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Influence of CYP3A4 inhibition on the tamoxifen metabolic pathway and the implications for breast cancer recurrence in a pre-menopausal cohort

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Influence of CYP3A4 inhibition on the tamoxifen metabolic pathway and the implications for breast cancer recurrence in a pre-menopausal cohort

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Abstract

Influence of CYP3A4 inhibition on the tamoxifen metabolic pathway and the implications for breast cancer recurrence in a pre-menopausal cohort

By Casey West

Background: Tamoxifen has been the guideline, most effective treatment for pre-menopausal breast cancer patients with non-metastatic estrogen receptor positive (ER+) tumors because it reduces the risk for breast cancer recurrence by almost fifty percent. Phase 1 metabolic enzymes, like CYP3A4, play a key role in metabolizing tamoxifen because the metabolites can compete with estrogen more effectively than the parent compound, and at lower concentrations. CYP3A4 expression can be decreased in patients due to a gene variant or by taking inhibiting drugs. Little is known about CYP3A4 and how its decreased expression may impact pre-menopausal patients who are taking tamoxifen and may be taking CYP3A4 inhibiting drugs.

Methods: This study used a cohort of strictly pre-menopausal Danish breast cancer patients, diagnosed between 2002 and 2011, split into ER+/TAM+ and ER-/TAM- groups who had genotyped tumor samples.

Results: The hazard ratios estimated for having one or no functional alleles for CYP3A4 and for taking a CYP3A4 inhibiting drug did not show a strong association for either group, which is in concordance with previous observations. When the gene variant and drug data were combined, a hazard ratio of 2.63 (95% CI 1.33, 5.20) was obtained in the ER+/TAM+ group for having the CYP3A4 variant and ever taking an inhibiting drug through modelling and was cross checked using the common referent approach. This interaction was not seen in the ER-/TAM- group (HR=1.45; 95% CI 0.49,4.26) through modelling, but interaction on the additive scale was suggestive for both strata when using the common referent approach.

Conclusion: Overall, these results agree with the recommendation against genotype-guided prescribing of tamoxifen and while the interaction hazard ratio is large, the minor allele frequency for the CYP3A4 variant is 8% in European ancestry populations so it is unlikely many patients would have the variant allele and take an inhibiting drug.

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Introduction

Personalized treatment using genetic data is an important growing field in combatting the differences in treatment efficacy among individual patients. This genetic data is even more important for cancer patients whose disease is caused by genetic mutation and whose treatment may be hindered the most by those same mutations or mutations that are not related to their cancer. Breast cancer has the highest incidence and mortality rate in women worldwide and is most common among women in Europe, the US, and Australia (1,2). With more than 3.8 million being treated for breast cancer or having completed treatment in the US alone, and even more across the globe, there is an increased need to not only treat the initial breast cancer, but also to prevent any recurrences (3). Around thirty percent of patients who were cleared of disease after the initial treatment have recurrence at a later follow-up time (4).

Tamoxifen has been the most effective treatment option for patients with nonmetastatic ER-positive (ER+) breast cancer, decreasing the risk of recurrence by fifty percent, as well as an effective treatment option for patients with metastatic ER+ breast cancer (5). Patients with estrogen receptor negative (ER-) tumors are not prescribed tamoxifen, at least according to treatment guidelines. Due to tamoxifen's high efficacy, it is the guideline treatment to prevent breast cancer recurrence in pre-menopausal women, but not for post-menopausal patients, which makes treatment optimization data from only pre-menopausal cohorts particularly important. Certain gene mutations, and drug interactions with these genes, can decrease Tamoxifen's efficacy or make the women not respond at all. The Tamoxifen metabolic pathway has been studied in detail to determine which genes and molecules are important biomarkers in determining Tamoxifen's efficacy. Some biomarkers, like CYP2D6, have been studied extensively; however, another metabolic biomarker involved in this pathway that has not been studied as much is CYP3A4, which metabolizes Tamoxifen to N-desmethyl tamoxifen and 4-hydroxytamoxifen and also converts 4-hydroxytamoxifen to 4-hydroxy-*N*-desmethyltamoxifen

(endoxifen) (6). CYP3A4's efficacy in metabolizing Tamoxifen can be decreased or blocked by certain drugs like anti-retroviral, antibiotics, anti-fungal, antidepressants, anti-nausea, antihypertensives, and antacids/antihistamines (7).

Previous studies have found a possible link between variants in the CYP3A4 gene and CYP2D6, CYP1A1, and CYP2C9 in women from the US, Europe, or Australia, but no significant findings were found in other populations (6,8). There is an overall lack of data on CYP3A4 variants by themselves and their effect on tamoxifen efficacy and subsequent breast cancer relapse or mortality, especially in pre-menopausal women. Due to the relatively high frequency (≥5%) of the rs10273424 variant used for this study among European populations, the Predictors of Breast Cancer Recurrence (ProBe CaRe) cohort obtained from the Danish Breast Cancer Cooperative Group (DBCG) will give the greatest sample size of any study of the variant mutation (9). Based on CYP3A4's involvement in the tamoxifen metabolism pathway it is important to know whether having one variant allele or two variant alleles, as well as the variant's interaction with certain drugs, has an effect on a premenopausal patient's hazard of breast cancer recurrence within 5-years of initial treatment compared to premenopausal patients who did not have a CYP3A4 variant mutation, take an inhibiting drug, or take tamoxifen.

Methods

Population

The ProBe CaRe cohort consisted of 5959 Danish premenopausal patients with stage I–III primary breast cancer followed from diagnosis to recurrence, loss to follow-up, death, diagnosis with another primary cancer, ten years, or September 25, 2017. The cohort was split into two groups based on estrogen receptor alpha (ERα) and tamoxifen (TAM) treatment status, either ERα+/TAM+ (n=4600) or ERα-/TAM- (n=1359). Patients who did not meet these criteria, or who received neoadjuvant chemotherapy or endocrine therapy, were excluded from the study. Genetic markers for Phase 1 metabolism were recorded for each stratum and ERα-/TAM- women were used as a negative control because the genetic markers should show null results when they do not interact with tamoxifen (10).

Data Sources

Patient information was collected from the Danish Breast Cancer Group (DBCG) clinical registry for women diagnosed between 2002 and 2011. The Danish National Pathology Registry and Data Bank was used to identify and collect formalin-fixed, paraffin-embedded (FFPE) primary tumor tissue blocks from the treatment hospitals (10).

Data Collection

The information gathered from the DBCG for each patient was for demographics (age and menopausal status), tumor characteristics (UICC stage, histological grade, and ER expression), and therapy characteristics (primary tumor surgical management, receipt of radiation therapy, receipt of adjuvant chemotherapy, receipt and completion of tamoxifen therapy). The Danish Civil Personal Registration (CPR) number was used to link this information with the

patient's tumor samples from the Danish National Pathology Registry and Data Bank (11). Personnel responsible for data and sample collection were blinded to any clinical information.

Genotyping (12)

The FFPE primary tumor tissue samples collected from the Danish National Pathology Registry and Data Bank had sections cut from each sample and DNA was extracted using the Omega Mag-Bind® FFPE DNA 96 Kit (M6958-01) with RNAse treatment and heat deparaffinization on the ThermoFisher KingFisher Flex with the Omega KF script (Omega_M6958_WaterDip_100uLElution_KF). There was almost perfect concordance between tumor sample genotypes and the genotypes of paired surrounding non-neoplastic tissue based on earlier comparison (13). Tamoxifen pharmacogenetic and pharmacokinetic literature review identified 126 genetic variants within 17 genes involved in tamoxifen metabolism or transport and after excluding variants with minor allele frequencies <5% in European ancestry populations left 32 variants within 15 genes. For this study only the CYP3A4 variant rs10273424 was analyzed.

Allelic discrimination using the TaqMan dry down method was conducted under manufacturer recommendations. ThermoFisher SDS v2.4 software was used to collect post-read fluorescent data and TaqMan Genotyper v1.3 software was used to make initial genotyping calls (auto-calls). Agreement from five investigators was needed to define genotype custom-calls by manual adjustment of genotype regions or point-by-point reclassification on TaqMan allelic discrimination plots. Observed genotypes from the same gene family along with patient and tumor characteristics were used to input missing genotype values. A single dataset was used for analysis which combed 50 data sets that were created using the 'MICE' package for R (14). Finally, the genotypes for each variant, for each calling protocol, were tested to ensure they were in Hardy-Weinberg Equilibrium (15).

Definitions of variables

Patients had either two, one, or no functional alleles for the CYP3A4 variant. To keep the power high for analysis, patients with one or no functional alleles were grouped together and compared to wildtype. Breast cancer recurrence was classified as any type of breast cancer or further metastases found after the initial therapy by the DBCG (13). The use of any CYP3A4 inhibiting drugs was classified as ever (within one year before or after diagnosis) and never. Five covariates were included: age at diagnosis, UICC tumor stage, surgery type (mastectomy vs. breast conserving), receipt of radiation therapy, and receipt of adjuvant chemotherapy.

Statistical Analysis (16)

Patients were grouped into ER+/TAM+ or ER-/TAM- strata and those strata were analyzed. Patient demographics for covariates, CYP3A4 genotype and the proportion taking CYP3A4 inhibiting drugs were calculated. Hazard ratios and 95% confidence intervals were calculated for genotype and breast cancer recurrence, inhibiting drug use and recurrence, and the combination of genotype and drug use on recurrence using Cox proportional hazard regression models. The CYP3A4 genotype was modelled as a factor variable for the initial hazard ratio and was modelled using dummy variables for the interaction model with drug inhibition. Drug inhibition was modelled as a dichotomous variable for both models. Both models used genetic data obtained from the auto-call and custom-call data and the homozygous wildtype genotype was used as the reference.

Cox proportional hazards modeling was done using SAS v.9.4 (SAS Institute, Cary, NC, USA). Permissions were obtained from the Institutional Review Board of Emory University, the ethics committee from Aarhus University and other review committees at participating institutions. Informed consent was not required per Danish laws on registry data use.

Results

The total cohort included 4600 ER+/TAM+ patients and 1359 ER-/TAM- patients and out of those patients, 3,480 and 874 had available data for their CYP3A4 genotype, respectively (Table 1). The ER+/TAM+ strata had 3,837 patients who had data on if they had taken a CYP3A4 inhibiting drug within the year before starting tamoxifen, while the ER-/TAM- strata had 989 patients. Out of the total cohort, there were 612 breast cancer recurrences within the follow-up time. Almost all the cofactors had similar proportions of patients between ER+/TAM+ and ER-/TAM-. The ER-/TAM- strata had a higher proportion of patients ever take a CYP3A4 inhibiting drug (27.2% vs. 9.7%), but the overall number of patients was about the same as ER+/TAM+ (372 vs. 269). CYP3A4 had a minor allele frequency of 8% and was found to be in Hardy-Weinberg equilibrium.

Table 2 shows the crude and adjusted hazard ratios obtained from the Cox proportional hazards model analyzing the effects from having one/no functional CYP3A4 alleles, having ever taken a CYP3A4 inhibiting drug, and a having one/no functional alleles in the ER+/TAM+ and ER-/TAM- strata using the wildtype and never taking drug patients as the references. The genotype by itself trended around the null while the inhibiting drug effect trended slightly below the null. When the genotype and drug data were combined to analyze interaction an HR of 0.88 (0.64, 1.20), 2.63 (1.33, 5.20), 0.92 (0.52, 1.61), and 1.45 (0.49, 4.26) were estimated for the ER+/TAM+ CYP3A4 variant/no drug and CYP3A4 variant/drug and ER-/TAM- CYP3A4 variant/no drug and CYP3A4 variant/drug strata, respectively.

Interaction was then analyzed using the common referent approach shown in Table 3. The expected values under no interaction for the patients with the CYP3A4 variant, who took an inhibiting drug, compared to wildtype patients, who did not take an inhibiting drug, in the ER+/TAM+ and ER-/TAM- strata were 0.56 and 0.26, respectively. The observed values for the

CYP3A4 variant and ever inhibiting drug groups were 1.46 (0.82,2.61) and 1.20 (0.30,4.89) for the ER+/TAM+ and ER-/TAM- strata, respectively. These values suggest there may be interaction on the additive scale in both strata. The HR was then estimated within the CYP3A4 variant strata to examine the effects of the inhibiting drug compared to no drug with a 63% and 32% increase being seen in the ER+/TAM+ and ER-/TAM- strata.

Discussion

Overall, the results for CYP3A4 inhibition by genotype or drug use showed trends on different sides of the null, although all results were near null and these patterns most likely reflected chance deviations from the null. This is in concordance with previous studies examining the effects of CYP3A4 genotype variants on the tamoxifen metabolic pathway and subsequent breast cancer recurrence (7,8,12). The modelled hazard ratio for the combination of CYP3A4 variant data and drug inhibition data gave a hazard ratio estimate of 2.63 (95% CI 1.33, 5.20) within the ER+/TAM+ strata and this significance or magnitude was not seen in the ER-/TAM- strata (HR=1.45; 95% CI 0.49, 4.26). Further evaluation of the interaction between gene variant and drug inhibition using the common referent approach yielded suggestive results for interaction on the additive scale for both ER+/TAM+ and ER-/TAM- strata. When the effect of taking the inhibiting drug was analyzed within the CYP3A4 variant groups with the no drug/variant being the reference, an increase in hazard for breast cancer recurrence was seen in both ER/TAM strata again.

While the common referent approach and the stratum specific estimates both showed suggestive interaction for both ER/TAM strata, the ER+/TAM+ strata showed greater interaction compared to the ER-/TAM-. This may suggest that while the CYP3A4 variant and drug inhibition on their own do not have an important effect on the tamoxifen metabolic pathway, when they are combined an important increase in hazard for breast cancer recurrence is seen. The suggestive additive interaction for the ER-/TAM- may be explained by CYP3A4 being a common phase 1 metabolic enzyme involved in many drug pathways and could interact with an oral drug therapy the ER- patients were taking. It would be beneficial to examine the overlap in common drug therapy pathways for ER- patients and the tamoxifen pathway for future study using an ER-/TAM- group as a negative control.

Strengths and Limitations

The main strength of this cohort was the availability of a large patient population that had data collected in a registry (DBCG and the Danish National Pathology Registry and Data Bank) that included FFPE tumor samples with DNA extracted, extensive patient demographics, a long follow-up time, and inhibiting drug usage data. It was also the first large cohort of strictly pre-menopausal patients, which is the breast cancer subgroup for which tamoxifen remains guideline adjuvant endocrine therapy. A concern with using DNA collected from neoplastic tissue is the misclassification of genotype that could occur from tumor growth, but this concern is mitigated with the evidence that paired non-neoplastic tissue often has the same genotype as the neoplastic tissue due to mixing in the tumor area (13, 17-22). This study looked at two different exposures, and their interaction, that could lead to inhibition of CYP3A4 and subsequently tamoxifen metabolic inhibition which adds to the sparse data on CYP3A4 inhibition and possible drug interactions.

A limitation of this study was the classification of CYP3A4 inhibiting drug usage. While it was still accurate as a dichotomous never/ever variable, it would have been more accurate to have a timeline of use before and during tamoxifen treatment in case there is increased inhibition of CYP3A4 when the inhibiting drug is taken at the same time as tamoxifen compared to taking it anytime in the year before tamoxifen treatment. A study to address this limitation would have to be conducted prospectively and have the drug data tracked, which is not protocol in many of the extensive cancer registries around the world. This may not be cost effective when the registries already provide a large patient pool and patient data. Another limitation is the use of a population of just European descent because the allele frequencies may be greater in other populations and may give differing results.

Public Health Implications

While the data from this study gave mostly near-null results, there was some importance for the interaction of CYP3A4 variant and drug inhibition on breast cancer recurrence. This data adds to the findings of other studies on gene-drug interaction and may suggest directions of future research on phase 1 metabolism genes and their interaction with drug therapies, but the clinical utility is at present not significant. Current recommendations are to not genotype breast cancer patients for drug metabolic pathway genes and this study does not go against that recommendation. CYP3A4 has a minor allele frequency in populations of European descent of 8% and the number of those who develop breast cancer, are treated with tamoxifen, and take a CYP3A4 inhibiting drug are scarce. Further research is still necessary for gene-drug interaction on a multitude of diseases because the clinical utility for personalized medication regiments has been suggested and may be the key to optimized care for individuals.

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Tables

Table 1. ER/TAM strata descriptive frequencies and proportions for CYP3A4 variant, inhibiting drug prescription, recurrence, and cofactors

	ER+/TAM+, n (%)	ER-/TAM-, n (%)
Total	4600 (100)	1359 (100)
CYP3A4 Genotype		
Two Functional Alleles	2903 (80)	739 (79)
One/No Functional Alleles	577 (15.5)	135 (14.4)
Missing	150 (4.1)	61 (6.5)
CYP3A4 Inhibiting Drug Prescription		
Ever	372 (9.7)	269 (27.2)
Never	3465 (90.3)	720 (72.8)
Recurrence		
Yes	396 (8.6)	216 (16)
No	4204 (91)	1143 (84)
Age at Diagnosis, y		
<35	222 (4.8)	182 (23)
35-39	487 (11)	229 (27)
40-44	1123 (24)	321 (24)
45-49	1668 (36)	385 (28)
50+	1100 (24)	242 (18)
UICC Tumor Stage at Diagnosis		
I	1184 (26)	402 (29.6)
II	2476 (54)	702 (51.7)
III	917 (20)	246 (18.1)
Unknown Stage	23 (0.5)	9 (0.7)
Surgery Type		
Breast-conserving Surgery	2567 (56)	732 (54)
Mastectomy	2033 (44)	627 (46)
Radiation Therapy		
Yes	3945 (86)	1092 (80)
No	655 (14)	267 (20)
Chemotherapy		
Yes	4163 (91)	1250 (92)
No	437 (9)	109 (8)

Table 2. Associated hazard between CYP3A4 inhibition and breast cancer recurrence within ER/TAM strata

	ER+/TAM+		ER-/TAM-	
CYP3A4 Genotype	Crude HR (95% CI)	Adjusted HR (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Two Functional Alleles	1 (reference)	1 (reference)	1 (reference)	1 (reference)
One/No Functional Alleles	1.05 (0.79, 1.39)	1.03 (0.78, 1.36)	1.17 (0.71, 1.92)	1.02 (0.62, 1.69)
CYP3A4 Inhibiting Drug Prescription				
Never	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Ever	0.94 (0.66, 1.32)	0.81 (0.53, 1.25)	0.81 (0.53, 1.23)	0.58 (0.31, 1.13)

Table 3. Common referent approach to analyze interaction between CYP3A4 mutation and drug inhibition compared to wildtype and no drug and within CYP3A4 variant strata

	ER+/TAM+		ER-/TAM-	
CYP3A4 Genotype	Never Drug	Ever Drug	Never Drug	Ever Drug
Two Alleles	1 (reference)	0.66 (0.43, 1.02)	1 (reference)	0.35 (0.14, 0.86)
One/No Allele	0.90 (0.66, 1.22)	**1.46 (0.82, 2.61)**	0.91 (0.54, 1.54)	**1.20 (0.30, 4.89)**
Stratum Specific Estimates				
Two Alleles	1 (reference)	0.66 (0.43, 1.02)	1 (reference)	0.35 (0.14, 0.86)
One/No Allele	1 (reference)	**1.63 (0.86, 3.07)**	1 (reference)	**1.32 (0.30, 5.76)**