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Breast cancer recurrence risk in relation to antidepressant use after diagnosis

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Abstract

Background—While laboratory data suggest that antidepressants may promote mammary tumor growth, there has been little research investigating whether antidepressant use after breast cancer diagnosis is associated with the risk of breast cancer recurrence.

Methods—We conducted a retrospective cohort study within Group Health, an integrated healthcare delivery system in Washington state. Women diagnosed with a first primary invasive, stage I, IIA, or IIB, unilateral breast carcinoma between 1990–1994 (aged 65 years) and 1996–1999 (aged 18 years) were eligible for the study (N=1306). Recurrence within 5-years of diagnosis was ascertained by medical chart review. We used the pharmacy database to identify antidepressant dispensings from Group Health pharmacies. We used multiple Cox regression to estimate the hazard ratio for recurrence and breast cancer mortality, comparing users and non-users antidepressant medications. Results for recurrence were examined separately in users and non-users of tamoxifen.

Results—We did not observe an association between antidepressant use after breast cancer diagnosis and the risk of recurrence either in general (hazard ratio for any antidepressant use: 0.8; 95% confidence interval: 0.5 to 1.4) or for specific types of antidepressant medication. Risk of death from breast cancer did not differ between non-users and users of antidepressants.

Conclusions—The results of this study suggest that women who use antidepressants after breast cancer diagnosis do not have an increased risk of recurrence or mortality.

Keywords

antidepressant medications; breast cancer; cancer epidemiology; pharmacoepidemiology; recurrence

Introduction

About a quarter of women with breast cancer suffer from depression [1, 2] and an estimated 15%-25% of American women use antidepressants after breast cancer diagnosis [3–5]. In

addition to depression and other psychological disorders, antidepressants are prescribed for other indications in women with breast cancer, including pain [6] and menopausal hot flashes [7], which can be caused by tamoxifen [8, 9].

Laboratory studies have suggested that antidepressants may promote breast cancer by binding to the antiestrogen binding site and triggering a histamine-mediated second messenger system [10, 11], increasing prolactin levels [12–15], or altering immune function [16, 17]. However, the accumulating epidemiologic evidence suggests no association of these drugs with breast cancer occurrence [18–23].

There has been little epidemiological research to investigate whether the use of antidepressants following breast cancer diagnosis might influence the risk of recurrence or mortality due to breast cancer [24–26]. Of particular importance to women who already have breast cancer, tamoxifen metabolism may be impaired by certain selective serotonin reuptake inhibitors (SSRIs), since certain SSRIs, particularly paroxetine and fluoxetine, inhibit CYP2D6, an enzyme that metabolizes tamoxifen to an active form [27–31].

We designed this study to assess the impact of antidepressant use on breast cancer recurrence by conducting a retrospective, population-based cohort study of women diagnosed with early stage breast cancer.

Methods

We conducted this study at Group Health, an integrated delivery system providing healthcare on a pre-paid basis to approximately 550,000 individuals in western Washington state [32]. Group Health is located within the geographic reporting region of the western Washington Cancer Surveillance System, a population-based cancer registry and member of the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute [33]. Women were eligible for this study if they were diagnosed with a first primary invasive, stage I, IIA, or IIB, unilateral breast carcinoma [34]. Women with stage III or IV breast cancer at diagnosis or women who developed a metastasis within 4 months of diagnosis were excluded because it is highly unlikely that they were cancer-free after treatment. The data were collected as part of two studies that linked Group Health data to the western Washington SEER cancer registry. The first study, Breast Cancer Treatment Effectiveness in Older Women (BOW), was restricted to women ≥ 65 years old diagnosed between January 1, 1990 and December 31, 1994 [35–37]. The second study, funded by the American Cancer Society (ACS), included women ≥ 18 years diagnosed between January 1, 1996 and December 31, 1999 [37]. All participants were required to be enrolled at Group Health during the year before diagnosis and one year after diagnosis unless they died within 12 months of diagnosis and all women had to have been free of any malignancies in the five years before entering the study. We also restricted our study to women who had received definitive surgical treatment (i.e. mastectomy or breast conserving surgery). With the exception of age at diagnosis and year of diagnosis, inclusion and exclusion criteria were the same for the both studies. Institutional review board approval and waivers of consent were obtained for both studies. Our analytic cohort (N=1306) consisted of 398 women from the BOW study and 908 women from the ACS study.

Data collection

We collected demographic data, information on American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging [34], tumor size, histology, tumor grade, definitive surgery, surgical margins, evaluation of lymph nodes, estrogen receptor (ER) and progesterone receptor (PR) status, and details on radiation, chemotherapy, and tamoxifen use. All charts were reviewed beginning one year before diagnosis and follow-up extended

through death, disenrollment from Group Health, or five years after diagnosis. Trained chart abstractors reviewed paper and electronic medical records and entered data directly into a computerized study database with preloaded SEER registry data (e.g. tumor stage and size) [38].

For all primary breast cancer treatments, we abstracted information on the beginning and end dates of the regimen. Radiation treatment and chemotherapy that began within six months of definitive surgery and tamoxifen initiated within one year of definitive surgery were defined as treatment of the primary tumor. We considered a woman to have used tamoxifen if it was recorded in either the pharmacy database or the medical record.

We also collected information on recurrences and second primary breast cancer. Recurrences were included if they were identified at least 120 days after the original diagnosis or completion of surgeries during the first course of treatment, whichever was longer [36]. A recurrence was defined as an invasive tumor in the ipsilateral breast, in the lymph nodes, skin, or chest muscle on the same side as the original tumor, or metastatic spread outside of the breast or axilla. A second primary was defined as an invasive cancer occurring in the contralateral breast. We also considered a woman as having a recurrence if she died of breast cancer without having had a documented recurrence (n=5). A woman was considered to have died of breast cancer if breast cancer was listed as the underlying cause of death (International Classification of Diseases version 9 (ICD-9) codes 174.0–174.9 [39] and ICD-10 codes C50.0–C50.9 [40]) in either the SEER or State death certificate data files.

We obtained data on antidepressant use and tamoxifen use from Group Health's electronic pharmacy database. The pharmacy database contains one record for each prescription dispensed at a Group Health pharmacy; each record includes a unique patient identifier, generic drug name, therapeutic class, form, strength, directions for use, date dispensed, number of pills dispensed, intended days supply of prescription (as of 1996), and National Drug Code [32]. We identified prescriptions for SSRIs, TCAs, miscellaneous antidepressants, and tamoxifen filled in the year before each woman's diagnosis through the end of follow-up. A woman was classified as a user of a particular class of antidepressants (SSRIs, TCA, miscellaneous) once she filled two or more prescriptions for a particular drug within that class within any 6-month interval after breast cancer diagnosis and before a recurrence or second primary breast cancer. This condition must have been met regardless of whether a woman had used antidepressants before her breast cancer diagnosis. The filling of two prescriptions within this relatively short time interval gives some assurance that the drug was actually taken [41–44]; the time between dispensings was generally less than two months.

For the purposes of secondary analyses, we computed the run-out date, or expected duration of the prescription, assuming 80% adherence, as the number of days' supply of the prescription multiplied by 1.25 [45]. When the days' supply variable was not available, we estimated the intended duration of the prescription based on prescription instructions or, if those were not available, the median duration of other prescriptions for that drug, quantity, and strength. Use was considered continuous if a woman filled a prescription on or before the run-out date of the previous prescription.

Analysis

We evaluated the risk of breast cancer recurrence in relation to ever-use of antidepressants after breast cancer diagnosis. We calculated the risk of recurrence associated with several post-diagnosis exposures: any antidepressant use, SSRI use only, any SSRI use, TCA use only, any TCA use, miscellaneous antidepressant use only, and any miscellaneous antidepressant use. In all analyses, women who had not used antidepressants after diagnosis

served as the reference group. At any given time point, the reference group included person-time from women who later went on to fill antidepressant prescriptions. Exposure variables were time-varying; a woman contributed person-time to a particular exposure category only after she met the definition of use. However, after meeting this definition, she remained in that exposure category even if she discontinued antidepressant use. We estimated unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CI) with Cox proportional hazards regression [46] with robust standard error estimates. The time scale for all analyses was time since diagnosis. We censored the follow-up of women at the first of the following: disenrollment from Group Health, death from a cause other than breast cancer, second primary breast cancer, or five years after initial diagnosis. We investigated whether or not hazards were proportional by including an interaction term between exposure and time. Since the evidence did not suggest a violation of the proportional hazards assumptions, we used a proportional hazards model. For the main analysis, we assessed each exposure in a separate model so that we could evaluate exposure categories that were not mutually exclusive (e.g. any SSRI use and SSRI use only). We also assessed SSRI use and TCA use in the same model and included an interaction between them. Models were adjusted for age at diagnosis, year of diagnosis, stage at diagnosis, hormone receptor status, tumor grade, and primary and adjuvant treatments received.

To investigate a potential interaction between concurrent antidepressant use and tamoxifen use, we restricted our analysis to women with hormone receptor positive cancer (positive for estrogen and/or progesterone receptors). We determined whether or not a woman had used antidepressants and tamoxifen concurrently based upon start and stop dates of their prescriptions. A woman was classified as a concurrent antidepressant and tamoxifen user on the day she filled prescription for an SSRI within six months while already taking tamoxifen or *vice versa*. She then remained classified as ever having concurrently used antidepressants and tamoxifen, regardless of subsequent use. We computed unadjusted rates of recurrence for each class of antidepressants and for the strongest CYP2D6 inhibitors (paroxetine and fluoxetine) stratified by tamoxifen use. All analyses were performed using Stata 9 (StataCorp LP, College Station, Texas).

Results

The mean age at diagnosis was 66 years and over 90% of participants were non-Hispanic white (Table 1). Most cancers were stage I (70.1%), ductal (78.5%), hormone receptor positive (79.1%), and either well- or moderately-differentiated (60.6%). Most women received either breast-conserving surgery plus radiation or mastectomy; 10% received breast conserving surgery without radiation. Approximately 60% of women were treated with adjuvant therapy (chemotherapy and/or tamoxifen). For those characteristics that we ascertained, women who used antidepressants after diagnosis did not differ substantially from non-users (Table 1). Women who used antidepressants following the diagnosis of breast cancer were more likely to have used antidepressants prior to diagnosis, to have received breast conserving surgery without radiation, and to have a higher Charlson index co-morbidity score.

One third of women met the definition of antidepressant user during follow-up (Table 2). Overall, similar percentages of cohort members used SSRIs (18.6%) and TCAs (16.8%). The most commonly used antidepressant was paroxetine (10.3%), followed by trazodone (9.0%), amitriptyline (6.8%), and fluoxetine (6.4%) (data not shown). Antidepressant use increased over the years of the study. Approximately one quarter of women diagnosed in 1990 used antidepressants during follow-up, compared to more than one third of women diagnosed in 1999. Additionally, the type of antidepressant used changed over the course of the study. Among women diagnosed in 1990, 5% used SSRIs and 17% used TCAs after

diagnosis, compared to 26% and 12%, respectively, for women diagnosed in 1999. The median durations of use of SSRIs and TCAs were 12.3 and 13.8 months, respectively.

There were 103 recurrences in 5303.7 years of follow-up, yielding an overall rate of 19.4 recurrences per 1,000 person-years (95% CI: 16.0 to 23.6). Overall, antidepressant use after diagnosis was not associated with risk of breast cancer recurrence during the first five years after diagnosis (Table 3). The rate of recurrence in non-users was 19.8 per 1,000 person-years (95% CI: 15.9 to 24.7) compared to 18.1 per 1,000 person-years (95% CI: 12.2 to 27.0) in users of any antidepressants. The point-estimate for the adjusted hazard ratio, 0.8 (95% CI: 0.5 to 1.4), was nearly the same as the unadjusted hazard ratio. The hazard ratio was slightly below 1.0 for use of SSRIs and TCAs and above 1.0 for miscellaneous antidepressant use. However, the 95% confidence intervals for all estimates were wide and included the null. When we required a one year lag after drug initiation to consider a woman “exposed”, the adjusted hazard ratio was 1.0 (95% CI: 0.6 to 1.7) for any antidepressant use, 1.3 (95% CI: 0.6 to 3.0) for SSRI use exclusively, and 0.6 (95% CI: 0.2 to 1.6) for TCA use exclusively (data not shown).

Among hormone receptor positive women, SSRI use (particularly use of the strongest CYP2D6 inhibitors, fluoxetine and paroxetine) was associated with a modest increase in risk of recurrence in users of tamoxifen (Table 4), but the number of observations was too small for any firm conclusions to be drawn. Due to the low number of recurrence events, we were unable to adjust our results.

Antidepressant use after diagnosis but before recurrence was not associated with breast cancer specific mortality (Table 5). The rate among women who did not use antidepressants was 8.5 per 1,000 person-years (95% CI: 6.1 to 11.8), compared to 8.1 per 1,000 person-years (95% CI: 4.5 to 14.7) among women who did.

Discussion

A number of epidemiological studies have investigated the relation between antidepressant use and the risk of breast cancer [19–22, 47–57]. Although laboratory studies have suggested mechanisms by which antidepressant medications could promote mammary tumor growth [10–17], little research has been conducted to assess whether antidepressant use after breast cancer is associated with an increased risk of breast cancer recurrence. We investigated this question and did not observe an association between antidepressant use after diagnosis and the risk of breast cancer recurrence.

There were several advantages to investigating the relationship between antidepressant use after breast cancer diagnosis and the risk of recurrence by conducting a population-based retrospective cohort study using the Group Health patient population [32]. Group Health serves a broad population base and is located within the geographic reporting region of SEER [33]. Through the SEER program and medical records review, we were able to collect nearly complete data on important predictors of breast cancer recurrence. Because we were able to obtain prospectively recorded data from the pharmacy database, our information on antidepressant use was uninfluenced by study outcomes or subject to recall bias. Furthermore, medication information was likely to be relatively complete; several studies suggest that about 97% of Group Health enrollees fill all or most of their prescriptions at Group Health pharmacies [32]. Additionally, our outcome data on breast cancer recurrence were likely to be complete since they were collected systematically via chart abstraction.

The results of our study do not support the hypothesis that women who use antidepressants after breast cancer diagnosis have an increased risk of breast cancer recurrence. However, we did not have sufficient power to detect small differences in risk and our results pertain

only to the first five years following the diagnosis of breast cancer. Also, women who filled prescriptions but did not subsequently take the medication may have been misclassified as users, however, this misclassification is likely to have been minor based on our definition of use as “use” as two or more dispensings within six months [41–44]. Though some subjects may have been misclassified as non-users if they obtained medications at non-Group Health pharmacies, this number is also likely to have been small.

An additional concern in this study was confounding by unmeasured variables, including indication for antidepressant use. Confounding by indication occurs when the indication for a prescription is associated with the outcome of interest [58]. Even if antidepressant use were not independently associated with the risk of breast cancer recurrence, it could appear to be if antidepressant users had a higher risk of recurrence due to depression and/or inadequate treatment. However, it is unclear whether psychosocial characteristics are independent risk factors for prognosis [59–61]. Removing any confounding by indication would likely decrease the hazard ratio; in other words, the lack of an observed association is unlikely to be due to confounding by indication.

Other potential unmeasured confounders include diet and physical activity. To confound our analyses, these factors would need to be associated with both the exposure and the outcome. Some, but not all, studies have suggested that these factors are modestly associated with prognosis [62, 63]. Our data suggest that antidepressant users are slightly heavier and have slightly more co-morbid conditions than non-users. However, it seems more likely that such associations would induce, rather than mask, an association between antidepressant use and breast cancer recurrence.

One prior study assessed the relationship between antidepressant or antihistamine use and cancer recurrence [64]; however, the application of results from that study is limited since it did not assess breast cancer recurrence separately from recurrences of colon cancer and melanoma or present data for antidepressant use separately from antihistamine use. Two studies looked specifically at concurrent use of CYP2D6 inhibitors and tamoxifen in relation to breast cancer recurrence [24, 25]. In one, a case-control study, the use of CYP2D6 inhibitors (paroxetine, fluoxetine, and sertraline) did not differ appreciably in the women whose breast cancer recurred (n=28) compared to those who did not (n=28) (OR: 0.75, 95% CI: 0.26 to 2.16) [24]. A recent cohort study found that women who were poor tamoxifen metabolizers, due to genetic variation and/or use of CYP2D6 inhibitors, had a two-fold increased risk of recurrence; however, it was not established whether increased risk of recurrence in women with decreased tamoxifen metabolism was due to genetic variation, use of CYP2D6 inhibitors, or both. In our study, women who used CYP2D6 inhibitors and tamoxifen concurrently had a slightly elevated risk of recurrence. However, our power for this secondary analysis was limited.

In summary, our results suggest that women who use antidepressants after a diagnosis of breast cancer do not have a different risk of recurrence or breast cancer mortality than women who do not have breast cancer. However, it will be important to confirm these results in studies with longer follow-up periods, and in studies with greater power to look at individual antidepressants and to investigate the association between recurrence and concurrent tamoxifen and CYP2D6 inhibitor use.

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Table 1

Characteristics of users and non-users of antidepressants after a diagnosis of breast cancer and before recurrence (Group Health, 1990–1994 and 1996–1999)^a

	<u>All</u>	<u>Antidepressant use after diagnosis</u>	
	(N=1306)	No (N=867)	Yes (N=439)
	n (%)	n (%)	n (%)
<u>Age at diagnosis (years)</u>			
18 – 39	23 (1.8)	16 (1.8)	7 (1.6)
40 – 49	142 (10.9)	88 (10.1)	54 (12.3)
50 – 59	214 (16.4)	128 (14.8)	86 (19.6)
60 – 69	332 (25.4)	231 (26.6)	101 (23.0)
70 – 79	413 (31.6)	284 (32.8)	129 (29.4)
80	182 (13.9)	120 (13.8)	62 (14.1)
<u>Year of diagnosis</u>			
1990	94 (7.2)	72 (8.3)	22 (5.0)
1991	57 (4.4)	46 (5.3)	11 (2.5)
1992	77 (5.9)	58 (6.7)	19 (4.3)
1993	80 (6.1)	56 (6.5)	24 (5.5)
1994	90 (6.9)	57 (6.6)	33 (7.5)
1996	201 (15.4)	137 (15.8)	64 (14.6)
1997	232 (17.8)	155 (17.9)	77 (17.5)
1998	240 (18.4)	137 (15.8)	103 (23.5)
1999	235 (18.0)	149 (17.2)	86 (19.6)
<u>Race</u>			
White, non-Hispanic	1213 (92.9)	793 (91.5)	420 (95.7)
Other	93 (7.1)	74 (8.5)	19 (4.3)
<u>Cancer characteristics</u>			
<u>Stage at diagnosis</u>			
I	916 (70.1)	607 (70.0)	309 (70.4)
IIA	303 (23.2)	201 (23.2)	102 (23.2)
IIB	87 (6.7)	59 (6.8)	28 (6.4)
<u>Nodal involvement</u>			
No	869 (66.5)	579 (66.8)	290 (66.1)
Yes	192 (14.7)	126 (14.5)	66 (15.0)
No surgical evaluation	245 (18.8)	132 (18.7)	83 (18.9)
<u>Tumor size</u>			
< 2.0 cm	931 (71.3)	613 (70.7)	318 (72.4)
2.0 cm	375 (28.7)	254 (29.3)	121 (27.6)
<u>Tumor histology</u>			
Ductal	1025 (78.5)	676 (78.0)	349 (79.5)
Lobular	128 (9.8)	88 (10.1)	40 (9.1)
Mixed/other	153 (11.7)	103 (11.9)	50 (11.4)

	<u>All</u>	<u>Antidepressant use after diagnosis</u>	
	(N=1306) n (%)	No (N=867) n (%)	Yes (N=439) n (%)
<u>Tumor grade</u>			
Well differentiated	319 (24.4)	214 (24.7)	105 (23.9)
Moderately differentiated	473 (36.2)	298 (34.4)	175 (39.9)
Poorly/undifferentiated	337 (25.8)	236 (27.2)	101 (23.0)
Not determined or stated	177 (13.6)	119 (13.7)	58 (13.2)
<u>Hormone receptor status</u>			
Estrogen receptor positive and/or progesterone receptor positive	1033 (79.1)	683 (78.8)	350 (79.7)
Estrogen receptor negative and progesterone receptor negative	180 (13.8)	123 (14.2)	57 (13.0)
Other/unknown	93 (7.1)	61 (7.0)	32 (7.3)
<u>Cancer treatment</u>			
<u>Primary therapy</u>			
Mastectomy with or without radiation	424 (32.5)	274 (31.6)	150 (34.2)
Breast conserving surgery with radiation	744 (57.0)	517 (59.6)	227 (51.7)
Breast conserving surgery without radiation	138 (10.6)	76 (8.8)	62 (14.1)
<u>Adjuvant treatment</u>			
Tamoxifen only	504 (38.6)	337 (38.9)	167 (38.0)
Chemotherapy only	146 (11.2)	93 (10.7)	53 (12.1)
Both chemotherapy and tamoxifen	142 (10.9)	80 (9.2)	62 (14.1)
Neither chemotherapy nor tamoxifen	514 (39.4)	357 (41.2)	157 (35.8)
<u>Health history</u>			
<u>Charlson Index (year prior to diagnosis)</u>			
0	906 (69.4)	616 (71.0)	290 (66.1)
1 or 2	352 (27.0)	226 (26.1)	126 (28.7)
3	48 (3.7)	25 (2.9)	23 (5.2)
<u>Body mass index at diagnosis</u>			
< 25 kg/m ²	439 (37.9)	296 (38.5)	143 (36.8)
25 – < 30 kg/m ²	379 (32.8)	263 (34.2)	116 (29.8)
30 kg/m ²	339 (29.3)	209 (27.2)	130 (33.4)
Missing	149	99	50
<u>Antidepressant use in year before diagnosis</u>			
No use	1126 (86.2)	848 (97.8)	278 (63.3)
SSRIs only	39 (3.0)	7 (0.8)	32 (7.3)
TCAs only	91 (7.0)	10 (1.2)	81 (18.5)
Miscellaneous only	20 (1.5)	1 (0.1)	19 (4.3)
Multiple classes	30 (2.3)	1 (0.1)	29 (6.6)

^aSSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

Table 2

Antidepressant prescriptions filled after breast cancer diagnosis and before recurrence in 1306 women diagnosed with early stage breast cancer (Group Health, 1990–1994 and 1996–1999)

	Number of users (%)	Median time to first use (months)	Median duration of use (months)
Any antidepressant ^a	439 (33.6)	10.7	16.6
Selective serotonin reuptake inhibitors	243 (18.6)	18.9	12.3
Tricyclic antidepressants	219 (16.8)	8.6	13.8
Miscellaneous antidepressants	138 (10.6)	14.9	11.9

^aCategories of antidepressants are not mutually exclusive.

Table 3

Five-year risk of breast cancer recurrence in relation to the use of antidepressants after a diagnosis of breast cancer (Group Health, 1990–1994 and 1996–1999)^a

	Person-years	Number of recurrences	Recurrence rate per 1,000 person-years (95% CI)	Unadjusted hazard ratio (95% CI)	Adjusted ^b hazard ratio (95% CI)
Overall	5303.7	103	19.4 (16.0 to 23.6)		
No antidepressant use	3980.0	79	19.8 (15.9 to 24.7)	1.0 (reference)	1.0 (reference)
Any antidepressant use	1323.7	24	18.1 (12.2 to 27.0)	0.9 (0.6 to 1.4)	0.8 (0.5 to 1.4)
SSRI use					
Only	369.3	7	19.0 (9.0 to 39.8)	0.9 (0.4 to 2.0)	0.8 (0.4 to 1.9)
Any	643.5	11	17.1 (9.5 to 30.9)	0.8 (0.4 to 1.6)	0.8 (0.4 to 1.5)
TCA use					
Only	468.2	7	15.0 (7.1 to 31.4)	0.7 (0.3 to 1.6)	0.8 (0.4 to 1.8)
Any	681.7	11	16.1 (8.9 to 29.1)	0.8 (0.4 to 1.5)	0.8 (0.4 to 1.6)
Miscellaneous antidepressant use					
Only	157.3	4	25.4 (9.5 to 67.7)	1.3 (0.5 to 3.5)	1.0 (0.3 to 3.2)
Any	374.5	9	24.0 (12.5 to 46.2)	1.2 (0.6 to 2.4)	1.0 (0.4 to 2.1)

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

^bAll estimates are from separate models. Adjusted for age at diagnosis (18–39, 40–49, 50–59, 60–69, 70–79, 80+ years); year of diagnosis (1990, 1991, 1992, 1993, 1994, 1996, 1997, 1998, 1999); stage (I, IIA, IIB); receptor status (estrogen receptor positive or progesterone receptor positive, estrogen receptor negative and progesterone receptor negative, other/unknown), tumor grade (well differentiated, moderately differentiated, poorly differentiated/undifferentiated, unknown tumor grade); primary therapy (mastectomy or breast conserving therapy with radiation, breast conserving therapy without radiation); and adjuvant therapy (chemotherapy and/or tamoxifen, neither). All variables were included as categorical variables. Treatment variables were included as time-varying covariates.

Table 4

Five-year risk of breast cancer recurrence in relation to antidepressant use after a diagnosis of hormone receptor positive breast cancer, stratified by tamoxifen use (Group Health, 1990–1994 and 1996–1999)^{a,b}

	Person-years	Number of recurrences	Recurrence rate per 1,000 person-years (95% CI)	Unadjusted hazard ratio (95% CI)
<u>Non-users of tamoxifen</u>				
No antidepressant use	1392.8	20	14.4 (9.3 to 22.3)	1.0 (reference)
Any antidepressant use	406.4	6	14.8 (6.6 to 32.9)	0.9 (0.4 to 2.2)
SSRI use exclusively	117.8	2	17.0 (4.2 to 67.9)	1.0 (0.2 to 4.3)
Paroxetine and/or fluoxetine exclusively	98.5	2	20.3 (5.1 to 81.2)	1.3 (0.5 to 3.4)
TCA use exclusively	142.2	2	14.0 (3.2 to 56.2)	0.9 (0.2 to 3.6)
Miscellaneous antidepressant use exclusively	49.6	1	20.2 (2.8 to 143.1)	1.3 (0.2 to 10.2)
<u>Tamoxifen users^c</u>				
No antidepressant use	1789.1	27	15.1 (10.3 to 22.0)	1.0 (reference)
Any concurrent antidepressant use	562.1	10	17.8 (9.6 to 33.1)	1.1 (0.5 to 2.4)
Concurrent SSRI use exclusively	154.9	3	19.4 (6.2 to 60.0)	1.2 (0.4 to 4.2)
Paroxetine and/or fluoxetine exclusively	112.5	3	26.7 (8.6 to 82.7)	1.7 (0.5 to 5.7)
Concurrent TCA use exclusively	187.1	3	16.0 (5.2 to 49.7)	1.0 (0.3 to 3.5)
Concurrent miscellaneous antidepressant use exclusively	54.1	1	18.5 (2.6 to 131.3)	1.2 (0.2 to 9.3)

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

^bRestricted to women with estrogen and/or progesterone positive hormone receptor status (n=1033).

^cExcludes person-time and events for non-concurrent tamoxifen and antidepressant use: 2 recurrences in 104.8 person-years for any antidepressant use, 0 recurrences in 27.5 person-years for exclusive SSRI use, 0 recurrences in 17.1 person-years for paroxetine and/or fluoxetine use exclusively, 0 recurrences in 48.1 person-years for exclusive TCA use, 1 recurrence in 14.9 person-years for exclusive miscellaneous antidepressant use.

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Table 5

Five-year risk of mortality from breast cancer in relation to the use of antidepressants after a diagnosis and before recurrence (Group Health 1990–1994 and 1996–1999)^a

	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 ^b hazard ratio (95% CI)
Overall	5470.7	46	8.4 (6.3 to 11.2)		
No use	4119.3	35	8.5 (6.1 to 11.8)	1.0 (reference)	1.0 (reference)
Any antidepressant use	1351.5	11	8.1 (4.5 to 14.7)	0.9 (0.5 to 1.8)	0.9 (0.4 to 1.9)
SSRI use					
Only	376.5	2	5.3 (1.3 to 21.2)	0.6 (0.1 to 2.4)	0.7 (0.2 to 3.0)
Any	655.3	5	7.6 (3.2 to 18.3)	0.8 (0.3 to 2.2)	1.0 (0.4 to 2.5)
TCA use					
Only	477.0	3	6.3 (2.0 to 19.5)	0.7 (0.2 to 2.3)	0.8 (0.2 to 3.0)
Any	694.4	5	7.2 (3.0 to 17.3)	0.8 (0.3 to 2.1)	0.8 (0.3 to 2.3)
Miscellaneous antidepressant use					
Only	163.2	2	12.3 (3.1 to 49.0)	1.4 (0.3 to 5.8)	1.0 (0.2 to 5.1)
Any	386.3	5	12.9 (5.4 to 31.1)	1.4 (0.6 to 3.6)	1.2 (0.4 to 3.4)

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

^bAdjusted for age at diagnosis (< 50, 50 years); year of diagnosis (1990, 1991, 1992, 1993, 1994, 1996, 1997, 1998, 1999); stage (I, IIA, IIB); receptor status (estrogen receptor positive or progesterone receptor positive other/unknown), tumor grade (well/moderately differentiated, poorly differentiated/undifferentiated/unknown tumor grade); primary therapy (mastectomy or breast conserving therapy with radiation, breast conserving therapy without radiation); and adjuvant therapy (chemotherapy and/or tamoxifen, neither). All variables were included as categorical variables. Treatment variables were included as time-varying covariates.