups [MD 3.54, 95% CI (− 9.77, 16.84), $p = 0.60$] (Table 2 and Fig. S1).

*CYP2D6*10* polymorphisms and 4-OH-TAM concentration

A total of five studies including 436 BC patients examined the relationship between *CYP2D6*10* polymorphisms and 4-OH-TAM concentration. Data for the CT vs. TT genotype comparison were heterogeneous ($I^2 = 89\%$, $p < 0.01$); therefore, a random effects model was used for meta-analysis. All other groups were analyzed with fixed effects models. The meta-analysis revealed significant differences in 4-OH-TAM concentrations between the CC and CT genotype groups [MD 0.30, 95% CI (0.01, 0.58), $p = 0.04$] and CC and TT genotype groups [MD 1.12, 95% CI (0.82, 1.41), $p < 0.01$]. There was no significant difference between the CT and TT

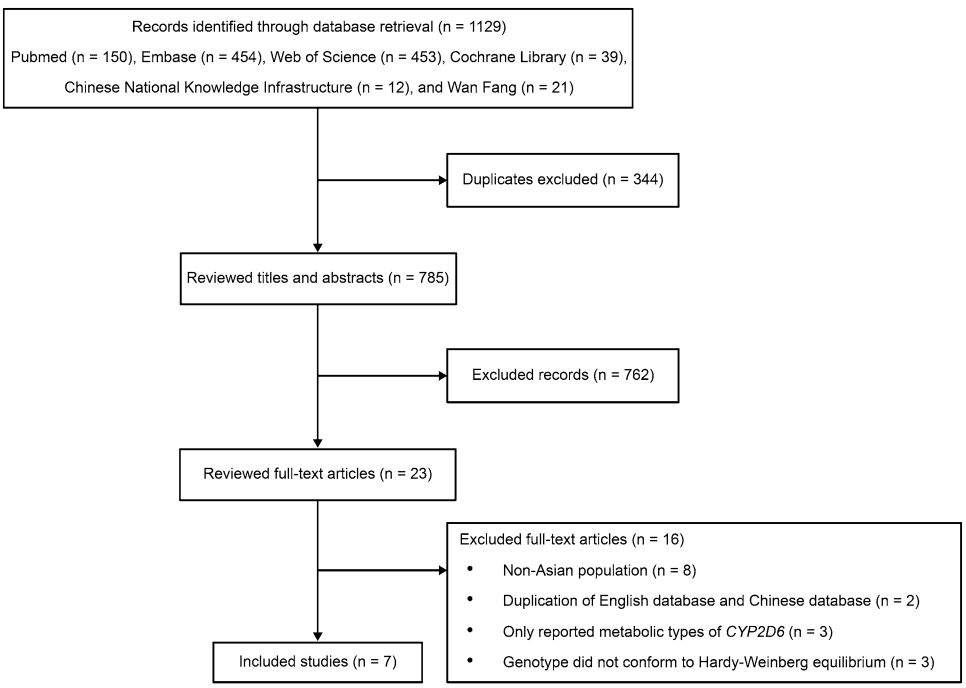


Fig. 1 Flow diagram of the study selection process

Table 1 Summary of the main characteristics of the included studies

Study	Year of publication	Country	Sample size	Age	Genotypic detection method	Plasma concentration detection method	Genotype (*n*)	Plasma concentration (ng/mL)			HWE		NOS score
								TAM	4-OH-TAM	Endoxifen	χ^2	*p*	
Lim et al. [25]	2007	Korea	202	47 (25–73)	Real-time PCR	HPLC-FLU	CC (64) CT (89) TT (49)	NG	2.63 (0.50–5.85) 2.47 (0.69–5.16) 1.25 (0.61–2.91)	19.35 (6.13–45.81) 17.74 (6.61–45.48) 7.90 (3.39–17.10)	2.62	0.27	7
Zhang et al. [26]	2010	China	30	46 (28–61)	Tetra-primer ARMS PCR	LC–MS/MS	CC (2) CT (18) TT (10)	245.5 ± 145.5 200.5 ± 90.5 184.7 ± 90.3	3.56 ± 1.55 2.57 ± 0.87 1.91 ± 0.46	NG	2.55	0.27	5
Lim et al. [27]	2011	Mixed[a]	84	49.3 (30–74)	Real-time PCR	HPLC-FLU	CC (13) CT (31) TT (40)	161.22 (50.06–369.89) 194.88 (51.80–421.16) 217.19 (84.27–599.91)	2.49 (0.97–3.36) 1.92 (0.86–4.51) 1.76 (0.72–3.82)	19.55 (4.18–39.47) 19.74 (7.26–33.24) 8.03 (1.74–34.68)	2.63	0.27	7
Kiyotani et al. [28]	2012	Japan	86	44 (29–65)	Taqman	LC-MS/MS	CC (24) CT (40) TT (22)	133 (39.60–272.28) 141.09 (44.55–338.39) 136.14 (69.31–259.90)	3.00 (1.25–6.48) 2.74 (0.96–4.65) 2.24 (1.35–5.72)	17.58 (4.65–37.17) 14.95 (5.45–39.19) 8.69 (5.86–14.62)	0.41	0.81	7
Yang et al. [29]	2013	China	57	44 (35–49)	Tetra-primer ARMS PCR	LC–MS/MS	CC (9) CT (25) TT (23)	348.12 ± 38.71 337.86 ± 30.03 326.05 ± 27.00	NG	34.82 ± 5.95 25.90 ± 3.93 23.55 ± 4.01	0.25	0.88	5
Areepium et al. [18]	2013	Thailand	59	50 ± 9.3	Real-time PCR	HPLC-FLU	CC (16) CT (23) TT (20)	323.6 ± 79.8 336.3 ± 151.1 437.3 ± 161.2	NG	21.55[b] 15.67[b] 9.62[b]	2.77	0.25	6
Lei et al. [30]	2016	China	34	42.11 ± 5.35 45.68 ± 7.40 43.96 ± 8.65	Pyrosequencing	LC–MS/MS	CC (12) CT (10) TT (12)	305.05 ± 158.37 336.42 ± 182.76 310.70 ± 128.03	3.90 ± 1.90 4.58 ± 1.93 3.14 ± 2.59	24.06 ± 12.07 25.68 ± 13.96 10.72 ± 4.00	5.76	0.06	6

ARMS amplification refractory mutation system, *HPLC-FLU* high performance liquid chromatography with fluorescence detection, *HWE* Hardy–Weinberg equilibrium, *LC–MS/MS* liquid chromatograph–mass spectrometry/mass spectrometry, *NG* not given, *NOS* Newcastle–Ottawa scale, *PCR* polymerase chain reaction, *TAM* tamoxifen

[a]Included a mixed population of Asian subjects (Chinese, Malay, and Indian)

[b]Endoxifen concentrations were reported as the median due to a non-normal distribution of data

Table 2 Summary of the meta-analysis and publication bias

Metabolite	Studies	Comparison	Mean difference (95% CI)	*Z*	*p* value	Heterogeneity		Publication bias	
						I^2, %	*p* value	Begg's test	Egger's test
TAM	6	CC vs. CT	4.65 (−14.85 to 24.14)	0.47	0.64	0.00	0.97	0.45	0.37
		CC vs. TT	−12.81 (−49.87 to 24.25)	0.68	0.50	55.00	0.05	1.00	0.40
		CT vs. TT	3.54 (−9.77 to 16.84)	0.52	0.60	34.00	0.18	0.45	0.24
4-OH-TAM	5	CC vs. CT	0.30 (0.01 to 0.58)	2.03	0.04	2.00	0.40	1.00	0.86
		CC vs. TT	1.12 (0.82 to 1.41)	7.41	< 0.01	39.00	0.16	0.81	0.45
		CT vs. TT	0.57 (−0.07 to 1.20)	1.75	0.08	89.00	< 0.01	0.81	0.40
Endoxifen	5	CC vs. CT	3.77 (0.29 to 7.25)	2.12	0.03	58.00	0.05	1.00	0.93
		CC vs. TT	11.13 (9.36 to 12.89)	12.38	< 0.01	0.00	0.89	0.46	0.39
		CT vs. TT	7.53 (6.41 to 8.66)	4.03	< 0.01	90.00	< 0.01	1.00	0.83

CI confidence interval, *TAM* tamoxifen

genotype groups [MD 0.57, 95% CI (−0.07, 1.20), $p = 0.08$] (Table 2; Fig. 2).

*CYP2D6*10* polymorphisms and endoxifen concentration

A total of five studies including 463 BC patients examined the relationship between *CYP2D6*10* polymorphisms and endoxifen concentration. Data for the CT vs. CC and CT vs. TT genotype comparisons were heterogeneous ($I^2 = 58\%$, $p = 0.05$ and $I^2 = 90\%$, $p < 0.01$, respectively); therefore, a random effects model was used for meta-analysis. Data for the CC and TT genotypes were analyzed with a fixed effects model. The meta-analysis results revealed significant differences in endoxifen concentrations between the CC and CT genotype groups [MD 3.77, 95% CI (0.29, 7.25), $p = 0.03$], CC and TT genotype groups [MD 11.13, 95% CI (9.36, 12.89), $p < 0.01$], and CT and TT genotype groups [MD 7.53, 95% CI (6.41, 8.66), $p < 0.01$] (Table 2; Fig. 3).

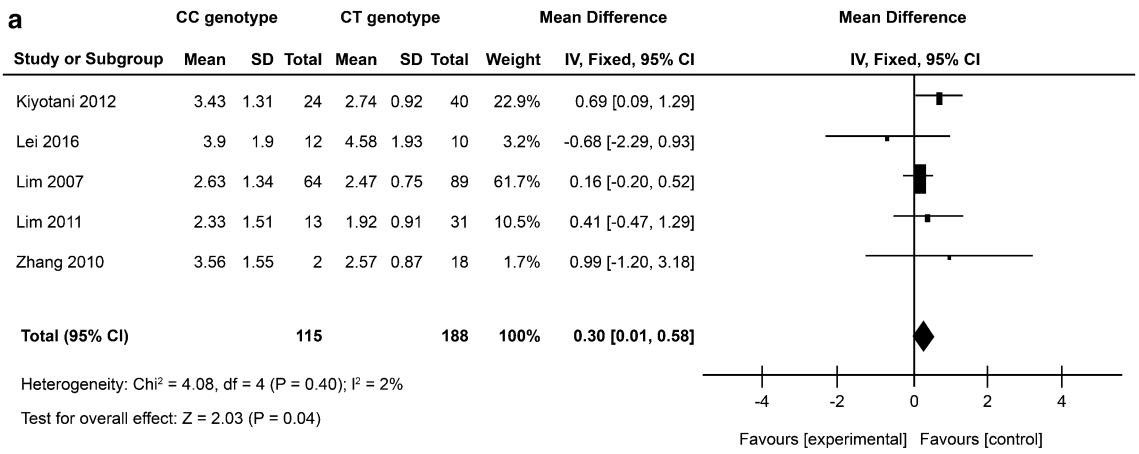
Publication bias and sensitivity analyses

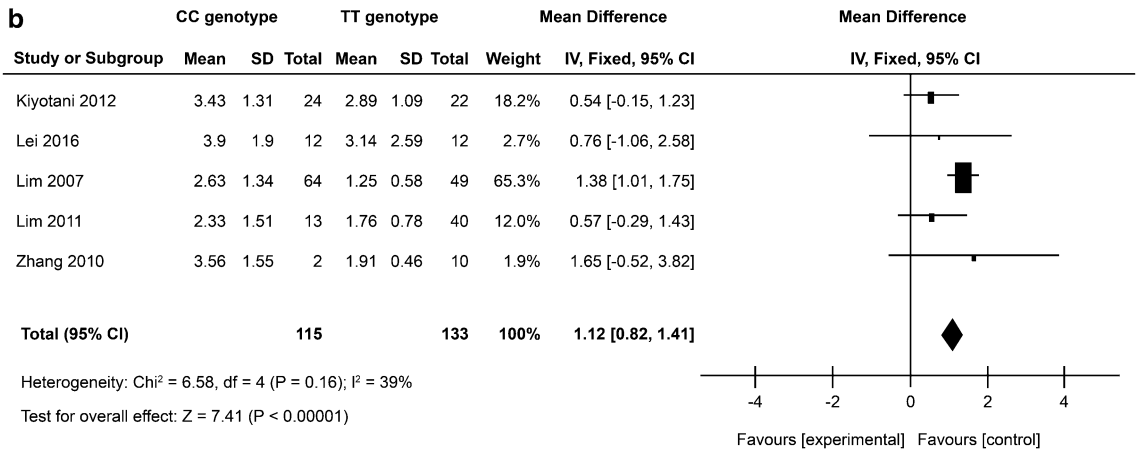
Publication bias was evaluated with both Begg's funnel plot and Egger's test. The results did not indicate any publication bias (Table 2 and Fig. S2). Moreover, a sensitivity analysis sequentially omitting each individual study revealed that most subgroups did not significantly affect pooled mean differences and no substantial changes in the results were identified, indicating that our results were statistically stable (Fig. S3).

Discussion

The development of precision medicine and an increasing demand for individualized therapy have spurred the progress of pharmacogenomic research [31]. Gene polymorphisms in drug-metabolizing enzymes can lead to individual differences in serum concentrations of drugs and their active metabolites, subsequently affecting treatment efficacy [7, 32]. Previous studies have shown that *CYP2D6* gene polymorphism can play a role in the metabolism of tamoxifen [33–35]. Therefore, in 2006, the United States Food and Drug Administration (FDA) Advisory Committee recommended the inclusion of pharmacogenomic biomarker information on *CYP2D6* in a revision of the label for TAM [7, 36, 37]. The *CYP2D6*10* gene mutation frequency is the highest among Asian populations, and there is an increasing research interest in the relationships between *CYP2D6* polymorphisms and TAM metabolism and efficacy [34, 35]. Previous studies have shown that the *CYP2D6* TT genotype has a greater impact on TAM metabolism and efficacy, but inconformity with concentration of TAM metabolism results in heterozygous mutagenesis [25, 26, 32].

In our screening of studies for inclusion in the meta-analysis, three articles had study populations with genotype distributions that did not conform to HWE and were excluded. Among them, Tian et al. [22] studied 200 cases of BC in China and found that patients with the TT genotype of *CYP2D6*10* had lower serum concentrations of 4-OH-TAM than other groups, but there were no other significant differences according to genotype. Xu et al. [23] evaluated 37 cases of BC in China and found that patients with the TT genotype of CYP2D6*10 had lower concentrations of 4-OH-TAM than those with the CC genotype, consistent with the results of our meta-analysis. Charoenchokthavee et al. [24] analyzed 133 cases of BC in Thailand and found no statistically difference between *CYP2D6*10* polymorphism and TAM metabolism. We analyzed and identified the reasons underlying the non-conformance of these three articles to HWE as follows: (1) Sample source: Tian et al. [22] used oral mucosal cells to extract DNA for sequencing, and Xu et al. [23] used blood sample, fresh-frozen tumors, or paraffin-embedded negative axillary nodes for extracted





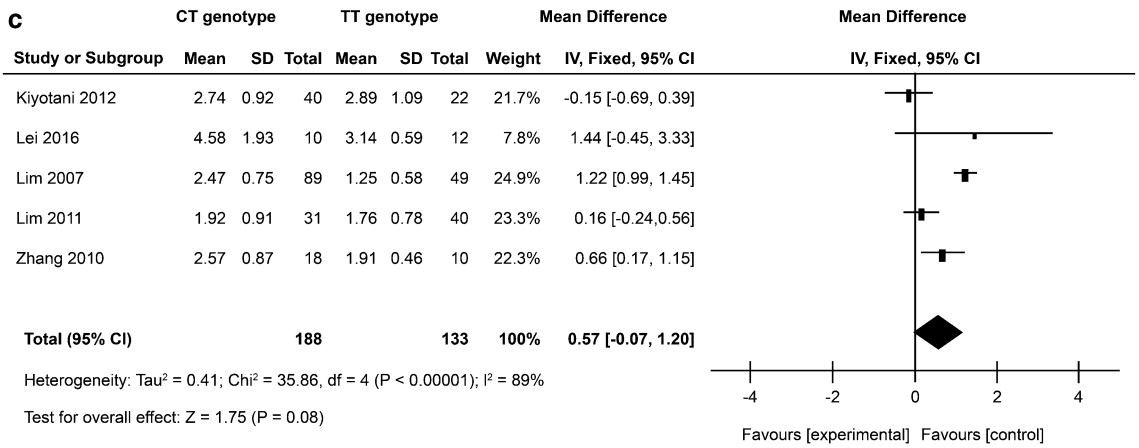
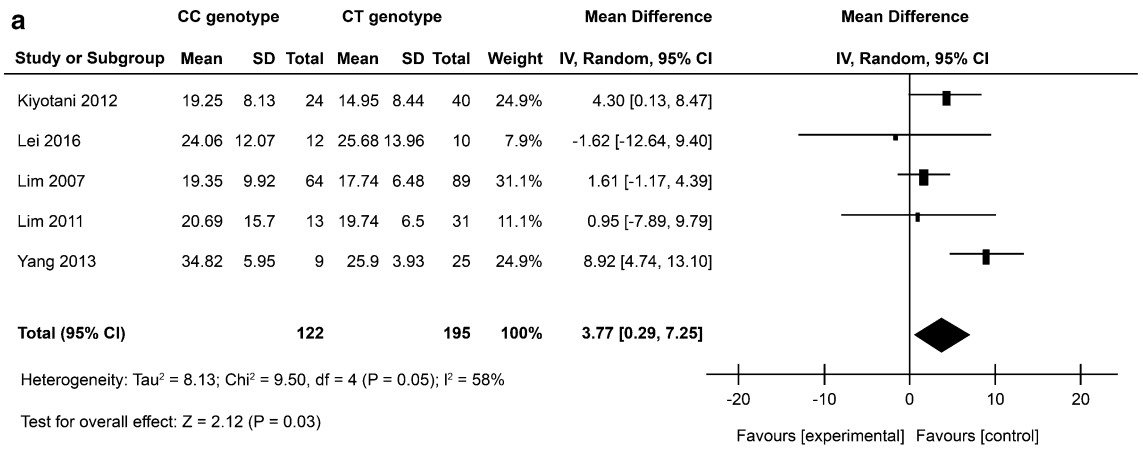
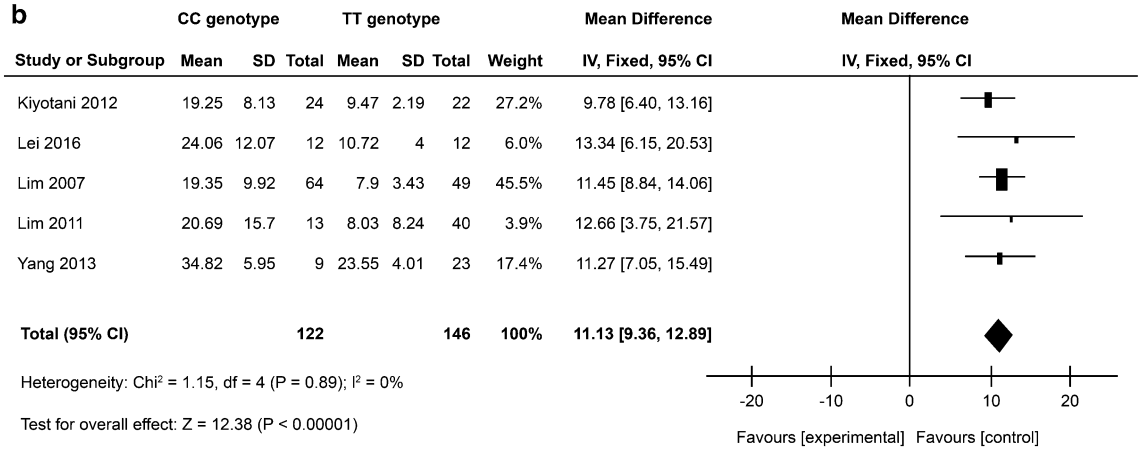


Fig. 2 Forest plots estimating the effects of *CYP2D6*10* polymorphisms on 4-OH-TAM concentrations. **a** CC genotype vs. CT genotype; **b** CC genotype vs. TT genotype; **c** CT genotype vs. TT genotype

DNA. However, the DNA samples were derived from blood sample in the included literature. (2) Genotype: Charoenchokthavee et al. [24] analysis of *CYP2D6* polymorphism was not only limited to *1/*1, *1/*10, and *10/*10, but also to *2/*2,*2/*10, and so on. However, we mainly focused on *1/*1, *1/*10, and *10/*10, which may affect HWE. (3) Ignoring HWE: The possibility that the researchers might have ignored HWE cannot be excluded.





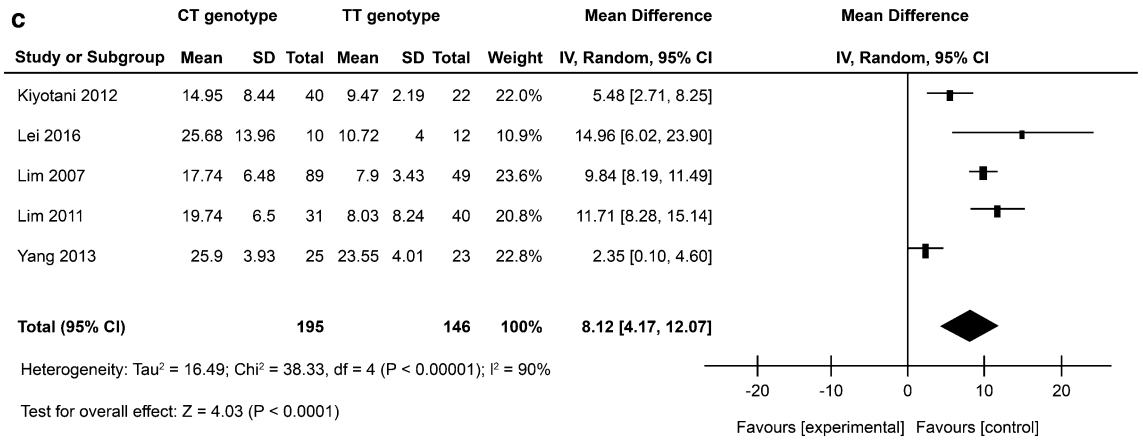


Fig. 3 Forest plots estimating the effects of *CYP2D6*10* polymorphisms on endoxifen concentrations. **a** CC genotype vs. CT genotype; **b** CC genotype vs. TT genotype; **c** CT genotype vs. TT genotype

Our meta-analysis may be the first to identify a correlation between *CYP2D6*10* polymorphism and tamoxifen pharmacokinetics in female Asian patients with BC receiving TAM adjuvant therapy (20 mg/day) for at least 1 month. There was no difference in serum TAM concentrations between genotype groups, and this is in agreement with other studies. In our meta-analysis, all genotypes showed variable concentrations of endoxifen ($p < 0.05$). Patients

carrying the TT genotype had lower endoxifen concentrations than those with the CC genotype in our pooled results, and these findings also agree with those of other studies. However, there were still some discrepancies; for example, the CT genotype also had a significantly lower concentration of endoxifen in our pooled results than the CC genotype and some previous research results also showed a significant difference [28, 29], but others showed no difference [25, 27, 30]. Additionally, an interesting trend was noted for the 4-OH-TAM concentration, where only Lim et al. [25] showed a significant difference between the CC and TT genotypes, whereas other studies showed no significant differences; however, our pooled results showed a difference with no heterogeneity. Therefore, large-scale clinical trials are still necessary to consolidate our meta-analysis. The discrepant conclusions mainly relate to the comparison of heterozygous with homozygous mutations, and the difference in the concentration of 4-OH-TAM. In fact, only a small part of tamoxifen would be converted to 4-OH-TAM by CYP2D6 and other metabolic enzymes; therefore, it may be difficult to obtain a statistically significant difference [5]. Additionally, the sensitivity analysis showed that the pooled study results did not depend significantly on any individual study, indicating that our results were statistically stable.

The present study had some limitations. First, we included several studies with small sample sizes that may have been underpowered to detect significant correlations between our study variables. Additionally, our analysis did not control for menopause status, time of blood sampling, and other important lifestyle factors. For example, whether tamoxifen was taken before blood collection and how long tamoxifen was taken before blood collection could affect the determination of drug concentration.

In summary, we conclude that although *CYP2D6*10* polymorphisms do not significantly affect serum concentrations of TAM, the serum concentrations of the active metabolites of TAM are influenced by *CYP2D6*10* polymorphisms. It is worth noting that even in patients with the CT genotype as well as CC genotype, the average serum concentration of endoxifen could be less than the threshold value of 5.97 ng/ml used in previous studies to predict tumor recurrence after treatment [10, 11]. However, the average endoxifen serum concentration of the CC/CT genotypes was still higher than that of the TT genotype. Per the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline [13], in patients with a TT genotype, the dose of TAM should be increased from 20 to 40 mg/day to ensure adequate serum concentrations. Kiyotani et al. [34] found that patients with the CT or TT genotype who received increasing doses of tamoxifen (30 or 40 mg/day from 20 mg/day) showed significant increases in serum concentrations of 4-OH-TAM and endoxifen ($p < 0.001$). However, it remains controversial whether there is a need to monitor endoxifen concentrations in patients. In a recent prospective multicenter trial by Neven et al. [38], no outcome was associated with endoxifen levels and the results do not suggest therapeutic drug monitoring of endoxifen to be of clinical value. Considering the possibility of racial differences, we still need similar prospective studies in Asia to validate the clinical significance and utility of our meta-analysis results.

Acknowledgements We would like to thank Editage (http://www.editage.com) for English language editing and publication support.

Funding This study was supported by grants from the National Key Technologies R&D Program (no. 2016YFC0904900).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval For this type of study, a formal consent is not required. This study does not involve any human participants or animals.

References

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A (2015) Global cancer statistics, 2012. CA Cancer J Clin 65:87–108. https://doi.org/10.3322/caac.21262
2. Shah R, O'Regan RM (2018) Adjuvant endocrine therapy. Cancer Treat Res 173:15–29
3. Early Breast Cancer Trialists'Collaborative Group (EBCTCG) (2005) Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patients-level meta-analysis of randomized trials. Lancet 378(9793):771–784
4. Klein DJ, Thorn CF, Desta Z, Flockhart DA, Altman RB, Klein TE (2013) PharmGKB summary: tamoxifen pathway, pharmacokinetics. Pharmacogenet Genom 23:643–647. https://doi.org/10.1097/FPC.0b013e3283656bc1
5. Woo HI, Lee SK, Kim J, Kim SW, Yu J, Bae SY, Lee JE, Nam SJ, Lee SY (2017) Variations in serum concentrations of tamoxifen metabolites and the effects of genetic polymorphisms on tamoxifen metabolism in Korean patients with breast cancer. Oncotarget 8:100296–100311. https://doi.org/10.18632/oncotarget.22220
6. Thota K, Prasad K, Basaveswara Rao MV (2018) Detection of Cytochrome P450 Polymorphisms in Breast Cancer Patients May Impact on Tamoxifen Therapy. Asian Pac J Cancer Prev 19:343–350. https://doi.org/10.22034/APJCP.2018.19.2.343
7. de Vries Schultink AH, Zwart W, Linn SC, Beijnen JH, Huitema AD (2015) Effects of Pharmacogenetics on the Pharmacokinetics and Pharmacodynamics of Tamoxifen. Clin Pharmacokinet 54:797–810. https://doi.org/10.1007/s40262-015-0273-3
8. Lim YC, Desta Z, Flockhart DA, Skaar TC (2005) Endoxifen (4-hydroxy-N-desmethyl-tamoxifen) has anti-estrogenic effects in breast cancer cells with potency similar to 4-hydroxy-tamoxifen. Cancer Chemother Pharmacol 55:471–478. https://doi.org/10.1007/s00280-004-0926-7
9. Johnson MD, Zuo H, Lee KH, Trebley JP, Rae JM, Weatherman RV, Desta Z, Flockhart DA, Skaar TC (2004) Pharmacological characterization of 4-hydroxy-N-desmethyl tamoxifen, a novel active metabolite of tamoxifen. Breast Cancer Res Treat 85:151–159. https://doi.org/10.1023/B:BREA.0000025406.31193.e8

10. Madlensky L, Natarajan L, Tchu S, Pu M, Mortimer J, Flatt SW, Nikoloff DM, Hillman G, Fontecha MR, Lawrence HJ, Parker BA, Wu AH, Pierce JP (2011) Tamoxifen metabolite concentrations, CYP2D6 genotype, and breast cancer outcomes. Clin Pharmacol Ther 89(5):718–725
11. Saladores P, Murdter T, Eccles D, Chowbay B, Zqheib NK, Winter S, Ganchew B, Eccles B, Gerty S, Tfayli A, Lim JS, Yap YS, Nq RC, Wong NS, Dent R, Habbal MZ, Schaeffeler E, Eichelbaum M, Schroth W, Schwab M, Brauch H (2015) Tamoxifen metabolism predicts drug concentrations and outcome in premenopausal patients with early breast cancer. Pharmacogenom J 15(1):84–94
12. Schroth W, Winter S, Mürdter T, Schaeffeler E, Eccles D, Eccles B, Chowbay B, Khor CC, Tfayli A, Zgheib NK, Eichelbaum M, Schwab M, Brauch H (2017) Improved prediction of endoxifen metabolism by CYP2D6 genotype in breast cancer patients treated with tamoxifen. Front Pharmacol 8:582. https://doi.org/10.3389/fphar.2017.00582
13. Goetz MP, Sangkuhl K, Guchelaar HJ, Schwab M, Province M, Whirl-Carrillo M, Symmans WF, McLeod HL, Ratain MJ, Zembutsu H, Gaedigk A, van Schaik RH, Ingle JN, Caudle KE, Klein TE (2018) Clinical pharmacogenetics implementation consortium (CPIC) guideline for CYP2D6 and tamoxifen therapy. Clin Pharmacol Ther 103:770–777. https://doi.org/10.1002/cpt.1007
14. Chin FW, Chan SC, Abdul Rahman S, Noor Akmal S, Rosli R (2016) CYP2D6 genetic polymorphisms and phenotypes in different ethnicities of malaysian breast cancer patients. Breast J 22:54–62. https://doi.org/10.1111/tbj.12518
15. Sirachainan E, Jaruhathai S, Trachu N, Panvichian R, Sirisinha T, Ativitavas T, Ratanatharathorn V, Chamnanphon M, Sukasem C (2012) CYP2D6 polymorphisms influence the efficacy of adjuvant tamoxifen in Thai breast cancer patients. Pharmgenom Pers Med 5:149–153. https://doi.org/10.2147/PGPM.S32160
16. Yin SJ, Ni YB, Wang SM, Wang X, Lou YQ, Zhang GL (2012) Differences in genotype and allele frequency distributions of polymorphic drug metabolizing enzymes CYP2C19 and CYP2D6 in mainland Chinese Mongolian, Hui and Han populations. J Clin Pharm Ther 37:364–369. https://doi.org/10.1111/j.1365-2710.2011.01298.x
17. Lan B, Ma F, Zhai X, Li Q, Chen S, Wang J, Fan Y, Luo Y, Cai R, Yuan P, Zhang P, Li Q, Xu B (2018) The relationship between the CYP2D6 polymorphisms and tamoxifen efficacy in adjuvant endocrine therapy of breast cancer patients in Chinese Han population. Int J Cancer. https://doi.org/10.1002/ijc.31291
18. Areepium N, Panomvana D, Rungwanonchai P, Sathaporn S, Voravud N (2013) Effects of CYP2D6 and UGT2B7 polymorphisms on pharmacokinetics of tamoxifen in Thai breast cancer patients. Breast Cancer (Dove Med Press) 5:73–78. https://doi.org/10.2147/BCTT.S47172
19. Zintzaras E, Ioannidis JP (2005) Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 28:123–137. https://doi.org/10.1002/gepi.20048
20. Hozo SP, Djulbegovic B, Hozo I (2005) Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 5:13. https://doi.org/10.1186/1471-2288-5-13
21. Harbord RM, Egger M, Sterne JA (2006) A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat Med 25:3443–3457. https://doi.org/10.1002/sim.2380
22. Tian C, Yang Y, Li H (2014) Clinical analysis of CYP2D6 gene polymorphism with serum concentration of tamoxifen and 4-hydroxytamoxifen. Sichuan Med J 35(1):4–6
23. Xu Y, Sun Y, Yao L, Shi L, Wu Y, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, He L, Li P, Xie Y (2008) Association between CYP2D6 *10 genotype and survival of breast cancer patients receiving tamoxifen treatment. Ann Oncol 19:1423–1429. https://doi.org/10.1093/annonc/mdn155
24. Charoenchokthavee W, Areepium N, Panomvana D, Sriuranpong V (2017) Effects of CYP2D6 and CYP3A5 polymorphisms on tamoxifen and its metabolites in Thai breast cancer patients. Breast Cancer (Dove Med Press) 9:249–256. https://doi.org/10.2147/BCTT.S125745
25. Lim HS, Ju Lee H, Seok Lee K, Sook Lee E, Jang IJ, Ro J (2007) Clinical implications of CYP2D6 genotypes predictive of tamoxifen pharmacokinetics in metastatic breast cancer. J Clin Oncol 25:3837–3845. https://doi.org/10.1200/JCO.2007.11.4850
26. Zhang YX, Li YF, Chen B, Zhang WX, Cai WM (2010) Correlation between polymorphisms of CYP3A5 and CYP2D6 genotypes with concentration of tamoxifen and its activity metabolism 4-hydroxy-tamoxifen in Chinese breast cancer patients. China Pharmacist 13(9):1229–1232
27. Lim JS, Chen XA, Singh O, Yap YS, Ng RC, Wong NS, Wong M, Lee EJ, Chowbay B (2011) Impact of CYP2D6, CYP3A5, CYP2C9 and CYP2C19 polymorphisms on tamoxifen pharmacokinetics in Asian breast cancer patients. Br J Clin Pharmacol 71:737–750. https://doi.org/10.1111/j.1365-2125.2011.03905.x
28. Kiyotani K, Mushiroda T, Imamura CK, Tanigawara Y, Hosono N, Kubo M, Sasa M, Nakamura Y, Zembutsu H (2012) Dose-adjustment study of tamoxifen based on CYP2D6 genotypes in Japanese breast cancer patients. Breast Cancer Res Treat 131:137–145. https://doi.org/10.1007/s10549-011-1777-7
29. Yang X, Luo B, Wu B (2013) Association between CYP2D6 polymorphism and serum concentration of endoxifen in breast cancer patients. Chin J Cancer Prev Treat 20(12):922–925
30. Lei L, Wang X, Wu XD, Wang Z, Chen ZH, Zheng YB, Wang XJ (2016) Association of CYP2D6*10 (c.100C>T) polymorphisms with clinical outcome of breast cancer after tamoxifen adjuvant endocrine therapy in Chinese population. Am J Transl Res 8:3585–3592
31. Johnson JA, Weitzel KW (2016) Advancing pharmacogenomics as a component of precision medicine: how, where, and who? Clin Pharmacol Ther 99:154–156. https://doi.org/10.1002/cpt.273
32. Lu J, Li H, Guo P, Shen R, Luo Y, Ge Q, Shi W, Li Y, Zhu W (2017) The effect of CYP2D6 *10 polymorphism on adjuvant tamoxifen in Asian breast cancer patients: a meta-analysis. Onco Targets Ther 10:5429–5437. https://doi.org/10.2147/OTT.S149197
33. Chamnanphon M, Pechatanan K, Sirachainan E, Trachu N, Chantratita W, Pasomsub E, Noonpakdee W, Sensorn I, Sukasem C (2013) Association of CYP2D6 and CYP2C19 polymorphisms and disease-free survival of Thai post-menopausal breast cancer patients who received adjuvant tamoxifen therapy. Pharmgenom Pers Med 6:37–47
34. Kiyotani K, Mushiroda T, Sasa M (2008) Impact of CYP2D6*10 on recurrence-free survival in breast cancer patients receiving adjuvant tamoxifen therapy. Cancer Sci 99(5):995–999
35. Helland T, Henne N, Bifulco E, Naume B, Borgen E, Kristensen VN, kvaløy JT, Lash TL, Alnæs GIG, van Schaik RH, Janssen EAM, Hustad S, Lien EA, Mellgren G, Søiland H (2017) Serum concentration of active tamoxifen metabolites predict long-term survival in adjuvantly treated breast cancer patients. Breast Cancer Res 19(1):125
36. Chau SB, Thomas RE (2015) The AmpliChip: a review of its analytic and clinical validity and clinical utility. Curr Drug Saf 10:113–124
37. de Leon J, Susce MT, Murray-Carmichael E (2006) The AmpliChip CYP450 genotyping test: Integrating a new clinical tool. Mol Diagn Ther 10:135–151
38. Neven P, Jongen L, Lintermans A, Van AK, Blomme C, Lambrechts D, Poppe A, Wildiers H, Dieudomne AS, Brouckaert O, Decloedt J, Berteloot P, Verhoeven D, Joerger M, Vuylsteke P, Wynendaele W, Casteels M, Van HS, Lybaert W, Van GJ, Paridaens R, Vergote I, Dezentje VO, Van CB, Guchelaar HJ (2018) Tamoxifen metabolism and efficacy in breast cancer: a prospective multicenter trial. Clin Cancer Res 24(10):2312–2318