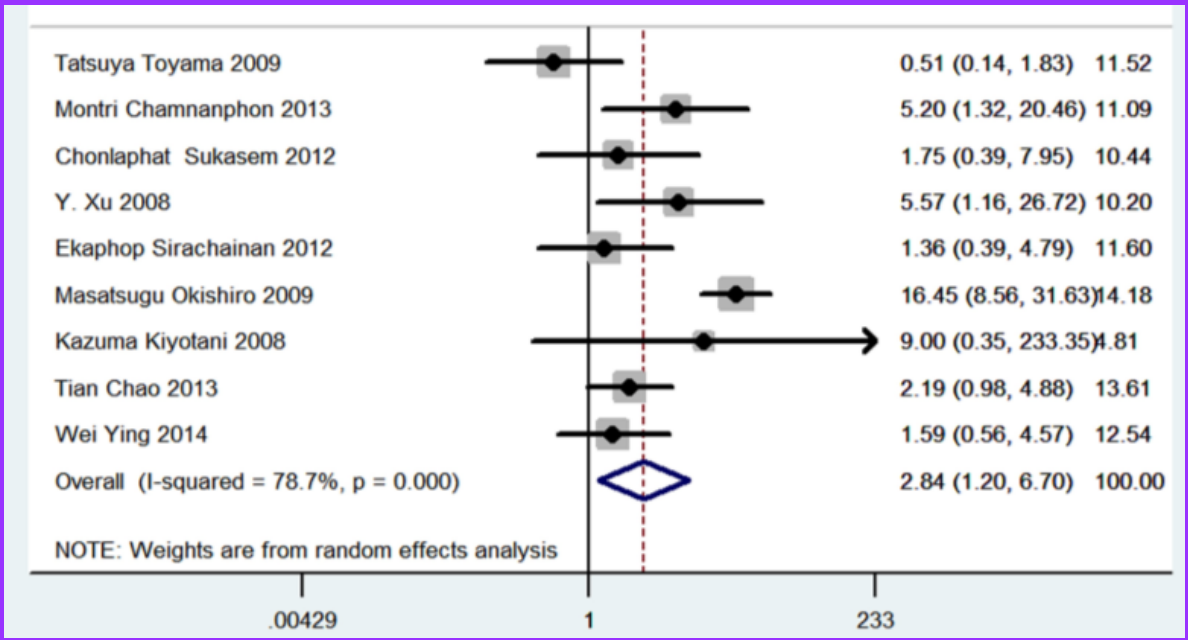

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Meta-Analysis

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Meta-analysis on the association between CYP2D6*10 gene polymorphism and disease free survival of breast cancer patients receiving tamoxifen treatment in Asia

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Abstract

Literatures about case-control study on the association between CYP2D6*10 gene polymorphism and breast cancer were searched from last updated on May, 2014. Odds ratio of CYP2D6*10 gene distributions in breast cancer patients against healthy control were analyzed. STATA 12 software was applied for investigating heterogeneity among individual studies and summarizing effects across studies by proper statistical methods. A total of 812 cases (case group) and 323 cases (control group) were included. Disease free survival of breast cancer patients with CYP2D6*10 wild-type homozygous and heterozygous is higher than that of CYP2D6*10/*10 patients after the tamoxifen treatment, with statistical significance. Disease free survival of breast cancer patients with CYP2D6*10/*10 gene is similar to those with other genotypes after the tamoxifen treatment. This study demonstrated that CYP2D6*10 genotype is unlikely to have any clinical significance for prognosis of breast cancer patients receiving tamoxifen alone.

Introduction

Breast cancer continues to be the most common cancer diagnosed among women in China, and it was estimated that approximately 232,340 new cases of invasive breast cancer in 2013. The American Cancer Society projected around 39,620 breast cancer related-deaths in 2013 (Li et al., 2012). In the past three decades, breast cancer is the second leading cause of cancer death after lung cancer (Ross et al., 2010). However, breast cancer is a complex disease entity with different biological characteristics and clinical behavior. Many studies showed that there are no treatment guidelines for triple -negative breast cancer.

Tamoxifen (TAM) is an important drug for treatment of estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive breast cancers, TAM, the first selective estrogen receptor modulators approved for the treatment of breast cancer (Serlin et al., 2011) has been used widely as a standard treatment for breast cancers (Tong et al., 2009). Adjuvant endocrine therapy is an important way of comprehensive treatment for breast cancer, and chemotherapy for breast cancer is closely associated with hormone levels of the body. TAM is non-synthetic antiestrogen, which is basic drug in adjuvant endocrine therapy for breast cancer (Li et al., 2014).

CYP2D6 is the key enzyme for the generation of endoxifen by catalyzing TAM. Because variant allele of CYP2D6 causes the decline in enzyme activity, the treatment and the prevention effects of TAM adjuvant therapy are decreased for breast cancer patients. It can be found that endoxifen blood concentrations of heterozygotes and homozygotes of CYP2D6*3, CYP2D6*4, CYP2D6*5 and CYP2D6*6 are 55 and 25% of wild-type

individuals respectively (Lin et al., 2011). No significant difference exists between TAM and 4-hydroxy-tamoxifen (HTAM). Endoxifen blood concen-tration of the patient with CYP2D6 gene enzymes defect decreases (Lee et al., 2010; Li et al., 2014). Endoxifen concentration in ultra-rapid metabolizer is significantly higher than that in the patient with other genotypes; the intermediary metabolism active heterozygous endoxi-fen concentration of CYP2D6*4 or CYP2D6*10 is higher than other chronic metabolic genotypes; endoxifen concentration shows in consistence with gradient phenomenon of genotype (Chang et al., 2013). The most common mutation of CYP2D6 is CYP2D6*10 in Chinese people, and the mutation rate is 57%. The decline of enzyme activity is caused by mutation.

Many studies have described the association between CYP2D6*10 gene polymorphism and disease free survi-val (DFS) of breast cancer patients receiving TAM treatment. However, the results remain controversial. However, the results remain controversial. Here, we reviewed the studies reporting the association between the CYP2D6*10 gene polymorphism and DFS of breast cancer patients receiving TAM treatment among the Asians.

Materials and Methods

Literature search

Literatures were identified by an electronic search on Embase, Pubmed, China National Knowledge Infra-structure and the Cochrane Library with a combination of the following key words: 'breast cancer', 'tamoxifen', 'CYP2D6*10 gene', 'CYP2D6*10 polymorphisms' or 'CYP2D6*10 gene polymer-phisms' (last updated on August, 2014). We estimated possibly relevant genetic association studies by censo-ring their titles and abstracts, and all published studies matching with the qualified criteria were recovered.

Study selection

For purpose of minimize heterogeneity and facilitate the appropriate interpretation and comprehending of the findings, studies were included in the meta-analysis if they had to meet the following inclusion criteria: (1) we appraised the potential combination between CYP2D6*10 polymorphism and TAM; (2) we were case-control studies (CCS); (3) gene polymorphism were available for cases and controls toward evaluate an odds ratio (OR) with 95% confidence interval (CI); (4) the distribution of genes in the control group was in line with Hardy-Weinberg equilibrium (HWE).

Data extraction

Two authors managed the literature searching, studied choice, and extracted data independently. Disagree-ment was resolved by discussion. The abstracted data included title and authors of study, study size, age, year of publication, details of methodological message, sex of the participants, name, specifics of the control interventions, genotype of the CYP2D6*10 polymor-phisms in cases and controls, treatment process, out-comes and adverse reaction for every research. Discrepancies were resolved by discussion to reach a consensus and were arbitrated by a third party when necessary.

Statistical analysis

Meta-analysis was performed according to the Coch-rane Handbook for Systematic Reviews of Interven-tions. The pooled OR and 95% CI were used to assess efficacy and safety endpoints. Heterogeneity was analyzed using the I2 statistic: $I2 = 100\% \times (Q\text{-}df)/Q$. I2 of 0–25% was considered to not have heteroge-neity; I2 of 25–50% may represent low heterogeneity; I2 of 50–75% may represent moderate heterogeneity; and I2 of 75–100% indicate high heterogeneity (Li et al., 2014). When No heterogeneity or low heterogeneity was present, the fixed effects model was used for meta-analysis. When moderate heterogeneity or high hetero-geneity was present, the random effects model was used for meta-analysis. Data was summarized using OR with 95% confidence intervals (CI) for binary outcomes. Publication bias was explored by way of a funnel-plot analysis (Shieh et al., 2011; Xiao et al., 2014). Missing or lost count data should be counted as treatment failure cases. OR, tests for heterogeneity, and forest plots for the relevant comparisons were performed using STATA 12. Tests for heterogeneity, and forest plots for the relevant comparisons were performed using STATA 12 with Beggr's bias test and Egger's bias test, with $p \leq 0.05$ indicating potential bias.

Results

Description of studies

We searched 304 documents from the 4 databases. 326 studies were eliminated by way of the title and abstract. The question/random method of 19 studies were not correct by reading full text. 25 studies without the inclusion criteria were eliminated by reading abstract. 15 studies were eliminated for duplicated publications. Finally full-text papers of 9 studies (Cai et al., 2014; Huang et al., 2013; Li et al., 2014; Malarde et al., 2014; Mao et al., 2014; Saracoglu et al., 2012; Wang et al., 2014; Wang et al., 2013; Zhu et al., 2007) were searched from all the citations. A flow chart described the search method and study chose (Figure 1).

General characteristics of included reviews

These 9 CCS included 1135 patients. There were 812 patients of case group and 323 patients of control group in all the included studies. The average number of case group was 90.2 cases and control group was 35.9 cases.

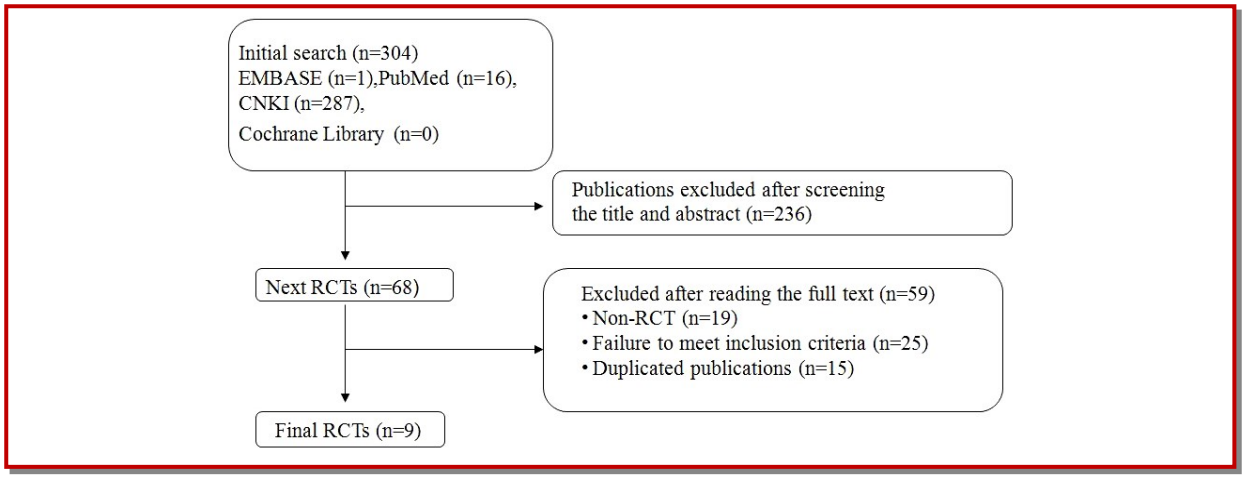

Figure 1: Flowchart of identification of studies included in the review

Table I

Characteristics of the studies included in the meta-analysis

Lead author, year, & Ref. #	Cases		Con-trols	Age (year)	Popula-tion	Ethnici-ty	Source of control	Gene method	HWE
	Wt/Wt	Wt/*10	*10/*10						
Toyama, 2009	64	62	28	59.1	Japan	Asian	Hospital	TaqMan	YES
Chamnanphon, 2013	13	21	13	50	Thailand	Asian	Hospital	PCR-RFLP	YES
Sukasem, 2012	16	22	10	>50	Thailand	Asian	Hospital	PCR-RFLP	YES
Xu, 2008	28	52	72	>50	China	Asian	Hospital	PCR-RFLP	YES
Sirachainan, 2012	19	14	6	35-55	Thailand	Asian	Hospital	PCR-RFLP	YES
Okishiro, 2008	74	59	40	47	Japan	Asian	Hospital	TaqMan	YES
Kiyotani, 2007	20	23	25	50	Japan	Asian	Research	PCR-RFLP	YES
Wei, 2014	114	105	38	58.4	China	Asian	Hospital	PCR-RFLP	YES
Tian, 2014	58	48	94	42.5	China	Asian	Hospital	PCR-RFLP	YES

The largest number was 257 cases and the least number was 47 cases in all the included studies. The study population of 5 studies (5/9) was ≥100 cases. The features of included studies were cataloged in Table I.

Meta-analysis results

*DFS of CYP2D6*10 wild-type homozygous and heterozygous vs CYP2D6*10/*10:* The nine trials evaluated the 5 years-DFS of breast cancer after the TAM treatment (1135 patients). I^2 statistic of heterogeneity was definite signifi-cant in these studies (I^2=78.7%, p=0.000). A random effects model (REM) was performed on outcome measurements. The potential sources of heterogeneity may caused by the clinical heterogeneity, such as patients from different states or the different treatment durations. This did not result in a change of the statistical significance between the effects of REM and that of fixed effects model (FEM). The result of REM (OR=2.84, 95% CI [1.20, 6.70], p=0.018) compared to that of FEM (OR=3.80, 95% CI [2.75, 5.25], p=0.000). The results showed, the 5 years DFS of breast cancer patients with CYP2D6*10 wild-type homozygous and heterozygous is slightly higher than that of CYP2D6*10/*10 patients after the TAM treatment, with statistical significance (Figure 2A).

The five trials evaluated the 10 years-DFS of breast cancer after the TAM treatment (675 patients). I^2 statistic of heterogeneity was definite significant in these studies (I^2=76.7%, p=0.001). REM was performed on outcome measurements. The potential sources of heterogeneity may caused by the clinical heterogeneity, such as patients from different states or the different treatment durations. This did not result in a change of the statistical significance between the effects of REM and that of FEM. The result of REM (OR=2.87, 95% CI [1.12, 7.34], p=0.028) compared to that of FEM (OR= 2.54, 95% CI [1.65, 3.64], p=0.000). The results showed, the 10 years DFS of breast cancer patients with CYP2D6*10 wild-type homozygous and heterozygous is higher than that of CYP2D6*10/*10 patients after the TAM treatment, with statistical significance (Figure 2B).

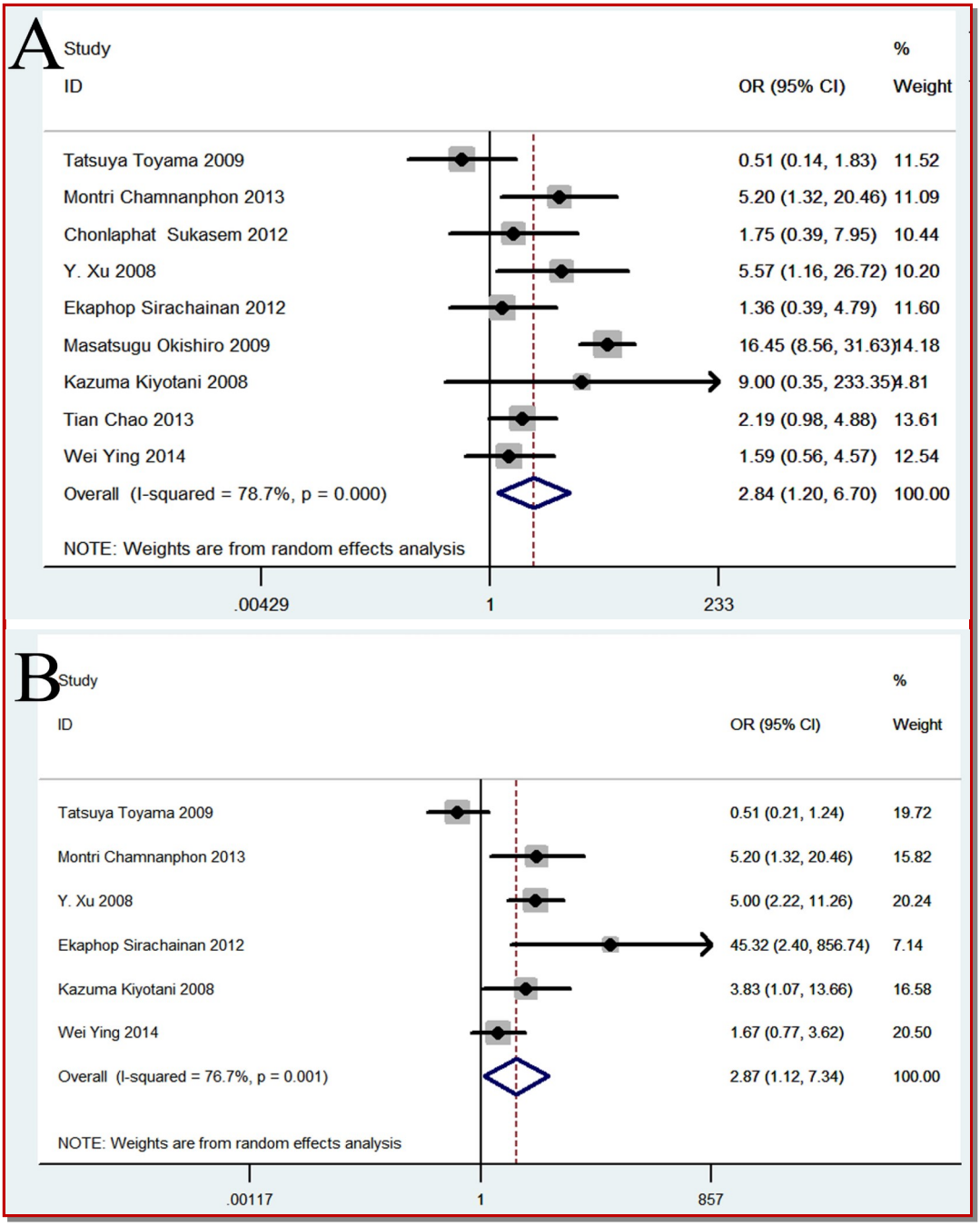

Figure 2: Meta-analysis for DFS of CYP2D6 Wt/Wt+Wt/*10 vs *10/*10. (A): 5 years-DFS; (B): 10 years-DFS

*DFS of CYP2D6*10 wild-type homozygous vs CYP2D6*10 wild-type heterozygous:* The five trials evaluated the 5 years-DFS of breast cancer patients after the TAM treatment (459 patients). I^2 statistic of heterogeneity was not significant in these studies (I^2=35%, p=0.203). FEM was performed on outcome measurements. The results showed, the 5 years DFS of breast cancer patients with CYP2D6*10 wild-type homozygous is slightly lower than that of wild-type heterozygous patients (OR=0.85, 95% CI [0.48, 1.50], p=0.571) after the TAM treatment, without statistical significance (Figure 3A).

The five trials evaluated the 10 years-DFS of breast cancer patients after the TAM treatment (310 patients). I^2 statistic of heterogeneity was a little significant in these studies (I^2=59.5%, p=0.085). REM was performed on outcome measurements. The potential sources of heterogeneity may caused by the clinical heterogeneity, such as patients from different states or the different treatment durations. This did not result in a change of the statistical significance between the effects of REM and that of FEM. The result of REM (OR=1.292, 95% CI [0.51, 3.29], p=0.591) compared to that of FEM (OR=

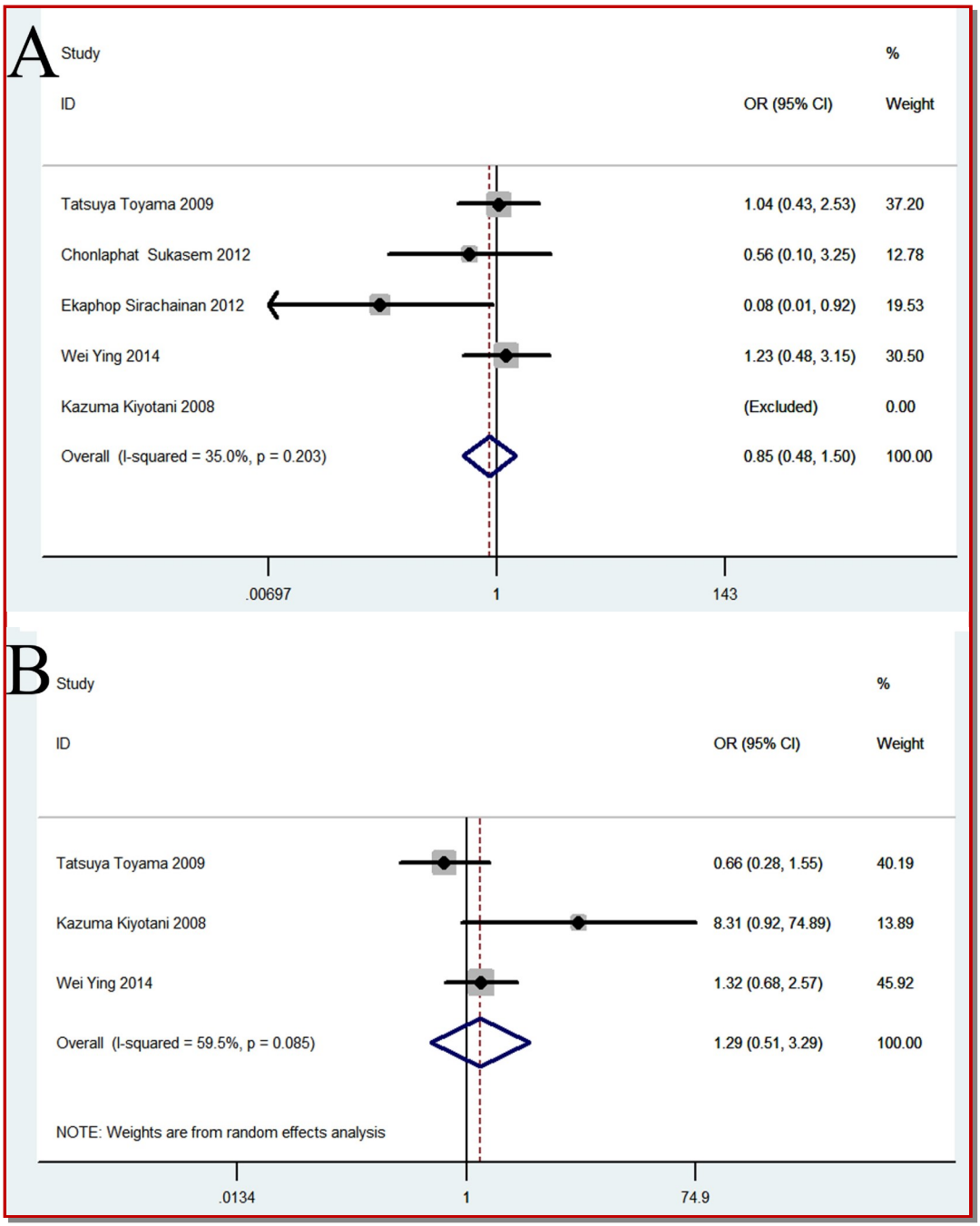

Figure 3: Meta-analysis for 5 years-DFS of CYP2D6 Wt/Wt vs Wt/*10. (A): 5 years-DFS; (B): 10 years-DFS

1.20, 95% CI [0.73, 1.96], p=0.470). The results showed, the 10 years DFS of breast cancer patients with CYP2D6*10 wild-type homozygous is similar to that of wild-type heterozygous patients after the TAM treatment, without statistical significance (Figure 3B).

*DFS of CYP2D6*10 wild-type homozygous vs CYP2D6*10/*10:* The five trials evaluated the 5 years-DFS of breast cancer patients after the TAM treatment (318 patients). I^2 statistic of heterogeneity was not significant in these studies (I^2=6.2%, p=0.371). FEM was performed on outcome measurements. The results showed, the 5 years DFS of breast cancer patients with CYP2D6*10 wild-type homozygous is slightly lower than that of CYP2D6*10/*10 patients (OR=0.931, 95% CI [0.46, 1.87], p=0.842) after the TAM treatment after the TAM treatment, without statistical significance (Figure 4A).

The five trials evaluated the 10 years-DFS of breast cancer patients after the TAM treatment (289 patients).

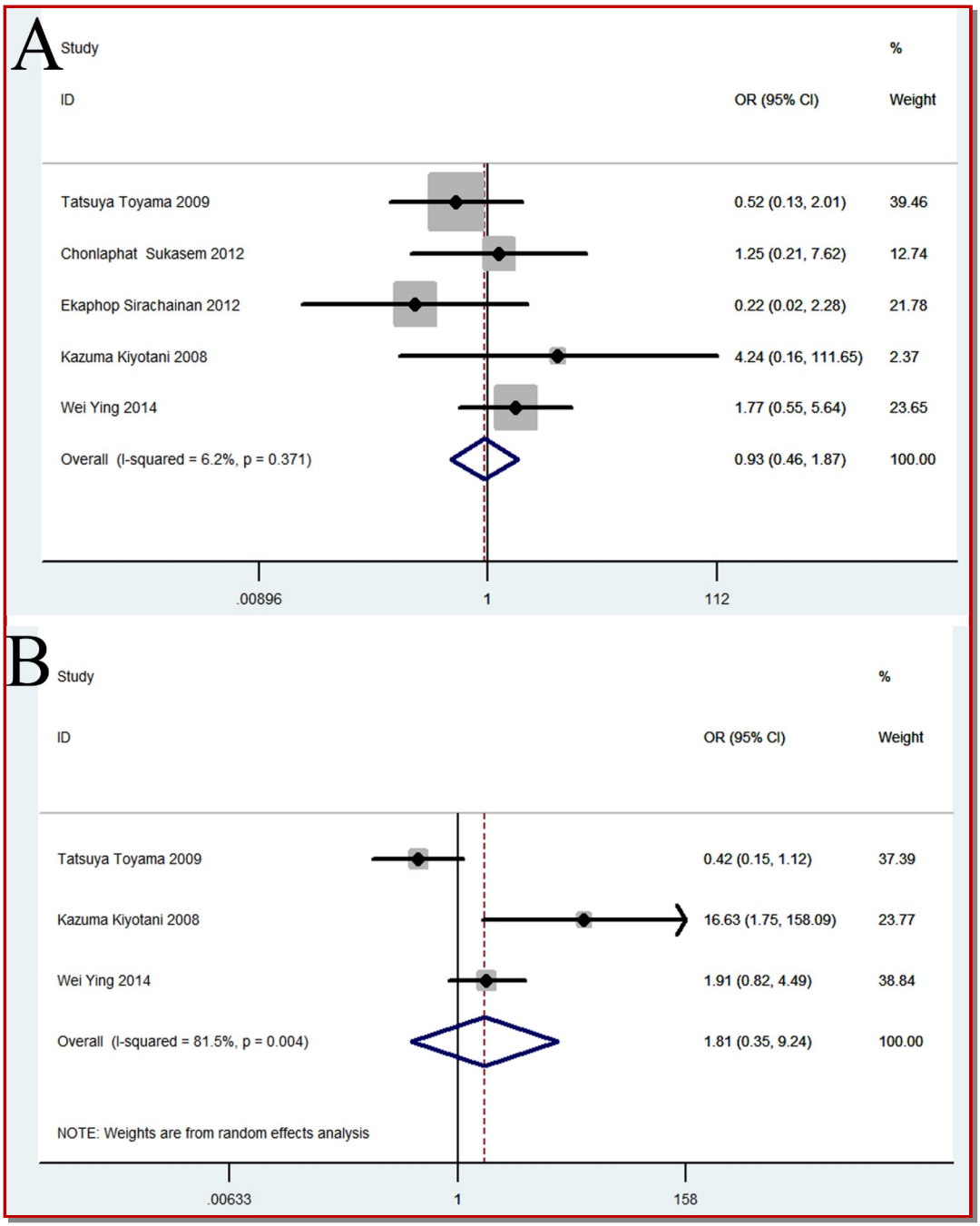

Figure 4: Meta-analysis for DFS of CYP2D6 Wt/Wt vs *10/*10. (A): 5 years-DFS; (B): 10 years-DFS

I^2 statistic of heterogeneity was definite significant in these studies (I^2=81.5%, p=0.004). FEM was performed on outcome measurements. The potential sources of heterogeneity may caused by the clinical heterogeneity, such as patients from different states or the different treatment durations. This did not result in a change of the statistical significance between the effects of REM and that of FEM. The result of REM (OR=1.81, 95% CI [0.35, 9.24], p=0.477) compared to that of FEM (OR= 1.37, 95% CI [0.76, 2.47], p=0.291). The results showed, the 10 years DFS of breast cancer patients with CYP2D6*10 wild-type homozygous is slightly higher than that of CYP2D6*10/*10 patients after the TAM treatment, without statistical significance (Figure 4B).

*DFS of CYP2D6*10 wild-type heterozygous vs CYP2D6*10/ *10:* The five trials evaluated the 10 years-DFS of breast cancer patients after the TAM treatment (333 patients). I^2 statistic of heterogeneity was not significant in these studies (I^2=0%, p=0.417). FEM was performed on

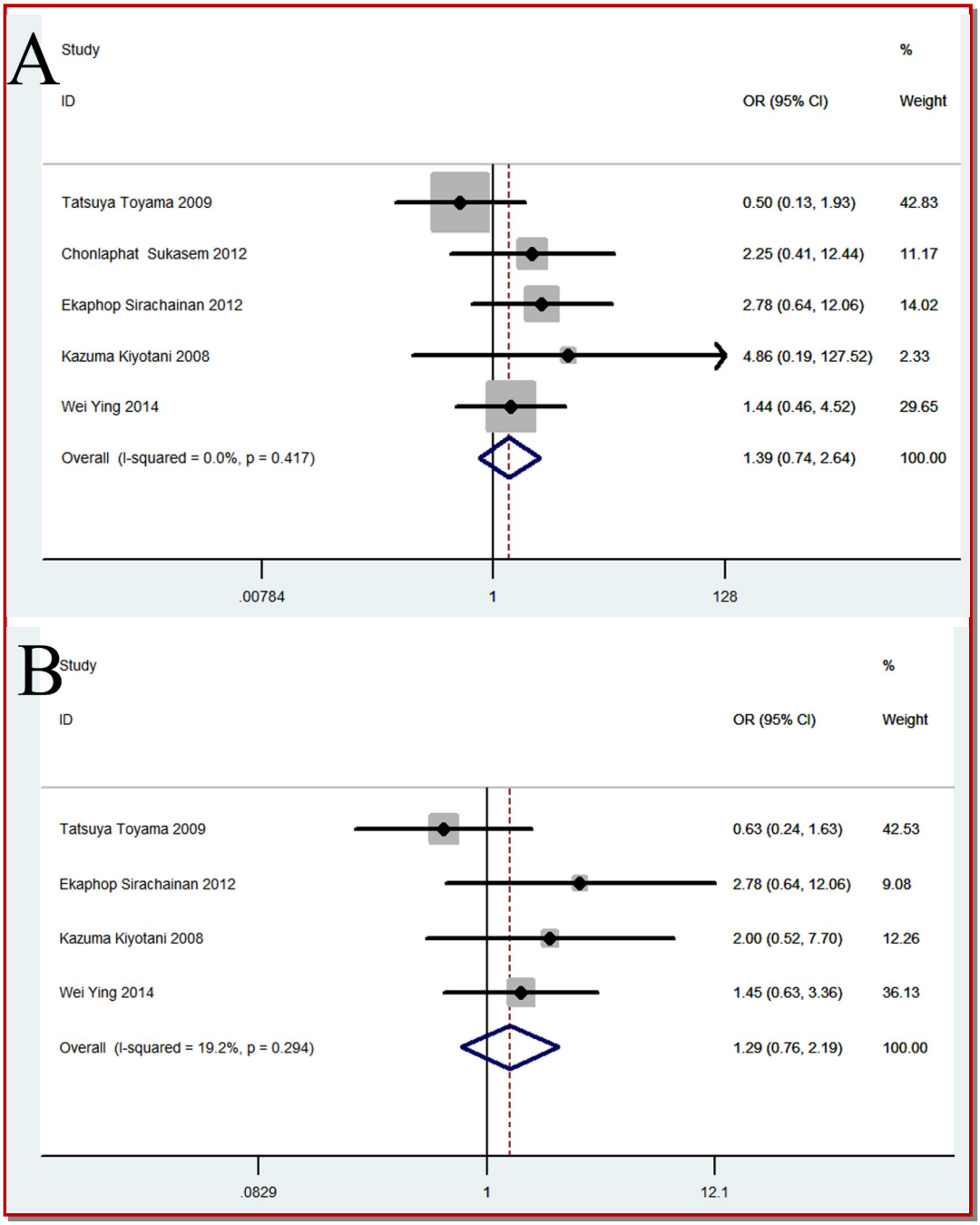

Figure 5: Meta-analysis for DFS of CYP2D6 Wt/*10 vs *10/*10. (A): 5 years-DFS; (B): 10 years-DFS

outcome measurements. The results showed, the 5 years DFS of breast cancer patients with CYP2D6*10 wild-type heterozygous is similar to that of CYP2D6*10/*10 patients (OR=1.395, 95% CI [0.74, 2.64], p=0.306) after the TAM treatment, without statistical significance (Figure 5A).

The five trials evaluated the 10 years-DFS of breast cancer patients after the TAM treatment (333 patients). I^2 statistic of heterogeneity was not significant in these studies (I^2=19.2%, p=0.294). FEM was performed on outcome measurements. The results showed, the 10 years OS of breast cancer patients CYP2D6*10 wild-type heterozygous is similar to that of CYP2D6*10/*10 patients (OR=1.288, 95% CI [0.76, 2.19], p=0.348) after the TAM treatment, without statistical significance (Figure 5B).

Adverse reaction

Two articles reported to the adverse reactions in this study, included bone mineral density, endometrial thickness, hot flashes and total cholesterol. These

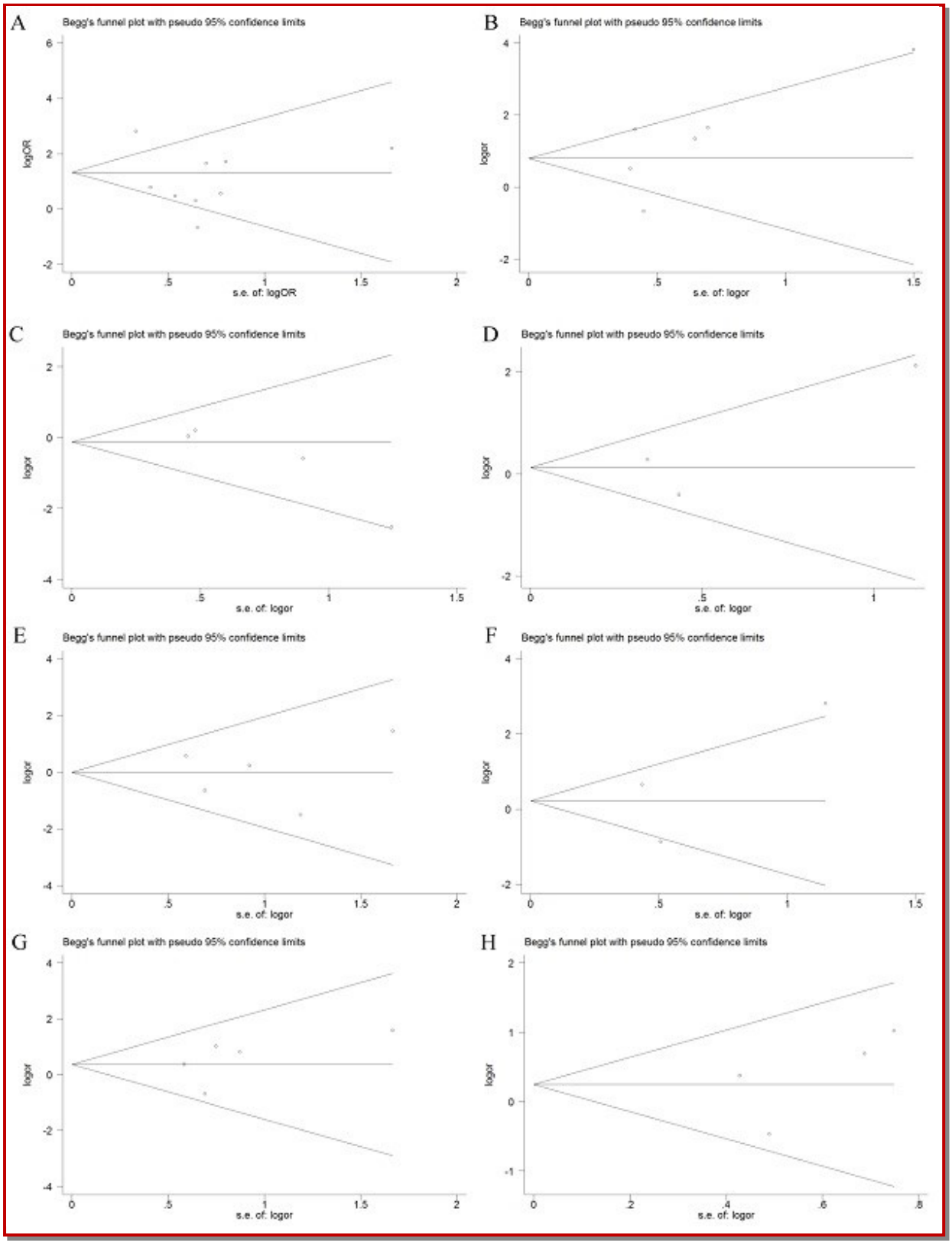

Figure 6: Funnel plot of the studies comparing the efficiency

(A) 5 years-DFS of CYP2D6 Wt/Wt + Wt/*10 vs *10/*10; (B)10 years-DFS of CYP2D6 Wt/Wt + Wt/*10 vs *10/*10; (C)5 years-DFS of CYP2D6 Wt/Wt vs Wt/*10; (D)10 years-DFS of CYP2D6 Wt/Wt vs Wt/*10; (E) 5 years-DFS of CYP2D6 Wt/Wt vs *10/*10; (F)10 years-DFS of CYP2D6 Wt/Wt vs *10/*10; (G)5 years-DFS of CYP2D6 Wt/*10 vs *10/*10; (H)10 years-DFS of CYP2D6 Wt/*10 vs *10/*10

adverse reactions did not appear the serious fatal report.

Sensitivity analysis

In the meta-analysis, sensitivity analysis was conducted to assess the degree that one individual study involved was deleted each time to reflect the influence of the individual data-set to the pooled OR. As stated above, the corresponding pooled OR were not materially altered, indicating that our results were statistically robust.

Evaluation of publication bias

The shape of the funnel Begg's plot for the homozygote comparison appeared to some asymmetry and no obvious bias in this meta-analysis, suggesting the possibility of publication bias (Figure 6). Publication bias was assessed by Begg's test and Egger's test (Figure 6; Table II). It showed a potential publication bias might caused by a language bias, inflated estimates by a flawed methodological design in smaller studies, and/or a lack of publication of small trials with opposite results.

Discussion

The catalytic activity of CYP2D6*1/*10 on HTAM is higher than that of CYP2D6*10/*10. Some adverse reactions may be caused by the gene polymorphism of CYP2D6 during TAM-treatment (Chen et al., 2014). These studies have shown that the breast cancer patients that receive TAM adjuvant therapy have increased incidence of adverse reactions such as cancer recurrence and flushing. The DFS for a patient of CYP2D6 G/A (1846G> A) and T/T (100C> T) is 22.7 months (Chang et al., 2013). The gene mutation of CYP2D6 can cause changes in the activity and quantity of the enzyme, resulting in the differences in specific drug metabolism and efficacy of human. Among Asian breast cancer patients, CYP2D6*10 is considered to be of relatively higher mutation frequency to reduce the expressive activity of metabolic enzymes.

Besides, it is found that the DFS of the patients with CYP2D6*10 wild-type homozygous has a statistically significant relationship with CYP2D6*10 wild-type heterozygous, but there is no difference with the CYP2D6*10/*10 genotype. The breast cancer patients with CYP2D6*10/*10 genotype had significantly worse DFS than those with the CYP2D6*10 wild-type homozygous and wild-type homozygous genotype (Shi et al., 2014). Patients with CYP2D6*10/*10 and CYP2D6*10 wild-type homozygous showed significant-ly shorter survival rate when compared to those with CYP2D6*10 wild-type homozygous.

Meta-analysis has been applied in this paper for the first time to make a comprehensive quantitative assessment on the relationship between CYP2D6*10 with the DFS of breast cancer patient after TAM treatment. It has been found from the meta analysis that the 5 years DFS of breast cancer patients with CYP2D6*10 wild-type homozygous and heterozygous is slightly higher than that of CYP2D6*10/*10 patients after the TAM treatment, with statistical significance; the 10 years DFS of breast cancer patients with CYP2D6*10 wild-type homozygous and heterozygous is higher than that of CYP2D6*10/*10 patients after the TAM treatment, with statistical significance. But, DFS of breast cancer patients with CYP2D6*10/*10 gene is similar to those with other genotypes after the TAM treatment.

Due to the variance in the race of researchers in the research centers, the variance in the experimental design, the variance in patient-selection criteria and the variance in sample size, etc., so that there is obvious

Table II

Meta-analysis on efficacy of DFS of breast cancer after the TAM treatment

Indicator	No. of trials	Combined effect size			Heterogeneity		Publication bias	
		OR	95% CI	Mode	I^2 (%)	P value	P value (Begg's)	P value (Eegg's)
5 years DFS: Wt/Wt+Wt/*10 vs *10/*10	9	2.84	1.20-6.70	R	78.7	0	0.466	0.278
10 years DFS: Wt/Wt+Wt/*10 vs *10/*10	5	2.87	1.12-7.34	R	76.7	0.001	0.452	0.282
5 years DFS: Wt/Wt vs Wt/*10	5	0.85	0.48-1.50	F	35	0.203	0.308	0.066
10 years DFS: Wt/Wt vs Wt/*10	3	1.29	0.51-3.29	R	59.5	0.085	1	0.541
5 years DFS: Wt/Wt vs *10/*10	4	0.93	0.46-1.87	F	6.2	0.371	0.806	0.902
10 years DFS: Wt/Wt vs *10/*10	3	1.81	0.35-9.24	F	81.5	0.004	1	0.613
5 years DFS: Wt/*10 vs *10/*10	5	1.39	0.74-2.64	F	0	0.417	0.462	0.416
10 years DFS: Wt/*10 vs *10/*10	5	1.29	0.76-2.19	F	19.2	0.294	0.308	0.419

Note: DFS: Disease free survival; Wt/Wt: CYP2D6*10 wild-type homozygous; Wt/*10: CYP2D6*10 wild-type heterozygous; *10/*10: CYP2D6*10/*10; F: Fixed effects model; R: Random effects model

controversy on the relevant findings of this polymorphism and the overall survival rate of breast cancer patients after TAM treatment (Renugadevi et al., 2010). From the comprehensive analysis on previous studies in accordance with the inclusion standard, it is found that both genotype and allele level of gene polymorphism of CYP2D6*10 may increase the risk extent in the TAM therapy for the Oriental patients. At the same time, due to genetic factors of different races and ethnic groups, only Oriental people are selected as the researching objects in this study to minimize population stratification bias.

Based on the combination of the results, it can be seen that the conclusion of meta-analysis is the same, while the difference is more significant, thus proving the validity of this conclusion further. Of course, the results of the meta-analysis may be influenced by publication bias, confounding factors and so on, which is mainly because the published literature are readily available, and it is easy to publish positive results. These reasons may interfere with the final evaluation of meta-analysis (Yen et al., 2009). Due to limitations of this study, only the published literature can be collected, which cannot be excluded as the potential influential element for the results of this study (Pari et al., 2006). However, according to funnel plot and B, E analysis, the possibility of suggesting publication bias is small, indicating that the approach quality of research included in the study for the oriental population is high, and the general results included in this study are reliable.

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Conflict of Interest

Authors declare no conflict of interest

References

Cai Q, Yao Z, Li H. Catalpol promotes oligodendrocyte survival and oligodendrocyte progenitor differentiation via the Akt signaling pathway in rats with chronic cerebral hypoperfusion. Brain Res. 2014; 1560: 27-35.

Chang XH, Liang LN, Zhan LB, Lu XG, Shi X, Qi X, Feng ZL, Wu MJ, Sui H, Zheng LP, Zhang FL, Sun J, Bai CC, Li N, Han GZ. The effect of Chinese Jinzhida recipe on the hippocampus in a rat model of diabetes-associated cognitive decline. BMC Complement Altern Med. 2013; 13: 161.

Chen J, Liang L, Zhan L, Zhou Y, Zheng L, Sun X, Gong J, Sui H, Jiang R, Zhang F, Zhang L. ZiBuPiYin recipe protects db/db mice from diabetes-associated cognitive decline through improving multiple pathological changes. PLoS One. 2014; 9: e91680.

Huang C, Cui Y, Ji L, Zhang W, Li R, Ma L, Xing W, Zhou H, Chen B, Yu J, Zhang H. Catalpol decreases peroxynitrite formation and consequently exerts cardioprotective effects against ischemia/reperfusion insult. Pharm Biol. 2013; 51: 463-73.

Lee KN, Seo MC, Bae IH, Oh SH, Jang WG, Jeong BC, Oh WM, Kim SH, Lee SE, Shim KM, Park BK, Koh JT. COMP-Ang1, a variant of angiopoietin 1, inhibits serum-deprived apoptosis of mesenchymal cells via PI3K/Akt and mitogen-activated protein kinase pathways. Pharmacology 2010; 86: 327-35.

Li H, Li J, Liu X, Chen J, Wu C, Guo X. Effect of PTEN and KAI1 gene overexpression on the proliferation, metastasis and radiosensitivity of ASPC1 pancreatic cancer cells under hypoxic conditions. Mol Med Rep. 2014; 10: 1973-77.

Li J, Wang Y, Zhou Y, Liu J. Gastric bypass surgery alters the mechanisms of insulin resistance in the adipose tissue of GK rats. Mol Med Rep. 2012; 6: 1111-16.

Li J, Yin LL, Su KL, Zhang GF, Wang J. Concomitant depletion of PTEN and p27 and overexpression of cyclin D1 may predict a worse prognosis for patients with post-operative stage II and III colorectal cancer. Oncol Lett. 2014; 8: 1543-50.

Li R, Zang A, Zhang L, Zhang H, Zhao L, Qi Z, Wang H. Chrysin ameliorates diabetes-associated cognitive deficits in Wistar rats. Neurol Sci. 2014; 35: 1527-32.

Li X, Xu Z, Jiang Z, Sun L, Ji J, Miao J, Zhang X, Li X, Huang S, Wang T, Zhang L. Hypoglycemic effect of catalpol on high-fat diet/streptozotocin-induced diabetic mice by increasing skeletal muscle mitochondrial biogenesis. Acta Biochim Biophys Sin (Shanghai). 2014; 46: 738-48.

Lin MS, Huang JX, Chen WC, Zhang BF, Fang J, Zhou Q, Hu Y, Gao HJ. Expression of PPARgamma and PTEN in human colorectal cancer: An immunohistochemical study using tissue microarray methodology. Oncol Lett. 2011; 2: 1219-24.

Malarde L, Groussard C, Lefeuvre-Orfila L, Vincent S, Efstathiou T, Gratas-Delamarche A. Fermented soy permeate reduces cytokine level and oxidative stress in streptozotocin-induced diabetic rats. J Med Food. 2014, 2014.

Mao XY, Cao DF, Li X, Yin JY, Wang ZB, Zhang Y, Mao CX, Zhou HH, Liu ZQ. Huperzine A ameliorates cognitive deficits in streptozotocin-induced diabetic rats. Int J Mol Sci. 2014; 15: 7667-83.

Pari L, Gnanasoundari M. Influence of naringenin on oxytetracycline mediated oxidative damage in rat liver. Basic Clin Pharmacol Toxicol. 2006; 98: 456-61.

Renugadevi J, Prabu SM. Cadmium-induced hepatotoxicity in rats and the protective effect of naringenin. Exp Toxicol Pathol. 2010; 62: 171-81.

Ross JH, Hardy DC, Schuyler CA, Slate EH, Mize TW, Huang Y. Expression of periodontal interleukin-6 protein is increased across patients with neither periodontal disease nor diabetes, patients with periodontal disease alone and patients with both diseases. J Periodontal Res. 2010; 45: 688-94.

Saracoglu I, Harput US. *In vitro* cytotoxic activity and structure activity relationships of iridoid glucosides derived from *Veronica* species. Phytother Res. 2012; 26: 148-52.

Serlin Y, Levy J, Shalev H. Vascular pathology and blood-brain barrier disruption in cognitive and psychiatric complications of type 2 diabetes mellitus. Cardiovasc Psychiatry Neurol. 2011; 2011: 609202.

Shi Y, Tan Y, Mao S, Gu W. Naringenin inhibits allergen-induced airway remodeling in a murine model of asthma. Mol Med Rep. 2014; 9: 1204-08.

Shieh JP, Cheng KC, Chung HH, Kerh YF, Yeh CH, Cheng JT. Plasma glucose lowering mechanisms of catalpol, an active principle from roots of *Rehmannia glutinosa*, in streptozotocin-induced diabetic rats. J Agric Food Chem. 2011; 59: 3747-53.

Tong M, Neusner A, Longato L, Lawton M, Wands JR, de la Monte SM. Nitrosamine exposure causes insulin resistance diseases: Relevance to type 2 diabetes mellitus, non-alcoholic steatohepatitis, and Alzheimer's disease. J Alzheimers Dis. 2009; 17: 827-44.

Wang SB, Jia JP. Oxymatrine attenuates diabetes-associated cognitive deficits in rats. Acta Pharmacol Sin. 2014; 35: 331-38.

Wang Y, He H, Li D, Zhu W, Duan K, Le Y, Liao Y, Ou Y. The role of the TLR4 signaling pathway in cognitive deficits following surgery in aged rats. Mol Med Rep. 2013; 7: 1137-42.

Xiao WQ, Yin GJ, Fan YT, Qiu L, Cang XF, Yu G, Hu YL, Xing M, Wu de Q, Wang XP, Hu GY, Wan R. Catalpol ameliorates sodium taurocholate-induced acute pancreatitis in rats via inhibiting activation of nuclear factor kappa B. Int J Mol Sci. 2014; 15: 11957-72.

Yen FL, Wu TH, Lin LT, Cham TM, Lin CC. Naringenin-loaded nanoparticles improve the physicochemical properties and the hepatoprotective effects of naringenin in orally-administered rats with CCl(4)-induced acute liver failure. Pharm Res. 2009; 26: 893-902.

Zhu X, Su B, Wang X, Smith MA, Perry G. Causes of oxidative stress in Alzheimer disease. Cell Mol Life Sci. 2007; 64: 2202-10.

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