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Breast cancer recurrence in relation to antidepressant use

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Abstract

Purpose—Women with breast cancer frequently use antidepressants; however, questions about the effect of these medications on breast cancer recurrence remain.

Methods—We identified 4216 women ≥18 years with an incident stage I or II breast cancer diagnosed between 1990–2008 in a mixed model healthcare delivery system linked to a cancer registry. Recurrences were ascertained from chart review. Medication exposures were extracted from electronic pharmacy records. We used multivariable Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) to assess the association between antidepressant use and breast cancer recurrence and mortality. We also conducted analyses restricted to tamoxifen users.

Results—Antidepressants overall, tricyclic antidepressants, and selective serotonin reuptake inhibitors were not associated with risk of breast cancer recurrence or mortality. Women taking paroxetine only (adjusted HR: 1.66; 95% CI: 1.02, 2.71) and trazadone only (adjusted HR: 1.76; 95% CI: 1.06, 2.92), but not fluoxetine only (adjusted HR: 0.92; 95% CI: 0.55, 1.53), had higher recurrence risks than antidepressant non-users. There was some suggestion of an increased recurrence risk with concurrent paroxetine and tamoxifen use compared to users of tamoxifen only (adjusted HR: 1.49; 95% CI: 0.79, 2.83).

Conclusions—In general, antidepressants did not appear increase risk of breast cancer recurrence; though there were some suggested increases in risk that warrant further investigation in other datasets. Our results combined systematically and quantitatively with results from other studies may be useful for patients and providers making decisions about antidepressant use after breast cancer diagnosis.

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CONFLICTS OF INTERST

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ETHICAL APPROVAL

For this type of study formal consent is not required.

Keywords

breast carcinoma; breast carcinoma recurrence; breast carcinoma mortality; antidepressants

INTRODUCTION

Antidepressant use is common among women with breast cancer in the United States, with upwards of one quarter to one third of women using these medications after their cancer diagnosis [1–3]. Thus, understanding the safety of antidepressants is important for the health of the growing number of breast cancer survivors.

Tamoxifen is an important treatment for breast cancer hormone receptor-positive breast cancer [4]. Inhibitors of the enzyme CYP2D6, such as the selective serotonin reuptake inhibitors (SSRIs) paroxetine and fluoxetine, may impair conversion of tamoxifen into its active form, endoxifen [5–8]. The clinical importance of their potential inhibitory effects is unknown and questionable, especially since studies suggest that even genetic variants of *CYP2D6* encoding reduced enzymatic activity do not result in worse outcomes [9–13]; however, there is much debate on the effects of these medications in women with breast cancer [14–19] and the Food and Drug Administration (FDA) has issued precautions regarding concomitant use of tamoxifen and paroxetine [20,21].

Epidemiologic research on antidepressant use and breast cancer outcomes varies considerably in exposures and outcomes studied [1,22–31]. Studies of antidepressants that weakly inhibit CYP2D6 (such as citalopram) have generally not been associated with breast cancer recurrence risk [22,23,31]. However, there has been some suggestion of increased risk of breast cancer recurrence [22] and breast cancer mortality [27] among patients who use tamoxifen with the strong CYP2D6 inhibitor paroxetine in some but not all studies [25]. Studies of CYP2D6 inhibitors in general (including medications other than antidepressants) [26], antidepressants with moderate/strong CYP2D6 affinity [30], and SSRIs in as a class [1,28,31] have generally not suggested an association with breast cancer outcomes among tamoxifen users. Of note, studies lacked statistical precision and little information was available on the commonly used antidepressant fluoxetine, which also inhibits CYP2D6. We therefore assessed the association between different classes of antidepressants and individual medications and the risk of breast cancer recurrence.

METHODS

Study overview

This cohort study, Commonly Used Medications and Breast Cancer Outcomes (COMBO), is described in detail elsewhere [32,33]. Briefly, we conducted this study within the western Washington region of Group Health, a mixed model health plan in Washington state and northern Idaho. Study participants had to reside in one of the 13 western Washington counties covered by the western Washington Surveillance, Epidemiology, and End Results program (SEER) registry. We used cancer registry files linked to Group Health enrollment files to identify women aged 18 years and older who were diagnosed with a first primary

stage I or II invasive breast cancer between 1990 and 2008, inclusive. Participants had to be enrolled in Group Health's Integrated Group Practice model for the year before and after their incident breast cancer diagnosis (unless they died during that year). Medical records of potentially eligible participants (N=4426) were reviewed. We excluded participants with no medical record (N=72), bilateral disease (N=6), recurrent or second primary breast cancers that were incorrectly identified as incident first breast cancers (N=79), and no definitive surgery (N=44). We required women be alive and recurrence-free for 120 days after surgery and therefore excluded people who died (N=5) or had metastases (N=4) within 120 days of surgery. The final cohort consisted of 4216 women. Five-year outcomes from a subset of this cohort (N=1306) were included in an earlier report on antidepressants and breast cancer outcomes [1]. The Group Health human subjects review committee approved all study procedures.

The SEER registry provided data on tumor characteristics and certain patient characteristics. When these were not available in SEER, we abstracted them from medical records as part of a detailed chart abstraction [31,32]. Charts were abstracted from one year before diagnosis through patient death, disenrollment from Group Health, or the date of chart abstraction. Data elements included treatment of the incident breast cancer, breast cancer recurrences and second primaries [34]. Data on comorbidity diagnoses (including mental health diagnoses [Supplemental Table 1] and the Charlson comorbidity score [35]), health history and medication use, height, weight, and date and cause of death, came primarily from administrative data sources and the electronic medical record at Group Health. A list of data elements and their sources was previously published by Boudreau and colleagues [32].

Exposure

Group Health's pharmacy database provided information on prescription fills at Group Health-owned pharmacies and pharmacy claims throughout the entire study period [36,37]. Each record contained information on the drug dispensed, including national drug code (NDC), quantity, strength, days' supply, date dispensed, and prescriber. Drug exposures of interest included use of the following after breast cancer diagnosis: 1) any antidepressant, 2) any SSRI, 3) any tricyclic antidepressant (TCA), and 4) any miscellaneous antidepressant. We further classified SSRI use into strong CYP2D6 inhibitors (paroxetine, fluoxetine, and buproprion) and weak/moderate CYP2D6 inhibitors (sertraline, citalopram, fluvoxamine, and escitalopram) [2,30].

For each drug and drug class, we defined episodes of use. We used the days' supply field to compute the intended duration of each prescription [1,32]. Assuming 80% adherence, we calculated prescriptions' run-out date by multiplying days' supply by 1.25 [38]. If a new prescription for the drug or class of interest was dispensed <60 days after the run-out date of the preceding prescription, it was included as part of the same episode of use. Episodes started on the dispensing day of the first prescription and ended on the run-out day of the last prescription [32]. Once someone became a user after breast cancer diagnosis, she remained a user, regardless of when she discontinued use. The rationale for this was that any use – not necessarily current use – could be related to recurrence risk. Concurrent use between

antidepressants and endocrine therapy (tamoxifen or aromatase inhibitors) was defined as an overlap of ≥60 days of use [28].

Information on endocrine therapy (tamoxifen and aromatase inhibitors) was obtained from prescription fills. Like all other exposure variables, concurrent antidepressant use was time-varying and unidirectional. Once someone became a concurrent user, she remained a concurrent user, even if she discontinued use of either the antidepressant or tamoxifen. A non-concurrent user could become a concurrent user if the 60 days of overlap was achieved (Supplemental Figure 1).

Outcomes

Recurrence was defined as a ductal carcinoma *in situ* or invasive cancer of the ipsilateral breast or in any regional or distant sites [32–34]. A cancer was classified as a recurrence only if it occurred more than 120 days after definitive surgery [34]. Date and cause of death were obtained from Washington State death files. Second cancers in the contralateral breast were obtained from the SEER program registry and chart abstraction. They were considered censoring events in the analysis of recurrence.

Statistical analysis

Analysis of breast cancer recurrence—We compared users and non-users of any antidepressant after diagnosis with respect to patient characteristics and features of their cancer using the Chi-square test for categorical variables and the t-test for continuous variables. We used multivariable Cox proportional hazards models to estimate hazard ratios (HR) and their 95% confidence intervals (CI) to assess the association between antidepressant use and breast cancer recurrence risk while accounting for competing risks [39]. Time from diagnosis was the analytic time scale [40] and women entered the analysis when they became at risk for recurrence, which was defined as 120 days after definitive surgery. Women were followed until the earliest of recurrence, second primary breast cancer diagnosis, death, disenrollment from Group Health, or end of study (chart abstraction date). Women were censored when they developed a second primary breast cancer and thus, any recurrence occurring after the second primary was not included as a recurrence outcome. Covariates in all models were selected *a priori* and included age (18–49, 50–59, 60–69, 70–79, ≥80 years) and year of diagnosis (1990–1994, 1995–1999, 2000–2004, 2005–2008), stage (I, IIA, IIB) [41], estrogen receptor (ER) and progesterone receptor (PR) status (ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR−), primary treatment (mastectomy, breast conserving surgery [BCS] with radiation, BCS without radiation), any chemotherapy treatment, any endocrine therapy, body mass index (BMI) (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, ≥35 kg/m^2) in the year before diagnosis, smoking in the year before diagnosis (current, past, never/unknown), menopausal status in the year before diagnosis (peri- or pre-menopausal, post-menopausal), and Charlson comorbidity score (0, 1, ≥2). All variables were included as categorical variables. Endocrine treatment and Charlson comorbidity score were included as time-varying covariates. Persons with unknown ER/PR status and BMI were excluded from the main recurrence and mortality models. We conducted an exploratory analysis with depression as a time-varying covariate.

In analyses of drug class and recurrence risk, we used two approaches to control for confounding by other antidepressants. We conducted one analysis in which we restricted (in a time-varying manner) to non-users of any antidepressant and users of only the antidepressant class of interest. In this analysis, exposure was time-varying in that women could switch from being a non-user to a user of one class, but were censored when they used an antidepressant from another class. In the tables, these are referred to as “restriction” analyses. Separate models were conducted for each antidepressant of interest and women were censored when they used another antidepressant. In the second approach, we included each class of antidepressants as a separate exposure variable in the model so that they were mutually adjusted for one another. In the tables, these are referred to as “adjustment” analyses.

We conducted an analysis limited to tamoxifen users (N=1902) to address the question of whether antidepressants modify tamoxifen’s effectiveness. For the analysis of concurrent tamoxifen use, women entered the analysis once they became at risk of recurrence and had used 60 days of tamoxifen (Supplemental Figure 1). Women with aromatase inhibitor use before tamoxifen use were excluded. Women could be non-users of antidepressants (i.e., tamoxifen only users), non-concurrent users of tamoxifen and antidepressants, or concurrent users of tamoxifen and antidepressants. Concurrent use of antidepressant and tamoxifen was time-varying and occurred once a woman had 60 days of overlap of tamoxifen and antidepressant use. We conducted separate models for concurrent use of tamoxifen and any antidepressant as well as with each antidepressant drug and drug class. Due to small sample size, we adjusted only for diagnosis age, diagnosis year, and stage at diagnosis in these models. Women were censored at the earliest of the start of an aromatase inhibitor, second primary breast cancer, death, disenrollment, and end of study follow-up.

Analysis of breast cancer mortality—In a secondary analysis, we examined the risk of breast cancer-specific mortality in relation to antidepressant use, using multivariable Cox models with the same exposures of interest as in the main analysis. Once a person started using an antidepressant, she was classified as a user; however, new use after a recurrence diagnosis or second primary was not included, as recurrences and second primaries were likely to be a strong time-varying confounders [42]. We followed women until the earliest of death from another cause, Group Health disenrollment, or end of study follow-up.

Proportional hazards assumptions—We evaluated proportional hazards assumptions by testing the interaction between the medication classes of interest and the logarithm of follow-up time. Separate tests were run for breast cancer recurrence and mortality outcomes. The assumptions held for all exposure-outcome pairs except for miscellaneous antidepressants and breast cancer mortality and any antidepressant and breast cancer mortality. To further assess the non-proportional hazards for, we divided the follow-up time into two periods each containing half the breast cancer deaths (≤4.24 years since diagnosis and >4.24 years). Separate HRs for exposures were estimated for each time period by including an interaction term between time period and the exposure in the multivariate Cox proportional hazards model. For both any antidepressant and miscellaneous antidepressants models, the HRs in the two time periods were not statistically significant and

the confidence intervals overlapped. Therefore, we report the overall results for both miscellaneous antidepressants and any antidepressant.

RESULTS

Among the 4216 women who met study eligibility criteria, more than half (N=2302, 54.6%) filled at least one prescription for an antidepressant sometime after their incident breast cancer diagnosis (but before recurrence or second primary). Antidepressant users were more often white, more likely to smoke at baseline, have a mental health diagnosis and filled prescriptions for antidepressants in the year before diagnosis, have lower education levels, more comorbidities, and higher BMI than participants who did not use antidepressants after breast cancer diagnosis (Table 1). Users and non-users were generally similar with respect to risk factors for recurrence, such as stage and other features of initial cancer. However, compared to non-users, antidepressant users were slightly more likely to receive mastectomy over breast conserving surgery with radiation and to receive chemotherapy.

The median duration of use after breast cancer diagnosis for all antidepressants was 23 months (Table 2) and median time to first use was 7.4 months (not shown). SSRIs were the most commonly used class of antidepressants. Of all individual antidepressants, fluoxetine and trazodone were the two most frequently used agents. Overall, use of antidepressants after incident breast cancer diagnosis was not associated with risk of recurrence (adjusted HR: 1.16, 95% CI: 0.94, 1.44) compared to non-users (Table 3). HRs for both SSRIs and TCAs were near 1.0 and were not statistically significant. Miscellaneous antidepressants were associated with a non-significant increased risk, possibly driven by the most commonly used of these medications, trazodone (adjusted HR: 1.76; 95% CI: 1.06, 2.92). We observed an increased recurrence risk among women taking paroxetine only (adjusted HR: 1.66; 95% CI: 1.02, 2.71), but not fluoxetine only (adjusted HR: 0.92; 95% CI: 0.55, 1.53). Risk estimates were elevated for citalopram users, but were based on only three events in the user group.

In the analysis restricted to tamoxifen users, concurrent use of most antidepressants was not associated with recurrence risk (Table 4). There was some suggestion of a decreased risk associated with concurrent weak CYP2D6-inhibitor use (adjusted HR: 0.51; 95% CI: 0.16, 1.62) and increased risk with concurrent paroxetine use (adjusted HR: 1.49; 95% CI: 0.79, 2.83). However, these estimates were based on only 6 and 16 events in the concurrent user groups, respectively. There were even fewer events among non-concurrent antidepressant users. For fluoxetine, recurrence risk was elevated with non-concurrent (adjusted HR: 2.21, CI: 1.04, 4.66) tamoxifen use, but not concurrent use.

Antidepressant use was not associated with breast cancer mortality (adjusted HR: 95% CI: 1.09; 95% CI: 0.83, 1.43) (Table 5). Confidence intervals for classes of antidepressants and individual drugs were wide. Post-hoc adjustment for depression did not change results meaningfully and are therefore not presented.

DISCUSSION

Our study provides some reassurance that many commonly used antidepressant medications are not associated with an increased risk of breast cancer recurrence. Results from this large, population-based retrospective cohort study are generally consistent with other studies that have generally not observed an increased risk of breast cancer recurrence with antidepressant use [6].

We hypothesized that paroxetine and fluoxetine would increase recurrence risk among tamoxifen users because these antidepressants inhibit the conversion of tamoxifen to its active form [5–7]. There was a suggestion of increased risk with concurrent paroxetine use among tamoxifen users. This finding is consistent with point estimates in one study (odds ratio for recurrence: 2.4, 95% CI: 0.6–9.5) [22], but not another (HR for disease free survival: 0.84; 95% CI: 0.34–2.05) [25]. Of note, all three studies (including ours) had wide confidence intervals.

Among tamoxifen users, we also observed that fluoxetine was associated with an increased risk of recurrence when taken separately from tamoxifen (i.e., non-concurrently) but not at the same time (i.e., concurrently). This is surprising and inconsistent with the biological hypothesis, which would suggest that fluoxetine, a strong CYP2D6 inhibitor, would affect breast cancer recurrence risk by reducing tamoxifen's effectiveness if the two medications were used concurrently. In general, our findings for non-concurrent antidepressant use among tamoxifen users should be cautiously interpreted due to small sample size.

We saw an increased risk of recurrence with trazodone use. Trazodone may be a weak/moderate CYP2D6 inhibitor [30,43], but to our knowledge, other studies have not looked specifically at the risk of recurrence in relation to trazodone use. Given trazadone is commonly used for insomnia [44], it is unclear whether our findings are due to chance or confounding by indication. The suggested increased risk of recurrence with citalopram should also be interpreted cautiously as it was based on only three events and is not consistent with findings from larger studies [22,23,31]. Similarly, the small number of deaths due to breast cancer in each drug exposure category limits our ability to draw conclusions.

Our study had relatively long follow-up and high-quality longitudinal, prospectively collected data on exposures, outcomes, and confounders with gold-standard chart-review for many of these variables. Variables were not subject to recall bias. A limitation was that we had very small number of events when examining individual drugs, particularly for analyses of non-concurrent use among patients taking tamoxifen. This has been a common issue in other studies of specific antidepressant use and breast cancer recurrence [22,23,25,26,31] and motivates the need for pooled meta-analyses on specific drugs. We anticipated this problem, but believed that these analyses were still important to conduct. Women will benefit from having information about the risk profiles of individual antidepressants to make decisions about which may be safer to use after breast cancer diagnosis. Last, COMBO uses data from a single health plan and includes an educated, primarily white population, and individuals with access to both medical care and prescription drug benefits. This may limit

generalizability to some populations if the biological effect of antidepressants differs by patient characteristics.

Having access to the most important predictors of cancer recurrence (i.e., disease characteristics) helped reduce confounding, but residual confounding may have been present. For example, there may be lifestyle risk factors for recurrence that are also associated with antidepressant use. Confounding by indication is also a possibility in this study; even though all medications studied are used for depression, some have other indications (e.g., anxiety, pain, sleep). We did not have information on the reasons for antidepressant use and therefore could not adjust for it. It is also possible that antidepressants were used for symptoms of an undiagnosed recurrence. Under such circumstances, they could appear to increase the risk of recurrence due to reverse causality (i.e., protopathic bias). To protect against confounding by indication in the breast cancer mortality analysis (i.e., a woman started using antidepressants because she had a recurrence), we counted only exposure initiated before recurrence [42].

Conclusions

Our results provide important information on antidepressant use after breast cancer diagnosis including information on individual drugs, which – when combined systematically and quantitatively with results from other studies – may be useful for patients and providers making decisions about whether to use these medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of users and non-users of any antidepressants after a diagnosis of breast cancer and before recurrence (Group Health, 1990–2008), N=4,216

	All	Any antidepressant use after diagnosis	
		No	Yes
	(N=4216) n (%)[a]	(N=1914) n (%)[a]	(N=2302) n (%)[a]
Age at diagnosis (years)			
Mean (SD)	62.2 (13.3)	62.5 (13.2)	62.6 (13.4)
18–39	139 (3.3)	65 (3.4)	74 (3.2)
40–49	646 (15.3)	285 (14.9)	361 (15.7)
50–59	995 (23.6)	438 (22.9)	557 (24.2)
60–69	1018 (24.1)	491 (25.7)	527 (22.9)
70–79	940 (22.3)	436 (22.8)	504 (21.9)
≥80	478 (11.3)	199 (10.4)	279 (12.1)
Year of diagnosis			
1990–1994	950 (22.5)	442 (23.1)	508 (22.1)
1995–1999	1191 (28.2)	520 (27.2)	671 (29.1)
2000–2004	1201 (28.5)	513 (26.8)	688 (29.9)
2005–2008	874 (20.7)	439 (22.9)	435 (18.9)
Follow-up time			
Mean (SD)	7.1 (4.3)	6.6 (4.3)	7.4 (4.3)
Median	6.3	5.7	6.7
Race			
White	3719 (88.5)	1640 (86.1)	2079 (90.5)
African American	136 (3.2)	73 (3.8)	63 (2.7)
American Indian/Alaska Native	113 (2.7)	44 (2.3)	69 (2.7)
Asian/Pacific Islander	233 (5.5)	148 (7.8)	85 (3.7)
Other	1 (0)	0 (0)	1 (0)
Unknown	14	9	5
Ethnicity			
Not Hispanic	3976 (94.6)	1798 (94.2)	2178 (94.8)
Hispanic	229 (5.4)	110 (5.8)	119 (5.2)
Unknown	11	6	5
Menopausal status at diagnosis			
Peri- or Premenopausal	1145 (27.2)	522 (27.3)	623 (27.1)
Postmenopausal	3071 (72.8)	1392 (72.7)	1679 (72.9)
Education			
High school or less	418 (23.4)	188 (22.1)	230 (24.5)
Some college	634 (35.4)	281 (33.0)	353 (37.6)
College or post graduate	737 (41.2)	382 (44.9)	355 (37.8)
Unknown	2427	1063	1364

	All	Any antidepressant use after diagnosis	
		No	Yes
	(N=4216) n (%)[a]	(N=1914) n (%)[a]	(N=2302) n (%)[a]
Cancer characteristics			
AJCC stage at diagnosis			
I	2648 (62.8)	1175 (61.4)	1473 (64.0)
IIA	1078 (25.6)	518 (27.1)	560 (24.3)
IIB	490 (11.6)	221 (11.5)	269 (11.7)
Lymph node status			
Unknown	451	195	256
Negative	2847 (75.6)	1304 (75.9)	1543 (75.4)
Positive (1–3 nodes)	680 (18.1)	309 (18)	371 (18.1)
Positive (≥4 nodes)	234 (6.2)	104 (6.1)	130 (6.4)
Positive (unknown number of nodes)	4 (0.1)	2 (0.1)	2 (0.1)
Tumor size			
<2.0 cm	3110 (73.8)	1392 (72.8)	1718 (74.7)
≥2.0 cm	1104 (26.2)	521 (27.2)	583 (25.3)
Unknown	2	1	1
Tumor histology			
Ductal	3315 (78.6)	1506 (78.7)	1809 (78.6)
Lobular	336 (8)	147 (7.7)	189 (8.2)
Mixed/other	565 (13.4)	261 (13.7)	304 (13.3)
Tumor grade			
Well differentiated	1041 (26.9)	471 (26.7)	570 (27.1)
Moderately differentiated	1600 (41.3)	714 (40.4)	886 (42.1)
Poorly/undifferentiated	1233 (31.9)	582 (33.0)	651 (30.9)
Not determined or stated	342	147	195
ER/PR status			
ER & PR unknown	217	93	124
ER−/PR−	667 (16.7)	313 (17.2)	354 (16.3)
ER+/PR−	383 (9.6)	177 (9.7)	206 (9.5)
ER−/PR+	61 (1.5)	24 (1.3)	37 (1.7)
ER+/PR+	2888 (72.2)	1307 (71.8)	1581 (72.6)
Her-2 test (diagnosis in 1998+ only)			
Test done	2074 (79.7)	950 (81.0)	1124 (78.7)
Her-2 test result among women with test done			
Positive/Borderline	353 (17.0)	152 (16.0)	201 (17.9)
Negative	1714 (82.6)	795 (83.7)	919 (81.8)
No result	7 (0.3)	3 (0.3)	4 (0.4)
Cancer treatment			
Primary therapy			
Mastectomy with or without radiation	1521 (36.1)	635 (33.2)	886 (38.5)

	All	Any antidepressant use after diagnosis	
		No	Yes
	(N=4216) n (%)[a]	(N=1914) n (%)[a]	(N=2302) n (%)[a]
Breast conserving surgery with radiation	2172 (51.5)	1039 (54.3)	1133 (49.2)
Breast conserving surgery without radiation	523 (12.4)	240 (12.5)	283 (12.3)
Adjuvant treatment (not mutually exclusive)			
Chemotherapy	1376 (32.6)	586 (30.6)	790 (34.3)
Tamoxifen	2057 (48.8)	884 (46.2)	1173 (51.0)
Aromatase Inhibitor	849 (20.1)	353 (18.4)	496 (21.6)
Health history in year prior to diagnosis			
Charlson Index			
0	3229 (76.6)	1541 (80.5)	1688 (73.3)
1	704 (16.7)	263 (13.7)	441 (19.2)
≥2	283 (6.7)	110 (5.7)	173 (7.5)
Body mass index (kg/m^2)			
<18.5	69 (1.6)	29 (1.5)	40 (1.7)
18.5 to <25 kg/m^2	1453 (34.6)	698 (36.6)	755 (33.0)
25 to <30 kg/m^2	1362 (32.5)	636 (33.4)	726 (31.7)
30 to <35 kg/m^2	766 (18.3)	330 (17.3)	436 (19.0)
≥35 kg/m^2	546 (13.0)	212 (11.1)	334 (14.6)
Unknown	20	9	11
Smoking status			
Current	253 (6.0)	83 (4.3)	170 (7.4)
Past	352 (8.3)	169 (8.8)	183 (7.9)
Never/Unknown	3611 (85.6)	1662 (86.8)	1949 (84.7)
Diagnosis of depression	402 (9.5)	39 (2.0)	363 (15.8)
Diagnosis of anxiety	174 (4.1)	30 (1.6)	144 (6.3)
Mental health diagnosis	795 (21.7)	166 (10.1)	629 (31.1)
Antidepressant use	935 (22.2)	53 (2.8)	882 (38.3)
SSRIs	452 (10.7)	17 (0.9)	435 (18.9)
TCAs	422 (10.0)	28 (1.5)	394 (17.1)
Miscellaneous	280 (6.6)	12 (0.6)	268 (11.6)

AJCC = American Joint Committee on Cancer; ER = estrogen receptor; PR = progesterone receptor; SD = standard deviation; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

[a]Column percents may not add to 100% due to rounding

Table 2

Antidepressant prescriptions filled after breast cancer diagnosis and before recurrence in 4216 women diagnosed with early stage breast cancer (Group Health, 1990–2008)

		Among users
	Number of users (%)[a]	**Median duration of use after diagnosis (months)**
Any antidepressant	2302 (54.6)	23.1
Selective serotonin reuptake inhibitors	1498 (35.5)	18.7
Strong CYP2D6 inhibitors	1245 (29.5)	13.8
Paroxetine	551 (13.1)	8.5
Fluoxetine	904 (21.4)	11.4
Weak/Moderate CYP2D6 inhibitors	579 (13.7)	12.0
Sertraline	301 (7.1)	10.0
Citalopram	337 (8.0)	9.3
Escitalopram	17 (0.4)	2.3
Fluvoxamine	3 (0.1)	35.0
Tricyclic antidepressants	1128 (26.8)	6.7
Amitriptyline	408 (9.7)	5.9
Nortriptyline	537 (12.7)	3.5
Desipramine	72 (1.7)	5.4
Doxepin	206 (4.9)	3.8
Imipramine	135 (3.2)	6.4
Protriptyline	1 (0.02)	1.3
Miscellaneous antidepressants	1099 (26.1)	6.8
Buproprion	261 (6.2)	6.5
Trazodone	785 (18.6)	4.4
Duloxetine	21 (0.5)	4.2
Mirtazapine	96 (2.3)	6.2
Nefazodone	11 (0.3)	6.3
Tranylcypromine	2 (0.1)	23.7
Venlafaxine	127 (3.0)	11.7

[a] Categories of antidepressants are not mutually exclusive

Table 3

Risk of breast cancer recurrence in relation to the use of antidepressants after a diagnosis of early stage breast cancer (Group Health, 1990–2008), N=4,216

	Person-years	Number of recurrences	Recurrence rate per 1,000 person-years (95% CI)	Unadjusted hazard ratio (95% CI)	Adjusted [a] hazard ratio (95% CI)
Overall	28063	415	14.8 (13.4, 16.3)	–	–
No antidepressant use	15662	228	14.6 (12.8, 16.6)	Reference	Reference
Any antidepressant use	12401	187	15.1 (13.1, 17.4)	1.13 (0.93, 1.38)	1.16 (0.94, 1.44)
SSRI use					
Only – restriction	2917	45	15.4 (11.5, 20.7)	1.05 (0.76, 1.45)	1.11 (0.79, 1.55)
Any – adjustment[b]	7315	110	15.0 (12.5, 18.1)	1.11 (0.89, 1.38)	1.14 (0.88, 1.48)
Paroxetine only	790	18	22.8 (14.4, 36.2)	1.55 (0.96, 2.50)	1.66 (1.02, 2.71)
Fluoxetine only	1235	18	14.6 (9.2, 23.1)	0.96 (0.60, 1.56)	0.92 (0.55, 1.53)
Sertraline only	255	3	11.8 (3.8, 36.5)	0.80 (0.26, 2.51)	0.88 (0.28, 2.76)
Citalopram only	183	3	16.4 (5.3, 51.0)	1.09 (0.35, 3.40)	1.60 (0.52, 4.92)
TCA use					
Only – restriction	3096	45	14.5 (10.9, 19.5)	1.04 (0.76, 1.44)	0.96 (0.67, 1.38)
Any – adjustment[b]	6527	93	14.2 (11.6, 17.5)	1.09 (0.87, 1.38)	1.04 (0.80, 1.35)
Amitriptyline only	1057	14	13.2 (7.8, 22.4)	0.94 (0.55, 1.61)	0.89 (0.50, 1.60)
Nortriptyline only	834	13	15.6 (9.0, 26.8)	1.11 (0.63, 1.94)	0.99 (0.53, 1.85)
Miscellaneous antidepressant use					
Only – restriction	1279	23	18.0 (12.0, 27.1)	1.27 (0.83, 1.95)	1.41 (0.89, 2.23)
Any – adjustment[b]	5125	75	14.6 (11.7, 18.4)	1.12 (0.87, 1.44)	1.12 (0.83, 1.51)
Bupropion only	180	0	0	–	–
Trazodone only	899	19	21.1 (13.5, 33.1)	1.55 (0.97, 2.48)	1.76 (1.06, 2.92)

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; CI = confidence interval

[a] All estimates are from separate models accounting for competing risks. Adjusted for age at diagnosis (18–49, 50–59, 60–69, 70–79, 80+ years), year of diagnosis (1990–1994, 1995–1999, 2000–2004, 2005–2008), American Joint Commission on Cancer stage (I, IIA, IIB), estrogen receptor (ER) and progesterone receptor (PR) status (ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR−), primary treatment (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation), chemotherapy treatment (yes, no), endocrine therapy (yes, no), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35+ kg/m^2), smoking at diagnosis (current, past, never/unknown), menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal), and Charlson score (0, 1, 2+). Total number of participants in adjusted model was 3979 due to exclusion of women with unknown ER/PR status or BMI.

[b] Unexposed groups for these analyses, i.e., non-users of specific antidepressants, are not shown in this table.

Table 4

Risk of breast cancer recurrence in relation to antidepressant use after a diagnosis of hormone receptor positive breast cancer among 1902 tamoxifen users (Group Health, 1990–2008)[a]

	Person-years	Number of recurrences	Recurrence rate per 1,000 person-years (95% CI)	Adjusted hazard ratio (95% CI)[c]
Any antidepressant				
Non-user (tamoxifen only)	7406	125	16.9 (14.1, 20.1)	Reference
Non-concurrent w/tamoxifen	799	12	15.0 (7.8, 26.2)	1.48 (0.75, 2.91)
Concurrent w/tamoxifen[b]	3464	54	15.6 (11.7, 20.3)	0.90 (0.64, 1.37)
SSRIs				
Non-user (tamoxifen only)	9240	150	16.2 (13.7, 19.1)	Reference
Non-concurrent w/tamoxifen	651	12	18.4 (9.5, 32.2)	1.82 (0.92, 3.61)
Concurrent w/tamoxifen[b]	1778	29	16.3 (10.9, 23.4)	1.10 (0.68, 1.79)
SSRI, Strong CYP2D6 inhibitor[d]				
Non-user	9654	155	16.1 (13.6, 18.8)	Reference
Non-concurrent w/tamoxifen	585	11	18.8 (9.4, 33.7)	1.84 (0.91, 3.73)
Concurrent w/tamoxifen[b]	1430	25	17.5 (11.3, 25.8)	1.15 (0.69–1.92)
SSRI, Weak/Moderate CYP2D6 inhibitor[f]				
Non-user (tamoxifen only)	10881	184	16.9 (14.6, 19.5)	Reference
Non-concurrent w/tamoxifen	241	1	4.2 (0.1, 23.1)	0.43 (0.06, 3.15)
Concurrent w/tamoxifen[b]	547	6	11.0 (4.0, 23.9)	0.51 (0.16, 1.62)
Paroxetine				
Non-user (tamoxifen only)	10659	172	16.1 (13.8, 18.7)	Reference
Non-concurrent w/tamoxifen	340	3	8.8 (1.8, 25.8)	0.95 (0.30, 3.05)
Concurrent w/tamoxifen[b]	670	16	23.9 (13.6, 38.8)	1.49 (0.79, 2.83)
Fluoxetine				
Non-user (tamoxifen only)	10367	170	16.4 (14.0, 19.1)	Reference
Non-concurrent w/tamoxifen	459	11	24.0 (12.0–42.9)	2.21 (1.04, 4.66)
Concurrent w/tamoxifen[b]	843	10	11.9 (5.7, 21.8)	0.73 (0.34, 1.59)
TCAs				
Non-user (tamoxifen only)	9451	153	16.2 (13.7, 19.0)	Reference
Non-concurrent w/tamoxifen	546	11	20.2 (10.1, 36.1)	1.26 (0.58, 2.74)
Concurrent w/tamoxifen[b]	1672	27	16.2 (10.6, 23.5)	0.79 (0.48, 1.31)
Miscellaneous antidepressant				
Non-user (tamoxifen only)	10229	170	16.6 (14.2, 19.3)	Reference
Non-concurrent w/tamoxifen	412	10	24.3 (11.6, 44.7)	1.99 (0.90, 4.40)
Concurrent w/tamoxifen[b]	1028	11	10.7 (5.3, 19.1)	0.74 (0.36, 1.52)

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; CI = confidence interval; w/ = with

[a] Restricted to 1902 women using tamoxifen for ≥60 days and no prior aromatase inhibitor use

[b] Concurrent use ≥60 days

[c] All estimates are from separate models accounting for competing risks. Censoring events were start of aromatase inhibitors, second primary breast cancer, death, Group Health disenrollment, and end of study follow-up. Adjusted for age at diagnosis (18–49, 50–59, 60–69, 70–79, 80+ years), year of diagnosis (1990–1994, 1995–1999, 2000–2004, 2005–2008), and American Joint Commission on Cancer stage

[d] Paroxetine and fluoxetine

[f] Sertraline, citalopram, fluvoxamine, and escitalopram

Table 5

Risk of breast-cancer specific death in relation to the use of antidepressants after a diagnosis and before recurrence (Group Health 1990–2008), N=4,216

	Person-years	Number of deaths due to breast cancer	Breast cancer mortality rate per 1,000 person-years (95% CI)	Unadjusted hazard ratio (95% CI)	Adjusted[a] hazard ratio (95% CI)
Overall	29900	264	8.8 (7.8, 10.0)	–	–
No use	16724	145	8.7 (7.4, 10.2)	Reference	Reference
Any antidepressant use	13176	119	9.0 (7.5, 10.8)	1.03 (0.81, 1.32)	1.09 (0.83, 1.43)
SSRI use					
Only – restriction	3024	18	6.0 (3.7, 9.4)	0.85 (0.52, 1.40)	0.89 (0.52, 1.50)
Any – adjustment	7714	70	9.1 (7.2, 11.5)	1.03 (0.78, 1.36)	1.14 (0.83, 1.56)
Paroxetine only	834	4	4.8 (1.8, 12.8)	0.76 (0.28, 2.08)	0.99 (0.35, 2.83)
Fluoxetine only	1268	7	5.5 (2.6, 11.6)	0.82 (0.38, 1.77)	0.71 (0.30, 1.67)
Sertraline only	258	3	11.7 (3.8, 36.1)	1.98 (0.63, 6.26)	2.42 (0.83, 7.02)
Citalopram only	189	2	10.6 (2.6, 42.3)	1.69 (0.42, 6.89)	2.52 (0.57, 11.20)
TCA use					
Only – restriction	3269	20	6.1 (3.9, 9.5)	0.92 (0.57, 1.49)	0.82 (0.48, 1.42)
Any - adjustment	7035	65	9.2 (7.2, 11.8)	1.06 (0.80, 1.41)	1.04 (0.77, 1.43)
Amitriptyline only	1101	5	4.5 (1.9, 10.9)	0.75 (0.30, 1.83)	0.71 (0.28, 1.81)
Nortriptyline only	889	6	6.7 (3.0, 15.0)	1.05 (0.46, 2.40)	0.81 (0.31, 2.08)
Miscellaneous antidepressant use					
Only – restriction	1312	10	7.6 (4.1, 14.2)	1.22 (0.64, 2.34)	1.55 (0.79, 3.04)
Any – adjustment	5407	43	8.0 (5.9, 10.7)	0.88 (0.63, 1.22)	0.92 (0.61, 1.38)
Bupropion only	180	1	5.6 (0.8, 39.5)	0.94 (0.13, 6.71)	1.70 (0.22, 13.10)
Trazodone only	929	6	6.5 (2.9, 14.4)	1.07 (0.47, 2.43)	1.25 (0.51, 3.00)

SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; CI = confidence interval

[a] All estimates are from separate models. Adjusted for age at diagnosis (18–49, 50–59, 60–69, 70–79, 80+ years), year of diagnosis (1990–1994, 1995–1999, 2000–2004, 2005–2008), American Joint Commission on Cancer stage (I, IIA, IIB), estrogen receptor (ER) and progesterone receptor (PR) status (ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR−), primary treatment (mastectomy, breast conserving surgery with radiation, breast conserving surgery without radiation), chemotherapy treatment (yes, no), endocrine therapy (yes, no), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35+ kg/m^2), smoking at diagnosis (current, past, never/unknown), menopausal status at diagnosis (peri- or pre-menopausal, post-menopausal), and Charlson score (0, 1, 2+). Total number of participants in adjusted model was 3924 due to exclusion of women with unknown ER/PR status or BMI.

[b] Unexposed groups for these analyses, i.e., non-users of specific antidepressants, are not shown in this table.