

Original Article

The outcomes of tamoxifen therapy in breast cancer patients and genotypes of SULT1A1 and glucuronosyltransferase

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Abstract: Background: The CYP2D6 genotype has been shown in previous meta-analysis to influence both the mortality and recurrence in breast cancer patients treated with tamoxifen. However, the effect of other drug-metabolizing enzymes on tamoxifen pharmacokinetics is uncertain. We aimed to assess the association between SULT1A1 and glucuronosyltransferase (UGT) genotypes and the outcome of breast cancer patients with tamoxifen therapy. Method: We performed a systematic search of Pubmed and Embase (Ovid) databases, and outcomes of overall survival, relapse/recurrence-free survival and disease-free survival were extracted and analyzed. Statistical analysis was performed by Engauge Digitizer 4.1, Revman4.2 and STATA 10.0. Results: A total of 4339 breast cancer cases in 14 studies were identified for data analysis. The results suggested a decrease in relapse/recurrence-free survival of breast cancer in patients carrying variant alleles of SULT1A1, while no increase or decrease in survival was observed when analyzed in combination with data of overall survival and disease-free survival. No statistically significant result was shown in the pooled-analysis of UGT2B15 genotypes and UGT2B7 genotypes. Conclusions: This current meta-analysis suggested the variant allele SULT1A1*2 might be an outcome predictive factor to assess the clinical responses of breast cancer patients towards tamoxifen therapy. Future studies are needed to validate our findings.

Keywords: Tamoxifen, breast cancer, SULT1A1, UGT, outcome

Introduction

Breast cancer is the most common prevalent cancer among females, accounting for 41% of incident cases in women in the United States [1-3]. Tamoxifen, a competitive inhibitor of estradiol, has been known as the standard treatment for estrogen receptor-positive (ER+) early-stage breast cancer, which accounts for approximately 75% of breast cancer cases [4]. However, estimations for the long term risk of recurrence showed that hormone receptor-positive breast cancer patients remain at a significant risk of recurrence until at least 15 years post diagnosis [5, 6]. The latest guidelines of American Society of Clinical Oncology recommends that women diagnosed with hormone receptor-positive breast cancer should be offered adju-

vant endocrine therapy with tamoxifen or aromatase inhibitor for a total duration of 10 years [7].

Genetic polymorphisms of drug-metabolizing enzymes involved in the metabolism of tamoxifen may affect clinical efficacy [8]. Tamoxifen is metabolized by the cytochrome P450 2D6 (CYP2D6) to 4-hydroxy tamoxifen (4-OH-TAM) and 4-hydroxy-Ndesmethyltamoxifen (endoxifen), which are 30-100 times more active as anti-estrogens than tamoxifen and N-desmethyltamoxifen [9]. Many studies have focused on CYP2D6 of cytochrome P450 which influence endoxifen formation as a predictive marker for clinical response [10, 11]. However, genetic variation in cytochrome P450 explains only partly the variability in clinical responses to

tamoxifen. Polymorphisms of other drug-metabolizing enzymes affecting tamoxifen pharmacokinetics should be considered. The Sulfotransferase (SULT) and glucuronosyltransferase (UGTs) are the phase II conjugating enzymes participating in the metabolism of the major active metabolites of tamoxifen [12]. Sulfotransferase 1A1 (SULT1A1) mainly participates in the elimination of 4-hydroxy-tamoxifen (4-OH-TAM) [13]. The SULT1A1 gene encodes a phenol sulfotransferase, which catalyzes the sulfate conjugation of catecholamine and of phenolic drugs [14]. It's reported that tamoxifen up-regulates SULT1A1, promoting clearance of 4-OH-TAM through sulfation [15, 16]. Studies showed breast cancer patients with the SULT1A1 rs9282861 homozygous variant AA genotype and treated with either adjuvant tamoxifen or chemotherapy had statistically significantly better overall survival (OS) compared with the carriers of other rs9282861 genotypes, indicating that SULT1A1 might play a role in variability of responses and resistance developed in tamoxifen-treated patients [13]. Besides, another major mode of metabolism of tamoxifen, 4-OH-TAM and endoxifen, is by glucuronidation via the UDP-glucuronosyltransferase, i.e. UGT, family of enzymes [17]. Researches elucidated that both 4-OH-TAM and endoxifen up-regulate UGT2B15 in breast cancer, while UGT2B15 facilitates the metabolism and clearance of 4-OH-TAM through glucuronidation, which might contribute to the increase of tamoxifen resistance [18]. Additionally, it suggested that functional polymorphisms in UGT2B15 and UGT2B7 may affect the individual variability in the response to tamoxifen therapy and the overall prognosis and survival of tamoxifen-treated patients with breast cancer [12, 19].

Studies assessing the role of SULT1A1, UGT2B15 and UGT2B7 in the survival and breast cancer recurrence of tamoxifen-treated patients, mostly randomized trials and retrospective studies, are small in sample size and the results are conflicting. A large retrospective study identified a shorter overall survival (OS) and a higher recurrence rate in patients with two variant polymorphisms in UGT2B15 and SULT1A1 [12], which is however not confirmed in studies published later [20, 21]. Thus, we aimed to gather all the available evidence on the topic in order to investigate the impact of SULT1A1, UGT2B15 and UGT2B7 genotypes on

survival of tamoxifen-treated patients with breast cancer.

Materials and methods

Search strategy and selection criteria

A systematic search of literature in Pubmed and Embase (Ovid) was carried out and the last search was updated on June 14th, 2015. The search terms were: Phenol sulfotransferase or Sulfotransferase1A1 or SULT1A1 or glucuronosyltransferase or UDP-glucuronosyltransferase or UGT, in combination with polymorphism or variant or mutation, and in combination with tamoxifen and breast cancer. Additionally, references of retrieved articles were manually reviewed for relevant studies. There was no limitation to the language restrictions.

The inclusion criteria were as follows: (a) studies investigating the association between outcomes of tamoxifen therapy and genotypes of SULT1A1 and UGT in breast cancer patients; (b) studies providing sufficient data or to extract or calculate a hazard ratio (HR) with its 95% confidence interval (95% CI) for OS, disease-free survival (DFS) or relapse/recurrence-free survival (RFS). The following exclusion criteria were adopted: (a) experimental discoveries only; (b) reviews, letters, case reports; (c) studies of patients with recurrent breast cancer; (d) pharmacodynamic studies; (e) studies without relevant biomarkers; (f) no interested outcome available.

Data extraction

Two investigators (YJQ and SJN) independently extracted the data. The following information was extracted: author, year of publication, country of origin, study design, age at diagnosis, number of participants, stage of breast cancer, status of estrogen receptor and progesterone receptor, daily dosage and intake duration of tamoxifen, duration of follow-up, genotypes compared, as well as OS, DFS and RFS. In case of discrepancies, consensus were obtained through discussion with a third investigator (LQ).

Statistical analysis

Summary HRs with their 95% CI was used to assess the association between the SULT1A1

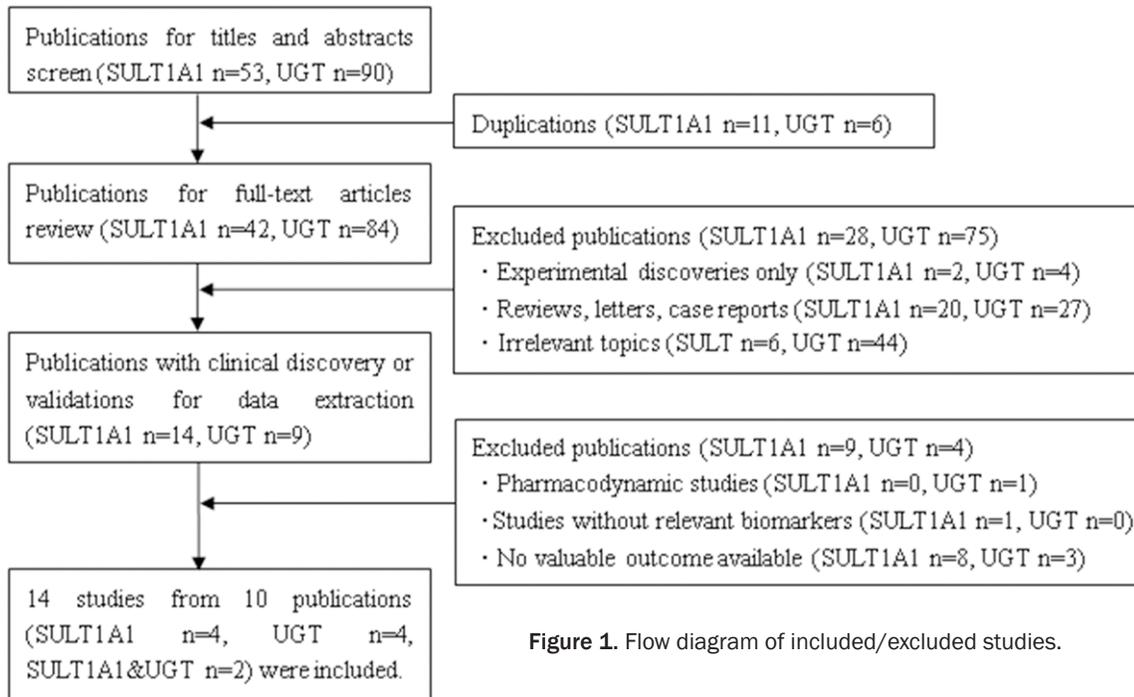


Figure 1. Flow diagram of included/excluded studies.

and UGT genotypes and the survival in breast cancer patients with tamoxifen treatment. The statistical significance of summary HR was determined with Z-test. Patients homozygous for wild type (wt) alleles were compared to those with heterozygous or homozygous for variant type (vt) alleles (i.e.wt/wt vs. wt/vt+vt/vt), if data was not presented in this format, other genotype comparisons such as (wt/wt+wt/vt vs. vt/vt) and (wt/wt vs. wt/vt) were adopted. If the survival was not reported in the pattern above, appropriate data such as the observed and expected events were extracted to calculate the corresponding HR with its 95% CI. If no data of value was presented digitally, the time-to-event data were read from Kaplan-Meier survival curves by the software “Engauge Digitizer 4.1” [22]. The results of data integration were presented as an HR with its 95% CI and *P*-value [23].

Between-study heterogeneity was assessed by chi-squared based *Q* statistic and was considered statistical significant at *P*<0.10. The data of HR were computed using the fixed effect model, unless there was significant evidence of unexplained heterogeneity, in which case a random effects model was adopted. The subgroup analysis was performed when there was significant heterogeneity. In addition, analysis by data type of survival was carried out to explore the data type-specific effects.

Publication bias was analyzed by visual inspection of asymmetry in funnel plots. Sensitivity analysis was conducted by sequentially deleting a single study each time in an attempt to identify the potential influence of the individual data set to the pooled estimates. Data combining was performed by software RevMan 4.2 and Stata 10.0 [24, 25].

Results

Study selection and characteristics

As is shown in **Figure 1**, a total of 143 results were identified after an initial search in the selected databases, among which 17 were duplication articles. After reading the titles and abstracts, 103 were excluded for being review, editorials, letters, case reports, animal experimental studies or with irrelevant content. Thus, 23 potential studies in proper article types which were relevant to outcomes of tamoxifen therapy in breast cancer patients and genotypes of SULT1A1 and UGT were included for full-text view. After reading the full text and extracting data of remaining articles, 13 studies were further excluded for not reporting usable data. Among the remaining 14 studies, 7 studies from 6 publications reported data on SULT1A1, 5 studies from 4 publications reported data on UGT2B15 and 2 studies from 2 pub-

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Table 1. Characteristics of publications included in meta-analysis

First author	Year	Country	Study design	Participants	Age at diagnosis	BCa stage	ER status	PR status	Daily dosage of TAM	Duration of TAM (year)	Follow-up (year)	Polymorphisms	Genotypes
Dezentje V.O [26]	2013	Netherlands	Randomized trial	731	66.1±9.2	I, II, III	+	+	20 mg	2.5-3	2.5	UGT2B15*2	wt/wt vs. wt/vt+vt/vt
Markiewicz A [27]	2013	Poland	Retrospective	281	56 (27-86)	I, II, III	+/-	+/-	20 mg	NS	4.5 (0.02-11.42)	UGT2B15*2	wt/wt vs. wt/vt+vt/vt
Moyer AM [28]	2011	US	Randomized trial	256	NS	I, II	+	NS	20 mg	5	14.3 (5.7-18.7)	SULT1A1	Copy number >2 vs. ≤2
Nowell S [31]	2002	US	Retrospective	337	NS	I, II, III, IV	+/-	+/-	NS	NS	5.4 (3-14)	SULT1A1*2	wt/wt+wt/vt vs. vt/vt
Nowell SA [12]	2005	US	Retrospective	337	NS	I, II, III, IV	+/-	+/-	NS	NS	5.4 (3-14)	SULT1A1*2, UGT2B15*2	Referent vs. variantsa for SULT1A1*2; wt/wt vs. wt/vt for UGT2B15*2
Parmar S [19]	2011	Austria	Cohort	305	55.6±12.6	I, II, III	NS	NS	NS	NS	6-10	UGT2B7*2	wt/wt+wt/vt vs. vt/vt
Rae JM [29]	2012	UK	Randomized trial	603	NS	I, II, IIIA	+	+	NS	NS	10	UGT2B7*2	wt/wt vs. wt/vt+vt/vt
Tengström M [13]	2012	Finland	Prospective case-control	65	56 (23-91)	I, II, III	+/-/NK	+/-/NK	20 or 40 mg	3 (0.25-6.25)	11.9 (0.1-20.4)	SULT1A1*2	wt/wt+wt/vt vs. vt/vt
Wegman P [30]	2005	Sweden	Randomized trial	679	≤70	NS	+/-	NS	40 mg	4	10.7 (0.24-18.6)	SULT1A1*2	wt/wt vs. wt/vt+vt/vt
Wegman P [20]	2007	Sweden	Randomised/Non-randomised	677	69 (50-96)	II, III	+	NS	20 or 40 mg	2 or 5	7.3 (0.04-17.9)	SULT1A1*2, UGT2B15*2	wt/wt vs. wt/vt+vt/vt

BCa: Breast cancer; TAM: tamoxifen; ER: Estrogen receptor; PR: Progesterone receptor; NS: not specified; NK: unknown. wt: wild-type; vt: variant-type. a: Data confounded with UGT2B15. Referent: SULT1A1*1/*1, UGT2B15*1/*1 or SULT1A1*1/*2, UGT2B15*1/*1; variants: SULT1A1*2/*2, UGT2B15*1/*2 or SULT1A1*2/*2, UGT2B15*2/*2.

Table 2. Genotypes compared and survival of studies included in meta-analysis

Gene	First author	Genotypes compared	OS		RFS		DFS	
			HR	95% CI	HR	95% CI	HR	95% CI
SULT1A1	Moyer AM	Copy number >2 vs. ≤2	NS		NS		1.18	0.76-1.83
	Nowell SA	Referent vs. variants ^a	4.40	1.17-16.55	3.79	1.18-12.15		NS
	Nowell S	wt/wt+wt/vt vs. vt/vt	3.18	0.97-10.4		NS		NS
	Tengström M	wt/wt+wt/vt vs. vt/vt	0.53	0.27-1.08		NS		NS
	Wegman P 2005	wt/wt vs. wt/vt+vt/vt	NS		1.35	0.49-3.76		NS
	Wegman P 2007	wt/wt vs. wt/vt+vt/vt	NS		3.03 ^b	1.04-8.33 ^b		NS
		wt/wt vs. wt/vt+vt/vt	NS		1.20 ^c	0.42-3.45 ^c		NS
UGT2B15	Dezentje V.O	wt/wt vs. wt/vt+vt/vt	NS		NS		0.47	0.25-0.89
	Markiewicz A	wt/wt vs. wt/vt+vt/vt	0.99	0.59-1.66		NS		NS
	Nowell SA	wt/wt vs. wt/vt	1.19	0.44-3.22		NS		NS
	Wegman P	wt/wt vs. wt/vt+vt/vt	NS		1.18 ^b	0.39-3.52 ^b		NS
		wt/wt vs. wt/vt+vt/vt	NS		1.94 ^c	0.53-7.06 ^c		NS
UGT2B7	Parmar S	wt/wt+wt/vt vs. vt/vt	NS		NS		5.22	1.67-26.04
	Rae JM	wt/wt vs. wt/vt+vt/vt	1.21	0.76-1.92		NS		NS

OS: overall survival; DFS: disease-free survival; RFS: relapse/recurrence-free survival; HR: hazard ratio; wt: wild-type; vt: variant type; NS: not specified. ^aData confounded with UGT2B15. Referent: SULT1A1*1/*1, UGT2B15*1/*1 or SULT1A1*1/*2, UGT2B15*1/*1; variants: SULT1A1*2/*2, UGT2B15*1/*2 or SULT1A1*2/*2, UGT2B15*2/*2. ^bData for 2 years follow-up; ^cData for 5 years follow-up.

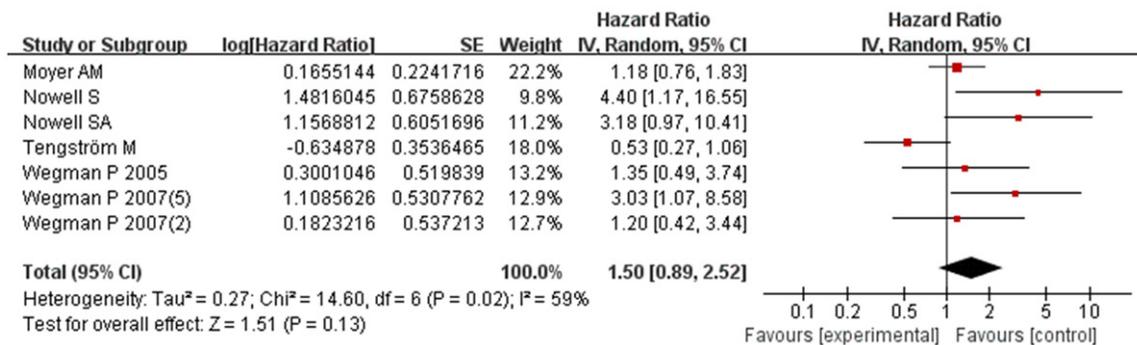


Figure 2. Meta-analysis of SULT1A1 genotype and survival of breast cancer patients with tamoxifen therapy (overall analysis).

lications reported data on UGT2B7. Only one study from one publication reported data on UGT1A8 [21]. Therefore, it was excluded from meta-analysis. Finally, a total of 14 studies from 10 publications were identified [12, 13, 19-21, 26-30]. The characteristics of publications included in meta-analysis are listed in **Table 1**.

Of these fourteen studies with a total of 4339 participants, 6 were eligible for the analysis of OS [12, 13, 27, 29, 31], another 6 were for RFS [12, 20, 30] and 3 more studies eligible for the analysis of DFS [19, 26], since one study reported both OS and RFS [12].

SULT1A1 genotype and survival of breast cancer patients with tamoxifen therapy

A total of seven studies with the total participants of 1337 included in the meta-analysis on the association between the SULT1A1 genotype and survival of breast cancer patients with tamoxifen therapy [12, 13, 20, 28, 30, 31]. HRs of single study ranged from 0.53 to 4.40 and were statistically significant in two of the seven studies (**Table 2**). Pooled analysis presented a non-significant trend toward an increase or decrease in survival (HR=1.50, 95% CI: 0.89-2.52, P=0.13) (**Figure 2**). Furthermore, moderate between-study heterogeneity was detected

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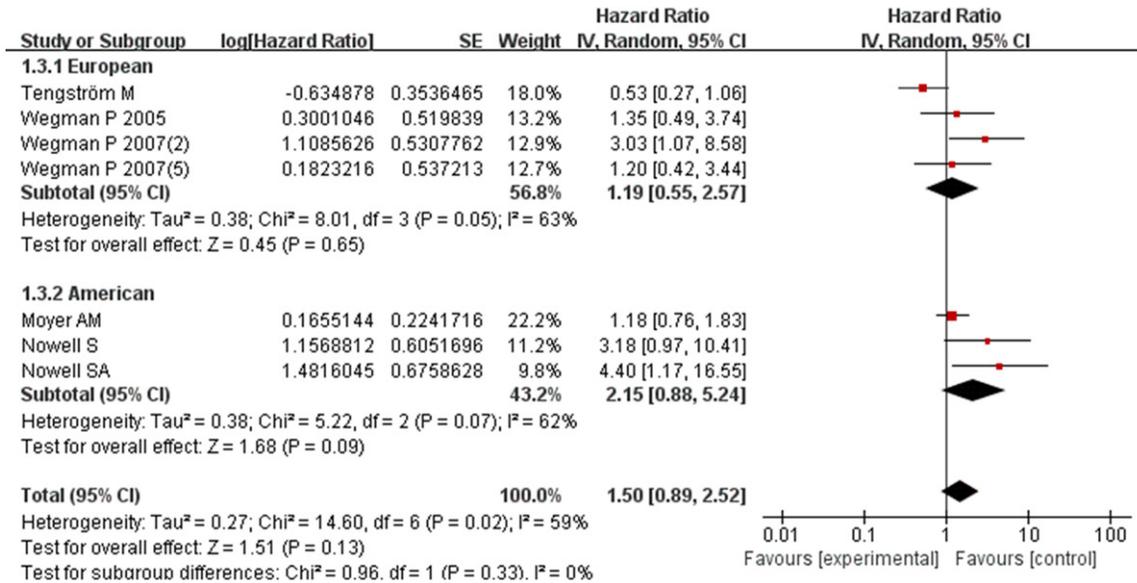


Figure 3. Meta-analysis of SULT1A1 genotype and survival of breast cancer patients with tamoxifen therapy (subgroup analysis by origin of cases).

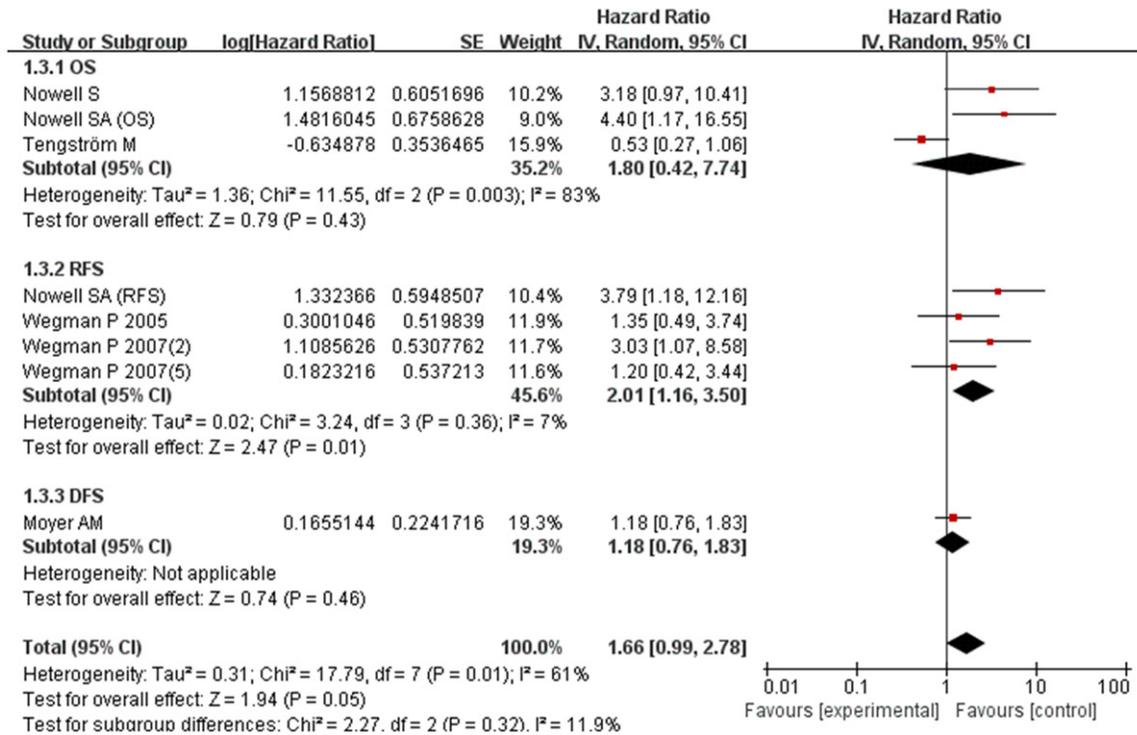


Figure 4. Meta-analysis of UGT2B15 genotype and survival of breast cancer patients with tamoxifen therapy (analysis of OS, RFS and DFS).

(I²=61%, P=0.02, Figure 2) for the analysis of 7 for SULT1A1. Thus, subgroup analysis by origin of cases was performed. However, no statistically significant result was found in subgroup of cases from European or American (Figure 3). In

addition, analysis by data type of survival suggested a trend toward an increased RFS of breast cancer in patients carrying wt alleles of SULT1A1 (HR=2.01, 95% CI: 1.16-3.50, P=0.01). No evidence of significant heterogeneity

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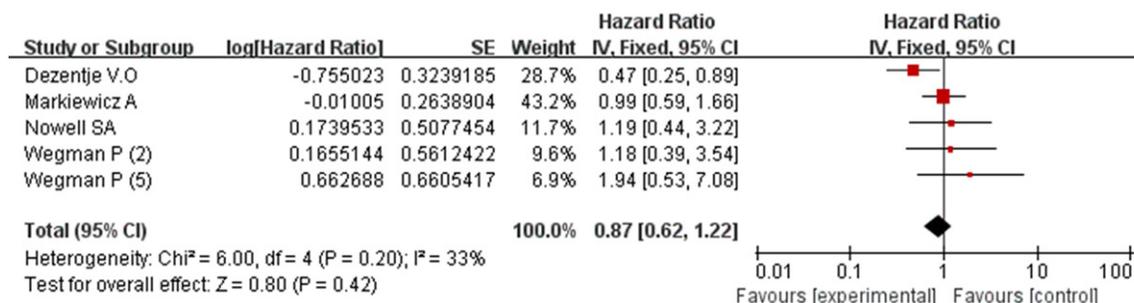


Figure 5. Meta-analysis of UGT2B15 genotype and survival of breast cancer patients with tamoxifen therapy.

was found in the result of RFS ($I^2=7\%$, $P=0.36$). However, the result indicated no association between SULT1A1 genotypes and OS (HR=1.80, 95% CI: 0.42-7.74, $P=0.43$) (Figure 4).

In order to assess the stability of the results of the current meta-analysis, we performed a one-study removed sensitivity analysis for dominant genetic model. It turned into a statistically positive result (HR=1.75, 95% CI: 1.12-2.75; $P=0.01$) with the study of Tengström M, et al excluded [13]. Nevertheless, relative statistically similar results were obtained after sequentially excluding each study, suggesting the stability of our meta-analysis in general. In addition, the shape of the funnel plots showed fair symmetry, suggesting a low-likelihood of publication bias (figure not shown).

UGT2B15 genotype and survival of breast cancer patients with tamoxifen therapy

A total of four studies with the total participants of 3108 were included in the meta-analysis on the association between the UGT2B15*2 genotype and survival of breast cancer patients with tamoxifen therapy [12, 20, 26, 27]. HRs of single study ranged from 0.47 to 1.94 and was statistically significant in one of the five studies (Table 2). Pooled analysis presented a non-significant trend toward an increase or decrease in survival (HR=0.87, 95% CI: 0.62-1.22, $P=0.42$) (Figure 5). There was no evidence of significant heterogeneity for UGT2B15 ($I^2=33\%$, $P=0.20$).

In order to assess the stability of the results of the current meta-analysis, we performed a one-study removed sensitivity analysis for dominant genetic model. Statistically similar results were obtained after sequentially excluding each study. In addition, the shape of the funnel

plots seemed symmetrical, indicating a lack of publication bias of the current analysis.

UGT2B7 genotype and survival of breast cancer patients with tamoxifen therapy

Two studies with the total participants of 1990 were included in the meta-analysis on the association between the UGT2B7*2 genotype and survival of breast cancer patients with tamoxifen therapy [19, 29]. HRs of single study ranged from 1.21 to 5.22 and was statistically significant in one of the two studies (Table 2). Pooled analysis presented a non-significant trend toward an increase or decrease in survival (HR=2.17, 95% CI: 0.53-8.81, $P=0.28$). Moderate between-study heterogeneity was detected ($I^2=74\%$, $P=0.05$).

Discussion

The SULT1A1, UGT2B15 and UGT2B7 genotypes have been reported to be associated with the outcomes of breast cancer patients with tamoxifen therapy, but the results remains inconclusive [12, 19, 20, 27, 30]. The current meta-analysis, including a total of 4339 participants from 14 studies, evaluated the outcomes of tamoxifen therapy in breast cancer patients and genotypes of SULT1A1, UGT2B15 and UGT2B7. The current results suggests that the recurrence-free survival of breast cancer patients with tamoxifen therapy might be decreased in patients with variant allele carriers of Sulfotransferase 1A1 (SULT1A1*2). However, when analyzed in combination with data of OS and DFS, the results turned statistically negative, indicating that the variant alleles may less likely to alter the survival of tamoxifen treated breast cancer. A p value being 0.05 in the analysis of OS, RFS and DFS (Figure 4) needs to be clarified. Since both RFS and OS were put into

statistical processing, this overall p value shall not be a worthwhile considering point although it seems a borderline positive result. Similar to overall analysis of SULT1A1, no statistically significant association between genotypes of UGT2B15 and UGT2B7 and breast cancer survivals were detected. These findings further indicated the sophistication in the mechanism of breast cancer development as well as the interactions with endocrine therapy. In addition, the correlation of ethnicity, intervention and other factors may be potentially influential.

In spite of a moderate heterogeneity in the analysis on SULT1A1, the heterogeneity was controllable and could be well explained. When analyzed by subgroup, there was still heterogeneity in both European and American subgroups. Thus the main heterogeneity might not lay in the origin of cases. In the analysis of OS, RFS and DFS, there was no heterogeneity in RFS while relatively strong heterogeneity in OS. The three out of four studies in RFS group were carried out by a same research team, although the data of participants were not confounded. This may explain the absent of heterogeneity in RFS. However, there might be other factors that may contribute to overall heterogeneity, such as the tamoxifen related intervention. To be specific, the daily dosage of tamoxifen was 20 mg in some of the studies while in others 40 mg [13, 26]. Additionally, there were studies in which patients received daily dosage of 40 mg before converting into 20 mg [20], which made the situation more intricate. Moreover, the duration of tamoxifen therapy was not consistent with the range being from 0.25 to the maximum of 6.25 years [13]. Another factor that might add to the heterogeneity is the design of studies. The designs included randomized trials, retrospective studies, cohort studies and so on. This also limited the potency of a quality evaluation of studies, thus the latter was not performed. Furthermore, the genotypes compared and hormone receptor status of patients may also be of potential concern.

In the investigation of association between SULT1A1 genotype and survival in breast cancer patients with tamoxifen, sensitivity analysis indicated that the data in study published by Tengström M had a significant influence on the overall result. The result synthesized from the rest of studies indicated a decreased survival

in tamoxifen treated breast cancer patients carried with variant genotypes of SULT1A1 ($P=0.01$). The reason to this noteworthy discordance was explained by discrepancy in genotyping related methodology and small sample size ($n=65$) of the very study [13]. Other methodological issues for the present meta-analysis were well investigated. There was no heterogeneity found in the analysis on UGT2B15 and moderate heterogeneity on SULT1A1. No publication bias was detected although there was still potential data omission which existed objectively and was unavoidable. In general, stability and accuracy of the present meta-analysis were guaranteed.

Some limitations of this meta-analysis should be considered. First, the sample size is relatively small in majority of studies and the evidence generated may be less powerful to draw the targeted conclusion. Second, country of origin all suggested a Caucasian or African-American ethnicities. Therefore, our results might be less predictable when applied to other ethnic groups such as Asian. Future studies are needed to investigate the association in Asian populations. Third, since statuses of menopausal and hormone receptors are key factors to tamoxifen response, menopausal status-specific and hormone receptor, especially ER-specific subgroup analyses should have been performed once the original data was sufficient. Furthermore, four defects in the study selection and data processing which may become origin of potential bias needs to be addressed: 1) In two studies published by Rae JM and Wegman P respectively, data were read from survival curves by Engauge [29, 30]. This procedure is time and investigator dependent, thus the data might not be exactly the same as the original one. To overcome this pitfall, investigators read the curve for as many times as needed until the corresponding survival curve of read data overlapped the curves in publications. 2) Although normally the patients with recurrence breast cancer were excluded in the original studies, such information was not declared in two studies. Results might be potentially biased if stage IV cancer were infused in these two studies [12, 31]. 3) In the study by Moyer AM, the data for SULT1A1 was mingled with that of UGT2B15 and could not be extracted separately [28]. 4) In the study performed by Parmar S, etc. Patients were given epirubicin before tamoxifen therapy was initiated, which may affect the

result [19]. Despite the limitations, we have minimized the bias based on methods in study identification, selection as well as statistical analysis, the soundness of results can be ensured.

In conclusion, the current study is the first meta-analysis to have assessed the association between SULT1A1, UGT2B15 and UGT2B7 genotypes and the survival of breast cancer patients with tamoxifen therapy. Our results suggested that recurrence-free survival of breast cancer might be decreased in patients with SULT1A1 variant alleles (SULT1A1*2), thus the later may possibly serve be an outcome predictive factor. Still, large-scale multicenter studies are needed to validate these conclusions.

Disclosure of conflict of interest

None.

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