Association between antidepressant use and second breast cancer event after ductal carcinoma in situ diagnosis; a nested case-control study.

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Abstract

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Controversy exists regarding the potential relationship between antidepressant use and risk of breast cancer. No previous studies have evaluated the relationship between antidepressant use and risk of a subsequent breast cancer among women with a history of ductal carcinoma in situ (DCIS). Using a nested case-control study design, we compared 338 cases of women diagnosed with DCIS and a subsequent breast cancer and 599 individually matched controls (on age, year of DCIS diagnosis, primary treatment, histology, grade, and disease-free survival time) who were diagnosed with DCIS but not a subsequent breast cancer. Information on antidepressant use after DCIS diagnosis was obtained from medical records. Antidepressant use after initial DCIS was not associated with risk of a subsequent breast cancer event (OR = 1.17, 95% CI: 0.84, 1.61). However, stratified analysis showed an increased risk among women without a first-degree family history of breast cancer (OR = 1.76, 95% CI: 1.11, 2.79). Similar results were seen when antidepressants were analyzed by drug class. Antidepressant use may be associated with an increased risk of a subsequent breast cancer event among women with a history of DCIS who do not have a first-degree history of breast cancer. This is the first study to evaluate the relationship between antidepressant use and risk of a subsequent breast cancer event among women with DCIS. Further studies are needed to confirm the associations observed.

Introduction:

Ductal carcinoma in situ (DCIS) is a non-invasive breast cancer with excellent prognosis after lumpectomy, with or without additional treatments such as mastectomy, radiation therapy, or adjuvant endocrine therapy. DCIS makes up about 20% of all new breast cancer diagnoses[1] and it is diagnosed increasingly in recent decades due to the rise of mammography screenings. What is most concerning about this diagnosis is that about one-third of women with DCIS will either have a recurrence of DCIS or be diagnosed with invasive breast cancer in the contralateral or ipsilateral breast within 10 years of the initial DCIS diagnosis.[2] Given this increased risk of subsequent events, identifying modifiable factors that affect risk could help with the development of preventive strategies. Recent observational studies suggest that alcohol use, physical activity[3], and BMI[2–4] may alter risk of a second breast cancer diagnosis after DCIS.

In the United States, 23% of women between the ages of 40-59 report current antidepressant use, and selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed class of antidepressants.[5,6] There is controversy regarding the potential relationship between antidepressant use and breast cancer risk. Some studies suggest that antidepressant treatment may increase the risk of breast cancer by elevating prolactin levels and promoting breast carcinogenesis,[7–9] but others report no association.[5,6,10–14] Further, untreated depression has also been speculated to increase the risk of breast cancer, but the data are also inconsistent.[5,6] No previous studies have evaluated the relationship between antidepressant use and risk of a subsequent breast cancer among women with DCIS. We evaluated this association in a population-based study designed specifically to characterize risk factors for second breast cancer events among women diagnosed with DCIS.

Methods:

Study Population

The study population has been described in previous publications.[4,15–17] Briefly, the original cohort consisted of women aged 30-79 years diagnosed with DCIS between January 1, 1995 and June 30, 2013 who were identified from the Surveillance, Epidemiology and End Results (SEER) cancer registry serving 13 counties in Western Washington State. Cases were defined as women with a second in situ or invasive breast cancer event at least six months following initial DCIS diagnosis. Controls were those women diagnosed with DCIS who did not have a second breast cancer event during the matched time period. Controls were individually matched 2:1 to cases by age and year of DCIS diagnosis (+/- two years), county of residence at initial diagnosis, initial surgical and radiation treatment, DCIS histology, grade, and reference date. For cases, the reference date was the date of second breast cancer event after initial DCIS diagnosis. For controls, matched reference dates were assigned based on the disease-free survival time of the case they were matched to. Of the eligible 705 cases and 1684 controls identified for this study, 497 cases (70.5%) and 965 controls (57.3%) gave written, informed consent and were enrolled. The study was approved by the Institutional Review Board at the Fred Hutchinson Cancer Research Center (Seattle, USA). This analysis was restricted to only women whose antidepressant use was available from medical record review (159 cases and 366 controls excluded), leaving 338 cases and 599 controls in this study.

Data Collection

Patient demographic, epidemiologic, and clinical data were collected from structured telephone interviews and detailed medical record reviews. Tumor characteristics, initial treatment of DCIS,

and medication data were obtained via medical records. Medical record review was limited to two years prior to first DCIS diagnosis through subsequent diagnosis or matched reference date.

Characterization of Exposures

Information on antidepressant use was collected from medical records for the period from two years before DCIS diagnosis until second breast cancer event or matched reference date. "Antidepressant non-users" were defined as both those women that discontinued antidepressants at the time of DCIS diagnosis and those that were non-users of antidepressants both before and after initial DCIS diagnosis. "Antidepressant users" were defined as both those women that continued antidepressants after initial DCIS diagnosis and those that started antidepressant use after initial DCIS diagnosis for a duration greater or equal to one month. Antidepressants were also categorized into the following classes: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs) and norepinephrine and dopamine reuptake inhibitors (NDRIs). No other classes of antidepressants were used by the study participants.

Statistical Analysis

Associations between antidepressant use (both by antidepressant class and by all classes combined) and the outcome of second breast cancer event among women with a history of DCIS were estimated using conditional logistic regression to implicitly adjust for matching variables given the matched case-control patient design. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated as estimates of relative risks. We then adjusted for adjuvant endocrine therapy use (e.g. tamoxifen) after initial DCIS diagnosis as this was not included in the matching criteria but has been shown to decrease the risk of second breast cancer event after DCIS in

randomized controlled trials.[18,19] Other possible confounders and interaction terms, including several established risk factors for breast cancer, were assessed (listed in Table 1). With respect to confounding, none of the possible confounders changed risk estimates ≥10% when included in our statistical models and thus none were added to our final models. The only potential effect modifier identified was first-degree family history of breast cancer (p for interaction <0.1). As such, we performed a stratified analysis of the study participants based on whether they had a first-degree family history of breast cancer. Analyses were performed using R Version 1.4.1103 and Stata/SE Version 16.0.

Results:

Cases and controls had similar median follow-up times (60 months (range: 6 - 213) and 58 months (range: 6 - 208), respectively) and similar distributions of age and year of DCIS diagnosis (Table 1). Cases were less likely to have used adjuvant endocrine therapy than controls (33.7% and 42.7%, respectively). Cases were also somewhat more likely than controls to have a history of depression (46.2% and 40.4%, respectively) and a first-degree family history of breast cancer (30.2% and 25.0%, respectively).

Overall, any antidepressant use after initial DCIS was not associated with risk of a subsequent breast cancer event when adjusted for adjuvant endocrine therapy (OR = 1.17, 95% CI: 0.84, 1.61) (Table 2). Similar trends were seen when the exposure was restricted to individual antidepressant classes (Table 2); there was no association with SSRI use (OR = 1.17; 95% CI: 0.82, 1.67), SNRI use (OR = 1.03, 95% CI: 0.68, 1.56), or NDRI use (OR = 1.29, 95% CI: 0.77, 2.15).

However, among women *without* a first-degree family history of breast cancer, antidepressant use after initial DCIS was associated with a 1.76-fold (95% CI: 1.11, 2.79) increased risk of a second breast cancer event, but no association was observed among women *with* a first-degree family history of breast cancer (OR = 0.50, 95% CI: 0.18, 1.36). Similar trends were seen when the exposure was restricted to individual antidepressant classes stratified by first-degree family history of breast cancer (Table 3).

Discussion:

A recent meta-analysis of 19 observational studies showed no association between the use of antidepressants and risk of breast cancer.[20] Our study corroborates that overall, antidepressant use after DCIS diagnosis was not associated with an increased risk of a second breast cancer event. However, our post hoc analysis does demonstrate an increased risk associated with antidepressant use in women without a first-degree history of breast cancer. To our knowledge, this is the first study to document that antidepressant use is associated with an increased risk of a subsequent breast cancer among women with a history of DCIS who do not have a first-degree family history of breast cancer.

A potential explanation for why this relationship was observed only among women without a first-degree family history is that those *with* a first-degree family history of breast cancer have an elevated baseline risk of breast cancer[15] and that adding the exposure of antidepressants does not significantly change that risk. However, among women with a lower baseline risk (those without first-degree family history of breast cancer), antidepressant use after DCIS diagnosis may observably increase risk. This could be possible via the potential for antidepressants to elevate

prolactin levels and promote angiogenesis.[5–7,9,11,12] However, as this is the first report of this association it requires confirmation in future studies.

Another important facet related to the use of antidepressants among breast cancer patients is the potential for drug-drug interactions between antidepressants and tamoxifen. This is noteworthy given that tamoxifen reduces the risk of recurrence by approximately half in estrogen-receptor positive (ER+) breast cancer survivors (not limited to DCIS).[8,21–23] In 2006, an FDA advisory committee recommended tamoxifen's label be changed to include a black box warning for SSRI and tamoxifen co-prescribing, indicating an increased risk of subsequent breast cancer[12,24] which was later removed.[25] Tamoxifen is a prodrug that requires metabolic conversion to endoxifen by the liver's cytochrome P450 enzymes, predominately CYP2D6, to become effective.[22] Some common SSRIs such as paroxetine and fluoxetine, and the NDRI bupropion are considered strong inhibitors of the CYP2D6 enzyme, probably influencing the effectiveness of tamoxifen.[13,26] However, there is conflicting data on whether this theoretical interaction has clinical relevance. Many studies investigating the association between CYP2D6 inhibition and the effectiveness of tamoxifen have produced inconsistent associations, with widely mixed results on either side of the null.[14,21] There is also genetic variation in people ranging from 'poor-metabolizers' to 'ultra-metabolizers' of CYP2D6 but this is not routinely tested prior to prescribing medications.[27] In our analysis, we adjusted for adjuvant endocrine therapy (75% of which was tamoxifen) as it was our a priori hypothesis that women with this exposure would have a significantly lower risk of second breast cancer event (which was noted in this study as well). Also, in analyses stratified by tamoxifen use we found similar results that lacked statistical significance due to limited sample size. We interpret this as no strong evidence of clinically relevant drug interaction between tamoxifen and antidepressants.

One limitation of this study is that antidepressants were analyzed by drug class but not by individual drug, duration, or dosage. Of note, antidepressants within the same class have varying levels of CYP2D6 inhibition. Additionally, concurrent use of other medications which may also influence CYP2D6 inhibition was not considered, nor were individual genetic differences in CYP2D6 metabolism determined. Our sample size also prohibited evaluations of risk across different subtypes of DCIS associated with clinical aggressiveness. Further, there is limited generalizability to different racial/ethnic populations given the limited diversity of our study population. Lastly, because the vast majority of women included in this study with a history of depression were classified as users of antidepressants, we could not conduct meaningful sensitivity analyses restricted to women with a history of depression to assess the risk of antidepressant use from non-use. Strengths of this study include its population-based study design and detailed medical record review. Since data on antidepressant use and adjuvant endocrine therapy after initial DCIS diagnosis came from medical records, they are not subject to recall bias.

The number of women with a history of DCIS continues to grow given the frequency of this diagnosis and its high survival rate. Our study is the first to suggest that among women without a first-degree family history of breast cancer, antidepressant use may confer an increased risk of a second breast cancer event. Further research is needed to evaluate how this relationship may vary across specific antidepressants, by dose, and influence of CYP2D6 metabolism. It is also important to emphasize that the results of this study require confirmation and should not impact clinical decision making particularly given the well-established benefits of antidepressants on improving mental health.

Table 1 Patient, pathology, and treatment characteristics of study participants

Patient characteristics	**Controls n=599 (%)**	**Cases n=338 (%)**
Age at initial diagnosis		
30-39	16 (2.7)	15(4.4)
40-49	169 (28.2)	90 (26.6)
50-59	216 (36.1)	126 (37.3)
60-69	139 (23.2)	70 (20.7)
70+	59 (9.8)	37 (10.9)
Year of initial diagnosis		
1995-2000	258 (43.1)	154 (45.6)
2001-2006	246 (41.1)	127 (37.6)
2007-2013	95 (15.9)	57 (16.9)
Race/ethnicity		
White	545 (91.0)	297 (87.9)
Asian/Pacific Islander	25 (4.2)	18 (5.3)
Black	9 (1.5)	9 (2.7)
Hispanic	8 (1.3)	7 (2.1)
Native American	12 (2.0)	7 (2.1)
First-degree family history of breast cancer		
No	428 (74.0)	229 (69.2)
Yes	150 (26.0)	102 (30.8)
Unknown	21	7
History of Depression		
No	336 (56.1)	178 (52.7)
Yes	242 (40.4)	156 (46.2)
Unknown	21	4
Body Mass Index (BMI) at initial diagnosis		
<25	252 (43.2)	129 (38.9)
25 to <30	188 (32.2)	110 (33.1)
>30	143 (24.5)	93 (28.0)
Unknown	16	6
Smoking Status at initial diagnosis		
Never	309 (53.3)	181 (54.7)
Former	209 (36.0)	106 (32.0)
Current smoker at initial diagnosis	62 (10.7)	44 (13.3)
Unknown	19	7
Reproductive Characteristics at initial diagnosis		
No history of live birth	109 (18.5)	73 (21.7)
History of live birth	480 (81.5)	263 (78.3)
Unknown	10	2
Age at first live birth (parous only; n=743)		
<20	63 (14.0)	35 (14.1)
20-24	176 (39.2)	101 (40.7)
25-29	129 (28.7)	64 (25.8)

30+	81 (18.0)	48 (19.4)
Unknown age	31	15
Menopausal status at initial diagnosis		
Pre- or perimenopausal	221 (37.4)	126 (37.8)
Postmenopausal	370 (62.6)	207 (62.2)
Unknown	8	5
Treatment history for initial tumor		
Biopsy only	6 (1.0)	4 (1.2)
Lumpectomy without radiation	137 (22.9)	77 (22.8)
Lumpectomy with radiation	328 (54.8)	190 (56.2)
Mastectomy	128 (21.4)	67 (19.8)
Adjuvant endocrine therapy after initial diagnosis		
No	343 (57.3)	224 (66.3)
Yes	256 (42.7)	114 (33.7)

Tumor characteristics		
Histology of initial tumor		
Mixed DCIS	229 (38.2)	118 (34.9)
DCIS, NOS	156 (26.0)	72 (21.3)
Comedo DCIS	77 (12.9)	53 (15.7)
Cribriform DCIS	67 (11.2)	40 (11.8)
Solid DCIS	50 (8.3)	41 (12.1)
Papillary DCIS	6 (1.0)	5 (1.5)
Micropapillary	14 (2.3)	9 (2.7)
Grade of initial tumor		
1	15 (3.0)	12 (4.4)
2	148 (29.9)	70 (25.8)
3	156 (31.5)	80 (29.5)
4	176 (35.6)	109 (40.2)
Unknown	104	67
Size of initial tumor		
<2 cm	363 (77.7)	216 (81.5)
2.1 - 5 cm	88 (18.8)	35 (13.2)
>5 cm	16 (3.4)	14 (5.3)
Unknown	132	73

DCIS: ductal carcinoma in situ; NOS: not otherwise specified; LCIS: lobular carcinoma in situ

Table 2 Risk of second breast cancer event associated with antidepressant medication use after initial DCIS

	Controls n=599 (%)	**Cases n=338 (%)**	**Adjusted OR* (95% CI)**
Never or discontinuers of any antidepressants after initial DCIS	318 (53%)	177 (52%)	Reference
Users of any antidepressants after initial DCIS	281 (47%)	161 (48%)	1.17 (0.84, 1.61)
Antidepressant users by antidepressant class†:			
Users of SSRIs after initial DCIS	189	107	1.17 (0.82, 1.67)
Users of SNRIs after initial DCIS	129	66	1.03 (0.68, 1.56)
Users of NDRIs after initial DCIS	54	39	1.29 (0.77, 2.15)

*All ORs are adjusted for adjuvant endocrine therapy use.
†Some women used more than one antidepressant type.
OR: odds ratio; CI: confidence interval; DCIS: ductal carcinoma in situ; SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin and norepinephrine reuptake inhibitors; NDRIs: norepinephrine and dopamine reuptake inhibitors

Table 3 Risk of second breast cancer event associated with antidepressant medication use after initial DCIS stratified by first-degree family history of breast cancer

Women *without* first-degree family history of breast cancer (n=656):

	Controls n=428 (%)	**Cases n=228 (%)**	**Adjusted OR* (95% CI)**
Never or discontinuers of any antidepressants after initial DCIS	227 (53%)	108 (47%)	Reference
Users of any antidepressants after initial DCIS	201 (47%)	120 (53%)	1.76 (1.11, 2.79)
Antidepressant users by antidepressant class†:			
Users of SSRIs after initial DCIS	135	81	1.82 (1.10, 3.00)
Users of SNRIs after initial DCIS	87	49	1.58 (0.88, 2.83)
Users of NDRIs after initial DCIS	40	27	2.10 (1.02, 4.33)

Women *with* first-degree family history of breast cancer (n=252):

	Controls n=150 (%)	**Cases n=102 (%)**	**Adjusted OR* (95% CI)**
Never or discontinuers of any antidepressants after initial DCIS	78 (52%)	64 (63%)	Reference
Users of any antidepressants after initial DCIS	72 (48%)	38 (37%)	0.50 (0.18, 1.36)
Antidepressant users by antidepressant class†:			
Users of SSRIs after initial DCIS	48	25	0.45 (0.15, 1.36)
Users of SNRIs after initial DCIS	39	16	0.24 (0.04, 1.38)
Users of NDRIs after initial DCIS	13	11	0.40 (0.07, 2.34)

*All ORs are adjusted for adjuvant endocrine therapy use.
†Some women used more than one antidepressant type.
OR: odds ratio; CI: confidence interval; DCIS: ductal carcinoma in situ; SSRIs: selective serotonin reuptake inhibitors; SNRIs: serotonin and norepinephrine reuptake inhibitors; NDRIs: norepinephrine and dopamine reuptake inhibitor

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