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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 (DBCG) 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 (95% CI) for each medication. The pooled recurrence odds ratio was null (OR: 1.0; 95% CI: 0.8, 1.3); recurrence odds ratios for individual drugs ranged from 0.3 to 3.4. The individual odds ratios 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.

Keywords

Epidemiology; breast neoplasms; tamoxifen; pharmacology and therapeutic use; tamoxifen; antagonists and inhibitors; cytochrome P-450 2D6

INTRODUCTION

Tamoxifen approximately halves the five-year recurrence risk among women treated for estrogen receptor-positive breast cancer (1). Cytochrome P450 (CYP) enzymes metabolize tamoxifen to 4-hydroxytamoxifen (4HT) and 4-hydroxy-N-desmethyltamoxifen (4HNDT), which exert the main pharmacologic effect (2–4). The gene encoding the CYP 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 (6–8). Tamoxifen-treated patients who also take

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potent *CYP2D6*-inhibiting drugs have low plasma concentrations of 4HNDT, equivalent to concentrations in women with no functional *CYP2D6* allele (4,9,10). Current epidemiologic evidence is inconclusive regarding the impact of compromised *CYP2D6* function on tamoxifen's effectiveness in preventing breast cancer recurrence (11). Here we examine whether 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 (12). To summarize, we used the Danish Breast Cancer Cooperative Group (DBCG) Registry to identify women diagnosed with UICC Stage I, II or III breast cancer between 1994 and 2001 (13). Women were followed from one year after their diagnosis date until breast cancer recurrence, death from any cause, loss to follow up, or 1 September 2006, whichever occurred first. We used the DBCG 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 recurrent case's risk set (14), matched on estrogen receptor expression, tamoxifen treatment status, county of residence, year of breast cancer surgery, menopausal status at diagnosis, and UICC 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 year, 2 years or 5 years, depending on the prevailing Danish treatment protocol at the time of diagnosis (15).

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 (ATC) system (16). We used ATC codes to ascertain prescriptions for medications known to be substrates for, or inhibitors of, *CYP2D6* activity (a full list of searched drugs and ATC codes is available from the corresponding author) (8,17). 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 and 95% confidence intervals 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 odds ratio estimates by >10% (18). We ranked the observed associations by magnitude and plotted the odds ratios against the inverse normal of rank percentile (19). On this plot, we overlaid predicted odds ratios 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 odds ratios to empirical Bayes adjustment for multiple comparisons (20,21). 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 odds ratios for the 15 drugs. Recurrence odds ratios ranged from 0.3 (for celecoxib; 95% CI: 0.1, 1.0) to 3.4 (for zuclopenthixol; 95% CI: 0.6, 23). The recurrence odds ratio pooled across all drugs was 1.0 (95% CI: 0.8, 1.3). Figure 1 shows the plot of odds ratios 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 (19). The observed drug associations fell almost perfectly along this line. Following empirical Bayes adjustment, no individual drug association differed appreciably from the pooled recurrence odds ratio.

DISCUSSION

Our results do not support the hypothesis that the studied *CYP2D6*-inhibiting medications diminish tamoxifen's effectiveness at reducing breast cancer recurrence among women treated for estrogen receptor-positive breast cancer. This study had 85% power to detect a statistically significant (α=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 (22). 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 the *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 HRT exposure classification by Danish prescription registries supports this expectation (23). Second, the duration of tamoxifen treatment differed within our study population according to prevailing treatment protocols during the study period (15). Since tamoxifen's protective effect 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.

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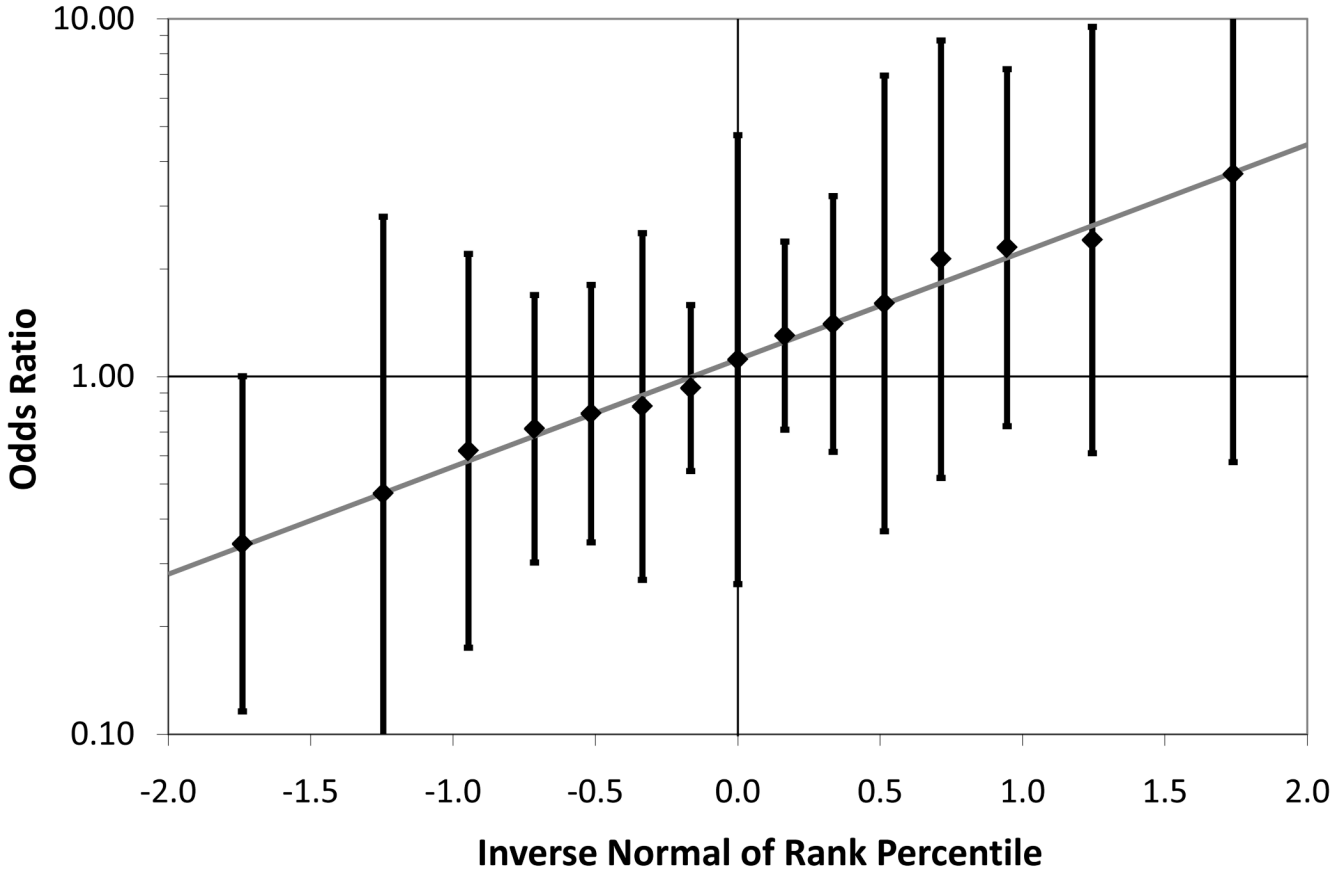

Figure 1.
Distribution of odds ratios estimating the association between breast cancer recurrence and concurrent use of tamoxifen and *CYP2D6*-inhibiting medications, plotted against the inverse normal of each estimate's rank percentile. From left to right, medications are presented in the same order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

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 Odds Ratio* (95% C.I.)	
***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 Odds Ratio† (95% C.I.)**	
Age at diagnosis:			
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 year	76/59	1.0	(Reference)
2 years	50/62	0.4	(0.2, 0.9)
5 years	240/245	0.4	(0.1, 1.2)

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

†Conditioned on matching factors.