Cytochrome P450 2D6 and Homeobox 13/Interleukin-17B Receptor: Combining Inherited and Tumor Gene Markers for Prediction of Tamoxifen Resistance

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Abstract

Purpose: Genetic variation in *cytochrome P450 2D6* (*CYP2D6*) and the gene expression ratio of the homeobox 13 (*HOXB13*) to interleukin-17B receptor (*IL17BR*) are associated with tamoxifen resistance. We sought to determine the combined effect of inherited (*CYP2D6*) and somatic (*HOXB13*/*IL17BR*) gene variation in tamoxifen-treated breast cancer.

Experimental Design: Retrospective analysis of women with node-negative breast cancer randomized to receive 5 years of tamoxifen (North Central Cancer Treatment Group 89-30-52). CYP2D6 metabolism (extensive or decreased) was based on CYP2D6*4 genotype and presence/absence of a CYP2D6 inhibitor. Reverse transcription-PCR profiles for *HOXB13* and *IL17BR* and the cut point separating patients into high- and low-risk categories according to disease-free survival (DFS) were used. A risk factor (CYP2D6:HOXB13/IL17BR) representing the four categories of combining CYP2D6 metabolism (extensive or decreased) and HOXB13/IL17BR (low or high) was created. The association between CYP2D6:HOXB13/IL17BR and DFS and overall survival (OS) was assessed using the log-rank test and proportional hazards modeling.

Results: CYP2D6 metabolism and *HOXB13*/*IL17BR* gene ratio was available in 110 of 160 (69%) patients. The combined CYP2D6:HOXB13/IL17BR risk factor was significantly associated with DFS (log-rank $P = 0.004$) and OS ($P = 0.009$). Relative to women with extensive CYP2D6 metabolism and low *HOXB13*/*IL17BR*, those with either decreased metabolism or a high *HOXB13*/*IL17BR* ratio had significantly worse OS (adjusted hazard ratio, 2.41; 95% confidence interval, 1.08-5.37; $P = 0.031$), whereas women with both decreased metabolism and high *HOXB13*/*IL17BR* ratio had the shortest survival (adjusted hazard ratio, 3.15; 95% CI, 1.17-8.52; $P = 0.024$).

Conclusions: An index composed of inherited (CYP2D6) and tumor (HOXB13/IL17BR) gene variation identifies patients with varying degrees of resistance to tamoxifen.

Genetic markers are increasingly used to identify patients at increased risk for relapse (prognosis) and to predict the likelihood of a therapeutic response (predictive markers). Given that both tamoxifen and aromatase inhibitors are effective therapies for the treatment of estrogen receptor (ER)-positive breast cancer (1, 2), there is great interest in identifying biomarkers that may allow the individualization of therapy.

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Cytochrome P450 2D6 (CYP2D6) is a polymorphic enzyme responsible for the metabolic activation of tamoxifen to metabolites (endoxifen and 4-OH tamoxifen) with a significantly greater affinity for the ER and greater ability to inhibit tumor cell proliferation compared with the parent drug (tamoxifen) or its primary metabolite, *N*-desmethyltamoxifen (3, 4). Both genetic (inherited traits) and environmental (drug induced) factors that alter CYP2D6 enzyme activity affect the concentrations of the active tamoxifen metabolites (5, 6). We and others have shown the importance of CYP2D6 as a predictor of tamoxifen benefit in the prevention (7), metastatic (8), and adjuvant settings (9–11). Based on these data, a Food and Drug Administration Clinical Pharmacology Subcommittee recently recommended that the tamoxifen label should be updated to reflect the increased risk of breast cancer recurrence for women who are CYP2D6 poor metabolizers, resulting from genetic variation or drug-induced inhibition of CYP2D6.

In a genome-wide microarray analysis of tumors from women with ER-positive breast cancer treated with adjuvant tamoxifen, Ma et al. (12) discovered the *homeobox 13* (*HOXB13*)/*interleukin-17B receptor* (*IL17BR*) gene ratio as an independent predictor of treatment outcome and showed that ectopic expression of *HOXB13* in a nontransformed human mammary epithelial cell confers increased cell migration and invasion. Follow-up studies have shown that both *HOXB13* and *IL17BR* are regulated by estradiol in an ER-dependent manner and this regulation is abrogated by tamoxifen (13). In hormone-sensitive cell lines, *HOXB13* expression rendered cells less sensitive to tamoxifen-induced apoptosis (14). Further clinical analysis of ~2,700 patients from four independent clinical databases (15–18) has repeatedly validated the HOXB13/IL17BR ratio as a prognostic marker (18) and a biomarker predictive of tamoxifen benefit (15–17), with the effect most pronounced in node-negative, ER-positive breast cancer (15, 16, 18).

In a cohort of postmenopausal women with resected ER-positive breast treated with adjuvant tamoxifen only, we reported that women with decreased CYP2D6 metabolism (defined as the presence of one or two *CYP2D6*4* alleles or the documented coprescription of a CYP2D6 inhibitor) had significantly shorter disease-free survival (DFS) compared with women with extensive CYP2D6 metabolism (defined as women who did not carry a *CYP2D6*4* allele and were not coprescribed a CYP2D6 inhibitor; ref. 9). In this same cohort, we showed that a high *HOXB13/IL17BR* ratio was associated with significantly worse DFS and overall survival (OS) but only in lymph node–negative patients (15).

We hypothesized that because CYP2D6 and *HOXB13/IL17BR* represent biologically independent markers of tamoxifen resistance, a combined index may provide a better indicator of tamoxifen treatment benefit. Therefore, using the same study population from which we derived our original findings about CYP2D6 (9, 10) and *HOXB13/IL17BR* (15), we evaluated the combined effect of CYP2D6 and *HOXB13/IL17BR* on the outcomes of DFS and OS in women with lymph node–negative breast cancer treated with adjuvant tamoxifen monotherapy.

Materials and Methods

Patients. The North Central Cancer Treatment Group (NCCTG) conducted a randomized phase III clinical trial in postmenopausal women with resected ER-positive breast cancer to assess the value of administering the androgen fluoxymesterone for 1 y during the standard 5 y of tamoxifen adjuvant therapy (NCCTG 89-30-52). A description of the clinical trial and its outcome has been published (19). The protocol was amended to assess genetic and environmental factors, which may be associated with increased risk of breast cancer relapse. The trial and its amendments were approved by the

Table 1. Baseline characteristics

Characteristic	HOXB13/IL17BR and CYP2D6 phenotype available (n = 110)	HOXB13/IL17BR and CYP2D6 phenotype not available (n = 50)
Median age (range)	65 (42-84)	63 (47-82)
Race		
Caucasian	105 (95%)	42 (84%)
African-American	1 (1%)	1 (2%)
Unknown	4 (4%)	7 (14%)
Extent of surgery		
Mastectomy	91(83%)	38 (76%)
Breast sparing	19 (17%)	12 (24%)
ER status		
10-49 fmol	27 (25%)	7 (14%)
≥50 fmol	65 (59%)	34 (68%)
Positive	18 (16%)	9 (18%)
Tumor size ≥3 cm	22 (20%)	7 (14%)
Tumor grade		
1-2	86 (78%)	22 (44%)
3	17 (15%)	5 (10%)
Unknown	7 (6%)	23 (46%)
Immunohistochemical HER2 expression		
0	13 (12%)	2 (4%)
1+	34 (31%)	10 (20%)
2+	35 (32%)	9 (18%)
3+	21 (19%)	6 (12%)
Unknown	7 (6%)	23 (46%)

Table 2. Risk groups as defined by CYP2D6 metabolism and HOXB13/IL17BR gene ratio

Risk group	HOXB13/IL17BR gene ratio	CYP2D6 metabolism phenotype (CYP2D6*4 genotype: CYP2D6 inhibitor use)	*n* = 110	Estimated 5-y DFS rate (95% CI)
1	<-1.339	Extensive	46	93.5% (86.6-99.9%)
		(Wt/Wt: no)	(46)	
2	<-1.339	Decreased	18	83.8% (67.8-99.9%)
		(Unknown: yes)	(2)	
		(Wt/Wt: yes)	(5)	
		(Wt/*4: yes)	(1)	
		(Wt/*4: no)	(9)	
		(*4/*4: no)	(1)	
3	≥-1.339	Extensive	32	75.0% (61.4-91.6%)
		(Wt/Wt: no)	(32)	
4	≥-1.339	Decreased	14	57.1% (36.3-89.9%)
		(Wt/Wt: yes)	(1)	
		(Wt/*4: no)	(11)	
		(*4/*4: no)	(2)	

NOTE: The Kaplan-Meier estimates of 5-y DFS rates and corresponding CIs for each group are given. CYP2D6 inhibitors coadministered during tamoxifen in nine patients were as follows: cimetidine (n = 4), fluoxetine (n = 2), paroxetine (n = 2), sertraline (n = 1), and haloperidol (n = 1); one patient was coprescribed two CYP2D6-inhibiting drugs.

institutional review board of Mayo Clinic Rochester and the individual NCCTG sites that enrolled patients onto the clinical trial.

The means by which *CYP2D6* genotyping (10) and *HOXB13/IL17BR* (15) were measured and quantified has been previously published. Additionally, we published a comprehensive analysis of both CYP2D6 genotype and CYP2D6 enzyme inhibition on tamoxifen treatment outcome (9). Briefly, a woman who carried either one or two *CYP2D6*4* alleles or had any *CYP2D6* genotype but coprescribed a CYP2D6 inhibitor was considered to have decreased CYP2D6 metabolism. A woman without a *CYP2D6*4* allele and who was not coprescribed a CYP2D6 inhibitor was considered to have extensive metabolism. A woman was said to have a low *HOXB13/IL17BR* gene ratio if her tumor HOXB13/IL17BR gene ratio fell below <-1.339 (15).

Study design and end points. The primary objective of this study was to assess the association of effect of CYP2D6 metabolism and the *HOXB13/IL17BR* gene ratio on DFS and OS in women with lymph node–negative breast cancer receiving adjuvant tamoxifen only. DFS was defined as the time from randomization to documentation of the first of the following events: any recurrence (local, regional, or distant) of breast cancer, a contralateral breast cancer, a second primary cancer, or death due to any cause. Patients who were alive without any of these events were censored at the date of their last disease evaluation. OS was estimated as the time from randomization to death due to any cause.

The overall distributions of DFS and OS were estimated using the Kaplan-Meier method. Log-rank tests and univariate proportional hazard models were used to assess whether the end point differed with respect to any one of the following factors: age >65 (yes versus no), ER status at time of entry into the trial (10-49 fmol versus ≥50 fmol versus positive by immunohistochemistry), tumor size ≥3 cm (yes versus no), Nottingham grade (3 versus 1 or 2), and HER2 expression (3+ versus 0, 1+, or 2+). For each clinical outcome, multivariate proportional hazard modeling was done to obtain a subset of the potential prognostic factors, which provided an adequate fit to the data. Residual plots were examined. A risk factor (CYP2D6:HOXB13/IL17BR) representing the four categories of combining CYP2D6 metabolism (extensive versus decreased) and *HOXB13/IL17BR* (low versus high) was created. Representing CYP2D6:HOXB13/IL17BR as three indicator variables, multivariate proportional hazard modeling was done to assess whether any one of these factors made a significant contribution to the previous established model for that clinical end point.

Results

Our study population is derived from women with node-negative breast cancer (n = 160) who were randomized from December 31, 1990 to April 6, 1995 to the tamoxifen only arm of NCCTG 89-30-52. In 110 of 160 patients, both *HOXB13/IL17BR* gene expression data and a comprehensive assessment of CYP2D6 metabolism (consisting of *CYP2D6*4* genotype and medication history) were known. The characteristics of these 110 patients are listed in Table 1 and the combined CYP2D6 and *HOXB13/IL17BR* phenotype is listed in Table 2.

As of October 25, 2006, 12 women were alive with disease progression, a second primary, or contralateral breast disease, and 37 women had died. The median length of follow-up for those women still alive is 12.5 years (range, 5.7-15.5 years).

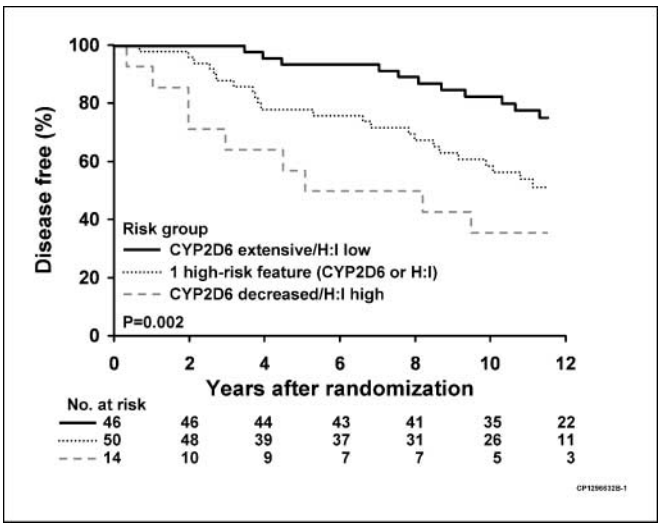

Fig. 1. Kaplan-Meier estimates of DFS in lymph node–negative patients according to the presence of no high-risk features (extensive CYP2D6 metabolism and HOXB13/IL17BR <-1.339), only one high-risk feature (either decreased CYP2D6 metabolism or HOXB13/IL17BR ≥-1.339), and two high-risk features (both decreased CYP2D6 metabolism and HOXB13/IL17BR ≥-1.339).

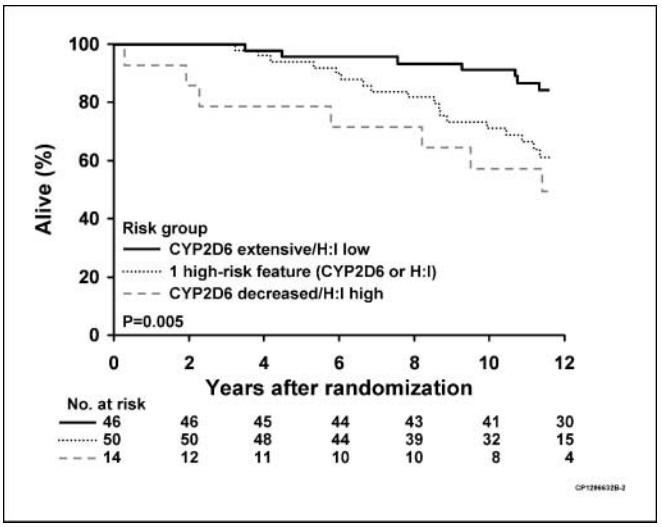

Fig. 2. Kaplan-Meier estimates of OS in lymph node–negative patients according to the presence of no high-risk features (extensive CYP2D6 metabolism and HOXB13/IL17BR <-1.339), only one high-risk feature (either decreased CYP2D6 metabolism or HOXB13/IL17BR ≥-1.339), and two high-risk features (both decreased CYP2D6 metabolism and HOXB13/IL17BR ≥-1.339).

Univariate analyses of clinical outcomes. Four risk groups were formed by combining CYP2D6 metabolism and *HOXB13/IL17BR* (Table 2). DFS and OS were found to differ significantly with respect to these four patient categories (P = 0.004 and 0.009, respectively). Table 2 presents the Kaplan-Meier estimates of 5-year DFS rate and its corresponding confidence interval (CI) for each risk group. To evaluate the cumulative effect of carrying one or more risk factors, we analyzed DFS and OS based on the absence of a risk factor (extensive CYP2D6 and *HOXB13/IL17BR* low), only one high-risk feature (either CYP2D6 metabolism decreased or *HOXB13/IL17BR* high), and finally two high-risk features (both CYP2D6 decreased and *HOXB13/IL17BR* high). In this analysis, both DFS (P = 0.001) and OS (P = 0.005) differed significantly according to risk groups (Figs. 1 and 2).

Multivariate analyses of clinical outcomes. For each end point, proportional hazard modeling was done using age, extent of surgery, ER status, tumor size, tumor grade, and HER2 expression. Once tumor size was accounted for, none of the other traditional factors made a significant contribution to explaining the variability in these clinical outcomes. Further multivariate proportional hazard modeling showed that after adjusting for tumor size, DFS and OS were significantly different among patients with zero, one, or two risk factors as determined by CYP2D6 and *HOXB13/IL17BR* gene ratio. Relative to women with no risk factors (extensive CYP2D6 and *HOXB13/IL17BR* low), women with at least one risk factor had significantly worse DFS [adjusted hazard ratio (HR), 2.03; 95% CI, 1.04-3.94; P = 0.037] and OS (adjusted HR, 2.41; 95% CI, 1.08-5.37; P = 0.031). An even greater effect was observed in women with two risk factors (decreased CYP2D6 metabolism and *HOXB13/IL17BR* high). These women had the shortest DFS (adjusted HR, 3.10; 95% CI, 1.34-7.17; P = 0.008) and OS (adjusted HR, 3.15; 95% CI, 1.17-8.52; P = 0.024; Table 3).

Discussion

Our analysis of this cohort of ER-positive, lymph node–negative patients treated with adjuvant tamoxifen strongly suggests that a combination of inherited (*CYP2D6*) and tumor (*HOXB13/IL17BR*) genetic variation influences the risk of breast cancer recurrence and death, independent of standard prognostic factors. Furthermore, we showed a stepwise increased risk of recurrence and death, with the greatest risk in those patients who carry both high-risk features (e.g., both decreased CYP2D6 metabolism and a high *HOXB13/IL17BR* gene ratio). In contrast to prior studies in lymph node–negative breast cancer that have simply focused on tumor genetic variation (20), the paradigm of accounting for host genetic variation affecting drug metabolism, as well as tumor somatic variation, offers the potential for a more accurate estimate of drug benefit and the identification of groups of patients for whom alternative or additional therapies could be considered.

The potential synergy between *HOXB13/IL17BR* and *CYP2D6* as biomarkers for tamoxifen resistance may be related to the differential effects of tamoxifen and its metabolites in the setting of tumor cells with dysfunctional estrogen signaling. Endoxifen exhibits a significantly greater affinity for the ER than tamoxifen (3) and multiple studies suggest that only two tamoxifen metabolites, endoxifen and 4-OH tamoxifen, have significant antiproliferative activity (3, 22). Tamoxifen and other metabolites exhibit only weak antagonist/agonist properties (23). The importance of these pharmacologic differences may be magnified in women with a high *HOXB13/IL17BR* gene ratio, as *in vitro*, *HOXB13* and *IL17BR* are regulated by estradiol, which suppresses *HOXB13* and augments *IL17BR*

Table 3. Results of multivariate modeling of DFS and OS

Factor	Clinical outcome	
	DFS	OS
Tumor size ≥3 cm	2.64 (1.42-4.92)	2.52 (1.23-5.14)
Either *HOXB13/IL17BR* high or decreased CYP2D6 metabolism	2.03 (1.04-3.94)	2.41 (1.08-5.37)
Both *HOXB13/IL17BR* high and decreased CYP2D6 metabolism	3.10 (1.34-7.17)	3.15 (1.17-8.52)

NOTE: Multivariate modeling based on tumor size, and the three risk group models comparing presence of one high-risk feature (defined as the presence of either decreased CYP2D6 metabolism or a *HOXB13/IL17BR* gene ratio ≥-1.339) or two high-risk features (defined as the presence of both decreased CYP2D6 metabolism and a *HOXB13/IL17BR* gene ratio ≥-1.339) relative to CYP2D6 extensive metabolizers with a *HOXB13/IL17BR* <-1.339 HRs and corresponding 95% CIs.

expression (13). In tumors with a high *HOXB13/IL17BR* ratio, the loss of both suppression of *HOXB13* expression and induction of *IL17BR* expression may not only be a marker for impaired ER signaling but also for increased growth factor signaling. Based on studies showing that ER-positive tumors with a high *HOXB13/IL17BR* ratio are more likely to overexpress HER2 (13), *in vivo* ER binding of tamoxifen and other nonpotent metabolites (as opposed to endoxifen) may activate growth factor signaling and thus tumor growth (18). This hypothesis is supported by preliminary data wherein nontransformed human mammary epithelial cells expressing *HOXB13* showed a synergistic increase in cell motility and invasion in the presence of epidermal growth factor (12).

Most of the published breast cancer gene signatures seem to provide similar information in the setting of ER-positive breast cancer (24) and proliferation-related genes seem to be an essential component accounting for the concordance between these expression signatures (12, 20, 25–28). Although "proliferation" signatures seem to identify those patients who derive the greatest benefit from adjuvant chemotherapy (29), the role of *HOXB13* and *IL17BR* as a tool for clinical decision making has been unclear. However, our data suggest that postmenopausal patients with decreased CYP2D6 metabolism (especially CYP2D6 poor metabolizers) may preferentially benefit from alternative hormonal therapy (e.g., aromatase inhibitor) in the setting of tumors with a high *HOXB13/IL17BR* ratio. Further retrospective studies of large adjuvant trials comparing tamoxifen with aromatase inhibitors are necessary to validate this hypothesis.

In summary, our data suggest that an index composed of CYP2D6 and *HOXB13/IL17BR* may provide a robust indicator of tamoxifen resistance. A prospective approach incorporating both factors may lead to the improved individualization of endocrine therapy.

Disclosure of Potential Conflicts of Interest

X-J. Ma, M.G. Erlander, and D.C. Sgroi are named inventors on a patent to use the HOXB13/IL17BR expression ratio to ascertain breast cancer prognosis. X-J. Ma and M.G. Erlander are employees of AviaraDx. M.P. Goetz, J.N. Ingle, M.M. Ames, and F.J. Couch are named inventors on a pending patent application about the combined index of CYP2D6 and *HOXB13/IL17BR* as a predictor for tamoxifen resistance. M.P. Goetz and J.N. Ingle have been consultants for Roche (2007). M.P. Goetz, J.N. Ingle, and F.J. Couch received research funding from Arcturus in 2005.

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