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ORIGINAL ARTICLE

Breast cancer recurrence risk related to concurrent use of SSRI antidepressants and tamoxifen

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Abstract

Background. Up to one-quarter of breast cancer patients suffer clinically significant depression in the year after diagnosis, which may respond to intervention. About half may be prescribed a psychotropic medication, such as a selective serotonin reuptake inhibitor (SSRI), while completing breast cancer therapy. Cytochrome P-450 2D6 (*CYP2D6*) metabolizes SSRIs and also metabolizes tamoxifen to more active forms. Therefore, concurrent use of SSRIs may reduce tamoxifen's effectiveness at preventing breast cancer recurrence. The SSRI citalopram has limited potency to inhibit *CYP2D6* activity, so has been recommended for breast cancer patients taking tamoxifen. This study provides epidemiologic evidence to support this recommendation. *Material and methods*. We conducted a case-control study of breast cancer recurrence nested in the population of female residents of Denmark who were diagnosed with non-metastatic estrogen-receptor positive breast cancers between 1994 and 2001 and who took tamoxifen for at least one year. We ascertained complete prescription histories by linking cases' and controls' civil registration numbers to the Danish national prescription registry. We estimated the association between SSRI use while taking tamoxifen and risk of recurrent breast cancer. *Results.* About the same proportion of recurrent cases (37 of 366) and matched controls (35 of 366) received at least one prescription for citalopram or its s-stereoisomer while taking tamoxifen (adjusted odds ratio=1.1, 95% confidence interval=0.7, 1.7). Breast cancer patients taking other SSRIs were also at no increased risk of recurrence (adjusted odds ratio=0.9, 95% confidence interval=0.5, 1.8). *Discussion*. Breast cancer patients with indications for an SSRI may be prescribed citalopram – and possibly other SSRI – without adversely affecting the outcome of adjuvant therapy with tamoxifen.

Almost all newly diagnosed breast cancer patients experience normal distress [1]. Up to one-quarter, however, suffer clinically significant depression in the year after diagnosis, which may respond to interventions [2]. Although no study has yet examined the effectiveness of psychotherapy and psychiatric drug therapy in cancer patients [2], the prevalence of prescriptions for psychotropic drugs among patients treated for breast cancer is high. For example, about half of the patients in a breast cancer waiting-room sample had received psychotropic medication during their breast cancer treatment [3]. One class of psychotropic medications, selective serotonin reuptake inhibitors (SSRI), may reduce both depressive symptoms and menopausal symptoms [4,5].

SSRIs are metabolized by cytochrome P450 2D6 (*CYP2D6*) [6], as is the selective estrogen-receptor modulator tamoxifen [7]. Tamoxifen reduces the risk of breast cancer recurrence by about half in patients with estrogen-receptor positive tumors [8].

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Tamoxifen's two 4-hydroxylated metabolites have the highest binding affinity for the estrogen receptor, and are the most important modulators of the estrogen receptor in the tamoxifen pathway [9,10]. Because both tamoxifen and SSRIs are metabolized by *CYP2D6*, SSRI inhibition of *CYP2D6* activity could reduce tamoxifen's prevention of breast cancer recurrence. Citalopram is among the least potent SSRI inhibitors of *CYP2D6* activity [6,11], which led Henry et al. to recommend citalopram (or similar low-inhibiting venlafaxine) for treatment of breast cancer patients taking tamoxifen [12]. Aside from a preliminary report from this research group [13], no clinical epidemiologic evidence has shown that these SSRI do not interfere with tamoxifen's effect on breast cancer recurrence risk.

We previously reported that Danish breast cancer patients with estrogen-receptor positive tumors who were treated with tamoxifen had no higher rate of recurrence if they were simultaneously taking the SSRI citalopram or its s-stereoisomer than if they were not [13]. This initial study was limited to four counties with local prescription registries. We have now extended the study to eight counties and use Danish national prescription data to ascertain exposure to SSRI and to control for exposure to a wide range of medications. The current study has substantially improved precision and has allowed more complete investigation of other *CYP2D6*-inhibiting SSRI medications.

Material and methods

The study was approved by the Boston University Medical Campus Institutional Review Board and the Regional Committee on Biomedical Research Ethics of Aarhus County, Denmark. Because the data are housed in medical registries, individual informed consent was not obtained.

Study population

The source population included female residents of eight Danish counties (Funen, South Jutland, Ribe, Vejle, Ringkøbing, Aarhus, Viborg, and North Jutland) 35–69 years old at diagnosis of stage I, II or III primary breast cancer between 1994–2001 and who were reported to the Danish Breast Cancer Cooperative Group (DBCG; [14]). We divided the source population into three groups: (a) ER+/TAM+ – estrogen-receptor positive and treated with tamoxifen for at least one year without recurrence in that year, (b) ER−/TAM− – estrogen-receptor negative, not treated with tamoxifen, and survived recurrence-free at least one year, and (c) group III women – all others, including patients who recurred in the first year, ER+ patients who did not receive tamoxifen, and ER− patients who did receive tamoxifen, all of whom were excluded from this analysis. Estrogen receptor expression was assayed at diagnosing hospitals by standard DBCG protocols. Clinical assay of estrogen receptor expression in pathology laboratories has shown high concordance with centralized testing in similar settings [15]. ER+/TAM+ women were assigned to tamoxifen therapy protocols of one year, two years, or five years, depending on the guideline current in Denmark when they were diagnosed [16]. Many of the women assigned to tamoxifen protocols shorter than five years took tamoxifen for much longer (unpublished validation data). Follow-up time began one year after breast cancer diagnosis and continued until the date of the first of breast cancer recurrence, death from any cause, loss to follow-up (e.g., emigration), 10 years of follow-up, or September 1, 2006.

Cases were women with local or distant breast cancer recurrence during their follow-up time. We used the DBCG definition of breast cancer recurrence as any type of breast cancer subsequent to the initial course of therapy. Using risk-set sampling, we matched one control to each case on (a) group membership (ER+/TAM+ or ER−/TAM−), (b) menopausal status at diagnosis (premenopausal or postmenopausal), (c) date of breast cancer surgery (caliper matched +/− twelve months), (d) county of residence at time of diagnosis, and (e) stage at diagnosis (stage I, II, or III). Controls were free of breast cancer recurrence at the same duration of post-surgery follow-up as their matched case. It was not possible to match controls to cases on duration of tamoxifen therapy, but the calendar time matching induced by risk-set sampling afforded good balance between cases and controls with regard to the duration of assigned tamoxifen protocol.

Data collection

We used the Danish civil registration number (CPR) assigned to all Danish citizens and residents to link data sets. We collected demographic information (age, menopausal status, and hospital of diagnosis), tumor characteristics (UICC stage, histologic grade, and estrogen-receptor expression), and therapy characteristics (primary surgical tumor management, receipt of radiation therapy, receipt of chemotherapy, and receipt of tamoxifen therapy) from the DBCG database. We collected data on receipt of citalopram prescriptions, prescriptions for other SSRIs, and prescriptions for other potential *CYP2D6* inhibitors by linking the CPR numbers of cases and controls to the prescription database maintained by Statistics Denmark as a component of the Danish national health care system.

Analytic variables

Prescription status. Prescription medications were coded by the Anatomical Therapeutic Chemical (ATC) classification system [17]. We defined SSRIs as all those classified in ATC group N06AB. We combined prescriptions for citalopram with prescriptions for its s-enantiomer escitalopram because escitalopram inhibits *CYP2D6* activity similarly to citalopram *in vitro* [18] and both have been shown to inhibit *CYP2D6* activity *in vivo* [11,19]. We classified cases and controls as those with no record of a citalopram prescription during their follow-up time (never citalopram) and those with any record of prescription for citalopram during their follow-up time (ever citalopram). We used a similar procedure to classify cases and controls as ever or never users of another SSRI or of another prescription medication that is a *CYP2D6* inhibitor or substrate.

For ER+/TAM+ women who ever had a citalopram prescription, we calculated the percentage of time on tamoxifen during which they were simultaneously taking citalopram. We created categories of (a) intermittent citalopram use, defined as citalopram use overlapping tamoxifen use for more than 0% but less than 30% of the time on tamoxifen, and (b) regular citalopram use, defined as citalopram use overlapping tamoxifen use for 30% or more of the time on tamoxifen. For this analysis, we used the full duration of their tamoxifen use as recorded in the DGCG registry, which was often longer than the duration anticipated by their original protocol assignment.

Covariates. We defined the following set of covariates: time period of breast cancer diagnosis, age at diagnosis, menopausal status at diagnosis, county of residence at diagnosis, UICC stage at diagnosis, histologic grade, surgery type, receipt of systemic adjuvant chemotherapy, and receipt of a prescription for another medication that is a *CYP2D6* inhibitor or substrate while taking tamoxifen (aside from those used to treat breast cancer recurrence or its effects).

Analytic strategy

We performed all analyses within strata of ER+/TAM+ and ER−/TAM− women. We calculated the number of cases and controls ever receiving each SSRI, the number of total prescriptions for each SSRI summed over all cases or controls, and the range of the number of prescriptions for each SSRI received by each individual case or control. Table I gives a complete list of SSRI medications and the frequency of their use in the study population. We also classified cases and controls as ever or never users of another prescription medication that is a *CYP2D6* inhibitor or substrate. Table II gives a complete list of these medications and the frequency of their use in the study population.

We then computed the frequency and proportion of cases and controls within categories of assigned protocol of tamoxifen duration, citalopram use, use of other SSRIs, use of other *CYP2D6* inhibitors or substrates, and the covariates.

We estimated the rate ratio associating citalopram prescription with breast cancer recurrence as the

Table I. Patterns of prescriptions for each SSRI.

	ERP+/TAM+n[a], (# of prescriptions[b]), [range of # per person[c]]		ERP−/TAM− n[a], (# of prescriptions[b]), [range of # per person[c]]	
SSRI name (ATC Code)	cases	controls	cases	controls
Zimeldine (N06AB02)	0	0	0	0
Fluoxetine (N06AB03)	5 (24) [2–11]	7 (60) [1–32]	2 (12) [1–11]	4 (19) [1–9]
Citalopram (N06AB04)[d]	33 (400) [1–53]	33 (163) [1–24]	12 (119) [1–35]	14 (120) [1–43]
Paroxetine (N06AB05)	6 (23) [1–13]	4 (16) [1–11]	1 (2) [2–2]	5 (39) [5–14]
Sertraline (N06AB06)	13 (86) [1–24]	15 (85) [1–18]	6 (28) [1–11]	4 (78) [1–48]
Alaproclate (N06AB07)	0	0	0	0
Fluvoxamine (N06AB08)	0	0	0	0
Etoperidone (N06AB09)	0	0	0	0
Escitalopram (N06AB10)[d]	5 (15) [1–6]	4 (18) [1–12]	0	0

[a]Number of cases and controls receiving any prescription for each SSRI.
[b]Total number of prescriptions for each SSRI.
[c]Range of number of prescriptions per person within women expressing the estrogen receptor and receiving at least one year of tamoxifen therapy (ERP+/TAM+), or not expressing the estrogen receptor, never receiving tamoxifen therapy, and surviving at least one year after diagnosis (ERP−/TAM−).
[d]In the analysis, we defined citalopram exposure as any prescription for citalopram (N06AB04) or its s-stereoisomer escitalopram (N06AB10).

Table II. *CYP2D6* inhibitors, substrates, and inducers used to adjust the association between breast cancer recurrence and ever/never use of citalopram or other SSRI.

Drug action & ATC Name	ATC code	ERP+/TAM+ cases/controls	ERP−/TAM− cases/controls
Histamine blocker			
Cimetidine	A02BA01	9/9	3/4
Ranitidine	A02BA02	0/2	2/0
Antiemetic			
Metoclopramide	A03FA01	12/5	12/1
Ondansetron	A04AA01	2/0	0/0
Antifungal			
Terbinafine	D01BA02	0/2	0/1
Antiarrythmia			
Flecainid	C01BC04	1/0	0/0
Amiodarone	C01BD01	0/0	0/1
Beta blocker			
Propranolol	C07AA05	5/0	2/1
Metoprolol	C07AB02	10/0	3/4
Timolol	S01ED01	3/0	0/0
Antihypertensive			
Carvedilol	C07AG02	1/0	1/0
Non-steroidal antiinflammatory			
Celecoxib	M01AH01	12/7	4/1
Analgesic			
Tramadol[a]	N02AX02	45/18	0/0
Codeine[a]	R05DA04	12/91	0/0
Oxycodone[a]	N02AA05	2/0	0/0
Antipsychotic			
Chlorpromazin	N05AA01	0/0	0/2
Levomepromazin	N05AA02	1/1	3/1
Haloperidol	N05AD01	1/0	1/0
Zuclopenthixol	N05AF05	1/1	2/2
Perphenazine	N05AB03	0/1	2/0
Risperidone	N05AX08	0/1	0/0
TCA Antidepressants			
Clomipramine	N06AA04	0/0	0/1
Amitriptyline	N06AA09	3/7	5/3
Nortriptyline	N06AA10	0/2	4/1
Other Antidepressants			
Moclobemid	N06AG02	1/0	0/0
Mirtazapin	N06AX11	9/10	4/2
Venlafaxin	N06AX16	6/2	0/1
Opioids			
Methadone[a]	N07BC02	0/1	0/0
Cough Suppressants			
Dexthromethorphan	R05DA09	0/1	0/0
Steroid Hormone			
Dexamethasone[a]	S01BA01	2/1	0/0

[a]Not included in the adjustment for ever/never use of a CPY2D6 inhibitor or substrate because the drug may be used to treat breast cancer recurrence or its symptoms.

odds ratio (OR) and its accompanying 95% confidence interval (CI) in a conditional logistic regression including only citalopram use as the exposure variable and conditioned on the matched factors. We then adjusted for additional confounding by covariates not included in the matching by including them as independent variables in a conditional logistic regression, retaining any covariate that affected the log odds ratio by more than ten percent. All analyses were performed using SAS version 9.

Results

Table I shows the pattern of SSRI prescriptions received by cases and controls. In both ER+/TAM+ and ER−/TAM− women, SSRI prescriptions were primarily written for citalopram or escitalopram. Table II shows the frequency and proportion of cases and controls who received prescriptions for other CYP2D6 substrates and inhibitors, within strata of ER+/TAM+ and ER−/TAM−. These frequencies and proportions were approximately the same among cases and controls, varying only as expected due to chance [20].

Table III shows the frequency and proportion of cases and controls, within strata of ER+/TAM+ and ER−/TAM−, in the categories of the covariates. Ten percent of ER+/TAM+ cases and 10% of ER+/TAM+ controls ever used citalopram while taking tamoxifen and about 6% of ER+/TAM+ cases and 6% of their controls ever used another SSRI while taking tamoxifen.

ER+/TAM+ women who ever used citalopram while taking tamoxifen had about the same rate of breast cancer recurrence as women who never used citalopram while taking tamoxifen (Table IV; adjusted OR=1.1, 95% CI=0.7, 1.7). These near-null results persisted within categories of intermittent and regular users of citalopram while taking tamoxifen. ER+/TAM+ women who ever used another SSRI (fluoxetine, paroxetine, or sertraline) while taking tamoxifen were also at no increased risk of breast cancer recurrence (Table IV; adjusted OR=0.9, 95% CI=0.5, 1.8). Neither citalopram use (adjusted OR=0.9, 95% CI=0.4, 2.2) nor use of another SSRI (adjusted OR=0.6, 95% CI=0.3, 1.6) had a substantial effect on recurrence in ER−/TAM− women, suggesting that these SSRI medications do not directly affect the risk of breast cancer recurrence.

Discussion

The results of this study provide clinical epidemiologic support for the hypothesis that citalopram, taken concurrently with tamoxifen, does not reduce tamoxifen's protective effect against breast cancer recurrence in early stage patients whose tumor cells express the estrogen receptor. This support is in agreement with recent recommendations that tamoxifen-treated breast cancer patients with indications for antidepressant medications may be safely prescribed citalopram or another SSRI with low potency to inhibit *CYP2D6* activity [12], and fills a void in the evidence base identified by the US

Table III. Frequency and proportion of cases of breast cancer recurrence and matched controls.

	ERP+/TAM+ [n, (%)]		ERP−/TAM− [n, (%)]	
	cases	controls	cases	controls
Citalopram prescription				
Ever	37 (10)	35 (10)	12 (5.3)	14 (6.1)
Ever, 0 to <30%[a]	24 (6.6)	25 (6.8)	7 (3.1)	10 (4.4)
Ever, 30 to ≤60%	6 (1.6)	7 (1.9)	1 (0.4)	1 (0.4)
Ever, >60%	7 (1.7)	3 (0.8)	4 (1.8)	3 (1.3)
Never	329 (90)	331 (90)	216 (95)	214 (94)
Other SSRI (ever exposed)				
Fluoxetine	5 (1.4)	7 (1.9)	2 (0.9)	4 (1.8)
Paroxetine	6 (1.6)	4 (1.1)	1 (0.4)	5 (2.2)
Sertraline	13 (3.6)	15 (4.1)	6 (2.6)	4 (1.8)
Other SSRI or *CYP2D6* inhibitor[c]				
Ever	103 (28)	95 (26)	53 (23)	54 (24)
Never	263 (72)	271 (74)	175 (77)	174 (76)
Diagnosis year[b]				
1985–1993	33 (9.0)	34 (9.3)	13 (5.7)	11 (4.8)
1994–1996	96 (26)	96 (26)	78 (34.2)	75 (33)
1997–2001	237 (65)	236 (65)	137 (60)	142 (62)
Age at diagnosis				
35–44	18 (4.9)	18 (4.9)	41 (18)	33 (15)
45–54	93 (25)	85 (23)	100 (44)	85 (37)
55–64	191 (52)	178 (49)	61 (27)	75 (33)
65–70	64 (18)	85 (23)	26 (11)	35 (15)
Menopausal status at diagnosis[b]				
Premenopausal	42 (12)	42 (12)	83 (36)	83 (36)
Postmenopausal	324 (89)	324 (89)	145 (64)	145 (64)
County of residence at diagnosis[b]				
Funen	61 (17)	61 (17)	47 (21)	47 (21)
South Jutland	41 (11)	41 (11)	29 (13)	29 (13)
Ribe	7 (1.9)	7 (1.9)	9 (3.9)	9 (3.9)
Vejle	38 (10)	38 (10)	43 (19)	43 (19)
Ringkøbing	13 (3.6)	13 (3.6)	4 (1.8)	4 (1.8)
Aarhus	83 (23)	83 (23)	42 (18)	42 (18)
Viborg	33 (9.0)	33 (9.0)	17 (7.5)	17 (7.5)
North Jutland	90 (25)	90 (25)	37 (16)	37 (16)
UICC tumor stage at diagnosis[b]				
Stage I	14 (3.8)	14 (3.8)	34 (15)	34 (15)
Stage II	148 (40)	148 (40)	111 (49)	111 (49)
Stage III	204 (56)	204 (56)	83 (36)	83 (36)
Histologic grade				
Grade I	59 (16)	89 (24)	19 (8.3)	13 (5.7)
Grade II	157 (43)	158 (43)	83 (36)	67 (29)
Grade III	78 (21)	45 (12)	90 (40)	90 (40)
Missing	72 (20)	74 (20)	36 (16)	58 (25)
Surgery type				
Breast conserving surgery	53 (15)	63 (17)	42 (18)	46 (20)
Mastectomy	313 (86)	303 (83)	186 (82)	182 (80)
Radiation therapy				
Yes	159 (43)	161 (44)	108 (47)	104 (46)
No	207 (57)	205 (56)	115 (50)	106 (47)
Missing			5 (2.2)	18 (7.9)
Tamoxifen protocol				
One year	76 (21)	59 (16)	Not Applicable	Not Applicable
Two years	50 (14)	62 (17)		
Five years	240 (66)	245 (67)		
Systemic adjuvant chemotherapy				
Yes	34 (9.3)	39 (11)	175 (77)	150 (66)
No	332 (91)	327 (89)	53 (23)	78 (34)

[a]Percent overlap of SSRI and tamoxifen prescription.
[b]Variable included in risk set sampling to match controls to cases.
[c]See Tables I and II for complete lists of SSRI and other *CYP2D6* inhibitors.

Table IV. Association between SSRI prescription and breast cancer recurrence.

Prescription	cases/controls	crude OR (95% CI)	adjusted OR (95% CI)[a]
ERP+/TAM+			
Never citalopram user	329/331	1 (reference)	1 (reference)
Ever citalopram user	37/35	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)
Intermittent use	24/25	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)
Regular use	13/10	1.3 (0.6, 3.0)	1.3 (0.6, 3.1)
ERP−/TAM−			
Never citalopram user	216/214	1 (reference)	1 (reference)
Ever citalopram user	12/14	0.8 (0.4, 1.9)	0.9 (0.4, 2.2)
ERP+/TAM+			
Never other SSRI user	345/344	1	1
Ever other SSRI[b] user	21/22	1.0 (0.5, 1.8)	0.9 (0.5, 1.8)
ERP−/TAM−			
Never other SSRI user	219/215	1	1
Ever other SSRI[b] user	9/13	0.7 (0.3, 1.6)	0.6 (0.3, 1.6)

[a]Adjusted for age category and other *CYP2D6* inhibiting medications (see Tables I and II for complete lists of these medications and the frequency of their use in the study population).
[b]Other SSRI are fluoxetine, paroxetine, and sertraline. See Table I for a description of their prescription frequencies.

National Comprehensive Cancer Network's treatment guidelines [21].

Most SSRI prescriptions in our study were for citalopram or its s-stereoisomer, which is a modest inhibitor of *CYP2D6* compared with some other SSRI medications [11,18,19]. Use of other SSRI medications (fluoxetine, paroxetine, or sertraline) while taking tamoxifen, some of which are more potent inhibitors of *CYP2D6* [11,22], was also unassociated with recurrence risk in our results. The frequencies of prescriptions for these other SSRIs were, however, too low to say with confidence that they do not reduce the effectiveness of tamoxifen.

This study extends our earlier results [13] by including 366 ER+/TAM+ cases and their 366 matched controls, resulting in 37 cases and 35 controls who ever used citalopram while taking tamoxifen. The earlier study included only 184 ER+/TAM+ cases and their 184 matched controls, resulting in only 17 cases and 21 controls who ever used citalopram while taking tamoxifen. Fifty-six percent of ER+/TAM+ cases and controls in this study were included in the earlier study, and 46% of citalopram-exposed cases were included in the earlier study. The present study's null result is, therefore, much more precisely measured than the null result of the earlier study. In addition, the large sample size and comprehensive prescription registry allowed investigation of, and control for, exposure to a wide range of prescription medications.

Despite the study's size and methodologic strength as a population-based case-control study, the results should be interpreted with the following limitations in mind. First, we do not know the reasons why SSRIs were prescribed to the study participants. SSRIs may have been prescribed to treat either depression or hot flashes [23], but SSRI prescriptions for hot flashes are very rare in Danish breast cancer patients. Second, we do not know whether participants carried *CYP2D6* variant alleles that reduce the enzyme's activity. Genetic variation in *CYP2D6* function, however, is not related to switching SSRI antidepressants or discontinuation of SSRI antidepressants [24], and does not affect response to, or tolerance of, citalopram in particular [25]. If *CYP2D6* genotype is unrelated to receipt or adherence to citalopram prescription, then the absence of genotyping data could not bias the results. Furthermore, clinicians caring for breast cancer patients who present with indications for SSRI antidepressants will seldom know the patient's *CYP2D6* genotype, so this study's result applies directly to the typical clinical setting.

Third, we have not confirmed that patients actually took either tamoxifen or a prescribed SSRI. In Denmark, tamoxifen is dispensed by breast cancer physicians to breast cancer patients at follow-up visits. SSRI medications recorded in the prescription registry are paid for and retrieved by patients, and then partly reimbursed by the national health care system. Both of these systems should assure good adherence to the registered medications. Fourth, most women taking SSRI prescription medications did not take them for the full duration of their tamoxifen therapy. This pattern reflects the clinical practice in this population during the study period. It would be very difficult to find a population in which a substantial proportion of tamoxifen-treated breast cancer patients took SSRI medications for the full five years of their tamoxifen therapy. Indeed, no such study has been reported. Finally, breast cancer patients with estrogen-receptor positive tumors were assigned treatment protocols calling for one, two, or five years of tamoxifen therapy, whereas cur-

rent guidelines recommend five years of tamoxifen therapy [21]. Many of the women assigned to tamoxifen protocols shorter than five years took tamoxifen for much longer (unpublished validation data), and we recorded the full duration of their use in the analysis of intermittent and regular use. In addition, recurrence risks between tamoxifen-treated and placebo-treated women differ as early as one year after initiation of tamoxifen treatment [8], so inhibition of tamoxifen effectiveness by concurrent SSRI prescriptions should have been apparent among all women included in our study.

While these results may seem at odds with the strong biologic rationale and *in vivo* evidence supporting the hypothesis that any *CYP2D6* inhibition would reduce tamoxifen's effectiveness, this information may not be as compelling as it first seems [26]. SSRI medications could reduce the plasma concentration of tamoxifen's secondary metabolites without reducing its anti-tumorigenicity [27]. Tamoxifen doses as low as 1 mg/day affect biomarkers of cardiovascular, bone, and tumor endpoints to about the same degree as the usual dose of 20 mg/day [28,29], so the three-fold reduction in the concentration of tamoxifen's secondary metabolites associated with receipt of the SSRI paroxetine [22] may have little consequence. Our results, combined with this emerging alternative view of the limited potential for *CYP2D6* inhibition to interact with tamoxifen, suggest that breast cancer patients with indications for an SSRI may be prescribed citalopram while taking tamoxifen with little effect, if any, on their risk of breast cancer recurrence.

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