Null Results in Brief

No Increase in Breast Cancer Recurrence with Concurrent Use of Tamoxifen and Some *CYP2D6*-Inhibiting Medications

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Abstract

Tamoxifen reduces recurrence risk among women treated for estrogen receptor–positive breast cancer. Its effectiveness partly depends on metabolic activation via cytochrome P450 2D6 (*CYP2D6*). Some medications compromise *CYP2D6* activity and may lower plasma concentrations of active tamoxifen metabolites. We studied the association between concurrent use of tamoxifen and *CYP2D6*-inhibiting medications and breast cancer recurrence among Danish women diagnosed with early-stage, estrogen receptor–positive breast cancer. Using the Danish Breast Cancer Cooperative Group Registry, we identified 366 cases with local or distant breast cancer recurrence and 366 matched breast cancer controls. We ascertained concurrent prescription of *CYP2D6*-inhibiting medications during tamoxifen treatment by linking to the national prescription database covering all Danish pharmacies. We computed the breast cancer recurrence odds ratio (OR) and 95% confidence interval for each medication. The pooled recurrence OR was null (OR, 1.0; 95% confidence interval, 0.8-1.3); recurrence ORs for individual drugs ranged from 0.3 to 3.4. The individual ORs followed the pattern expected under a null-centered Gaussian distribution. Null associations were apparent for all drugs after empirical Bayes adjustment for multiple comparisons. Together, these results provide evidence for a null association between drug-compromised *CYP2D6* activity and breast cancer recurrence among tamoxifen-treated women. (Cancer Epidemiol Biomarkers Prev 2009;18(9):2562–4)

Introduction

Tamoxifen approximately halves the 5-year recurrence risk among women treated for estrogen receptor–positive breast cancer (1). Cytochrome P450 enzymes metabolize tamoxifen to 4-hydroxytamoxifen and 4-hydroxy-*N*-desmethyltamoxifen, which exert the main pharmacologic effect (2-4). The gene encoding the cytochrome P450 enzyme chiefly responsible for 4-hydroxylation of tamoxifen, *CYP2D6*, is polymorphic and variant genotypes confer varying degrees of enzymatic impairment (5). Other medications inhibit, or are competing substrates for, *CYP2D6* activity (6, 7).[3] Tamoxifen-treated patients who also take potent *CYP2D6*-inhibiting drugs have low plasma concentrations of 4-hydroxy-*N*-desmethyltamoxifen, equivalent to concentrations in women with no functional *CYP2D6* allele (4, 8, 9). Current epidemiologic evidence is inconclusive regarding the effect of compromised *CYP2D6* function on the effectiveness of tamoxifen in preventing breast cancer recurrence (10). Here, we examine whether the use of *CYP2D6*-inhibiting medications was associated with higher breast cancer recurrence rates among tamoxifen-treated Danish women diagnosed with estrogen receptor–positive breast cancer.

Materials and Methods

This study was approved by the Boston University Medical Campus Institutional Review Board, the Regional Committee on Biomedical Research Ethics of Aarhus County, and by the Danish Registry Board.

Study Population. A description of study enrollment criteria and data collection procedures appear in an earlier publication (11). To summarize, we used the Danish Breast Cancer Cooperative Group Registry to identify women diagnosed with International Union Against Cancer stage I, II, or III breast cancer between 1994 and 2001 (12). Women were followed from 1 y after their diagnosis date until breast cancer recurrence, death from any cause, loss to follow-up, or September 1, 2006, whichever occurred first. We used the Danish Breast Cancer Cooperative Group Registry to identify cases of local or distant breast cancer recurrence among women with estrogen receptor–positive tumors who were treated with tamoxifen (n = 366). We selected one breast cancer control from each

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[3] http://www.medicine.iupui.edu/clinpharm/ddis/table.asp

Table 1. Observed associations between concurrent use of tamoxifen and *CYP2D6*-inhibiting medications and recurrence among Danish women diagnosed with estrogen receptor–positive breast cancer

	Exposed cases/ controls	Recurrence, OR* (95% CI)
CYP2D6-inhibiting medications (ever vs. never exposed)		
Celecoxib	8/15	0.3 (0.1-1.0)
Levomepromazine	2/4	0.5 (0.1-2.8)
Fluoxetine	5/7	0.6 (0.2-2.2)
Sertraline	13/15	0.7 (0.3-1.7)
Mirtazapine	14/16	0.8 (0.3-1.8)
Amitriptyline	6/8	0.8 (0.3-2.5)
Citalopram	33/33	0.9 (0.5-1.6)
Escitalopram	5/4	1.1 (0.3-4.7)
Metoclopramide	31/22	1.3 (0.7-2.4)
Cimetidine	16/14	1.4 (0.6-3.2)
Timolol	5/3	1.6 (0.4-6.9)
Propranolol	8/4	2.1 (0.5-8.7)
Venlafaxine	11/5	2.3 (0.7-7.2)
Paroxetine	6/4	2.4 (0.6-9.5)
Zuclopenthixol	5/2	3.4 (0.6-23)
	Total cases/ controls	Recurrence, OR† (95% CI)
Age at diagnosis (y)		
35-44	18/18	1.0 (Reference)
45-54	93/85	1.0 (0.5-2.2)
55-64	191/178	1.0 (0.4-2.3)
65-70	64/85	0.7 (0.3-1.7)
Tamoxifen protocol		
1 y	76/59	1.0 (Reference)
2 y	50/62	0.4 (0.2-0.9)
5 y	240/245	0.4 (0.1-1.2)

*Conditioned on matching factors and adjusted mutually for listed medications.
†Conditioned on matching factors.

recurrent case's risk set (13), matched on estrogen receptor expression, tamoxifen treatment status, county of residence, year of breast cancer surgery, menopausal status at diagnosis, and International Union Against Cancer stage at diagnosis. We defined the index date for each matched pair as the date of the case's breast cancer recurrence. Women received tamoxifen treatment for durations of 1, 2, or 5 y, depending on the prevailing Danish treatment protocol at the time of diagnosis (14).

Prescription Data Collection. We used the unique civil registration numbers of our breast cancer cases and controls to link the study roster to the national prescription database, which records drugs dispensed at all Danish pharmacies according to the Anatomical Therapeutic Chemical system.[4] We used Anatomical Therapeutic Chemical codes to ascertain prescriptions for medications known to be substrates for, or inhibitors of, *CYP2D6* activity[5] (a full list of searched drugs and Anatomical Therapeutic Chemical codes is available from the corresponding author). For each drug evaluated, cases and controls were classified as "ever exposed" to the drug if it was prescribed during their tamoxifen treatment; otherwise, they were classified as "never exposed."

Statistical Analysis. We tabulated the frequency of cases and controls according to use of *CYP2D6*-inhibiting medications, age group at diagnosis, and duration of tamoxifen use. We estimated breast cancer recurrence odds ratios (OR) and 95% confidence intervals (95% CI) associated with use of each of the concurrently prescribed medications using conditional logistic regression models, which addressed the matched factors and adjusted for confounders that changed the log OR estimates by >10% (15). We ranked the observed associations by magnitude and plotted the ORs against the inverse normal of rank percentile (16). On this plot, we overlaid predicted ORs from the inverse variance-weighted regression of observed log-odds values on the inverse normal of rank percentile. Finally, we subjected the vector of observed ORs to empirical Bayes adjustment for multiple comparisons (17, 18). Empirical Bayes adjustment shrinks individual associations toward the mean of a larger population of associations, in proportion to the ratios of the individual variances to the population variance. The method thus de-emphasizes imprecisely measured associations of otherwise striking magnitude, helping to avoid unproductive follow-up on what are likely to be false-positive findings.

Results

Of the candidate *CYP2D6*-inhibiting drugs we considered, 15 were prescribed to study subjects while they were taking tamoxifen. There were 120 cases and 103 controls who were exposed to at least one of the *CYP2D6*-inhibiting drugs while taking tamoxifen. Table 1 lists the conditional recurrence ORs for the 15 drugs. Recurrence ORs ranged from 0.3 (for celecoxib; 95% CI, 0.1-1.0) to 3.4 (for zuclopenthixol; 95% CI, 0.6-23). The recurrence OR pooled across all drugs was 1.0 (95% CI, 0.8-1.3). Figure 1 shows the plot of ORs against the inverse normal of rank percentile. The ascending diagonal line depicts the pattern under this plotting scheme that one would expect to observe if the vector of associations were drawn from an underlying null-centered Gaussian distribution (16). The observed drug associations fell almost perfectly along this line. Following empirical Bayes adjustment, no individual drug association differed appreciably from the pooled recurrence OR.

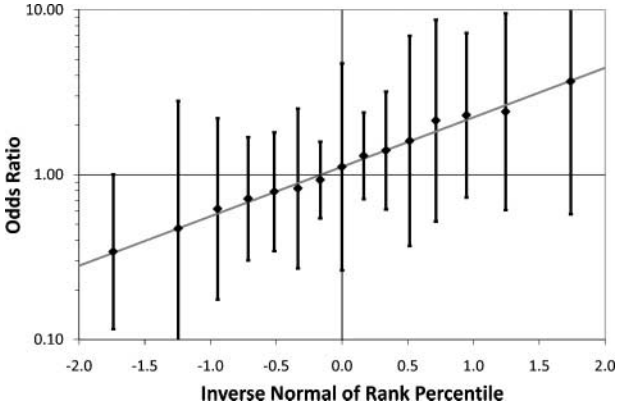

Figure 1. Distribution of ORs estimating the association between breast cancer recurrence and concurrent use of tamoxifen and *CYP2D6*-inhibiting medications, plotted against the inverse normal of each estimate's rank percentile. Medications are presented in the same order (*left to right*) as in Table 1.

[4] http://www.whocc.no/atcddd/
[5] http://www.medicine.iupui.edu/clinpharm/ddis/table.asp

Discussion

Our results do not support the hypothesis that the studied *CYP2D6*-inhibiting medications diminish the effectiveness of tamoxifen at reducing breast cancer recurrence among women treated for estrogen receptor–positive breast cancer. This study had 85% power to detect a statistically significant ($\alpha = 0.05$) 1.6-fold increase in the breast cancer recurrence rate among tamoxifen-treated women exposed to at least one of the drugs we examined. Furthermore, we had 99% power to detect a 1.9-fold increase in recurrence rate, which is the effect size observed in a recent report of concurrent use of tamoxifen and SSRI antidepressants (19). Because our study drew from the entire Danish breast cancer patient population during the study period, with complete follow-up, the study was not susceptible to selection bias. The prospectively collected Danish registry data reduced the risk of differential measurement error.

Nevertheless, the study has some limitations. First, we could not directly observe prescription compliance for both tamoxifen and *CYP2D6* inhibitors. Because prescriptions are only recorded in the registry after a medication has been paid for and dispensed, we expect prescription compliance to be high. An earlier validation study of hormone replacement therapy exposure classification by Danish prescription registries supports this expectation (20). Second, the duration of tamoxifen treatment differed within our study population according to prevailing treatment protocols during the study period (14). Because the protective effect of tamoxifen on recurrence manifests after the first year of treatment (1), we would expect ample opportunity for a modifier of its effectiveness to exert an effect, even among the small proportion of those in our study with the shortest assigned tamoxifen treatment regimen.

Disclosure of Potential Conflicts of Interest

The Department of Clinical Epidemiology at Aarhus University is involved in studies with funding from various companies as research grants to, and administered by, Aarhus University. These include a grant from the Lundbeck Foundation to study meningococcal disease and collaborations with the Centre for Registry Research, which receives grants from H. Lundbeck A/S (the manufacturer of citalopram and escitalopram). None of these studies have direct relation to the present study or supported any of the work reported herein.

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