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Original Article

Association of CYP2D6*10 (c.100C>T) polymorphisms with clinical outcome of breast cancer after tamoxifen adjuvant endocrine therapy in Chinese population

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Abstract: Tamoxifen is the most widely used adjuvant endocrine therapy for breast cancer. However, the pharmacogenetic effect of CYP2D6 on its efficacy remains unclear. Therefore, this study aimed to evaluate the association of CYP2D6*10 (c.100C>T) polymorphisms with clinical outcome in Chinese breast cancer patients. A total of 72 tamoxifen-treated early breast cancer patients were included in this study. CYP2D6*10 (c.100C>T) polymorphisms (C/C: wild type; T/T: homozygous mutant genotype T; C/T: heterozygote genotype C) were detected by pyrosequencing. The plasma concentrations of tamoxifen and its two major active metabolites were determined by liquid chromatography tandem mass spectrometry (LC-MS). Disease-free survival (DFS) and overall survival (OS) were assessed by Kaplan-Meier analysis, while the Cox proportional hazards model was used in multivariate tests for prognostic significance. We found that T/T carrier showed the lowest serum concentration of endoxifen as compared to C/C and C/T carriers ($p<0.01$). In the subgroup of patients below 40 years of age, T/T carriers appeared to have the shortest DFS and OS as compared to other genotype carriers ($p<0.01$). When genotypes (C/C, C/T and T/T carriers) and other clinical characteristics were adjusted, tumor size (>2 cm) and grades were independent prognostic factors for DFS but not OS (tumor size >2 cm: HR: 3.870, 95% CI: 1.045-14.330, P = 0.043; tumor grades: HR: 2.230, 95% CI: 1.090-4.562, P = 0.028). In conclusion, the T/T genotype is a negative prognostic factor in young breast cancer patients using tamoxifen. Tumor size (>2 cm) and grades are independent prognostic factors for DFS, when genotype of CYP2D6*10 (c.100C>T) is adjusted.

Keywords: CYP2D6, genotyping, tamoxifen, breast cancer

Introduction

According to the latest epidemiological data of the United States, breast cancer has the highest incidence among all cancers in women [1]. The selective estrogen receptor (ER) modulator tamoxifen (TAM) is critical for adjuvant endocrine therapy in ER-positive breast cancer patients, regardless of their menopausal status [2]. TAM needs to be converted into active metabolites, (Z)-4-hydoxytamoxifen and (Z)-endoxifen, by the cytochrome P450 enzyme CYP2D6 to exert its anti-tumor effect [3]. The latest CYP2D6 allele nomenclature (http://www.cypalleles.ki.se/cyp2d6.htm) has reported 109 genetic variants, which result in different inter-individual enzyme activity. Based on this, poor metabolizers (PMs), extensive metabolizers (EMs), intermediate metabolizers (IMs) and ultra-rapid metabolizers (UMs) were classified across populations worldwide [4]. Thus, CYP2D6 polymorphisms may influence outcomes of TAM treatment in patients with breast cancer [5]. However, some studies reported adverse results [6, 7]. Based on these contradictory results, current guidelines have not yet recommended routine genetic testing of CYP2D6 [8].

To pursue a personalized strategy of adjuvant endocrine therapy for breast cancer in a Chinese cohort, we studied the possible association of CYP2D6*10 (c.100C>T) polymor-

Table 1. Association between genotypes and clinical characteristics

		C/C (N = 18)	T/T (N = 23)	C/T (N = 31)	Significance
Age (mean ± SD, year)		42.11 ± 5.35	43.96 ± 8.65	45.68 ± 7.40	P^* = 0.084 $P^\#$ = 0.213 P^Δ = 0.475
Tumor size (cm)	≤2	6	7	10	P = 0.979
	>2	12	16	21	
Tumor grades	1	12	12	17	P = 0.904
	2	3	6	8	
	3	3	5	6	
LN status	Negative	6	7	11	P = 0.927
	Positive	12	16	20	
Clinical stage	I	3	7	8	P = 0.831
	II	10	9	15	
	III	5	7	8	
ER	Negative	0	1	2	P = 0.552
	Positive	18	22	29	
PR	Negative	2	2	4	P = 0.888
	Positive	16	21	27	
HER2	Negative	12	16	21	P = 0.979
	Positive	6	8	10	
Menopausal status	Pre-menopause	18	20	27	P = 0.275
	Menopause	0	3	4	
Hot flashes	Yes	3	9	14	P = 0.126
	No	15	14	17	
Tamoxifen (mean ± SD, ng/ml)		305.05 ± 158.37	310.70 ± 128.03	336.42 ± 182.76	t^* = -0.093, P^* = 0.927 $t^\#$ = -0.425, $P^\#$ = 0.675 t^Δ = -0.399, P^Δ = 0.693
4-OH-TAM (mean ± SD, ng/ml)		3.90 ± 1.90	3.14 ± 2.59	4.58 ± 1.93	t^* = 0.763, P^* = 0.455 $t^\#$ = -0.830, $P^\#$ = 0.416 t^Δ = -1.538, P^Δ = 0.138
Endoxifen (mean ± SD, ng/ml)		24.06 ± 12.07	10.72 ± 4.00	25.68 ± 13.96	t^* = 3.345, P^* = 0.007 $t^\#$ = -0.287, $P^\#$ = 0.777 t^Δ = -3.567, P^Δ = 0.004

*C/C vs. T/T; #C/C vs. C/T; ΔC/T vs. T/T. ER, estrogen receptor; PR, progesterone; HER2, human epidermal growth factor receptor-2.

phism with plasma concentrations of TAM and its active metabolites as well as the occurrence of TAM-induced hot flashes and clinical outcomes.

Materials and methods

Ethics statement

The Zhejiang Cancer Hospital Ethics Institution Office approved this study, and all participants provided informed consent. This study strictly conformed to the principles outlined in the Declaration of Helsinki.

Study population

We retrieved data of 72 breast cancer patients who had received surgical treatment at the Zhejiang Provincial Cancer Hospital between January 1993 and October 2008. The inclusion criteria were: (1) Chinese females of Han ethnicity; (2) histological diagnosis of ER+/PR+; (3) diagnosed with invasive breast cancer; and (4) received (38 patients) or receiving TAM (> four weeks, 34 patients) as adjuvant endocrine therapy after surgery; (5) median follow-up was 85 months (range: 20-144 months). The follow-up period was defined as the time from diagnosis to the last visit or death. Disease-free survival (DFS) was defined as the time from diagnosis of breast cancer to the relapse or metastasis. Overall survival (OS) was defined as the time from diagnosis to the last visit or death. The breast cancer-related clinicopathological data were collected including age at diagnosis, tumor size, tumor grades, meno-

Table 2. Association of genotypes with plasma concentrations of TAM and its metabolites

	C/C (N = 12)	T/T (N = 12)	C/T (N = 10)	Significance
Tamoxifen (mean ± SD, ng/ml)	305.05 ± 158.37	310.70 ± 128.03	336.42 ± 182.76	P^{*} = 0.927 $P^{\#}$ = 0.675 P^{Δ} = 0.693
4-OH-TAM (mean ± SD, ng/ml)	3.90 ± 1.90	3.14 ± 2.59	4.58 ± 1.93	P^{*} = 0.455 $P^{\#}$ = 0.416 P^{Δ} = 0.138
Endoxifen (mean ± SD, ng/ml)	24.06 ± 12.07	10.72 ± 4.00	25.68 ± 13.96	P^{*} = 0.007 $P^{\#}$ = 0.777 P^{Δ} = 0.004

*C/C vs. T/T; #C/C vs. C/T; ΔC/T vs. T/T. ER, estrogen receptor; PR, progesterone; HER2, human epidermal growth factor receptor-2.

pausal status, hot flashes, metastatic lymph nodes (LNs), clinical stage (AJCC 7th ed.), estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER2), and p53 expression. All patients underwent a standard operation, and follow-up treatments such as chemotherapy, endocrine therapy and radiotherapy according to the NCCN guidelines.

All pathological and immunohistochemistry (IHC) assessments were confirmed by two pathologists, and were performed according to the typical standard.

Genotyping and metabolic concentration tests

DNA was extracted from whole blood using the Qiagen DNA Midi kit (Qiagen, Valencia, CA), according to the manufacturer's guidelines. Plasma was isolated from whole blood by centrifugation for testing metabolic concentration by liquid chromatography-tandem mass spectrometry (LC-MS-MS) as previously described [9]. Genomic DNA was extracted from 2 mL of whole blood using a Qiagen kit (QIAGEN, Hilden, Germany). The oligonucleotide forward (F) and reverse (R) primers used to amplify the CYP2D6*10 alleles were ordered from TAKARA (Tokyo, Japan), and the sequences were as follows: F: 5'-biotin-GCCATCTTCCTGCTCCTG-3' and R: 3'-GGTTTCACCCACCATCCAT-5'. PCR was performed at 94°C for 3 min, followed by these steps, repeated 30 times: 94°C for 20 s, 56°C for 30 s, 68°C for 30 s; and finally 72°C for 10 min. The presence of amplified fragments was checked by 2% agarose gel electrophoresis. Pyrosequencing was performed as previously described using the PyroMark Q24 kit (Qiagen, Hilden, Germany) [10]. Briefly, PCR reactions

ous clinicopathological parameters. Overall, baseline characteristics of the patients including menopausal status, tumor size, and lymph node metastasis were comparable (P>0.05). Concentrations of TAM and its two major active metabolites were determined in 34 patients receiving TAM for more than four weeks.

Frequencies of genotypes

CYP2D6*10 (c.100C>T) genotype was assessed in all patients, of which 18 (25.0%) were homozygous wild genotype (C/C), 23 (31.9%) were homozygous mutant genotype (T/T) and 31 (43.1%) were heterozygous genotype (C/T) (**Table 1**).

Relationship between metabolic concentration and genotype

T/T carriers presented the lowest concentration of endoxifen as compared to C/C or C/T carriers (P<0.01, **Table 2**). No significant difference in endoxifen concentration was detected between C/C and C/T carriers (P = 0.777, **Table 2**).

Relationship between genotypes and clinical outcomes

The intermediate survival time was 85 months (range: 20-144 months, n = 72). At the end of follow-up, there were 28 deaths among 72 breast cancer patients taking TAM after surgery, with a 5-year OS of 80.6% (58/72), and 7-year OS of 69.4% (50/72). The CYP2D6 C100T genotype was significantly associated with DFS and OS in the subgroup of patients below 40 years of age. T/T carriers had shorter DFS and OS than C/C and C/T carriers (P = 0.015 for both DFS and OS, **Figures 1** and **2**).

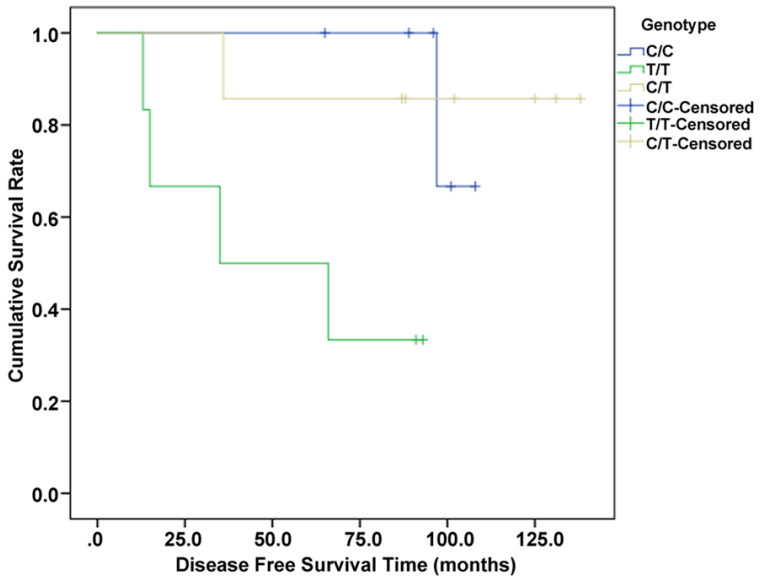

Figure 1. DFS of genotype C/C, C/T and T/T carriers. Log-rank test showed that the T/T carrier had worse DFS than the C/C and C/T carriers (χ^2 = 8.371, P = 0.015) in the subgroup of patients below 40 years of age.

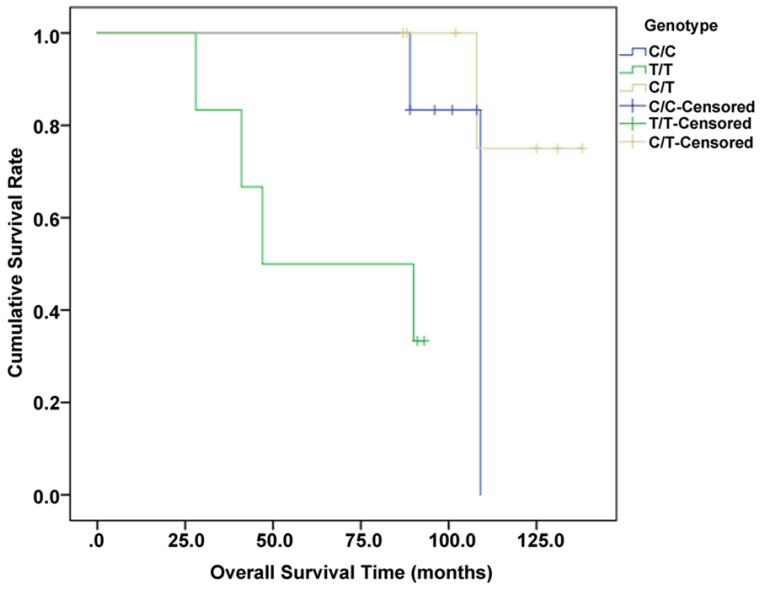

Figure 2. OS of genotype C/C, C/T and T/T carriers. Log-rank test showed that the T/T carrier had worse OS than the C/C and C/T carriers (χ^2 = 8.347, P = 0.015) in the subgroup of patients below 40 years of age.

The Cox proportional hazards regression model indicated that tumor size (>2 cm) and tumor grades were independent negative prognostic factors for DFS but not OS in ER-positive breast cancer patients when the diagnosed age, number of LN+ (lymph node metastasis), ER/PR/HER-2 status, menopause, hot flashes and genotype-grouping (three groups for genotype C/C, C/T and T/T carriers) were adjusted (**Tables 3** and **4**).

Discussion

Tamoxifen (TAM) has been clinically shown to reduce the relapse-risk of breast cancer for at least 15 years after surgery, particularly in young and ER-positive women with early breast cancer [2]. CYP2D6 enzyme facilitates conversion of TAM to its active metabolites, and its activity depends on CYP2D6 gene polymorphism [12]. CYP2D6*10 (c.100C>T) was reported as the most frequent mutant allele (52.53-56.2%) in normal Chinese Han subjects, and plays an important role in the biotransformation of TAM to IM metabolite phenotypes [13, 14]. CYP2D6*10 has a potentially negative effect on the clinical outcome of TAM treatment in ER-positive patients [15, 16]. According to the International Tamoxifen Pharmacogenomics Consortium (ITPC) consensus, abnormal CYP2D6 genotype was associated with a higher risk of metastasis in some postmenopausal patients operated for invasive ER-positive breast cancer. However, the impact of heterogeneity of CYP2D6 genotype on the clinical outcome of TAM-treated young or premenopausal breast cancer patients remains unknown [17].

In the subgroup of patients below 40 years of age, we observed a definite relationship between CYP2D6*10 (c.100C>T) T/T genotype and lower plasma endoxifen concentrations as compared to the C/C and C/T genotypes. Saladores P et al. showed that high steady-level of endoxifen and normal CYP2D6 genotype were related to lower risk of breast cancer

Table 3. Cox proportional hazards regression model test for DFS of all patients

	B	Wald	*P*	Exp (B)	EXP (B) 95% CI	
					Lower	Upper
Age	0.005	0.020	0.889	1.005	0.934	1.082
Tumor Size (>2 cm)	1.353	4.106	0.043	3.870	1.045	14.330
Tumor Grade	0.802	4.825	0.028	2.230	1.090	4.562
Number of LN+	0.007	0.017	0.895	1.007	0.913	1.110
ER+	-0.198	0.039	0.843	0.820	0.115	5.848
PR+	-0.305	0.256	0.613	0.737	0.226	2.406
HER-2+	0.263	0.330	0.566	1.301	0.530	1.583
Menopause	0.188	0.039	0.843	1.207	0.188	7.745
Hot flashes	-0.401	0.858	0.354	0.670	0.287	1.564
Genotype	0.333	0.680	0.409	1.396	0.632	3.081

LN+, lymph node metastasis; ER, estrogen receptor; PR, progesterone; HER2, human epidermal growth factor receptor-2; Genotype-grouping, three groups for genotype C/C, C/T and T/T carriers.

Table 4. Cox proportional hazards regression model test for OS of all patients

	B	Wald	*P*	Exp (B)	EXP (B) 95% CI	
					Lower	Upper
Age	0.029	0.563	0.453	1.030	0.954	1.111
Tumor Size (>2 cm)	0.692	1.814	0.178	1.998	0.730	5.469
Tumor Grade	0.574	3.186	0.074	1.776	0.945	3.335
Number of LN+	0.005	0.013	0.910	1.005	0.924	1.092
ER+	-1.005	1.304	0.253	0.366	0.065	2.054
PR+	0.175	0.078	0.780	1.191	0.349	4.064
HER-2+	0.209	0.237	0.626	1.232	0.532	2.853
Menopause	-0.921	0.948	0.330	0.398	0.062	2.542
Hot flashes	-0.720	2.884	0.089	0.487	0.212	1.117
Genotype-grouping	-0.109	0.189	0.663	0.897	0.549	1.465

LN+, lymph node metastasis; ER, estrogen receptor; PR, progesterone; HER2, human epidermal growth factor receptor-2; Genotype-grouping, three groups for genotype C/C, C/T and T/T carriers.

recurrence regardless of ethnicity in premenopausal patients [18]. In contrast to Caucasian women, breast cancer is often diagnosed in young Chinese patients, irrespective of the cut-off age (35 y or 40 y). Younger patients frequently showed larger tumor size, more LN-metastasis and triple-negative subtype, which led to worse prognosis [19]. Previous genetic testing for CYP2D6 mainly included postmenopausal patients [17, 20, 21]. However, the relationship between CYP2D6 and clinical outcome in premenopausal and younger patients was unclear [22-24]. Our research suggests that younger age is an important factor to predict TAM efficacy by CYP2D6 genotyping.

Increasing evidence has shown that (Z)-endoxifen is the main active metabolite for evaluating the overall clinical outcome of TAM [25, 26]. The additional and extinct mechanism of anti-ER-positive-breast cancer cell growth by endoxifen has also been recently discovered *in vitro* in the presence of high estrogen concentrations equivalent to premenopausal patients [27]. Although the validity of CYP2D6 as a predictor of TAM outcome remains controversial, the definite association between plasma concentrations of endoxifen and CYP2D6 genetic polymorphism has been consistently demonstrated by prospective pharmacological studies [28]. Increasing the regular TAM dose (from 20 to 40 mg daily) could significantly increase endoxifen exposure in patients with CYP2D6 PMs or IMs but not in EMs metabolism [24]. The threshold of 5.97 ng/ml has been reported as the potential concentration for (Z)-endoxifen to predict the benefit from adjuvant TAM therapy [29]. Higher metabolite concentrations of endoxifen were related to 26% lower breast cancer recurrence rate [30]. Although the trends of the mean concentrations of TAM and its primary metabolites in our study were consistent with previous reports [29, 31], the values were higher in Chinese than in Caucasian breast cancer patients, which could be because among the mutant phenotypes of CYP2D6, IM phenotype is more frequent in Chinese while PM phenotype is more reported in Caucasians [17]. However, no association between metabolic concentration and clinical outcome was observed in our study probably because of the small sample size.

Despite the significant relationship between clinical outcome and TAM-induced hot flashes, CYP2D6*10 (c.100C>T) and metabolic concentrations of TAM and its main effective metabolites was not observed in our study. Tumor size (>2 cm) and pathological grades were found to be independent prognostic factors for DFS in

ER-positive breast cancer patients. Our study had several limitations. Firstly, it was not a prospective cohort, had limited sample size and focused on analyzing the relationship between CYP2D6 phenotype and TAM-treated breast cancer outcome in China. Secondly, the definition of CYP2D6*10 should include the detection of two mutant alleles. However, we chose only one allele C100T because of its high frequency in Chinese population. Thirdly, apart from CYP2D6, other factors and drug-metabolizing enzymes, such as polymorphic CYP2C9, CYP3A5, CYP2B6, CYP2C19, SULT1A2 and UGTs [26], age [32], body mass index [29, 33], and seasonal variation [34] may also influence the steady level of (Z)-endoxifen. Furthermore, CYP2D6 activity is not the only factor for TAM-associated hot flashes. Instead, estrogen metabolism and signaling, polymorphisms in the estrogen receptor-2 gene [35] and the time of menopause [36] are known to be related to the occurrence of TAM-induced hot flashes. Until more evidence is available, the presence or absence of hot flashes in TAM-treated women cannot be recommended to predict the possible long-term clinical benefits from TAM [37]. Concomitant medications are also needed. Especially, selective serotonin reuptake inhibitors (SSRIs) are used to relieve hot flashes induced by TAM, and are also well-known for their CYP2D6-inhibiting properties [38, 39]. However, Chinese patients prefer to take traditional Chinese medicine (TCM) instead of SSRIs. The impact of TCM on CYP2D6 enzyme activity or clinical outcome of TAM treatment remains unknown. The concomitant medications and compliance with the therapy were not recorded in our study.

While a definite positive relationship between CYP2D6*10 (c.100C>T) polymorphisms and clinical outcome was not found in this cohort, we found that T/T genotype might be a potential negative prognostic factor for breast cancer patients below 40 years of age. If other high-risk factors for recurrence or metastasis are present in these patients, higher dose of TAM or other endocrine therapy, such as ovarian function suppression plus aromatase inhibitor might be rational choices for adjuvant endocrine therapy. Prospective studies could demonstrate the value of CYP2D6 genotyping in TAM therapy for all ages.

Clinicians should be cautious about selecting TAM as the adjuvant endocrine therapy in female Chinese patients below 40 years of age and carrying homozygous mutant T/T of CYP2D6*10 (C100T) genotype, which is related to lower endoxifen level. In addition, tumor size (>2 cm) and pathological grades are independent prognostic factors for DFS of ER-positive breast cancer patients.

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Disclosure of conflict of interest

None.

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