Depression, Antidepressant Use, and Postmenopausal Breast Cancer Risk

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Abstract

Background: Whether depression and antidepressant (AD) use might influence breast cancer risk is unclear, and these exposures have not been evaluated together in a single, prospective cohort study of breast cancer risk.

Methods: Among 71,439 postmenopausal women in the Women’s Health Initiative Observational Study (WHI-OS), we estimated multivariable-adjusted HRs for the independent and joint effects of depressive symptoms and AD use on breast cancer risk using Cox proportional hazards regression.

Results: When analyzed separately, neither depressive symptoms nor AD use at baseline were associated with a significantly increased risk of total breast cancer (HR = 0.96, 95% CI, 0.85–1.08; HR = 1.04, 95% CI, 0.92–1.20, respectively) or invasive breast cancer (HR = 0.98, 95% CI, 0.86–1.12; HR = 1.00, 95% CI, 0.86–1.16, respectively). Current AD use was associated with a borderline-significant increase of in situ breast cancer (HR = 1.30, 95% CI, 0.99–1.75) after adjustment for depressive symptoms; however, this relationship was attenuated after adjustment for mammographic screening (HR = 1.08, 95% CI, 0.76–1.51). No significant variation in total breast cancer risk was observed when the separate and joint effects of depressive symptoms and AD use were explored (P for interaction = 0.14).

Conclusion: We found no evidence that either depression or AD use influences breast cancer risk. An elevated risk of in situ disease among AD users could not be ruled out, though is likely due to increased screening in this subgroup.

Impact: Given the high prevalence of these exposures, these results may provide reassurance to the millions of women who are depressed and/or use ADs each year. Cancer Epidemiol Biomarkers Prev; 25(1): 1–7. ©2015 AACR.

Introduction

Breast cancer is the most prevalent cancer and second leading cause of cancer mortality among women in the United States (1). Depression and antidepressant (AD) use also are common, with 9% to 11% of middle-aged women reporting depression (2) and 23% of U.S. women of ages 40 to 59 reporting current AD use (3). Depression is a serious chronic medical condition hypothesized to increase breast cancer risk through inflammation and a suppressed immune response characterized by decreased cytotoxic T cell, natural killer cell, and inflammatory cytokine activity (4–10). Compared with healthy individuals, women with depression have higher cortisol levels (6, 9, 11–13), and in vitro evidence suggests that cortisol may increase proliferation of mammary cancer cells and contribute to tumor growth (14, 15).

ADs are often taken as part of a long-term treatment regimen for depression, mood disorders, anxiety spectrum conditions, and chronic pain, with approximately 78% of AD prescriptions indicated for treatment of depressive disorders (16, 17). Over the last 20 years, the rate of AD use has quadrupled; ADs are now the top prescription drug used by adults of ages 18 to 44 years, and selective serotonin reuptake inhibitors (SSRIs) are the most commonly used class of AD medication (3). Although ADs have anti-inflammatory properties that may mitigate an effect of depression on breast cancer risk, concern has mounted that AD treatment, specifically SSRIs, may increase circulating prolactin levels and thereby increase breast cancer risk. Prolactin has been shown to stimulate cellular proliferation, differentiation, and angiogenesis (18, 19), and prior prospective studies have linked prolactin with increased premenopausal and postmenopausal breast cancer risk, particularly in postmenopausal women (20–22).

Whether depression or AD use might influence breast cancer risk remains unclear. In two prospective studies with 10 or more years of follow-up, women with depression had either a borderline significant or significant 2 to 4 times increased risk of breast cancer compared with healthy women (23, 24), whereas other prospective studies with shorter follow-up have observed no association (25–27). Similarly, two prospective studies found that women using ADs, specifically SSRIs, had a significant 39% to 53% increased risk of breast cancer (28, 29), whereas several case–control studies have reported no association (30–34).

Prior epidemiologic studies have not, however, considered depression and AD use in a single analysis even though there is high concordance between these exposures. Thus, any effect of depression on breast cancer risk may actually be due to use of ADs, or vice versa. We evaluated both the independent and joint effects of depression and AD use on breast cancer risk among postmeno- pausal women in the Women’s Health Initiative Observational Study (WHI-OS). The WHI-OS is a large population with up to

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17 years of follow-up data available for analysis and presents a unique opportunity to prospectively evaluate the impact of these exposures at a time when the prevalence of both depression and AD use were increasing.

Materials and Methods

Study population
The WHI-OS recruited a total of 93,676 women in 40 clinical centers throughout the United States from October 1, 1993, to December 31, 1998. Eligible women were between the ages of 50 and 79 years old, postmenopausal at enrollment, and intended to reside in the area for at least 3 years. Details about the WHI-OS study design, recruitment, and data collection methods have been previously published (35, 36). Briefly, participants provided written informed consent and completed baseline questionnaires about demographic and lifestyle factors, medical history, and current medication use. During follow-up, participants completed mailed questionnaires each year and attended clinic visits every 3 years. We utilized publicly available data from the WHI-OS through the National Heart, Lung, and Blood Institute’s Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC). Human subjects review committees at each participating institution reviewed and approved the study, and the Institutional Review Board of the University of Massachusetts Amherst approved this analysis.

Assessment of depressive symptoms
Depressive symptoms were assessed at baseline using the Burns eight-item scale for depressive disorders (37), which consists of six items from the Center for Epidemiologic Studies Depression Scale about the frequency of depressive symptoms during the past week and two items from the National Institute of Mental Health’s Diagnostic Interview Schedule about symptoms over the past 1 to 2 years. Specifically, participants were asked to indicate how often they felt depressed, had restless sleep, enjoyed life, had crying spells, felt sad, or felt that people disliked them over the past week, scored from 0 “rarely or none of the time (<1 day)” to 3 “most or all of the time (5–7 days).” In addition, participants indicated if they experienced two or more weeks in the past year during which they felt sad, blue, depressed, or lost pleasure in things they usually cared about or enjoyed, or two or more years in their life during which they felt depressed or sad most days, including if they felt depressed or sad much of the time in the past year. These items were scored as 0 “no” or 1 “yes.” Responses from the Burnam scale were used to calculate an overall score ranging from 0 to 0.99, with higher scores indicative of greater depressive symptoms (37). Consistent with prior studies in the WHI (38–40), the continuous Burnam score was categorized into two groups using the standard cut point of 0.06 to separately classify women experiencing depressive symptoms consistent with disorders such as major depression and dysthymia from women without these symptoms. In a reliability study of WHI participants, the Burnam scale was found to have 74% sensitivity and 87% specificity when compared with a clinical diagnosis of depression (41).

Measurement of antidepressant use
Participants were asked to bring all current medications to their baseline interview and year 3 clinic visit. For medications used regularly (i.e., for more than 2 weeks), clinic interviewers entered the medication names and dose directly from containers into a database that assigned drug codes using the Medi-Span software (First DataBank Inc.). For our primary analysis, women were categorized as AD users or non-AD users at baseline. For secondary analyses, we additionally considered AD use by drug class [e.g., SSRIs, tricyclic antidepressants (TCA)] and evaluated the impact of consistency of AD use (e.g., never AD use, AD use at baseline only, AD use at year 3 only, AD use at baseline and year 3) on breast cancer risk.

Diagnosis of breast cancer
Details of breast cancer outcomes, including adjudication procedures, in the WHI-OS have been described elsewhere (42). Briefly, participants self-reported incident breast cancer diagnoses on annual questionnaires. Breast cancer diagnoses were adjudicated by physicians who confirmed the self-reported outcomes using relevant medical records and pathology reports, and breast cancer outcomes were then centrally adjudicated by the WHI’s Clinical Coordinating Center. Information on invasiveness and hormone receptor subtype also was extracted and included with the adjudication reports. Only adjudicated breast cancer cases were included in this analysis.

Statistical analysis
Women were excluded from this analysis if they reported a history of cancer except for non-melanoma skin cancer at baseline (n = 11,726), if they were missing information on the Burnam depression scale (n = 2,546), or if they had missing data on one or more of the potential confounders included in our multivariable model (n = 7,965), resulting in a final sample of 71,439 women.

We categorized participants by depressive symptom status (<0.06, ≥0.06 Burnam score) and AD use (AD user, non-AD user) at baseline to examine the distribution of covariates using t tests and χ² tests. To visually depict the breast cancer experience of study participants stratified by depressive symptom status and AD use, we used Kaplan–Meier curves and the log rank test to examine the distribution of survival times. Women in this analysis were followed from enrollment through September 2010; participants contributed person-time to the analysis until diagnosis of breast cancer, death, loss to follow-up, or the end of the study/administrative censor date defined as the participant’s last available visit, whichever happened first.

We used multivariable Cox proportional hazards regression to estimate HRs and 95% CIs of the association between depressive symptoms, AD use, and time to breast cancer diagnosis with adjustment for confounders. We separately examined the relationship between depression, AD use, and the risk of total breast cancer, invasive breast cancer, in situ breast cancer, estrogen receptor (ER)þ breast cancer, and ER– breast cancer. In the subgroup analyses by breast cancer outcome, women who developed other types of breast cancer were censored at the time of their diagnosis (i.e., for the ER– subgroup analysis, ER– women were censored at the time of diagnosis) per the assumption that the risks of different types of breast cancer are independent. Further, we created a time-varying covariate to capture mammogram screening during follow-up (collected via annual mailed questionnaire), including only mammograms prior to diagnosis, to explore the impact of screening on the relationship between depressive symptoms, AD use, and in situ breast cancer.
We conducted a stratified analysis to evaluate whether the risk of total breast cancer, invasive breast cancer, or in situ breast cancer varied by strata of AD use (AD user, non-AD user) and depressive symptom status (depressive symptoms, no depressive symptoms). To test the overall statistical significance of the interaction, we included an interaction term in our multivariable model and utilized the likelihood ratio test to compare the full and reduced models. In addition, dummy variables were used in our multivariable model to examine the association for each level of the interaction.

We also evaluated the association between the drug classes used most commonly in this cohort (i.e., SSRIs, TCAs) and breast cancer risk. Given that some women used SSRIs and TCAs at the same time, we adjusted for TCA use in the SSRI analysis and vice versa, and we explored these relationships among women with and without depressive symptoms. We additionally examined the effect of consistency of AD use, including SSRI and TCA use specifically, from baseline to year 3. For these analyses, follow-up began at year 3 and cases diagnosed prior to this time were excluded.

Potential confounders were identified using prior literature and subject area knowledge about variables associated with depression, AD use, and/or breast cancer; any covariate that changed the estimate for the exposure by greater than 10% was retained in the final multivariable model. All models were adjusted for the following variables collected at baseline: age (years, continuous); BMI (kg/m², continuous); alcohol use (0, 0.1 to <2, 2 to <4, 4 to <7, ≥7 servings/week); smoking status (never, past, current); physical activity (MET-hours/week, continuous); parity (nulliparous, 1 child, 2 children, ≥3 children); age at first birth (never had a term pregnancy, <20 years, 20–29 years, ≥30 years); breastfeeding (ever, never); oophorectomy (ever, never); postmenopausal hormone (PMH) use (never, past, current); age at menopause (years, continuous); and race (American Indian or Alaskan Native, Asian or Pacific Islander, Black or African American, Hispanic/Latino, White not of Hispanic origin, Other). Further, to examine the independent relationships of depressive symptoms and AD use with breast cancer risk, we adjusted depression analyses for AD use and vice versa.

All analyses were performed in the SAS version 9.2 software (SAS Institute). All statistical tests were two-sided; \( P < 0.05 \) was used to define statistical significance.

### Results

Characteristics of WHI-OS participants by depressive symptom status and AD use at baseline are presented in Table 1. At baseline, 7,941 women (11.1%) were experiencing depressive symptoms and 5,238 women (7.3%) were current AD users. Overall, women with depressive symptoms and women currently using ADs were younger at enrollment, slightly heavier, and were more likely to have a younger age at first birth, be less physically active, be a past or current smoker, and report PMH use as compared with women without depressive symptoms or AD use, respectively.

During the study follow-up period, 2,566 women developed invasive breast cancer and 605 women developed in situ breast cancer, resulting in a total of 3,171 total breast cancer cases. Results from the age-adjusted and multivariable-adjusted Cox proportional hazards regression models are presented in Table 2. We found no association between depressive symptoms and the risk of total breast cancer (HR = 0.96, 95% CI, 0.85–1.08), invasive breast cancer (HR = 0.98, 95% CI, 0.86–1.12), or in situ breast cancer (HR = 0.86, 95% CI, 0.65–1.14), with no evidence of confounding by AD use. Risk of ER+ and ER- disease specifically was also not associated with depression status at baseline. These relationships were largely unchanged after further adjustment for mammographic screening (data not shown).

Likewise, we observed no association between AD use and total breast cancer risk (HR = 1.04, 95% CI, 0.92–1.20) or invasive breast cancer risk (HR = 1.00, 95% CI, 0.86–1.16) in multivariable models, which was not affected by additional adjustment for depression status (Table 2). We also observed no meaningful change in these estimates after additional adjustment for mammogram utilization (data not shown). We did observe a borderline-significant increase in the risk of in situ breast cancer among current AD users, which remained after additional adjustment for depression (HR = 1.30, 95% CI, 0.99–1.75). This association was attenuated after additional adjustment for mammogram usage (HR = 1.08, 95% CI, 0.76–1.51). No association was observed between current AD use and risk of ER+ breast cancer. However, current AD users had a significant increase in ER- breast cancer risk (HR = 1.52, 95% CI, 1.11–2.08) that remained following adjustment for depression (HR = 1.51, 95% CI, 1.10–2.08).

We did not observe significant variation in the risk of total breast cancer when the association was examined by the joint

### Table 1. Distribution of baseline characteristics by depressive symptoms and AD use in the Women’s Health Initiative Observational Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Depressive symptoms</th>
<th>No depressive symptoms</th>
<th>Current AD user</th>
<th>Non-AD user</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>7,941 (11.1)</td>
<td>63,498 (88.9)</td>
<td>5,238 (7.3)</td>
<td>66,201 (92.7)</td>
</tr>
<tr>
<td>Mean age at enrollment (years, SD)</td>
<td>61.8 (7.4)</td>
<td>63.5 (7.5)</td>
<td>62.0 (7.5)</td>
<td>63.4 (7.3)</td>
</tr>
<tr>
<td>Mean age at menopause (years, SD)</td>
<td>47.1 (6.8)</td>
<td>48.4 (6.2)</td>
<td>46.9 (6.7)</td>
<td>48.4 (6.3)</td>
</tr>
<tr>
<td>Mean body mass index (kg/m², SD)</td>
<td>28.4 (6.4)</td>
<td>27.0 (5.5)</td>
<td>28.5 (6.3)</td>
<td>27.0 (5.6)</td>
</tr>
<tr>
<td>Race, White (%)</td>
<td>6,275 (79.0)</td>
<td>53,961 (84.9)</td>
<td>4,948 (7.8)</td>
<td>55,550 (83.9)</td>
</tr>
<tr>
<td>Mean parity (among parous women only, SD)</td>
<td>2.5 (0.7)</td>
<td>2.5 (0.7)</td>
<td>2.5 (0.7)</td>
<td>2.5 (0.7)</td>
</tr>
<tr>
<td>Age at first birth (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 years</td>
<td>1,377 (17.3)</td>
<td>6,750 (10.6)</td>
<td>817 (5.6)</td>
<td>7,310 (11.0)</td>
</tr>
<tr>
<td>20–29 years</td>
<td>4,267 (53.7)</td>
<td>38,732 (61.0)</td>
<td>3,004 (67.4)</td>
<td>39,995 (60.4)</td>
</tr>
<tr>
<td>≥30 years</td>
<td>538 (6.8)</td>
<td>4,948 (7.8)</td>
<td>340 (6.5)</td>
<td>5,146 (7.7)</td>
</tr>
<tr>
<td>History of breastfeeding, ever (%)</td>
<td>3,484 (45.3)</td>
<td>29,385 (46.3)</td>
<td>2,396 (45.7)</td>
<td>30,473 (46.0)</td>
</tr>
<tr>
<td>Mean total energy expenditure (MET-hours/week, SD)</td>
<td>10.8 (13.0)</td>
<td>14.2 (14.5)</td>
<td>11.2 (13.1)</td>
<td>14.1 (14.4)</td>
</tr>
<tr>
<td>Smoking status, past or current (%)</td>
<td>4,933 (52.8)</td>
<td>30,866 (48.6)</td>
<td>2,867 (54.7)</td>
<td>32,992 (48.6)</td>
</tr>
<tr>
<td>Alcohol use, past or current (%)</td>
<td>7,032 (88.6)</td>
<td>56,410 (88.8)</td>
<td>4,713 (90.0)</td>
<td>58,729 (88.7)</td>
</tr>
<tr>
<td>PMH use, past or current (%)</td>
<td>5,959 (75.0)</td>
<td>45,822 (72.2)</td>
<td>4,471 (85.4)</td>
<td>47,310 (71.5)</td>
</tr>
</tbody>
</table>
distribution of depressive symptoms and AD use at baseline. \( P \) for interaction = 0.14, Table 3). Specifically, compared with non-AD users without depressive symptoms, no association with total breast cancer risk was observed among women experiencing depressive symptoms without AD use (HR = 0.98, 95% CI, 0.86–1.11), women using ADs without depressive symptoms (HR = 1.10, 95% CI, 0.94–1.28), or women using ADs with depressive symptoms (HR = 0.91, 95% CI, 0.70–1.18).

We also evaluated if the consistency of AD use at baseline and year 3 was associated with total breast cancer risk, separately within strata defined by depressive symptom status during year 3 (Table 4). Overall, total breast cancer risk was similar among women who never used ADs, used ADs only at baseline or year 3, and those who used them at both timepoints, among both depressed and nondepressed women.

**Discussion**

In this prospective cohort study of postmenopausal women, we observed no association between depressive symptoms or AD use at baseline and total or invasive breast cancer risk. A nonsignificant positive relationship was observed between AD use at baseline and in situ breast cancer, which was attenuated after adjustment for mammogram screening during follow-up. When the exposures were evaluated together, neither depression nor AD use nor their combined exposure appeared to influence total breast cancer risk. To our knowledge, this is the first study to examine both the separate and the combined relationship between depressive symptoms and AD use and subsequent breast cancer risk, which is important given the overwhelming overlap in these exposures among U.S. women.

Prior epidemiologic studies support a potential relationship between depression and breast cancer risk, but the data are inconsistent. The direct comparison of results from prior studies is complicated by the multitude of exposures ranging from depression, personality traits, psychosis, and dysthymia, as few studies have focused specifically on the association between depressive symptoms and breast cancer risk. In a meta-analysis of the available prospective data on depression and breast cancer risk, depressed women had a nonsignificant 59% increased risk of breast cancer (RR = 1.59, 95% CI, 0.74–3.44) compared with women without depression (43). However, results of the individual studies included in this meta-analysis varied widely, and few studies included information on important potential confounders. Additionally, many studies had short follow-up times, which is problematic as the impact of depression on breast cancer risk likely occurs over a period of many years. In the prospective studies with at least 10 years of follow-up, a three to four times increased breast cancer risk was observed among women with depression (23, 24). Confounding may explain at least part of these associations, as no adjustment was made for BMI, PMH therapy, or mammography use. Further, given that these studies did not account for AD use, it is possible that the positive association observed between depression and breast cancer risk is due to AD use for treatment of depressive symptoms rather than depression itself. Also, we measured only depressive symptoms, while other studies defined depression via a documented clinical diagnosis; our inclusion of lower severity depression may have attenuated effect estimates.

Our finding of no association between ADs and breast cancer risk overall is in agreement with many retrospective case-control studies (30–33, 44, 45) and two retrospective cohort studies

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**Table 2. HR and 95% CIs for depressive symptoms and AD use at baseline and the risk of breast cancer in the WHI-OS**

<table>
<thead>
<tr>
<th></th>
<th>Depressive symptoms</th>
<th>No depressive symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years</td>
<td>80,725</td>
<td>683,409</td>
</tr>
<tr>
<td><strong>Breast cancer cases, ( n )</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total breast cancer</td>
<td>313</td>
<td>2,858</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>259</td>
<td>2,307</td>
</tr>
<tr>
<td>In situ breast cancer</td>
<td>54</td>
<td>551</td>
</tr>
<tr>
<td>ER⁺ breast cancer</td>
<td>222</td>
<td>2,049</td>
</tr>
<tr>
<td>ER⁻ breast cancer</td>
<td>52</td>
<td>394</td>
</tr>
<tr>
<td><strong>Current AD user</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Person-years</td>
<td>54,088</td>
<td>710,046</td>
</tr>
<tr>
<td><strong>Breast cancer cases, ( n )</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total breast cancer</td>
<td>238</td>
<td>2,933</td>
</tr>
<tr>
<td>Invasive breast cancer</td>
<td>183</td>
<td>2,383</td>
</tr>
<tr>
<td>In situ breast cancer</td>
<td>55</td>
<td>550</td>
</tr>
<tr>
<td>ER⁺ breast cancer</td>
<td>162</td>
<td>2,019</td>
</tr>
<tr>
<td>ER⁻ breast cancer</td>
<td>45</td>
<td>401</td>
</tr>
</tbody>
</table>

*Multivariable models for depression and AD use adjusted for: age (years, continuous); smoking status (never, past, current); alcohol use (0, 0.1 to <2, 2 to <4, 4 to <7, >7 servings/week); parity (nulliparous, 1 child, 2 children, ≥3 children); age at first birth (never had a term pregnancy, <20 years, 20–29 years, ≥30 years); breastfeeding (ever, never); oophorectomy (ever, never); PMH use (never, past, current); age at menopause (years, continuous); race (American Indian or Alaskan Native, Asian or Pacific Islander, Black or African American, Hispanic/Latino, White not of Hispanic origin, other); physical activity (MET-hours/week); BMI (kg/m², continuous).

*Multivariable model for depression adjusted for covariates in model 1 and AD use; model for AD use adjusted for covariates in model 1 and depression.
based on pharmacy/healthcare records (46, 47), but not with two recent prospective cohort studies (28, 29). In the prospective New York University Women’s Health Study, the use of any type of psychotropic medication at baseline was associated with a significant 39% increase in breast cancer risk (29). Psychotropic medications include antipsychotics, which are well known to cause elevations in circulating prolactin levels (48, 49), and could be responsible for the observed increase in risk. The investigators reported a statistically significant 75% increase in breast cancer risk among AD users, which was limited to premenopausal women upon further analysis. The number of breast cancer cases with AD use specifically was quite small (n = 16), however, and these results should be interpreted cautiously. A nationwide record linkage study in Finland reported a significant 53% increase in total breast cancer risk associated with >4 years of SSRI use (28). Our results may differ from these recent studies due to our focus on older, postmenopausal women compared with younger populations of women. Another important distinction between the present analysis and prior prospective studies relates to the assessment of AD data. Prior work has measured AD use through registry data (28) or self-administered questionnaire (29). In WHI-OS, however, women were asked to bring pill bottles for their medications to the clinic visit, and AD use was derived from these data. Although this has the advantage of capturing actual usage, as opposed to written prescriptions, a disadvantage is that only current AD use was measured. Women who have used ADs in the past or who recently discontinued AD use were therefore classified as nonusers in our analyses. This nondifferential misclassification may have attenuated a true association between AD use and breast cancer risk, and may, in part, account for our null findings.

Interestingly, we observed a small association between AD use and in situ breast cancer risk, although this result was only of borderline significance. This association was attenuated after adjustment for mammography screening. Compared with healthy individuals, women with AD use maintain regular contact with their health care providers to fulfill treatment and prescription needs, and thus may also be referred for regular screening mammography at these visits. It is known that screening mammography results in increased diagnosis of in situ breast cancer compared with unscreened populations (50). Given the attenuation we observed after adjustment for mammography screening, the relationships observed with in situ breast cancer are likely attributable, at least in part, to screening artifacts rather than true etiologic associations. Future research is warranted to confirm these results as prior prospective studies have not examined the relationships between these exposures and breast cancer subtypes, nor have previous studies considered the potential impact of screening mammography specifically with regard to the relationships between depressive symptoms, AD use, and in situ breast cancer risk.

We also observed a statistically significant 50% increase in risk of ER− disease among AD users. Prior epidemiologic work has rarely evaluated depression or AD use in relation to hormone receptor subtypes of breast cancer. Two studies reported no association with ER+ or ER− disease (32, 51), whereas another reported a 2-fold increase in risk of ER+/PR− disease associated with SSRI use (52). We had hypothesized that depression and AD

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### Table 3. HR and 95% CIs for the joint distribution of depressive symptoms and AD use at baseline and the risk of total breast cancer in the WHI-OS (1993–2010)

<table>
<thead>
<tr>
<th>Group</th>
<th>Breast cancer cases, n</th>
<th>Person years</th>
<th>Multivariable model HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-AD user, no depressive symptoms</td>
<td>2,679</td>
<td>644,891</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Non-AD user, depressive symptoms</td>
<td>254</td>
<td>65,156</td>
<td>0.98 (0.86–1.11)</td>
</tr>
<tr>
<td>Current AD user, no depressive symptoms</td>
<td>179</td>
<td>38,518</td>
<td>1.10 (0.94–1.28)</td>
</tr>
<tr>
<td>Current AD user, depressive symptoms</td>
<td>59</td>
<td>15,569</td>
<td>0.91 (0.70–1.18)</td>
</tr>
</tbody>
</table>

*Multivariable model adjusted for age; smoking status; alcohol use; parity; age at first birth; breastfeeding; oophorectomy; PMH use; age at menopause; race; physical activity; and BMI.

**P** for interaction = 0.14.

### Table 4. HR and 95% CIs for the risk of total breast cancer by consistency of AD use and strata of depressive symptoms at year 3 in the WHI-OS (1993–2010)

<table>
<thead>
<tr>
<th>Group</th>
<th>Depressive symptoms</th>
<th>Person years</th>
<th>Multivariable model HR (95% CI)</th>
<th>No depressive symptoms</th>
<th>Person years</th>
<th>Multivariable model HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall AD use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never use</td>
<td>219</td>
<td>45,690</td>
<td>1.00 (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline only</td>
<td>22</td>
<td>4,196</td>
<td>1.01 (0.62–1.66)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 3 only</td>
<td>57</td>
<td>7,874</td>
<td>0.99 (0.67–1.44)</td>
<td></td>
<td></td>
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<tr>
<td>Consistent use</td>
<td>33</td>
<td>7,327</td>
<td>0.94 (0.63–1.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Never use</td>
<td>258</td>
<td>53,657</td>
<td>1.00 (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline only</td>
<td>12</td>
<td>2,862</td>
<td>0.52 (0.19–1.04)</td>
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<tr>
<td>Year 3 only</td>
<td>27</td>
<td>5,525</td>
<td>1.01 (0.65–1.62)</td>
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<tr>
<td>Consistent use</td>
<td>14</td>
<td>3,043</td>
<td>0.73 (0.41–1.43)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TCAS</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Never use</td>
<td>267</td>
<td>59,699</td>
<td>1.00 (ref)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline only</td>
<td>16</td>
<td>2,273</td>
<td>1.25 (0.68–2.31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 3 only</td>
<td>11</td>
<td>1,657</td>
<td>0.91 (0.41–2.06)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consistent use</td>
<td>12</td>
<td>1,458</td>
<td>1.07 (0.46–2.33)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*Multivariable model adjusted for age; smoking status; alcohol use; parity; age at first birth; breastfeeding; oophorectomy; PMH use; age at menopause; race; physical activity; and BMI.
use might only increase risk of ER+ disease, given that both obesity and circulating prolactin levels are more strongly related to ER+ breast cancer (53–56). We observed no association between depression and either ER+ or ER- disease. The increased risk of ER- disease among AD users requires confirmation in future studies, and may be due to chance.

Limitations of this study primarily relate to the measurement of depressive symptoms and AD use. Data on depressive symptoms were gathered via self-report instead of the gold standard structured psychiatric interview or clinical diagnosis of depression, and information on the duration of depressive symptoms and prior history of depression was not available. In addition, given that we only had data on depressive symptoms, not on clinical diagnoses of depression, we may have captured a less severe spectrum of depression in this study, which may have contributed to our null findings. However, the Burnam scale has been shown to have good to excellent sensitivity and specificity with a threshold score that is well correlated with clinical depression (37). Also, women effectively treated for depression with ADs would score low on the depressive symptoms scale and would not have been classified as "depressed" in our analysis. With regard to AD use, actual use may be underestimated if women failed to bring their pill bottles to visits, and we additionally lacked information on AD indication and compliance. We also lacked information on duration of use, and we therefore were unable to explore whether ADs might have effects observable only after extended duration of use. As noted earlier, these limitations might have attenuated true associations and contributed to our null findings.

Strengths of our study include the prospective design, large sample size, comprehensive data on potential confounders, and up to 17 years of follow-up. In addition, data for this study were collected when the prevalence of both depression and AD use were rising, and the large number of exposed women in this study is a significant strength over prior studies.

In summary, these results do not support an overall association between depression or AD use and breast cancer risk, though there is suggestive evidence that AD use may be related to increased risk of ER- or in situ disease, specifically. At least part of the association between AD use and in situ breast cancer risk can be explained by differential mammography utilization between AD users and nonusers. The findings from this study contribute considerably to a better understanding of the safety profile of ADs in women, and may provide some reassurance to the millions of women who are depressed and/or use ADs each year. Given the high prevalence of both depression and AD use, future work to understand and verify these associations, and to explore the impact of their duration, is warranted.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Authors’ Contributions
Conception and design: S.B. Brown, K.W. Reeves
Development of methodology: S.B. Brown, K.W. Reeves
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.W. Reeves
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.B. Brown, S.E. Hankinson, J. Qian, K.W. Reeves
Writing, review, and/or revision of the manuscript: S.B. Brown, S.E. Hankinson, K.F. Arcaro, J. Qian, K.W. Reeves
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): S.B. Brown, K.W. Reeves
Study supervision: S.E. Hankinson

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