Breast Cancer Res Treat (2008) 112:123–132
DOI 10.1007/s10549-007-9828-9

EPIDEMIOLOGY

Breast cancer recurrence risk in relation to antidepressant use after diagnosis

Jessica Chubak · Diana S. M. Buist · Denise M. Boudreau · Mary Anne Rossing · Thomas Lumley · Noel S. Weiss

Received: 13 November 2007 / Accepted: 15 November 2007 / Published online: 6 December 2007

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-year 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 of 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: 0.5–1.4) 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

J. Chubak (✉) · D. S. M. Buist · D. M. Boudreau
Group Health Center for Health Studies, 1730 Minor Ave, Suite 1600, Seattle, WA 98101-1448, USA
e-mail: chubak.j@ghc.org

J. Chubak · D. S. M. Buist · M. A. Rossing · N. S. Weiss
Department of Epidemiology, University of Washington, Seattle, WA, USA

J. Chubak · D. S. M. Buist · M. A. Rossing · N. S. Weiss
Fred Hutchinson Cancer Research Center, Seattle, WA, USA

D. M. Boudreau
School of Pharmacy, University of Washington, Seattle, WA, USA

T. Lumley
Department of Biostatistics, University of Washington, Seattle, WA, USA

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 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 6 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 2 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 a prescription for an SSRI within 6 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 [47].

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

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]

	All	Antidepressant use after diagnosis	
	(N = 1,306) n (%)	No (N = 867) n (%)	Yes (N = 439) n (%)
Age at diagnosis (years)			
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)
Year of diagnosis			
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)
Race			
White, non-Hispanic	1,213 (92.9)	793 (91.5)	420 (95.7)
Other	93 (7.1)	74 (8.5)	19 (4.3)
Cancer characteristics			
Stage at diagnosis			
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)
Nodal involvement			
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)
Tumor size			
<2.0 cm	931 (71.3)	613 (70.7)	318 (72.4)
≥2.0 cm	375 (28.7)	254 (29.3)	121 (27.6)
Tumor histology			
Ductal	1,025 (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)
Tumor grade			
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)
Hormone receptor status			
Estrogen receptor positive and/or progesterone receptor positive	1,033 (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)

Table 1 continued

	All (N = 1306) n (%)	Antidepressant use after diagnosis	
		No (N = 867) n (%)	Yes (N = 439) n (%)
Cancer treatment			
Primary therapy			
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)
Adjuvant treatment			
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)
Health history			
Charlson Index (year prior to diagnosis)			
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)
Body mass index at diagnosis			
<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
Antidepressant use in year before diagnosis			
No use	1,126 (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)

[a] SSRI, 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

[a] Categories of antidepressants are not mutually exclusive

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 5,303.7 years of follow-up, yielding an overall rate of 19.4 recurrences per 1,000 person-years (95% CI: 16.0–23.6). Overall, antidepressant use after diagnosis was not associated with risk of breast

cancer recurrence during the first 5 years after diagnosis (Table 3). The rate of recurrence in non-users was 19.8 per 1,000 person-years (95% CI: 15.9–24.7) compared to 18.1 per 1,000 person-years (95% CI: 12.2–27.0) in users of any antidepressants. The point-estimate for the adjusted hazard ratio, 0.8 (95% CI: 0.5–1.4), 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: 0.6–1.7) for any antidepressant use, 1.3 (95% CI: 0.6–3.0) for SSRI use exclusively, and 0.6 (95% CI: 0.2–1.6) 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: 6.1–11.8), compared to 8.1 per 1,000 person-years (95% CI: 4.5–14.7) 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, 48–58]. 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

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	5,303.7	103	19.4 (16.0–23.6)		
No antidepressant use	3,980.0	79	19.8 (15.9–24.7)	1.0 (reference)	1.0 (reference)
Any antidepressant use	1,323.7	24	18.1 (12.2–27.0)	0.9 (0.6–1.4)	0.8 (0.5–1.4)
SSRI use					
Only	369.3	7	19.0 (9.0–39.8)	0.9 (0.4–2.0)	0.8 (0.4–1.9)
Any	643.5	11	17.1 (9.5–30.9)	0.8 (0.4–1.6)	0.8 (0.4–1.5)
TCA use					
Only	468.2	7	15.0 (7.1–31.4)	0.7 (0.3–1.6)	0.8 (0.4–1.8)
Any	681.7	11	16.1 (8.9–29.1)	0.8 (0.4–1.5)	0.8 (0.4–1.6)
Miscellaneous antidepressant use					
Only	157.3	4	25.4 (9.5–67.7)	1.3 (0.5–3.5)	1.0 (0.3–3.2)
Any	374.5	9	24.0 (12.5–46.2)	1.2 (0.6–2.4)	1.0 (0.4–2.1)

[a] SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; CI, confidence interval

[b] All 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)
Non-users of tamoxifen				
No antidepressant use	1,392.8	20	14.4 (9.3–22.3)	1.0 (reference)
Any antidepressant use	406.4	6	14.8 (6.6–32.9)	0.9 (0.4–2.2)
SSRI use exclusively	117.8	2	17.0 (4.2–67.9)	1.0 (0.2–4.3)
Paroxetine and/or fluoxetine exclusively	98.5	2	20.3 (5.1–81.2)	1.3 (0.5–3.4)
TCA use exclusively	142.2	2	14.0 (3.2–56.2)	0.9 (0.2–3.6)
Miscellaneous antidepressant use exclusively	49.6	1	20.2 (2.8–143.1)	1.3 (0.2–10.2)
Tamoxifen users[c]				
No antidepressant use	1,789.1	27	15.1 (10.3–22.0)	1.0 (reference)
Any concurrent antidepressant use	562.1	10	17.8 (9.6–33.1)	1.1 (0.5–2.4)
Concurrent SSRI use exclusively	154.9	3	19.4 (6.2–60.0)	1.2 (0.4–4.2)
Paroxetine and/or fluoxetine exclusively	112.5	3	26.7 (8.6–82.7)	1.7 (0.5–5.7)
Concurrent TCA use exclusively	187.1	3	16.0 (5.2–49.7)	1.0 (0.3–3.5)
Concurrent miscellaneous antidepressant use exclusively	54.1	1	18.5 (2.6–131.3)	1.2 (0.2–9.3)

[a] SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; CI, confidence interval

[b] Restricted to women with estrogen and/or progesterone positive hormone receptor status (n = 1033)

[c] Excludes 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

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	5,470.7	46	8.4 (6.3–11.2)		
No use	4,119.3	35	8.5 (6.1–11.8)	1.0 (reference)	1.0 (reference)
Any antidepressant use	1,351.5	11	8.1 (4.5–14.7)	0.9 (0.5–1.8)	0.9 (0.4–1.9)
SSRI use					
Only	376.5	2	5.3 (1.3–21.2)	0.6 (0.1–2.4)	0.7 (0.2–3.0)
Any	655.3	5	7.6 (3.2–18.3)	0.8 (0.3–2.2)	1.0 (0.4–2.5)
TCA use					
Only	477.0	3	6.3 (2.0–19.5)	0.7 (0.2–2.3)	0.8 (0.2–3.0)
Any	694.4	5	7.2 (3.0–17.3)	0.8 (0.3–2.1)	0.8 (0.3–2.3)
Miscellaneous antidepressant use					
Only	163.2	2	12.3 (3.1–49.0)	1.4 (0.3–5.8)	1.0 (0.2–5.1)
Any	386.3	5	12.9 (5.4–31.1)	1.4 (0.6–3.6)	1.2 (0.4–3.4)

[a] SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; CI, confidence interval

[b] Adjusted 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

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 5 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 two or more dispensing within 6 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 [59]. 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 [60–62]. Removing any confounding by indication would likely decrease the hazard ratio; in other words, the lack of an observed is 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 [63, 64]. 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 [65]; 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: 0.26–2.16) [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 twofold increased risk of recurrence; however, it is 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.

Acknowledgments We would like to thank Rebecca Silliman, MD, PhD for developing the data abstraction instrument, leading the BOW study, helping to secure funding and providing guidance throughout the project; and Soe Soe Thwin, PhD for developing the data abstraction instrument and sharing common programs from BOW. We would also like to thank project manager Linda Shultz, MPH and our colleagues who collected data for this study: Kristin Delaney, MPH; Margaret Farrell-Ross, MPH; Mary Sunderland; Millie Magner; Beth Kirlin, Srabani Dutta, Chester Pabiniak, and Julia Hecht, PhD. This research was supported by: National Cancer Institute (R01 CA09377, T32 CA09168 to JC); American Cancer Society (CRTG-03–024-01-CCE). The contents of this publication are soley the responsibility of the authors and do not necessarily represent the official views of the NCI, NIH.

References

1. McDaniel JS, Musselman DL, Porter MR, Reed DA, Nemeroff CB (1995) Depression in patients with cancer. Diagnosis, biology, and treatment. Arch Gen Psychiatry 52:89–99
2. van't Spijker A, Trijsburg RW, Duivenvoorden HJ (1997) Psychological sequelae of cancer diagnosis: a meta-analytical review of 58 studies after 1980. Psychosom Med 59:280–293
3. Meeske K, Smith AW, Alfano CM, McGregor BA, McTiernan A, Baumgartner KB et al (2007) Fatigue in breast cancer survivors two to five years post diagnosis: a HEAL Study report. Qual Life Res 16:947–960
4. Ashbury FD, Madlensky L, Raich P, Thompson M, Whitney G, Hotz K et al (2003) Antidepressant prescribing in community cancer care. Support Care Cancer 11:278–285
5. Coyne JC, Palmer SC, Shapiro PJ, Thompson R, DeMichele A (2004) Distress, psychiatric morbidity, and prescriptions for psychotropic medication in a breast cancer waiting room sample. Gen Hosp Psychiatry 26:121–128
6. MacDonald RN, Hugi MR, Graydon JE, Beaulieu M-D, Caines J, Firth LA et al (1998) The management of chronic pain in patients with breast cancer. The steering committee on clinical practice guidelines for the care and treatment of breast cancer. CMAJ 158 (Suppl 3):S71–S81

7. Bordeleau L, Pritchard K, Goodwin P, Loprinzi C (2007) Therapeutic options for the management of hot flashes in breast cancer survivors: An evidence-based review. Clin Ther 29:230–241
8. Ganz PA (2001) Impact of tamoxifen adjuvant therapy on symptoms, functioning, and quality of life. J Natl Cancer Inst Monogr 2001:130–134
9. Love RR, Cameron L, Connell BL, Leventhal H (1991) Symptoms associated with tamoxifen treatment in postmenopausal women. Arch Intern Med 151:1842–1847
10. Brandes LJ, Arron RJ, Bogdanovic RP, Tong J, Zaborniak CL, Hogg GR et al (1992) Stimulation of malignant growth in rodents by antidepressant drugs at clinically relevant doses. Cancer Res 52:3796–3800
11. Brandes LJ, Bogdanovic RP, Cawker MD, LaBella FS (1987) Histamine and growth: interaction of antiestrogen binding site ligands with a novel histamine site that may be associated with calcium channels. Cancer Res 47:4025–4031
12. Turkington RW (1972) Prolactin secretion in patients treated with various drugs: phenothiazines, tricyclic antidepressants, reserpine, and methyldopa. Arch Intern Med 130:349–354
13. Krulich L (1975) The effect of a serotonin uptake inhibitor (Lilly 110140) on the sercretion of prolactin in the rat. Life Sci 17:1141–1144
14. Urban RJ, Veldhuis JD (1991) A selective serotonin reuptake inhibitor, fluoxetine hydrochloride, modulates the pulsatile release of prolactin in postmenopausal women. Am J Obstet Gynecol 164:147–152
15. Leatherman ME, Ekstrom RD, Corrigan M, Carson SW, Mason G, Golden RN (1993) Central serotonergic changes following antidepressant treatment: a neuroendocrine assessment. Psychopharmacol Bull 29:149–154
16. Eisen JN, Irwin J, Quay J, Livnat S (1989) The effect of antidepressants on immune function in mice. Biol Psychiatry 26:805–817
17. Laudenslager ML, Clarke AS (2000) Antidepressant treatment during social challenge prior to 1 year of age affects immune and endocrine responses in adult macaques. Psychiatry Res 95:25–34
18. Bahl S, Cotterchio M, Kreiger N (2003) Use of antidepressant medications and the possible association with breast cancer risk. A review. Psychother Psychosom 72:185–194
19. Chien C, Li CI, Heckbert SR, Malone KE, Boudreau DM, Daling JR (2006) Antidepressant use and breast cancer risk. Breast Cancer Res Treat 95:131–140
20. Coogan PF, Palmer JR, Strom BL, Rosenberg L (2005) Use of selective serotonin reuptake inhibitors and the risk of breast cancer. Am J Epidemiol 162:835–838
21. Fulton-Kehoe D, Rossing MA, Rutter C, Mandelson MT, Weiss NS (2006) Use of antidepressant medications in relation to the incidence of breast cancer. Br J Cancer 94:1071–1078
22. Gonzalez-Perez A, Garcia Rodriguez LA (2005) Breast cancer risk among users of antidepressant medications. Epidemiology 16:101–105
23. Lawlor DA, Juni P, Ebrahim S, Egger M (2003) Systematic review of the epidemiologic and trial evidence of an association between antidepressant medication and breast cancer. J Clin Epidemiol 56:155–163
24. Goetz MP, Knox SK, Suman VJ, Rae JM, Safgren SL, Ames MM et al (2007) The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat 101:113–121
25. Lehmann D, Nelsen J, Ramanath V, Newman N, Duggan D, Smith A (2004) Lack of attenuation in the antitumor effect of tamoxifen by chronic CYP isoform inhibition. J Clin Pharmacol 44:861–865
26. Steingart AB, Cotterchio M (1995) Do antidepressants cause, promote, or inhibit cancers? J Clin Epidemiol 48:1407–1412
27. Stearns V, Johnson MD, Rae JM, Morocho A, Novielli A, Bhargava P et al (2003) Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst 95:1758–1764
28. Jin Y, Desta Z, Stearns V, Ward B, Ho H, Lee KH et al (2005) CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. J Natl Cancer Inst 97:30–39
29. Borges S, Desta Z, Li L, Skaar TC, Ward BA, Nguyen A et al (2006) Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. Clin Pharmacol Ther 80:61–74
30. Goetz MP, Rae JM, Suman VJ, Safgren SL, Ames MM, Visscher DW et al (2005) Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol 23:9312–9318
31. Hemeryck A, Belpaire FM (2002) Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. Curr Drug Metab 3:13–37
32. Saunders KW, Davis RL, Stergachis A (2005) Group health cooperative. In: Strom BL (ed) Pharmacoepidemiology. 4th edn. Wiley, Chichester
33. National Cancer Institute. Surveillance, epidemiology, and end results. http://seer.cancer.gov/
34. Fleming ID, Cooper JS, Henson DE, Hutter RVP, Kennedy BJ, Murphy GP et al (1997) AJCC cancer staging manual, 5th edn. Lippincott Williams & Wilkins, Philadelphia
35. Enger SM, Thwin SS, Buist DS, Field T, Frost F, Geiger AM et al (2006) Breast cancer treatment of older women in integrated health care settings. J Clin Oncol 24:4377–4383
36. Geiger AM, Thwin SS, Lash TL, Buist DS, Prout MN, Wei F et al (2007) Recurrences and second primary breast cancers in older women with initial early-stage disease. Cancer 109:966–974
37. Buist DSM, Ichikawa L, Prout MN, Ulcickas Yood M, Field TS, Owusu C et al (2007) Receipt of primary breast cancer therapy and adjuvant therapy are not associated with obesity in older women with access to health care. J Clin Oncol 25:3428–3436
38. Thwin SS, Clough-Gorr KM, McCarty MC, Lash TL, Alford SH, Buist DS et al (2007) Automated inter-rater reliability assessment and electronic data collection in a multi-center breast cancer study. BMC Med Res Methodol 7:23
39. ICD-9-CM (2006) International classification of diseases, 9th Revision: Clinical Modification. Available via 6th STAT!Ref Online Electronic Medical Library
40. World Health Organization. (2007) International statistical classification of diseases and related health problems 10th Revision. http://www.who.int/classifications/apps/icd/icd10online/. Cited June 9, 2007
41. Rossing MA, Scholes D, Cushing-Haugen KL, Voigt LF (2000) Cimetidine use and risk of prostate and breast cancer. Cancer Epidemiol Biomarkers Prev 9:319–323
42. O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS (2001) Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. J Natl Cancer Inst 93:754–762
43. Dublin S, Rossing MA, Heckbert SR, Goff BA, Weiss NS (2002) Risk of epithelial ovarian cancer in relation to use of antidepressants, benzodiazepines, and other centrally acting medications. Cancer Causes Control 13:35–45
44. Buist DS, Newton KM, Miglioretti DL, Beverly K, Connelly MT, Andrade S et al (2004) Hormone therapy prescribing patterns in the United States: prevalence and rates of initiation and discontinuation, 1999–2002. Obstet Gynecol 104:1042–1050
45. Smith NL, Heckbert SR, Lemaitre RN, Reiner AP, Lumley T, Weiss NS et al (2004) Esterified estrogens and conjugated equine

estrogens and the risk of venous thrombosis. JAMA 292:1581–1587
46. Kalbfleisch JD, Prentice RL. (2002) The statistical analysis of failure time data, 2nd edn. Wiley, Chichester
47. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40:373–383
48. Cotterchio M, Kreiger N, Darlington G, Steingart A (2000) Antidepressant medication use and breast cancer risk. Am J Epidemiol 151:951–957
49. Davis S, Mirick DK (2007) Medication use and the risk of breast cancer. Eur J Epidemiol 22:319–325
50. Danielson DA, Jick H, Hunter JR, Stergachis A, Madsen S (1982) Nonestrogenic drugs and breast cancer. Am J Epidemiol 116: 329–332
51. Haque R, Enger SM, Chen W, Petitti DB (2005) Breast cancer risk in a large cohort of female antidepressant medication users. Cancer Lett 221:61–65
52. Kato I, Zeleniuch-Jacquotte A, Toniolo PG, Akhmedkhanov A, Koenig K, Shore RE (2000) Psychotropic medication use and risk of hormone-related cancers: the New York University Women's Health Study. J Public Health Med 22:155–160
53. Kelly JP, Rosenberg L, Palmer JR, Rao RS, Strom BL, Stolley PD et al (1999) Risk of breast cancer according to use of antidepressants, phenothiazines, and antihistamines. Am J Epidemiol 150:861–868
54. Kreiger N, Cotterchio M, Steingart A, Buchan G (2000) Antidepressant medication use and breast cancer. Am J Epidemiol 151:S27
55. Moorman PG, Grubber JM, Millikan RC, Newman B (2003) Antidepressant medications and their association with invasive breast cancer and carcinoma in situ of the breast. Epidemiology 14:307–314
56. Sharpe CR, Collet JP, Belzile E, Hanley JA, Boivin JF (2002) The effects of tricyclic antidepressants on breast cancer risk. Br J Cancer 86:92–97
57. Steingart A, Cotterchio M, Kreiger N, Sloan M (2003) Antidepressant medication use and breast cancer risk: a case-control study. Int J Epidemiol 32:961–966
58. Wallace RB, Sherman BM, Bean JA (1982) A case-control study of breast cancer and psychotropic drug use. Oncology 39:279–283
59. Csizmadi I, Collet JP, Boivin JF (2005) Bias and confounding in pharmacoepidemiology. In: Strom BL (ed) Pharmacoepidemiology, 4th edn. Wiley, Chichester
60. Groenvold M, Petersen MA, Idler E, Bjorner JB, Fayers PM, Mouridsen HT (2007) Psychological distress and fatigue predicted recurrence and survival in primary breast cancer patients. Breast Cancer Res Treat 105:209–219
61. Goodwin PJ, Ennis M, Bordeleau LJ, Pritchard KI, Trudeau ME, Koo J et al (2004) Health-related quality of life and psychosocial status in breast cancer prognosis: analysis of multiple variables. J Clin Oncol 22:4184–4192
62. Watson M, Homewood J, Haviland J, Bliss JM (2005) Influence of psychological response on breast cancer survival: 10-year follow-up of a population-based cohort. Eur J Cancer 41:1710–1714
63. Rock CL, Demark-Wahnefried W (2002) Nutrition and survival after the diagnosis of breast cancer: a review of the evidence. J Clin Oncol 20:3302–3316
64. Kushi LH, Kwan ML, Lee MM, Ambrosone CB (2007) Lifestyle factors and survival in women with breast cancer. J Nutr 137:236S–242S
65. Weiss SR, McFarland BH, Burkhart GA, Ho PT (1998) Cancer recurrences and secondary primary cancers after use of antihistamines or antidepressants. Clin Pharmacol Ther 63:594–599