Impaired Tamoxifen Metabolism Reduces Survival in Familial Breast Cancer Patients

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Abstract

Purpose: Tamoxifen has been the mainstay adjuvant hormonal treatment for breast cancer for many years. Conversion of tamoxifen to its active metabolite, endoxifen, is reduced by low activity of the cytochrome P450 enzyme, CYP2D6. We examined the effect of reduced CYP2D6 activity on the response to tamoxifen in patients with familial early-onset breast cancer.

Experimental Design: We conducted a case note review and genotyping for the CYP2D6*3, CYP2D6*4, CYP2D6*5, and CYP2D6*41 alleles in 115 patients (47 BRCA1, 68 BRCA2) with familial breast cancer who had been treated with 20-mg tamoxifen following surgery.

Results: Eight (7%) individuals had genotypes consistent with poor metabolizer status, and 4 (3.5%) individuals took CYP2D6 inhibitor drugs concomitant with their tamoxifen and were also considered poor metabolizer. Time to tumor recurrence, disease-free survival, and overall survival were reduced in the patient group with poor metabolizer CYP2D6 activity. However, a significant effect was confined to patients with BRCA2 mutations with a worse overall survival (median survival, 7 versus 28 years; \( P = 0.008 \); adjusted hazard ratio, 9.7).

Conclusions: Poor metabolizer status for CYP2D6 predicts worse overall survival in patients with familial breast cancer. Therefore, CYP2D6 inhibitor drugs should not be prescribed concomitantly with tamoxifen. Prospective studies should be undertaken to establish the effect of CYP2D6 status on outcome in familial breast cancer patients treated with tamoxifen.

Breast cancer is the most common cancer in females, with more than 1 million women worldwide diagnosed every year (1). In the United States, ~170,000 new diagnoses of invasive breast cancer are expected in 2007 (2). Familial susceptibility to breast cancer accounts for ~10% to 25% of all breast cancer cases, with the majority of high risk familial breast cancer cases due to mutations in the BRCA1 and BRCA2 genes (3, 4). The lifetime risks for developing breast cancer are 65% to 85% and 45% to 85% for BRCA1 and BRCA2 mutation carriers, respectively (5). In addition, BRCA1 and BRCA2 mutation carriers have increased lifetime risks of ovarian cancer of 37% to 62% and 11% to 23%, respectively (6). Importantly, breast cancer due to BRCA1 and BRCA2 mutations accounts for a disproportionately high number of life-years lost because of the early onset of disease.

Currently, the treatment of breast cancer in women with BRCA1 or BRCA2 mutations does not differ from the treatment in women with sporadic breast cancer (7). However, trials of poly(ADP-ribose) polymerase inhibitors and platinum- versus taxane-based chemotherapy are under way in patients with metastatic BRCA1- and BRCA2-related breast cancer, aiming to exploit impaired DNA damage response pathways (8). Often, the presence of a BRCA1 or BRCA2 mutation is unknown at the time of primary treatment and so is unavailable to guide treatment decisions (9). In the majority of studies, ipsilateral and contralateral breast cancer rates of recurrence have been increased in women with BRCA1 or BRCA2 mutations compared with women with sporadic breast cancer (10, 11). Histopathologic analyses have shown important differences between BRCA1- and BRCA2-related breast tumors (12). Notably, sporadic and BRCA2-related breast cancers are more likely to be estrogen receptor (ER) positive than those with BRCA1 mutations (13).

Tamoxifen is a selective ER modulator and its antagonist properties predominate in breast tissue. It remains the standard adjuvant therapy for premenopausal women and a significant proportion of postmenopausal women with ER-positive breast cancer. Multiple trials have shown its positive influence on disease-free survival and overall survival from breast cancer (14, 15). Specifically, tamoxifen is associated with a 50% reduction in the incidence of contralateral breast cancer in both BRCA1 and BRCA2 mutation carriers, independent of the ER status of the primary tumor (16, 17).

A number of studies have considered the role of pharmacogenetics in breast cancer treatment (18) and recent focus has...
been directed at tamoxifen metabolism. Importantly, pharmacokinetic analyses have indicated that the cytochrome P450 enzyme CYP2D6 is the rate-limiting step in the conversion of tamoxifen to its active metabolite, 4-hydroxy-N-desmethyltamoxifen (endoxifen; ref. 19). Endoxifen is up to 100 times more potent than the parent drug in suppressing estrogen-dependent cell proliferation (20). Reduction in CYP2D6 activity due to polymorphisms in the CYP2D6 gene or to drug inhibitors, including some selective serotonin reuptake inhibitors including fluoxetine and paroxetine, has been shown to reduce endoxifen levels and be associated with poorer outcome in women with breast cancer who have been treated with tamoxifen (21-24). Therefore, we undertook to establish the effect of variation in CYP2D6 and concomitant medication on the outcome of a cohort of patients with familial breast cancer, due to BRCA1 and BRCA2 mutations, treated with tamoxifen.

### Materials and Methods

Of our entire cohort of 456 probands with pathogenic BRCA1 or BRCA2 mutations at a single U.K. cancer genetics center, we ascertained 125 unrelated White Caucasian women (7.8% of Ashkenazi Jewish ethnicity) on whom we had complete clinical data with a range of pathogenic BRCA1 (51) or BRCA2 (74) mutations with breast cancer and who had been treated with tamoxifen following surgery. Germ-line DNA samples extracted from lymphocytes were available from 115 patients (47 BRCA1 and 68 BRCA2 mutations). We genotyped the patient cohort and a healthy ethnically matched control population without cancer (90 individuals) for the common CYP2D6 null alleles, CYP2D6*3 (c.2549delA), and CYP2D6*4 (c.1934G>A+1), and the intermediate allele CYP2D6*41 (c.2988G>A) by TaqMan allelic discrimination methods (Applied Biosciences). Quality assurance was ensured by sequence analysis of 10% of samples. In addition, the CYP2D6 gene deletion CYP2D6*5 was genotyped by a TaqMan assay (25).

Data were abstracted from medical records about outcome, dose of tamoxifen, duration of treatment, other treatments including radiotherapy and chemotherapy, tumor size and grade, ER status at diagnosis with primary breast cancer, and concomitant medication especially selective serotonin reuptake inhibitors. The primary outcome measure for this retrospective study was time to tumor recurrence with contralateral, ipsilateral, or metastatic disease. Secondary outcome measures included recurrence-free survival and overall survival.

CYP2D6 genotypes were evaluated by χ² tests for consistency with Hardy-Weinberg equilibrium, and allele frequencies compared between groups using Fisher's exact tests. Kaplan-Meier survival curves were constructed for time to tumor recurrence, relapse-free survival, and overall survival, and groups compared using log-rank tests. Cox proportional hazard models were used to compute hazard ratios (HR) and to compare groups allowing for nodal status (0, 1-3, and >3). Subgroup differences in genetic effects (BRCA1 versus BRCA2) were determined by testing appropriate interaction terms in the Cox regression model. There was insufficient data to adjust the analyses for more than the dominant predictor (nodal status) but additional selective confirmatory analyses were undertaken adjusting for ER status and tumor size. For the analyses presented here, patients with two null alleles for CYP2D6*3, CYP2D6*4, or CYP2D6*5 were defined as poor metabolizers and pooled with those on concomitant inhibitory medication, but these groups were also considered separately. The R statistical package was used for all computations (26).

The study was approved by Salford and Trafford (06/Q1404/155) and University of Manchester (07046) research ethics committees.

### Results

The characteristics of the 115 familial breast cancer patients for whom samples and data were available for analysis are presented in Table 1. Importantly, there were no significant differences in the age at diagnosis, nodal status at presentation, chemotherapy and/or radiotherapy received, tumor size, type of surgery, or tumor grade between the BRCA1- and BRCA2-related breast cancer patients. Tumors from patients with BRCA2 mutations were more likely to have ER-positive tumors (91% versus 57.5%, P < 0.001). Patients were followed up for a median duration of 10 years or until death. All patients were treated with 20-mg tamoxifen with a median duration of treatment of >4 years.

Overall, in the 115 patients there were 43 (37.4%) breast cancer recurrences with a median time to recurrence of 19.3 years (Kaplan-Meier estimate), and 21 (18.3%) deaths with a median time to death of 28.1 years. Of the recurrence events, 12 were second primary tumors, 18 were locoregional, and 13 were metastatic. Ten (8.7%) patients also developed ovarian cancer, consistent with the familial nature of tumor predisposition in this cohort; one patient developed endometrial cancer; and six patients underwent prophylactic mastectomy. Importantly, four patients were coprescribed drugs reported to inhibit CYP2D6 (two fluoxetine, one trazodone, and one thioridizone; refs. 21, 27) concomitant with tamoxifen treatment.

Nodal status was predictive of recurrence (P = 0.026) but not overall survival (P = 0.3). However, ER tumor positivity, BRCA1 versus BRCA2 mutation, grade of tumor, type of surgery, chemotherapy and/or radiotherapy, and tumor size were not significantly associated with recurrence or survival in our cohort, although this small data set has limited power to detect such effects.

### Table 1. Baseline familial breast cancer patient and tumor characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>BRCA1 positive (n = 47)</th>
<th>BRCA2 positive (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>42 (28-68)</td>
<td>44 (27-68)</td>
</tr>
<tr>
<td>Surgery (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastectomy</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>Breast conserving</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Tumor size (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;3 cm</td>
<td>72.3</td>
<td>79.4</td>
</tr>
<tr>
<td>&gt;3 cm</td>
<td>27.7</td>
<td>20.6</td>
</tr>
<tr>
<td>Positive lymph nodes at diagnosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>53.3</td>
<td>63.1</td>
</tr>
<tr>
<td>1-3</td>
<td>37.8</td>
<td>29.2</td>
</tr>
<tr>
<td>&gt;3</td>
<td>8.9</td>
<td>7.7</td>
</tr>
<tr>
<td>ER status (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>57.5</td>
<td>91</td>
</tr>
<tr>
<td>Negative</td>
<td>42.5</td>
<td>9</td>
</tr>
<tr>
<td>Tumor grade (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>32.6</td>
<td>41.8</td>
</tr>
<tr>
<td>3</td>
<td>67.4</td>
<td>58.2</td>
</tr>
<tr>
<td>Other treatment (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>17</td>
<td>14.8</td>
</tr>
<tr>
<td>Radiotherapy only</td>
<td>7.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Chemotherapy and radiotherapy</td>
<td>17</td>
<td>9.2</td>
</tr>
<tr>
<td>Neither</td>
<td>58.6</td>
<td>66.6</td>
</tr>
</tbody>
</table>
There were no significant differences between allele and genotype frequencies in the control and patient populations (Table 2), indicating that CYP2D6 is not associated with susceptibility to breast cancer in high-risk individuals with BRCA1 and BRCA2 mutations. Control genotype frequencies were consistent with Hardy-Weinberg equilibrium (P > 0.05).

Following previous studies (24), we separated patients into four groups: poor CYP2D6 metabolizers based on two copies of the CYP2D6*3, CYP2D6*4, or CYP2D6*5 alleles; a group with concomitant use of a potent CYP2D6 inhibitor in wild-type individuals or moderate inhibitor in heterozygous patients; individuals with two CYP2D6*41 alleles or one null allele and one CYP2D6*41 allele were designated as intermediate metabolizers; and a group of extensive metabolizers who were wild type or heterozygous for CYP2D6*3, CYP2D6*4, CYP2D6*5, or CYP2D6*41, and where there was no recorded use of a CYP2D6 inhibitor. Of the four patients taking a CYP2D6 inhibitor, two were heterozygous for CYP2D6*4 and two were wild-type homozygous.

Eight (7%) women in the familial breast cancer cohort were CYP2D6 poor metabolizers. This patient group had a trend to earlier time to tumor recurrence [P = 0.076; HR, 2.9; 95% confidence interval (95% CI), 0.9-9.4] and reduced overall survival (P = 0.079; HR, 3.5; 95% CI, 0.8-15.4; Fig. 1). In the patient group with reduced CYP2D6 activity due to concomitant use of an inhibitor, there was also earlier time to tumor recurrence (P = 0.044; HR, 3.2; 95% CI, 0.98-10.5) and a trend to reduced overall survival (P = 0.084; HR, 3.4; 95% CI, 0.77-14.9; Fig. 1). Combination of the individuals with two CYP2D6 null alleles or with presumed reduced CYP2D6 activity due to concomitant use of an inhibitor defined an overall poor metabolizer group, which showed a reduced time to tumor recurrence and reduced overall survival compared with all other individuals (Table 3), but these differences did not reach statistical significance. The median time to tumor recurrence in the overall poor metabolizer patients was 5.2 years compared with 17.3 years in the normal activity group (P = 0.14; adj HR, 2.1; 95% CI, 0.84-5.4). Overall survival was similarly reduced (P = 0.17; adj HR, 2.5; 95% CI, 0.8-8.2). Importantly, there were no significant differences in the prognostic cofounders including age at diagnosis, nodal status at presentation, chemotherapy and/or radiotherapy, tumor

Table 2. Combined CYP2D6*3, CYP2D6*4, and CYP2D6*5 genotype frequencies in BRCA1 and BRCA2 patients and healthy controls

<table>
<thead>
<tr>
<th>CYP2D6 genotype</th>
<th>BRCA1 group, n = 47</th>
<th>BRCA2 group, n = 68</th>
<th>Healthy controls, n = 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wt/wt</td>
<td>23 (49)</td>
<td>44 (65)</td>
<td>58 (64)</td>
</tr>
<tr>
<td>Wt/*3, *4, or *5</td>
<td>21 (45)</td>
<td>19 (28)</td>
<td>26 (29)</td>
</tr>
<tr>
<td>*3, *4, or *5/*3, *4, or *5</td>
<td>3 (6)</td>
<td>5 (7)</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>

NOTE: Values in table expressed as n (%).

Fig. 1. Kaplan-Meier plots of time to recurrence (A) and overall survival (B) in the entire group of familial breast cancer patients treated with tamoxifen. Earlier disease recurrence and decreased survival is shown in both patients with reduced CYP2D6 activity due to two null alleles (-----) and on concomitant CYP2D6 inhibitors (-----) compared with individuals with normal activity (- - -)

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size, type of surgery, or tumor grade between the individuals designated as CYP2D6 poor metabolizers and all others (Supplementary Table 1).

DNA was sufficient to only genotype 98 of the 115 patients for the CYP2D6*41 allele. We identified one individual homozygous for CYP2D6*41 and six individuals who were compound heterozygotes of a null allele/CYP2D6*41. These seven individuals were considered intermediate metabolizers of CYP2D6 in our analysis. However, either independently or in combination with the poor metabolizer group, the intermediate metabolizer group did not define a relationship with outcome to tamoxifen treatment. We therefore confined our further analysis to the poor metabolizer group compared with all others.

### Table 3. Breast cancer recurrence, recurrence-free survival, and overall survival in the entire cohort and stratified for BRCA1 or BRCA2 status

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>RFS</th>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall low CYP2D6 activity group adjusted for nodal status</td>
<td>2.1 (0.84-5.4)</td>
<td>1.9 (0.8-4.8)</td>
<td>2.5 (0.8-8.2)</td>
</tr>
<tr>
<td>Cox HR</td>
<td>0.14</td>
<td>0.19</td>
<td>0.17</td>
</tr>
<tr>
<td>BRCA1 group adjusted for nodal status</td>
<td>1.3 (0.3-6.2)</td>
<td>1.1 (0.2-5.5)</td>
<td>0 (NA)</td>
</tr>
<tr>
<td>Cox HR</td>
<td>0.73</td>
<td>0.90</td>
<td>0.18</td>
</tr>
<tr>
<td>BRCA2 group adjusted for nodal status</td>
<td>3.8 (1.0-14.5)</td>
<td>3.6 (0.9-13.4)</td>
<td>9.7 (2.3-41.0)</td>
</tr>
<tr>
<td>Cox HR</td>
<td>0.083</td>
<td>0.094</td>
<td>0.008</td>
</tr>
</tbody>
</table>

NOTE: The confidence intervals are not computable as there were no deaths in the BRCA1 group with low CYP2D6 activity.
Abbreviations: RFS, recurrence-free survival; NA, not applicable

Fig. 2. Kaplan-Meier plots of time to recurrence (A and B) and overall survival (C and D) in the BRCA1-related (A and C) and BRCA2-related (B and D) breast cancer patients treated with tamoxifen. Earlier disease recurrence and decreased survival are shown in both patients with reduced CYP2D6 activity either due to polymorphisms or concomitant medication (—) compared with individuals with normal activity (—).
Stratification for BRCA1 or BRCA2 status defined two distinct groups in terms of response to tamoxifen in the context of poor metabolizer CYP2D6 activity (Table 3). There was a significant effect of low CYP2D6 activity on overall survival in the BRCA2 patient group (Fig. 2) with no effect in the BRCA1 group. The median time to tumor recurrence in the BRCA2 patients with low CYP2D6 activity was 4.1 years compared with 19.3 years (P = 0.083; adj HR, 3.8; 95% CI, 1.0-14.5) in the normal activity group, and the median overall survival was 6.9 years compared with 28.1 years (P = 0.008; adj HR, 9.7; 95% CI, 2.3-41.0). A formal test of the interaction showed that this difference between BRCA1 and BRCA2 patients was significant between the two groups for survival (P = 0.022 after adjustment for nodal status). This difference remained significant if we additionally adjusted for ER status. Importantly, when we considered the entire ER-positive group, CYP2D6 status was not associated with outcome, but the positive association persisted in the ER-positive BRCA2 tumor group.

**Discussion**

Tamoxifen is the standard adjuvant hormonal treatment for premenopausal women with ER-positive breast cancer (28). Tamoxifen is also a valuable treatment option in postmenopausal women with early breast cancer, either alone or followed by a third-generation aromatase inhibitor (14, 15, 29). Tamoxifen chemopreventative trials have been undertaken for women at high risk of breast cancer due to family history (30, 31). Importantly, tamoxifen has been shown to reduce the risk of contralateral breast cancer in women with BRCA1 and BRCA2 mutations and therefore is the current treatment of choice in this patient group (16). Although BRCA1-related tumors are often ER negative, some studies suggest that tamoxifen may also show reduced recurrence in ER-negative tumors and, therefore, it is occasionally used in this context (16, 17, 32).

Our study shows a significant influence of low CYP2D6 activity on outcome with tamoxifen treatment in women with familial breast cancer. The decreased overall survival was confined to women receiving adjuvant treatment for BRCA2-related breast cancer.

The results are consistent with previous studies showing the relevance of CYP2D6 null alleles or reduced activity due to medications that inhibit CYP2D6 activity on reducing the efficacy of tamoxifen treatment in the adjuvant setting in postmenopausal breast cancer (21–24, 33). However, this is the first time that CYP2D6 activity and tamoxifen response have been considered in a patient group with familial breast cancer. This is particularly pertinent due to the early age of disease onset and premenopausal or perimenopausal status of a large number of the patients considered here. In familial breast cancer, there exists the potential for multiple relatives to be affected, and therefore the risk of inherited susceptibility to low CYP2D6 activity is especially relevant.

It is not clear why there is a difference in outcome to tamoxifen between patients with BRCA1- and BRCA2-related tumors. The study is small and may reflect the smaller number of patients with BRCA1 tumors and the fact that only 56% of these were ER positive. BRCA1-related tumors are less likely to be ER positive (13), and in our study, we confirm that a higher proportion of BRCA2-positive individuals had ER-positive tumors, although a greater number of both BRCA1- and BRCA2-related tumors were ER positive compared with a recent survey (34). This disparity may be reflected by differences in detection methods for ER status, which have evolved over the past two decades. However, despite these caveats, the outcome is not strongly dependent on ER status, and the difference between BRCA1 and BRCA2 patients persisted when we adjusted for ER status or considered ER-positive individuals alone.

Analysis in our cohort considering only the CYP2D6*4 allele, as undertaken by Goetz et al. (24) in their study of postmenopausal breast cancer patients, provided a much stronger relationship between recurrence and overall survival, especially in the BRCA2 group. This emphasizes the importance of considering all major CYP2D6 null alleles (35) in future prospective studies of tamoxifen pharmacogenetics. We also considered the effect of the intermediate metabolizer CYP2D6 activity both alone and in combination with poor metabolizer cases. No relationship between intermediate metabolizer status and outcome was determined, which contrasts with the study of Schroth et al. (33), but may be attributable to the small numbers in our study and needs further examination in larger patient cohorts. In addition, other genes important in tamoxifen metabolism including CYP3A4, CYP3A5, CYP2C19, and sulfotransferase 1A1 (SULT1A1) should be considered in these future studies (36). Importantly, there were no differences in CYP2D6 allele frequencies between healthy female controls and breast cancer patients, consistent with a review of multiple previous studies stating that altered CYP2D6 activity is not associated with a risk of breast cancer per se (37).

Nonfunctional CYP2D6 allels are much less common in non-Caucasian populations (38), and therefore direct extrapolation of these findings to Asian and African breast cancer patients is inappropriate. However, a recent report in a Chinese breast cancer population showed a relationship between CYP2D6*10 variants and worse outcome following tamoxifen (39).

Nonadherence with tamoxifen treatment is a major consideration and has been reported in up to one half of patients by 4 years of treatment (40). As this was a retrospective analysis, we were unable to accurately determine the level of adherence, but this must be rigorously assessed in prospective studies to establish the true utility of CYP2D6 pharmacogenetic testing.

Clearly, multiple factors are associated with outcome in patients with familial breast cancer. In our patient group, CYP2D6 activity nodal status is a strong predictor as well. However, consistent with a recent study of patients with BRCA1- and BRCA2-related breast cancer, we did not see an association between tumor size and outcome (34).

Recent studies have focused on comparisons of tamoxifen with aromatase inhibitors as adjuvant treatment for breast cancer in postmenopausal women (41–43). These suggest an absolute reduction in recurrence and increase in overall survival with aromatase inhibitors compared with tamoxifen (41–43). Importantly, aromatase inhibitors do not sufficiently inhibit ovarian estrogen synthesis to be a viable monotherapy in premenopausal women, and a high proportion of women with familial tumors will be premenopausal at presentation. Therefore, the use of luteinizing hormone-releasing hormone analogues, including goserelin, has been considered either alone or in combination with aromatase inhibitors in this patient group (44, 45), and major international studies are...
under way to test this hypothesis (46). The results of our study suggest that in patients with BRCA2 mutations and low CYP2D6 activity, who are postmenopausal, an aromatase inhibitor would be the drug of choice. In premenopausal or perimenopausal women, further studies are required to establish the optimum treatment. Furthermore, drugs that strongly inhibit CYP2D6 should be avoided whenever possible in patients with familial cancer receiving tamoxifen.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References
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