ORIGINAL RESEARCH

The effect of *CYP2D6 *10* polymorphism on adjuvant tamoxifen in Asian breast cancer patients: a meta-analysis

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Objective: To evaluate the effect of *CYP2D6 *10* polymorphism (C 100C>T, rs1065852) on clinical outcomes of female Asian breast cancer patients with tamoxifen adjuvant treatment.
Methods: Meta-analysis of retrospective cohort studies published in July 2017 was performed. Fifteen studies with 1,794 Asian breast cancer patients were included, using strict eligibility requirements. Associations of disease-free survival (DFS), overall survival (OS) and recurrence rate after tamoxifen intake, with *CYP2D6 *10* polymorphism were investigated through random effects models.
Results: *CYP2D6 *10* polymorphism was found to have effect on DFS and recurrence rate in various comparison models, but not on overall survival in the female Asian breast cancer patients.
Conclusion: In conclusion, our meta-analysis suggests that significant association of *10/*10 (*TT*) genotype with poorer DFS and recurrence exists in female Asian breast cancer patients with tamoxifen 20 mg/day adjuvant treatment. In the future, large and well-designed studies are required to illustrate the interactions of *CYP2D6* genetic variants, including *10 polymorphism and tamoxifen response on female breast cancer patients.
Keywords: *CYP2D6 *10*, polymorphism, breast cancer, Asia, tamoxifen adjuvant treatment

Introduction

Tamoxifen has been widely used for >30 years as adjuvant treatment for women operated for estrogen receptor-positive breast cancer. It is reported that postoperative 5-year tamoxifen therapy effectively reduces the risk of breast cancer recurrence by 39%[1] and breast cancer mortality.[1]

The clinical efficacy of tamoxifen adjuvant treatment varies among individuals. Tamoxifen itself has weak affinity for the estrogen receptor and undergoes considerable first-pass oxidative metabolism to more potent metabolites, such as 4-hydroxytamoxifen and 4-hydroxy-N-desmethyl tamoxifen (endoxifen), which is the main active tamoxifen, and has up to a 33-fold higher affinity for the estrogen receptor than tamoxifen itself.[2] The rate-limiting step in tamoxifen metabolism is mediated primarily by the highly polymorphic *CYP2D6*.[3]

Several studies have reported that *CYP2D6* genetic mutations leading to the absence of functional enzyme are related to the decrease in 4-hydroxytamoxifen and endoxifen levels.[4] However, it is still highly controversial on the clinical association of *CYP2D6* genetic variants as predictors of tamoxifen efficacy at the standard dose of 20 mg/day. Nonfunctional allele variants of *CYP2D6* gene were reported to be associated with increased risk of breast cancer relapse in female breast cancer patients[4–8] and increased

risk of breast cancer occurrence in unaffected women.[9] Meanwhile, other studies do not support such an association.[10–13] The causes of these conflicting results might be clarified by some newly emerged evidence,[14,15] such as inclusion criteria for patients, source of deoxyribonucleic acid and genotyping method, coverage of genetic mutations and polymorphisms, as well as serological concentrations of endoxifen.

The classical *CYP2D6*-predicted phenotype is commonly divided into 4 levels of enzyme activity: poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers and ultrarapid metabolizers.[16] To date, more than 100 allelic variants have been described for *CYP2D6* gene.[17] *CYP2D6 *10* is a major variant and produces an unstable CYP2D6 enzyme, with an allele frequency of ~50% in Asians[18] but only 2% in Caucasians.[19] Mutation of *CYP2D6 *10* generates a 188 C to T transition in exon 1, leading to a Proline 34 to Serine amino acid substitution and resulting in an unstable enzyme with lower activity and metabolic conversion rate.[20]

It would be of great interest to investigate whether *CYP2D6 *10* genotype affects the efficacy of tamoxifen in female Asian breast cancer patients. To test this hypothesis, we investigated whether the *CYP2D6 *10* genotype is associated with the clinical outcome in a particular population subgroup of female Asian breast cancer patients by meta-analysis.

Methods
Literature and search strategy
The PubMed, MEDLINE, Cochrane, Embase, Wan Fang and Chinese National Knowledge Infrastructure database searches were conducted for all the pertinent trials. The search terms were: "*CYP2D6*" and "polymorphism" and "tamoxifen" and "breast cancer". Manual scrutiny for eligible articles was conducted according to the bibliography of the original and review reports. The literature search was updated in July 2017.

Study selection
Retrieved studies were deemed eligible provided that they met all the following criteria: 1) studies on human beings; 2) in a cohort design or randomized controlled trial design; 3) investigated the effect of *CYP2D6 *10* polymorphism with outcome of breast cancer patients taking tamoxifen; 4) in Asian population; 5) treated with 20 mg/day adjuvant tamoxifen for 2–5 years; 6) detailed outcomes could be obtained or calculated on the outcome of disease-free survival (DFS), overall survival (OS) or recurrence rate; 7) the number of

women with breast cancer was >30; 8) and received more than 4 points in the Newcastle–Ottawa Scale (NOS), which was considered to be of high quality.

Data extraction
Three reviewers screened titles and abstracts for relevance to the topic independently (Junjun Lu, He Li and Peng Guo). All potential publications were independently evaluated in full text. The following information was sought for reaching consensus on all of the items: the first author's name, year of publication, design of trial, comparison, number of patients, and the endpoints of clinical prognosis. Any disagreements were resolved by the fourth investigator (Zhu Weikang).

Statistical analysis
Five genic comparison models (TT vs CC, CT vs CC, TT vs CT/CC, TT/CT vs CC, and TT vs CT) for 3 endpoints (DFS, OS and reference) were analyzed. A χ^2-test based on the Q test and I^2 metric were used to quantify the heterogeneity.[21] When $I^2 > 50\%$ and $p < 0.1$, the between-study heterogeneity was considered to be significant and the random-effects model was used. Otherwise, for homogeneous studies, the fixed effects model was used. The mean hazard ratios (HRs) and 95% CIs were obtained from the original article by using survival analysis.[22,23] If a publication did not provide HR values, Engauge Digitizer version 4.1 was used to obtain the HR values and 95% CIs.[23] The pooled HR was initially demonstrated using forest plots graphically. Begg's Funnel plot and Egger's test were conducted to evaluate the potential publication bias.[24] Sensitivity analysis was performed to assess the stability of our outcomes by omitting each study sequentially. Hardy–Weinberg equilibrium was examined with goodness-of-fit χ^2-test. Two-sided $p < 0.05$ was considered to be statistically significant. STATA version 12.0 (StataCorp LLC, College Station, TX, USA) was used for all the data analyses and graphs.

Results
Characteristics of studies included in this meta-analysis
Initial search yielded a total of 221 potentially relevant citations. Finally, 15 studies[7,25–38] were included in our meta-analysis to meet the inclusion criteria (Figure 1). Publication years ranged from January 2008 to July 2017; the number of breast cancer patients varied from 39 to 296 (Table 1). As a result, data for our meta-analysis were available from 15 studies with a total of 1,794 Asian breast cancer patients. The eligible studies were assessed by the NOS. Each of the
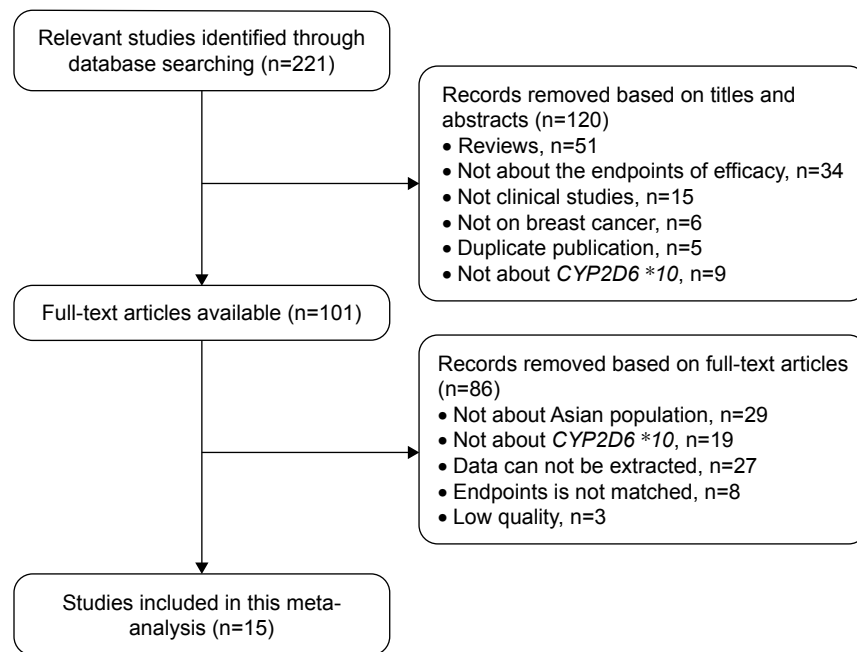
Relevant studies identified through
database searching (n=221)

Records removed based on titles and
abstracts (n=120)
• Reviews, n=51
• Not about the endpoints of efficacy, n=34
• Not clinical studies, n=15
• Not on breast cancer, n=6
• Duplicate publication, n=5
• Not about *CYP2D6 *10*, n=9

Full-text articles available (n=101)

Records removed based on full-text articles
(n=86)
• Not about Asian population, n=29
• Not about *CYP2D6 *10*, n=19
• Data can not be extracted, n=27
• Endpoints is not matched, n=8
• Low quality, n=3

Studies included in this meta-
analysis (n=15)

Figure 1 Study flow diagram for the process of selecting the final 15 studies.

studies scored >4, which suggested that all the research was of high quality (Table 1).

Meta-analysis results

The pooled effect of *CYP2D6 *10* genotype on the DFS of breast cancer patients treated with tamoxifen is shown in Figure 2 and Table 2. *CYP2D6 *10* polymorphism (C 100C>T, rs1065852) significantly influences DFS in various comparison models (TT vs CC: HR =1.79, 95% CI =1.14–2.80, p=0.011; CT vs CC: HR =2.02,

95% CI =1.04–3.19, p=0.037; TT vs CC: HR =1.79, 95% CI =1.14–2.80, p=0.011; TT vs CT: HR =2.03, 95% CI =1.41–2.93, p<0.001; TT vs CT/CC: HR =2.19, 95% CI =1.07–4.50, p=0.033) except the dominant model (TT/CT vs CC: HR =1.80, 95% CI =0.81–4.00, p=0.147).

Heterogeneity

There was no significant between-study heterogeneity for the endpoint of DFS in the comparison model of TT vs CC (I^2=44.5%, p=0.114), CT vs CC (I^2=36.3%, p=0.194) and

Table 1 Characteristics and quality assessment of the included studies

Study ID	Country	Sample size	Menopause status (pre + post)	Follow-up (months)[a]	Endpoints	Genotyping method	HWE	NOS
Xu et al[35]	China	152	–	63 (4–122)	DFS	RT-PCR	Y	6
Kiyotani et al[26]	Japan	67	35+32	96 (19.2–259.2)	RFS, recurrence	TaqMan	Y	7
Sirachainan et al[29]	Thailand	39	31+8	52.3–97.4	DFS	Pyrosequencing	Y	6
Sukasem et al[30]	Thailand	48	30+18	67.2	DFS	Microarray	Y	7
Teh et al[7]	Mixed*	95	33+62	–	Recurrence	TaqMan	Y	7
Chamnanphon et al[25]	Thailand	57	38+19	48 (2–172)	DFS, recurrence	Microarray	Y	6
Tian et al[31]	China	200	–	31.5 (9–58)	DFS	TaqMan	Y	7
Wei and Xu[33]	China	257	–	–	DFS, OS	RT-PCR	Y	5
Xiao et al[34]	China	87	0+87	35 (12–43)	DFS, recurrence	TaqMan	Y	6
Wang et al[32]	China	171	–	60	OS	RT-PCR	Y	5
Zhang et al[38]	China	296	174+122	–	OS	Sequencing	#	6
Lei et al[27]	China	72	65+7	85 (20–144)	DFS, OS	Pyrosequencing	Y	6
Sensorn et al[28]	Thailand	73	47+26	87.6 (60–171.6)	DFS	RT-PCR	Y	7
Yu et al[36]	China	106	–	–	DFS	RT-PCR	Y	5
Zeng et al[37]	China	76	–	30.5 (5–40)	Recurrence, OS	RT-PCR	Y	5

Notes: *Mixed includes patients in Malaysia, China, and India. #HWE of Zhang et al[38] was unknown and could not be estimated. [a]Data presented as median (range).
Abbreviations: DFS, disease-free survival; HWE, Hardy–Weinberg equilibrium; NOS, Newcastle–Ottawa scale; OS, overall survival; RFS, relapse-free survival; RT-PCR, real time-polymerase chain reaction.
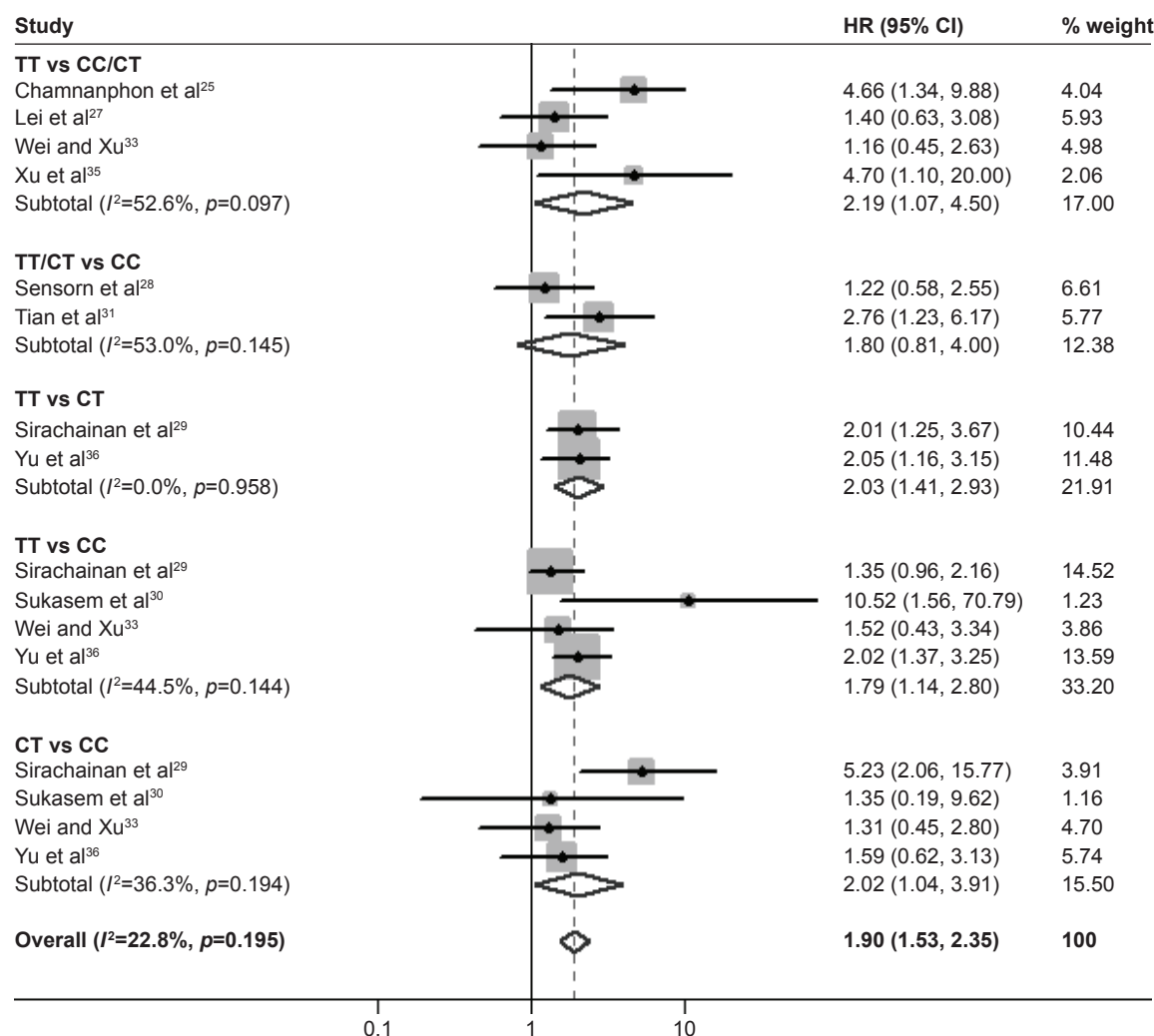
Study	HR (95% CI)	% weight

TT vs CC/CT
Chamnanphon et al[25] — 4.66 (1.34, 9.88) — 4.04
Lei et al[27] — 1.40 (0.63, 3.08) — 5.93
Wei and Xu[33] — 1.16 (0.45, 2.63) — 4.98
Xu et al[35] — 4.70 (1.10, 20.00) — 2.06
Subtotal (I^2=52.6%, p=0.097) — 2.19 (1.07, 4.50) — 17.00

TT/CT vs CC
Sensorn et al[28] — 1.22 (0.58, 2.55) — 6.61
Tian et al[31] — 2.76 (1.23, 6.17) — 5.77
Subtotal (I^2=53.0%, p=0.145) — 1.80 (0.81, 4.00) — 12.38

TT vs CT
Sirachainan et al[29] — 2.01 (1.25, 3.67) — 10.44
Yu et al[36] — 2.05 (1.16, 3.15) — 11.48
Subtotal (I^2=0.0%, p=0.958) — 2.03 (1.41, 2.93) — 21.91

TT vs CC
Sirachainan et al[29] — 1.35 (0.96, 2.16) — 14.52
Sukasem et al[30] — 10.52 (1.56, 70.79) — 1.23
Wei and Xu[33] — 1.52 (0.43, 3.34) — 3.86
Yu et al[36] — 2.02 (1.37, 3.25) — 13.59
Subtotal (I^2=44.5%, p=0.144) — 1.79 (1.14, 2.80) — 33.20

CT vs CC
Sirachainan et al[29] — 5.23 (2.06, 15.77) — 3.91
Sukasem et al[30] — 1.35 (0.19, 9.62) — 1.16
Wei and Xu[33] — 1.31 (0.45, 2.80) — 4.70
Yu et al[36] — 1.59 (0.62, 3.13) — 5.74
Subtotal (I^2=36.3%, p=0.194) — 2.02 (1.04, 3.91) — 15.50

Overall (I^2=22.8%, p=0.195) — **1.90 (1.53, 2.35)** — **100**

0.1   1   10

Figure 2 Forest plot to estimate the effect of *CYP2D6 *10* polymorphism on the DFS of breast cancer patients taking tamoxifen.
Note: Weights are from random effects analysis.
Abbreviations: DFS, disease-free survival; HR, hazard ratio.

TT vs CT (I^2=0%, p=0.958). Meanwhile, for the dominant model and recessive model, heterogeneity was detected to be significant. Thus, random-effects estimates would be more appropriate for data analysis. Similarly, the random-effect model was conducted for the comparison of TT vs CC for OS and T allele vs C allele for recurrence (Tables 3 and 4).

Publication bias and sensitivity analysis
The publication bias of literature was assessed with both funnel plots and Egger's test. As shown in Tables 2–4 and Figure 4, our results did not reveal any obvious asymmetry in the funnel plots. Moreover, the Egger's test, which was used to provide statistical evidence of publication bias, suggested

Table 2 Results of the effect of *CYP2D6 *10* polymorphism on the DFS of breast cancer patients taking tamoxifen

Comparison	Studies	Overall effect			Heterogeneity		Publication bias	
		HR (95% CI)	Z	p-value	I^2, %	p-value	Begg's test	Egger's test
TT vs CC	4	1.79 (1.14–2.80)	2.54	0.011	44.50	0.144	1	0.91
CT vs CC	4	2.02 (1.04–3.91)	2.09	0.037	36.30	0.194	0.734	0.351
TT vs CT/CC	4	2.19 (1.07–4.50)	2.13	0.033	52.60	0.097	0.308	0.012
TT/CT vs CC	2	1.80 (0.81–4.00)	1.45	0.147	53.00	0.145	1	–
TT vs CT	2	2.03 (1.41–2.93)	3.79	0	0.00	0.958	1	–

Notes: Different from DFS, the pooled results of the endpoint of OS showed that there was no relationship between *CYP2D6 *10* polymorphism and OS of female breast cancer patients with adjuvant tamoxifen. As shown in Table 3, all the genetic models did not support any evidence of association (TT vs CC: HR =1.05, 95% CI =0.35–3.11, p=0.934; CT vs CC: HR =1.29, 95% CI =0.83–2.00, p=0.225; TT vs CT/CC: HR =0.96, 95% CI =0.62–1.48, p=0.858; TT/CT vs CC: HR =1.57, 95% CI =0.89–2.77, p=0.119). For the additive comparison model of TT vs CT, which was reported by only one study, the result was negative as well.
Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

Table 3 Results of the effect of *CYP2D6 *10* polymorphism on the OS of female breast cancer patients taking tamoxifen

Comparison	Studies	Overall effect			Heterogeneity		Publication bias	
		HR (95% CI)	Z	*p*-value	*I²*, %	*p*-value	Begg's test	Egger's test
TT vs CC	3	1.05 (0.35–3.11)	0.08	0.934	73.10	0.024	1.00	0.320
CT vs CC	3	1.29 (0.83–2.00)	1.14	0.255	0.00	0.844	1.00	0.751
TT vs CT/CC	2	0.96 (0.62–1.48)	0.18	0.858	0.00	0.578	1.00	–
TT/CT vs CC	2	1.57 (0.89–2.77)	1.56	0.119	0.00	0.468	1.00	–
TT vs CT	1	1.36 (0.58–3.18)	0.71	0.478	–	–	–	–

Notes: The results of the endpoint of recurrence are shown in Figure 3 and Table 4. *CYP2D6 *10* polymorphism was found to be associated with the increased risk of relapse of breast cancer in different genetic models (TT vs CC: OR =4.07, 95% CI =1.88–8.80, *p*<0.001; TT vs CT/CC: OR =3.69, OR =2.13–6.41, *p*<0.001; TT/CT vs CC: 2.52, 95% CI =1.24–5.13, *p*=0.011; T allele vs C allele: 2.99, 95% CI =1.46–6.11, *p*=0.029). However, in the heterozygous model, heterozygous variant of *CYP2D6 *10* gene did not increase the risk of relapse (CT vs CC: OR =1.39, 95% CI =0.62–3.13, *p*=0.427).
Abbreviations: HR, hazard ratio; OS, overall survival.

that no evidence of publication bias existed in the overall analysis (*p*>0.05 for all the comparisons). Sensitivity analyses showed that omitting each individual study from all the analyses did not affect the pooled odds ratios significantly, and no substantial change was detected, indicating that our results were statistically robust (Figure 5).

Discussion

The *CYP2D6* gene has earned special attention because an increasing number of studies have revealed that polymorphisms of the *CYP2D6* gene were associated with the outcomes following tamoxifen treatment for breast cancer.[39] However, the results across studies have been equivocal.[40,41] Previous meta-analyses were performed by Jung and Lim,[17] Province et al[42] and Johansson et al.[43] These meta-analyses were designed to evaluate the effect of *CYP2D6* metabolizer types on outcome of breast cancer patients with tamoxifen treatment, for all the ethnicities. Different from these previous studies, our investigation aimed to assess the effect in a certain population and for a certain polymorphism, and was conducted in Asian breast cancer patients for *CYP2D6 *10* polymorphism. Therefore, to our knowledge, it would be the first meta-analysis to report the unique association between *CYP2D6 *10* and efficacy of tamoxifen in Asian breast cancer patients.

Ethnic difference in genetic background is one of the most important biological factors that might influence the patients' clinical response and efficacy.[44] *CYP2D6 *10* variant is commonly reported in Asian population, but not in other ethnicities.[19] The genetic discrepancies might be one of the reasons for the dispute on effect of *CYP2D6* variants on tamoxifen response. Besides, the coverage of *CYP2D6* mutations in the different studies might also play a role in the dispute.[20] Most research studies reported *CYP2D6* metabolizer types with their effect of tamoxifen efficacy, however, *CYP2D6*-predicted phenotype classified system was too variable to reach a consensus. Therefore, it is of great clinical significance to conduct this meta-analysis to reveal the effect of *CYP2D6 *10* polymorphism on the tamoxifen efficacy in Asian patients. It might provide a new insight on a range of outcomes, investigating a potential gene dose-response relationship, and an assessment of data from trials that investigated effect modification of tamoxifen by *CYP2D6* genotype status.

In the process of study inclusion, we selected several indicators, including DFS, OS, and recurrence rate as the endpoints of our meta-analysis. These indicators were commonly reported by various studies and were suitable to be pooled. In fact, 2 of the studies included[26,45] reported the outcome of relapse-free survival (RFS). However, we failed to pool the results of RFS because these studies were with a different genetic comparison model. Similarly, data of disease-specific survival, time to progression, recurrence-free time were also reported by some studies but not available to be pooled.

Table 4 Results of the effect of *CYP2D6 *10* polymorphism on the recurrence of breast cancer in patients taking tamoxifen

Comparison	Overall effect			Heterogeneity		Publication bias	
	OR (95% CI)	Z	*p*-value	*I²*, %	*p*-value	Begg's test	Egger's test
TT vs CC	4.07 (1.88–8.80)	3.57	0	40.20	0.154	0.22	0.11
CT vs CC	1.39 (0.62–3.13)	0.79	0.427	0.00	0.725	0.462	0.331
TT vs CT/CC	3.69 (2.13–6.41)	4.65	0	40.90	0.148	0.806	0.51
TT/CT vs CC	2.52 (1.24–5.13)	2.55	0.011	14.10	0.325	0.22	0.073
T vs C*	2.99 (1.46–6.11)	3	0.003	63.10	0.029	0.462	0.141

Note: *Random effects model was used for the comparison of allele genetic model as heterogeneity is significant.
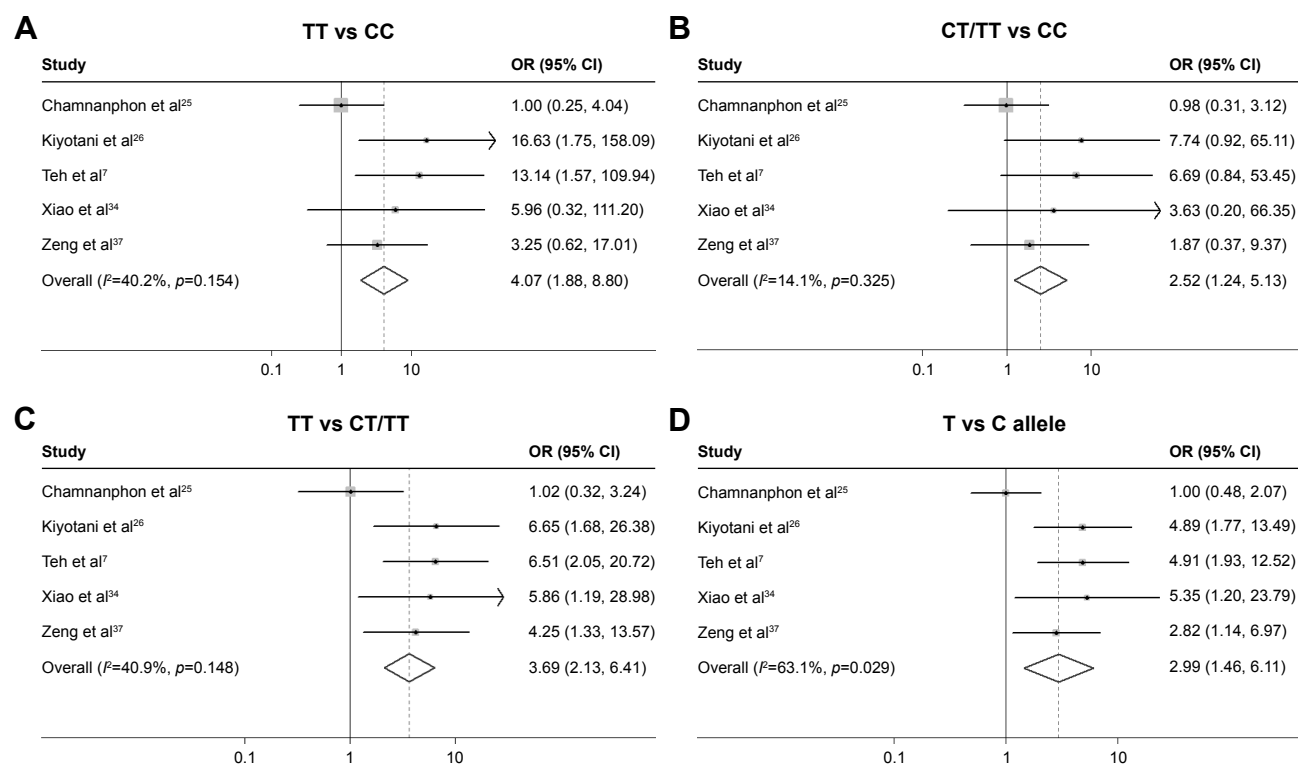**Abbreviation:** OR, odds ratio.

Figure 3 Forest plot to estimate the effect of *CYP2D6 *10* polymorphism on the recurrence of breast cancer in patients taking tamoxifen in the comparison of (**A**) TT vs CC; (**B**) CT/TT vs CC; (**C**) TT vs CT/TT and (**D**) T vs C allele.
Note: Weights are from random effects analysis.
Abbreviations: CI, confidence interval; OR, odds ratio.

Tamoxifen will still be commonly used in both premenopausal and postmenopausal women in the foreseeable future. Therefore, analysis of *CYP2D6 *10* genotype may be useful in identifying patients who are more likely to benefit from tamoxifen treatment. In fact, men with breast cancer are also an important subgroup who are treated in adjuvant setting preferentially with tamoxifen. *CYP2D6 *4* polymorphism was reported to be associated with a probability of recurrence in male breast cancer.[46] Therefore, analysis of *CYP2D6 *10* variant in male breast

cancer would also be of great clinical significance. Our meta-analysis indicated the relationship of *CYP2D6 *10* polymorphism with tamoxifen response existed both on the endpoints of DFS and recurrence rate in female Asian breast cancer patients, with tamoxifen 20 mg/day adjuvant therapy. It is consistent in direction with the hypothesis that reduced tamoxifen metabolism is associated with poorer outcome.[5,11,30] In the genetic models of TT/CT vs CC in DFS and CT vs CC in recurrence, pooled results were negative for revealing the association of *CYP2D6 *10* and

Figure 4 Begg's funnel plots to examine publication bias for reported comparisons of *CYP2D6 *10* polymorphism with recurrence in the comparison of (**A**) CT vs CC and (**B**) TT vs CC in Asian breast cancer patients treated with tamoxifen.
Abbreviations: OR, odds ratio; SE, standard error.

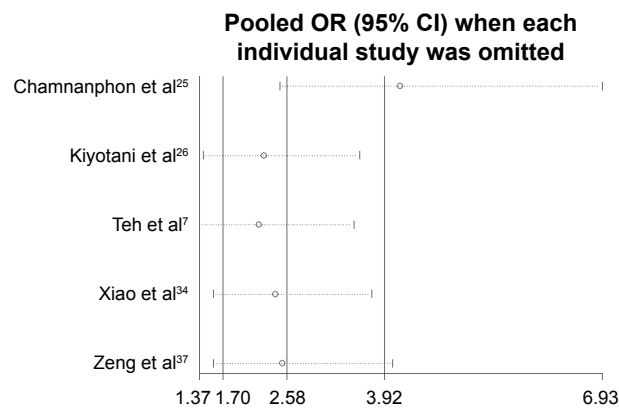**Pooled OR (95% CI) when each individual study was omitted**

Figure 5 Sensitivity analysis of the comparison of allele genetic model (T vs C allele) in the recurrence analysis.

tamoxifen efficacy. The former might be invalid, because this comparison contains only 2 studies, with significant heterogeneity (I^2=53%, p=0.145), and is in contradiction to the other comparison, especially in TT vs CC and CT vs CC. For the CT vs CC comparison in recurrence, the results are without any between-study heterogeneity, and considered to be reliable. Our results suggests the decrease in enzyme activity caused by heterozygous mutation of *CYP2D6 *10* does not translate into a significant poorer clinical outcome. Meanwhile, *CYP2D6 *10* polymorphism was not associated with OS after pooled analysis, which was not consistent with the hypothesis. Given that OS is defined as the time from randomization to all-cause mortality, which is different from DFS, it might include in some death records that is irrelevant to cancer. Besides, for the endpoint of OS, 3 studies and 2 studies were pooled in different comparisons, which is relatively few and may have underpowered the results.

The heterogeneity between the studies was very low in our analysis. This suggested that the results from these studies were suitable to be pooled. The sensitivity analysis indicated that studies contributing to the heterogeneity did not significantly alter the pooled results. This suggested that our results were statistically robust. Taken together, our results might provide insights into the individualized therapy of breast cancer in Asian women. In patients with **10/*10* (*TT*) genotype, CYP2D6 enzyme activity and metabolic conversion rate was low. It is reported that increasing the regular tamoxifen dose could significantly increase endoxifen exposure in patients with CYP2D6 PMs or IMs.[47] Therefore, female breast cancer patients with **10* variant should increase their tamoxifen dose to >20 mg/day. However, the optimal dose of tamoxifen for **10* carriers needs to be explored.

Several limitations in our meta-analysis should be acknowledged. First, several studies with small sample size

included in our analysis might be underpowered to detect the relationship. Second, our results are based on the unadjusted parameters. A more accurate analysis should be performed, in which the outcomes should be adjusted by some related parameters, including age, menopause status, and other important lifestyle factors.

In summary, our meta-analysis might be the first meta-analysis to estimate the association of *CYP2D6 *10* polymorphism with the efficacy of tamoxifen treatment in female Asian breast cancer patients. Significant association of **10/*10* (*TT*) genotype with poorer DFS and recurrence was found in the Asian population. In the future, large and well-designed studies are required to illustrate the interactions of *CYP2D6* genetic variants, including **10* polymorphism and tamoxifen response in female breast cancer patients.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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