

# Depression, Antidepressant Use, and Breast Cancer Risk in Pre- and Postmenopausal Women: A Prospective Cohort Study



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## Abstract

**Background:** Depression and antidepressant use is highly prevalent among U.S. women and may be related to increased breast cancer risk. However, prior studies are not in agreement regarding an increase in risk.

**Methods:** We conducted a prospective cohort study within the Nurses' Health Study (NHS) and NHSII among females age 25 and older. Over more than 10 years of follow-up in each cohort, 4,014 incident invasive breast cancers were diagnosed. We used Cox proportional hazards regressions with updating of exposures and covariates throughout follow-up to estimate HRs and 95% confidence intervals (CIs) for associations between clinical depression and antidepressant use with invasive breast cancer risk. Analyses were repeated separately for *in situ* disease, as well as stratified by estrogen receptor (ER) subtype and menopausal status at diagnosis.

**Results:** No statistically significant associations were observed between clinical depression (HR for reporting  $\geq 3$  times vs. 0, 1.13; 95% CI, 0.85–1.49) or antidepressant use (HR for reporting  $\geq 3$  times vs. 0, 0.92; 95% CI, 0.80–1.05) and invasive breast cancer risk in multivariable analyses. Likewise, we observed no significant associations between clinical depression or antidepressant use and risk of *in situ*, ER<sup>+</sup>, ER<sup>-</sup>, premenopausal, or postmenopausal breast cancer.

**Conclusions:** In the largest prospective study to date, we find no evidence that either depression or antidepressant use increase risk of breast cancer.

**Impact:** The results of this study are reassuring in that neither depression nor antidepressant use appear to be related to subsequent breast cancer risk. *Cancer Epidemiol Biomarkers Prev*; 27(3); 306–14. ©2017 AACR.

## Introduction

An estimated 12.3% of U.S. women ages 40 to 59 experience moderate or severe depressive symptoms (1). Depression increases inflammation and suppresses appropriate immune responses (2–5). These effects, and the strong relationship between depression and obesity (6, 7), raise concerns that depression may increase breast cancer risk. Indeed, some (8–10), but not all (11–13), prior prospective studies reported a 2- to 4-fold increased breast cancer risk among women with depression.

Antidepressants are commonly prescribed to women with depression and can effectively treat this condition. Antidepressant use within the U.S. population has quadrupled in recent decades, with 22.8% of women ages 40 to 59 reporting current

antidepressant use (1). Antidepressants have anti-inflammatory effects (14, 15), which might mitigate hypothesized influences of depression on breast cancer risk. However, treatment with selective serotonin reuptake inhibitors (SSRIs), the most commonly used class of antidepressant (16), may increase circulating prolactin levels (17–19), which in turn could potentially increase breast cancer risk (20–22). Two prospective studies suggest a 50% to 75% increased risk of breast cancer associated with antidepressant use or SSRI use specifically (23, 24), although other studies reported no association (25–27).

There is a strong biologic rationale linking depression and antidepressant use to breast cancer risk, yet epidemiologic studies of these relationships have important limitations. Prior work has largely included clinical samples of depressed women and/or antidepressant users; thus, observed estimates may not be generalizable to broader populations of women. In addition, few studies have evaluated risk of breast cancer subtypes defined by invasiveness, estrogen receptor (ER) status, or menopausal status. Such factors are important for disease prognosis, and differences in risk factors for specific subtypes have been noted (28). Importantly, depression and antidepressant use has rarely been evaluated together, despite the high concordance between these two exposures. The possibility that any increased risk associated with antidepressant use might actually be due to the depression for which the antidepressant is prescribed rather than the antidepressant itself, or vice versa, has not been fully explored. A recent analysis of 313 breast cancer cases within the Women's Health Initiative (WHI; ref. 25) was the first prospective study to jointly evaluate depression and antidepressant use with breast cancer risk

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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and reported no significant association with either exposure [HR = 0.96; 95% confidence intervals (CIs), 0.85–1.08; HR = 1.04; 95% CI, 0.92–1.20, respectively]. However, this analysis utilized a single measurement of depressive symptoms, as opposed to clinically diagnosed depression and antidepressant use.

Understanding whether either depression or antidepressant use increases subsequent breast cancer risk remains an important question. We evaluated associations between these common exposures and breast cancer risk within two large prospective cohort studies, the Nurses' Health Study (NHS) and NHSII, each with more than 10 years of follow-up data and biennial assessments of depression and antidepressant use.

## Materials and Methods

### Study population

The NHS ( $n = 121,700$ , ages 30–55 in 1976) and NHSII ( $n = 116,429$ , ages 25–42 in 1989) are two ongoing prospective cohort studies of registered nurses with follow-up through mailed biennial questionnaires. We included all NHS and NHSII participants who completed a study questionnaire and had no history of cancer other than nonmelanoma skin cancer prior to baseline for our analysis. Participants were excluded if they did not have information on clinical depression status or antidepressant use at the beginning of the follow-up period (NHS: 2000, NHSII: 2003), resulting in 66,692 NHS women and 89,820 NHSII women available for analysis (NHS: through 2012, NHSII: through 2013).

### Measurement of depression

NHS and NHSII participants self-reported clinical diagnoses of depression (hereafter, "clinical depression") on each biennial questionnaire beginning in 2000 and 2003, respectively (Fig. 1). Participants reported diagnoses occurring after the date of the previous questionnaire cycle. We created a variable counting the cumulative number of times a participant reported being clinically diagnosed with depression, which we categorized as 0, 1, 2, and  $\geq 3$  times. Because depression can be an episodic condition, we utilized this count variable to measure the intensity of clinical depression (i.e., women reporting clinical depression diagnoses more frequently were assumed to have chronic depression).

Depressive symptoms were assessed via the Mental Health Inventory-5 (MHI-5) scale on the 1992, 1996, and 2000 questionnaires for NHS and the 1993, 1997, and 2001 questionnaires for NHSII.

for NHSII, with scores  $\leq 52$  indicating severe depressive symptoms (29). As a secondary exposure definition, we counted the number of times (0, 1, 2, 3) each participant reported severe depressive symptoms. All participants provided written informed consent at the time of enrollment, and the study was approved by institutional review boards at Brigham and Women's Hospital and the University of Massachusetts Amherst (Amherst, MA). This research was conducted in accordance with the Belmont Report.

### Measurement of antidepressant use

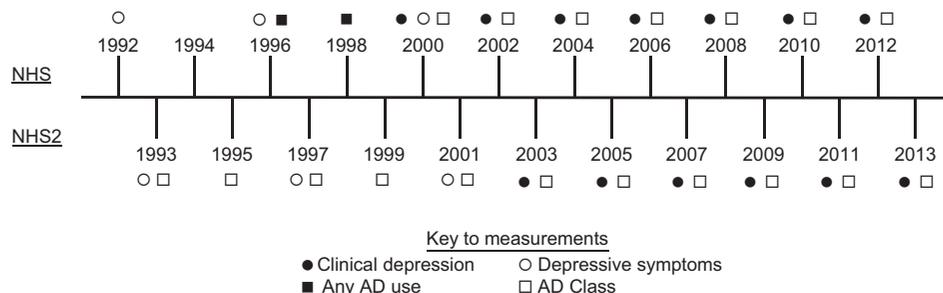
NHS participants self-reported any current antidepressant use (yes, no) on the 1996 and 1998 questionnaires; starting with the 2000 questionnaire, NHS participants separately reported use of Prozac, Zoloft, Paxil, Celexa (SSRIs), or use of "other" antidepressants [with given examples of Elavil, Tofranil, and Pamelor, which are tricyclic antidepressants (TCA)]. NHSII participants self-reported use of SSRIs, TCAs, or other antidepressants, separately, beginning in 1993 (Fig. 1). We created a variable counting the cumulative number of times a participant reported using antidepressants, categorized as 0, 1, 2, and  $\geq 3$  times, to measure the intensity of antidepressant use. As a secondary analysis, we also modeled the type of antidepressant used (none, SSRI only, other antidepressant only, SSRI, and other antidepressant) at each questionnaire.

### Breast cancer ascertainment

Breast cancer cases were initially self-reported by NHS and NHSII with subsequent confirmation using hospital records and pathology reports and extraction of stage and hormone receptor status. Medical records were obtained for 93% and 82% of NHS and NHSII breast cancer cases, respectively, with pathology reports confirming 99% of the self-reported cases. We included only confirmed breast cancer cases through 2012 (NHS) or 2013 (NHSII).

### Statistical analysis

We examined age-adjusted differences within each cohort (NHS, NHSII) by clinical depression status and antidepressant use status in potential confounders derived from study questionnaires at the beginning of follow-up: age (continuous), race (white, other), antidepressant use (yes, no), depressive symptoms count (0, 1, 2, 3), history of breast cancer in first-degree relative (yes, no), mammogram since previous cycle (yes, no), age at



**Figure 1.**

Timeline of assessment of depression and antidepressant use in the NHS and NHSII. Depressive symptoms were assessed in 1992, 1996, and 2000 in NHS and in 1993, 1997, and 2001 in NHSII. Clinical depression was assessed biennially starting in 2000 in NHS and 2003 in NHSII. Antidepressant use was assessed biennially starting in 1996 in NHS, with specificity of antidepressant class beginning in 2000. Antidepressant use by class was assessed biennially beginning in 1993 in NHSII.

menarche ( $\leq 12$ , 13,  $\geq 14$ ), combined parity/age at first birth (nulliparous, 1–2 children/ $<25$  years, 1–2 children/ $25$ – $29$  years, 1–2 children/ $\geq 30$  years, 3–4 children/ $<25$  years, 3–4 children/ $25$ – $29$  years, 3–4 children/ $\geq 30$  years,  $\geq 5$  children/ $<25$  years,  $\geq 5$  children/ $25$ – $29$  years,  $\geq 5$  children/ $\geq 30$  years), breastfeeding history (none/ $<1$  month, 1– $<2$  years,  $\geq 2$  years), menopausal status (postmenopausal, premenopausal), age at menopause ( $<50$ , 50– $<55$ ,  $\geq 55$ ), history of biopsy-confirmed benign breast disease (BBD; yes, no), current oral contraceptive use (NHSII only: yes, no), type of postmenopausal hormone therapy use (premenopausal, never user, unopposed estrogen, estrogen + progesterone, progesterone only, other), body mass index (BMI;  $<25$  kg/m<sup>2</sup>, 25– $<30$  kg/m<sup>2</sup>,  $\geq 30$  kg/m<sup>2</sup>), early life somatotype (ordinal; ref. 30), diabetes (yes, no), total physical activity ( $<3$  MET/wk, 3– $<9$  MET/wk, 9– $<18$  MET/wk, 18– $<27$  MET/wk,  $\geq 27$  MET/wk), alcohol intake (none,  $<5$  g/day, 5– $<15$  g/day,  $\geq 15$  g/day), alternative healthy eating index score (continuous), and smoking status (never, past, current).

We used Cox proportional hazards regressions with updating of exposure and covariates throughout follow-up to estimate HRs and 95% CIs for associations between: (i) clinical depression; (ii) depressive symptoms; (iii) antidepressant use; and (iv) type of antidepressant use, and invasive breast cancer risk. Women diagnosed with *in situ* breast cancer also were censored at the time of their diagnosis. We first examined associations adjusted only for age and calendar year and then for age, calendar year, and BMI. To assess potential confounding by antidepressant use on estimates of clinical depression and depressive symptoms, we fit models adjusted for antidepressant use in addition to age and BMI; similarly, we also fit models evaluating antidepressant use and antidepressant type adjusted for age, BMI, and clinical depression. Finally, we fit models for each exposure adjusted for all the covariates listed above and in Tables 1 and 2. Because these adjustments minimally affected the estimates for our primary exposures, we report herein the age-adjusted and fully adjusted HRs and 95% CIs. We further examined risk of *in situ* disease, censoring women with diagnosis of invasive breast cancer, following a similar approach.

We repeated analyses among invasive breast cancer cases with subtypes defined by ER status and menopausal status at diagnosis. Also, we repeated analyses incorporating inverse probability weighting based on probabilistic models of mammogram receipt (31). Separately, we repeated analyses restricting to women with a mammogram since the previous questionnaire cycle.

Analyses were conducted separately in each cohort and heterogeneity assessed by random-effects meta-analysis (32, 33). Analyses were conducted using SAS, version 9.3 (SAS Corporation).

## Results

At the beginning of follow-up, 7.3% of NHS participants and 14.1% of NHSII participants self-reported clinical depression. In both cohorts, current antidepressant use was more common among women with clinical depression than those without, as was a history of BBD, obesity, diabetes, and past and current smoking (Table 1). Antidepressant use was reported during 1, 2, or  $\geq 3$  cycles by 6.0%, 3.3%, and 3.8% of the NHS cohort in 2000 and 8.7%, 8.5%, 11.1% of the NHSII cohort in 2003, respectively. Similar patterns with descriptive characteristics were noted for antidepressant use (Supplementary Tables S1 and S2).

During 12 years of follow-up in NHS, 2,667 invasive breast cancers and 658 *in situ* breast cancers were identified among 66,692 women; during 10 years of follow-up in NHSII, 1,347 invasive and 491 *in situ* breast cancers were identified among 89,820 NHSII participants.

The association between clinical depression and invasive breast cancer was similar between the two cohorts ( $P_{\text{heterogeneity}} > 0.43$ ; Table 2). In pooled analyses, we observed no association between the number of times women self-reported clinical depression and risk of invasive breast cancer (HR for  $\geq 3$  times vs. 0, 1.13; 95% CI, 0.85–1.49). Likewise, clinical depression was not significantly associated with invasive disease defined by ER status or menopausal status at diagnosis. The small number of premenopausal cases ( $n = 519$ ) resulted in instability in HR estimates, although no association with clinical depression was apparent (HR = 0.79; 95% CI, 0.45–1.39 for  $\geq 3$  times vs. 0). We also explored the effect of depressive symptoms prior to the beginning of the follow-up period on subsequent breast cancer risk. We observed no association between depressive symptoms and invasive breast cancer overall (HR = 0.86; 95% CI, 0.63–1.17 for  $\geq 3$  times vs. 0) or defined by ER or menopausal status subtypes (Table 3). We also observed no association between clinical depression (HR = 1.10; 95% CI, 0.84–1.46 for  $\geq 3$  times vs. 0) or depressive symptoms (HR = 0.84; 95% CI, 0.57–1.25) and risk of *in situ* disease.

Associations between antidepressant use and invasive breast cancer also were similar across cohorts ( $P_{\text{heterogeneity}} > 0.29$ ; Table 4). We observed no statistically significant association between the number of times antidepressant use was reported and invasive breast cancer risk, although estimates were suggestive of an inverse association for those with the most frequent reports of antidepressant use ( $\geq 3$  times vs. 0 times, HR = 0.92; 95% CI, 0.80–1.05). Antidepressant use was not associated with invasive disease defined by ER subtype, although the suggestion of an inverse effect was apparent only among ER<sup>+</sup> cases and not among ER<sup>−</sup> cases. Antidepressant use was not associated with postmenopausal invasive breast cancer when separately evaluated. Again, small numbers of premenopausal cases in each antidepressant use group led to instability in the HR estimates, although no associations with antidepressant use were apparent (HR = 1.30; 95% CI, 0.65–2.60 for  $\geq 3$  times vs. 0). Type of antidepressant currently used also was not significantly associated with invasive breast cancer overall or defined by ER or menopausal status (Table 5). We observed no association between concurrent use of SSRI and other antidepressant with invasive breast cancer (HR = 0.81; 95% CI, 0.55–1.21), which persisted among ER<sup>−</sup>, postmenopausal, and premenopausal subgroups. Interestingly, we observed a statistically significant positive association between concurrent use of SSRI and other antidepressant with *in situ* disease (HR = 1.72; 95% CI, 1.00–2.94).

We observed similar results in analyses restricted to women with a mammogram since the previous cycle (e.g., HR = 0.76; 95% CI, 0.55–1.04 for depressive symptoms  $\geq 3$  vs. 0 times).

## Discussion

In these large prospective cohorts with 4,014 invasive breast cancer cases, we observed no evidence that either clinical depression or antidepressant use are associated with subsequent risk of breast cancer. The lack of association persisted among *in situ* cases

**Table 1.** Age-standardized characteristics of study population at beginning of follow-up period, by clinical depression status<sup>a</sup> (NHS: 2000, NHSII: 2003)

	NHS		NHSII	
	Not depressed <i>n</i> = 61,818	Clinically depressed <i>n</i> = 4,874	Not depressed <i>n</i> = 77,132	Clinically depressed <i>n</i> = 12,688
Age, years <sup>b</sup>	66.4 (7.1)	65.2 (7.0)	48.3 (4.7)	48.7 (4.6)
White race, %	97.5	98.5	95.7	97.5
Number of times reported antidepressant use, %				
0, %	91.9	22.9	80.7	16.3
1, %	4.3	27.2	6.6	21.4
2, %	2.0	20.9	6.9	18.8
≥3, %	1.8	29.0	5.8	43.6
Number of times with severe depressive symptoms, as assessed by MHI-5				
0, %	93.2	69.9	86.6	60.5
1, %	4.8	16.0	9.1	22.2
2, %	1.4	8.4	3.1	11.2
≥3, %	0.7	5.7	1.3	6.1
History of breast cancer in first-degree relative, %	17.4	17.2	14.7	15.5
Mammogram in previous 2 years, %	93.3	94.4	85.3	85.2
Age at menarche				
≤12, %	35.1	32.3	54.6	56.9
13, %	39.6	41.4	27.6	25.9
14+, %	25.3	26.3	17.8	17.2
Nulliparous, %	5.2	6.0	17.1	19.8
Age at first birth, years <sup>c</sup>	25.1 (3.3)	24.9 (3.3)	26.6 (4.7)	26.1 (4.9)
Parity <sup>c</sup>	3.2 (1.5)	3.1 (1.4)	2.3 (1.0)	2.2 (0.9)
Breastfeeding history				
None/<1 month, %	47.1	45.6	19.1	19.9
1 month-<1 year, %	34.2	36.2	34.1	36.9
1-<2 years, %	12.2	12.5	24.7	24.0
≥2 years, %	6.6	5.7	22.1	19.2
Postmenopausal, %	98.8	98.9	42.1	49.0
Age at menopause, years <sup>d</sup>				
<50 years, %	42.3	44.6	60.9	66.6
50-<55 years, %	48.5	47.6	36.9	31.8
≥55 years, %	9.2	7.8	2.2	1.6
History of benign breast disease, %	49.9	61.2	50.2	58.0
Current oral contraceptive use, %	—	—	86.7	90.8
Type of postmenopausal hormone therapy use				
Premenopausal, %	1.4	1.3	62.4	56.0
Never user, %	24.2	13.0	15.0	13.3
Unopposed estrogen, %	34.4	44.3	11.4	16.6
Estrogen + progesterone, %	30.1	29.0	8.4	9.9
Other, %	10.0	12.4	2.8	4.1
Body mass index, kg/m <sup>2</sup>				
<25 kg/m <sup>2</sup> , %	42.1	34.7	46.6	34.2
25-<30 kg/m <sup>2</sup> , %	34.9	33.2	28.3	27.6
≥30 kg/m <sup>2</sup> , %	23.0	32.2	25.1	38.2
Early life somatotype <sup>e</sup>	2.7 (1.2)	2.8 (1.2)	2.9 (1.1)	3.1 (1.2)
Diabetes, %	8.7	13.0	3.6	6.8
Total physical activity, MET-hrs/wk				
<3 MET-hrs/wk, %	24.2	32.7	19.4	25.9
3-<9 MET-hrs/wk, %	22.4	24.1	20.9	22.2
9-<18 MET-hrs/wk, %	20.3	17.8	20.0	19.0
18-<27 MET-hrs/wk, %	12.7	10.2	13.3	11.8
≥27 MET-hrs/wk, %	20.4	15.3	26.4	21.1
Alcohol intake, g/d <sup>f</sup>				
None, %	41.6	49.7	35.7	40.9
<5 g/d, %	30.1	27.0	32.6	31.5
5-<15 g/d, %	19.4	15.6	20.7	17.2
≥15 g/d, %	9.0	7.7	10.9	10.4
Alternative healthy eating index score <sup>f</sup>	54.2 (10.5)	53.7 (10.8)	54.6 (13.2)	53.4 (13.1)
Smoking status				
Never smoker, %	45.0	39.3	66.0	57.0
Past smoker, %	45.9	49.9	25.7	30.4
Current smoker, %	9.0	10.9	8.3	12.6

NOTE: Values are means (SD) or percentages and are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding.

<sup>a</sup>Clinical depression defined as self-reported of having been diagnosed with depression by a physician or other medical professional.

<sup>b</sup>Value is not age adjusted.

<sup>c</sup>Among parous women only.

<sup>d</sup>Among postmenopausal women with a natural or surgical menopause.

<sup>e</sup>Average of reported somatotype at ages 10 and 20.

<sup>f</sup>Based on data from 1998 (NHS) or 2001 (NHSII) questionnaire.

**Table 2.** Association between cumulative number of times reported clinical depression diagnosis<sup>a</sup> at each cycle and invasive breast cancer risk, NHS (2000–2012), and NHSII (2003–2013)

	All invasive cases		ER positive		ER negative		Postmenopausal at diagnosis		
	Cases/ person-years	Age- and calendar year adjusted	Fully adjusted <sup>b</sup>	Cases/ person-years	Fully adjusted <sup>b</sup>	Cases/ person-years	Fully adjusted <sup>b</sup>	Cases/ person-years	Fully adjusted <sup>b</sup>
NHS (n = 2,667 cases)									
0	2,400/734,139	1 (ref)	1 (ref)	1,975/734,139	1 (ref)	302/734,139	1 (ref)	2,391/734,127	1 (ref)
1	219/72,768	0.97 (0.84–1.11)	0.95 (0.81–1.12)	176/72,768	0.97 (0.81–1.17)	32/72,768	0.89 (0.58–1.38)	219/72,768	0.96 (0.81–1.13)
2	39/12,083	1.16 (0.84–1.59)	1.13 (0.80–1.58)	31/12,083	1.14 (0.78–1.67)	6/12,083	1.14 (0.48–2.72)	39/12,083	1.13 (0.80–1.58)
3+	9/2,508	1.49 (0.77–2.88)	1.44 (0.73–2.82)	5/2,508	1.00 (0.41–2.44)	3/2,508	2.96 (0.89–9.90)	9/2,508	1.44 (0.74–2.82)
NHS II (n = 1,347 cases)									
0	1,078/570,394	1 (ref)	1 (ref)	858/570,394	1 (ref)	178/570,394	1 (ref)	635/569,475	1 (ref)
1	138/73,815	0.98 (0.82–1.17)	1.04 (0.85–1.28)	113/73,815	1.05 (0.84–1.31)	21/73,815	1.06 (0.64–1.76)	83/73,712	1.00 (0.77–1.29)
2	72/38,637	0.94 (0.74–1.19)	1.00 (0.76–1.31)	56/38,637	0.94 (0.69–1.27)	15/38,637	1.51 (0.81–2.79)	54/38,601	1.08 (0.78–1.48)
3+	59/29,276	1.02 (0.78–1.35)	1.07 (0.78–1.46)	54/29,276	1.11 (0.80–1.55)	3/29,276	0.50 (0.15–1.69)	46/29,252	1.11 (0.77–1.59)
Pooled (n = 4,014 cases)									
0	3,478/1,304,533	1 (ref)	1 (ref)	2,833/1,304,533	1 (ref)	480/1,304,533	1 (ref)	3026/1,303,602	1 (ref)
1	357/146,583	0.97 (0.87–1.09)	0.99 (0.87–1.12)	289/146,583	1.01 (0.87–1.16)	53/146,583	0.96 (0.69–1.33)	302/146,480	0.97 (0.84–1.11)
2	111/50,720	1.01 (0.83–1.24)	1.05 (0.85–1.29)	87/50,720	1.01 (0.80–1.28)	21/50,720	1.37 (0.83–2.27)	93/50,684	1.10 (0.87–1.39)
3+	68/31,784	1.09 (0.82–1.45)	1.13 (0.85–1.49)	59/31,784	1.10 (0.81–1.50)	6/31,784	1.22 (0.21–6.99)	55/31,760	1.18 (0.85–1.62)

<sup>a</sup>Clinical depression defined as self-reported of having been diagnosed with depression by a physician or other medical professional.

<sup>b</sup>Adjusted for age, calendar year, BMI, count of antidepressant use, age at menarche, current oral contraceptive use (NHSII only), type of PMH use, age at menopause, age at first birth and parity, history of biopsy-confirmed benign breast disease, family history of breast cancer, mammogram in prior 2 years, smoking status, physical activity, alcohol intake, and AHEI score.

**Table 3.** Association between cumulative number of times reported severe depressive symptoms<sup>a</sup> at each cycle and invasive breast cancer risk, NHS (2000–2012), and NHSII (2003–2013)

	All invasive cases		ER positive		ER negative		Postmenopausal at diagnosis		
	Cases/ person-years	Age and calendar year adjusted	Fully adjusted <sup>b</sup>	Cases/ person-years	Fully adjusted <sup>b</sup>	Cases/ person-years	Fully adjusted <sup>b</sup>	Cases/ person-years	Fully adjusted <sup>b</sup>
NHS (n = 2,667 cases)									
0	2,301/760,269	1 (ref)	1 (ref)	2,028/760,269	1 (ref)	313/760,269	1 (ref)	2,461/751,889	1 (ref)
1	137/45,587	0.93 (0.78–1.10)	0.91 (0.77–1.09)	109/45,587	0.90 (0.74–1.09)	21/45,587	1.05 (0.67–1.65)	137/45,587	0.92 (0.77–1.09)
2	39/14,887	0.79 (0.58–1.09)	0.79 (0.57–1.09)	31/14,887	0.79 (0.55–1.13)	7/14,887	1.02 (0.48–2.20)	39/14,887	0.79 (0.58–1.09)
3+	20/8,394	0.74 (0.48–1.15)	0.76 (0.48–1.18)	18/8,394	0.89 (0.55–1.42)	2/8,394	0.51 (0.12–2.06)	20/8,394	0.76 (0.49–1.19)
NHS II (n = 1,347 cases)									
0	1,089/557,035	1 (ref)	1 (ref)	873/557,035	1 (ref)	178/557,035	1 (ref)	667/556,146	1 (ref)
1	125/73,582	0.87 (0.73–1.05)	0.88 (0.73–1.06)	102/73,582	0.89 (0.72–1.09)	18/73,582	0.81 (0.49–1.32)	74/73,496	0.83 (0.65–1.06)
2	58/28,254	1.04 (0.80–1.36)	1.11 (0.85–1.45)	53/28,254	1.24 (0.94–1.65)	3/28,254	0.39 (0.12–1.22)	37/28,210	1.08 (0.77–1.52)
3+	22/12,914	0.86 (0.57–1.31)	0.97 (0.63–1.48)	15/12,914	0.81 (0.48–1.35)	7/12,914	2.18 (1.00–4.71)	15/12,901	1.01 (0.60–1.70)
Pooled (n = 4,014 cases)									
0	3,390/1,317,304	1 (ref)	1 (ref)	2,901/1,317,304	1 (ref)	491/1,317,304	1 (ref)	3,122/1,308,035	1 (ref)
1	262/119,169	0.90 (0.79–1.02)	0.90 (0.79–1.02)	211/119,169	0.89 (0.77–1.03)	39/119,169	0.93 (0.67–1.30)	211/119,083	0.89 (0.77–1.02)
2	97/43,141	0.92 (0.71–1.21)	0.95 (0.68–1.32)	84/43,141	1.01 (0.65–1.56)	10/43,141	0.69 (0.27–1.77)	76/43,097	0.92 (0.68–1.25)
3+	42/21,308	0.80 (0.59–1.09)	0.86 (0.63–1.17)	33/21,308	0.85 (0.60–1.20)	9/21,308	1.19 (0.29–4.85)	35/21,295	0.86 (0.61–1.20)

<sup>a</sup>Severe depressive symptoms defined as a score  $\leq 2$  on the MHI-5 scale.

<sup>b</sup>Adjusted for age, calendar year, BMI, count of antidepressant use, age at menarche, current oral contraceptive use (NHSII only), type of PMH use, age at menopause, age at first birth and parity, history of biopsy-confirmed benign breast disease, family history of breast cancer, mammogram in prior 2 years, smoking status, physical activity, alcohol intake, and AHEI score.

**Table 4.** Association between cumulative number of times reported antidepressant use at each cycle and invasive breast cancer risk, NHS (2000–2012), and NHSII (2003–2013)

	All invasive cases			ER positive			ER negative			Postmenopausal at diagnosis		
	Cases/ person-years	Age- and calendar year adjusted	Fully adjusted <sup>a</sup>	Cases/ person-years	Age- and calendar year adjusted	Fully adjusted <sup>a</sup>	Cases/ person-years	Age- and calendar year adjusted	Fully adjusted <sup>a</sup>	Cases/ person-years	Age- and calendar year adjusted	Fully adjusted <sup>a</sup>
NHS (n = 2,667 cases)												
0	2,194/666,501	1 (ref)	1 (ref)	1,816/666,501	1 (ref)	1 (ref)	269/666,501	1 (ref)	1 (ref)	2,186/666,489	1 (ref)	1 (ref)
1	159/52,826	0.94 (0.80–1.11)	0.93 (0.79–1.10)	126/52,826	0.93 (0.79–1.10)	0.90 (0.75–1.09)	23/52,826	1.01 (0.65–1.58)	1.01 (0.65–1.58)	158/52,825	0.93 (0.78–1.10)	0.93 (0.78–1.10)
2	100/30,851	1.03 (0.84–1.26)	0.99 (0.80–1.23)	77/30,851	1.03 (0.84–1.26)	0.93 (0.73–1.18)	15/30,851	1.10 (0.63–1.92)	1.10 (0.63–1.92)	100/30,851	1.00 (0.81–1.23)	1.00 (0.81–1.23)
3+	214/71,179	1.03 (0.89–1.19)	0.97 (0.82–1.15)	168/71,179	1.03 (0.89–1.19)	0.91 (0.76–1.10)	36/71,179	1.26 (0.82–1.94)	1.26 (0.82–1.94)	214/71,179	0.98 (0.82–1.16)	0.98 (0.82–1.16)
NHS II (n = 1,347 cases)												
0	905/478,115	1 (ref)	1 (ref)	716/478,115	1 (ref)	1 (ref)	151/478,115	1 (ref)	1 (ref)	524/477,328	1 (ref)	1 (ref)
1	127/61,702	1.09 (0.90–1.31)	1.06 (0.87–1.29)	103/61,702	1.09 (0.87–1.35)	1.09 (0.87–1.35)	21/61,702	1.03 (0.63–1.68)	1.03 (0.63–1.68)	78/61,620	1.06 (0.83–1.37)	1.06 (0.83–1.37)
2	109/61,140	0.92 (0.75–1.12)	0.88 (0.71–1.08)	85/61,140	0.88 (0.71–1.08)	0.87 (0.68–1.10)	21/61,140	0.99 (0.61–1.61)	0.99 (0.61–1.61)	71/61,061	0.87 (0.67–1.14)	0.87 (0.67–1.14)
3+	206/111,165	0.94 (0.80–1.09)	0.85 (0.69–1.03)	177/111,165	0.85 (0.69–1.03)	0.91 (0.73–1.13)	24/111,165	0.62 (0.36–1.05)	0.62 (0.36–1.05)	145/111,031	0.84 (0.66–1.07)	0.84 (0.66–1.07)
Pooled (n = 4,014 cases)												
0	3,099/1,144,616	1 (ref)	1 (ref)	2,532/1,144,616	1 (ref)	1 (ref)	420/1,144,616	1 (ref)	1 (ref)	2,710/1,143,817	1 (ref)	1 (ref)
1	286/113,988	1.01 (0.87–1.16)	0.98 (0.86–1.12)	229/113,988	1.01 (0.87–1.16)	0.98 (0.82–1.18)	44/113,988	1.02 (0.73–1.42)	1.02 (0.73–1.42)	236/114,445	0.97 (0.84–1.11)	0.97 (0.84–1.11)
2	209/91,991	0.97 (0.84–1.12)	0.93 (0.80–1.08)	162/91,991	0.97 (0.84–1.12)	0.90 (0.76–1.06)	36/91,991	1.03 (0.72–1.50)	1.03 (0.72–1.50)	171/91,912	0.95 (0.80–1.12)	0.95 (0.80–1.12)
3+	420/182,344	0.99 (0.89–1.09)	0.92 (0.80–1.05)	345/182,344	0.99 (0.89–1.09)	0.91 (0.79–1.05)	60/182,344	0.90 (0.44–1.81)	0.90 (0.44–1.81)	359/182,210	0.93 (0.81–1.07)	0.93 (0.81–1.07)

<sup>a</sup>Adjusted for age, calendar year, BMI, count of clinical depression, age at menarche, current oral contraceptive use (NHSII only), type of PMH use, age at menopause, age at first birth & parity, history of biopsy-confirmed benign breast disease, family history of breast cancer, mammogram in prior 2 years, smoking status, physical activity, alcohol intake, and AHEI score.

**Table 5.** Association between type of antidepressant use at each cycle and invasive breast cancer risk, NHS (2000–2012), and NHSII (2003–2013)

	All invasive cases			ER positive			ER negative			Postmenopausal at diagnosis		
	Cases/ person-years	Age and calendar year adjusted	Fully adjusted <sup>a</sup>	Cases/ person-years	Age and calendar year adjusted	Fully adjusted <sup>a</sup>	Cases/ person-years	Age and calendar year adjusted	Fully adjusted <sup>a</sup>	Cases/ person-years	Age and calendar year adjusted	Fully adjusted <sup>a</sup>
NHS (n = 2,667 cases)												
None	2,345/726,654	1 (ref)	1 (ref)	1,931/726,654	1 (ref)	1 (ref)	295/726,654	1 (ref)	1 (ref)	2,337/726,642	1 (ref)	1 (ref)
SSRI	194/59,047	1.04 (0.90–1.21)	0.99 (0.84–1.17)	153/59,047	1.04 (0.90–1.21)	0.95 (0.79–1.14)	28/59,047	1.04 (0.67–1.61)	1.04 (0.67–1.61)	193/59,046	0.99 (0.84–1.17)	0.99 (0.84–1.17)
Other AD	93/25,544	1.16 (0.94–1.43)	1.13 (0.91–1.40)	76/25,544	1.16 (0.94–1.43)	1.13 (0.89–1.44)	14/25,544	1.20 (0.68–2.11)	1.20 (0.68–2.11)	93/25,544	1.13 (0.91–1.41)	1.13 (0.91–1.41)
SSRI + Other AD	13/4,480	0.95 (0.55–1.65)	0.93 (0.53–1.62)	8/4,480	0.95 (0.55–1.65)	0.69 (0.34–1.39)	3/4,480	1.62 (0.50–5.25)	1.62 (0.50–5.25)	13/4,480	0.93 (0.54–1.63)	0.93 (0.54–1.63)
NHS II (n = 1,347 cases)												
None	1,118/588,420	1 (ref)	1 (ref)	893/588,420	1 (ref)	1 (ref)	182/588,420	1 (ref)	1 (ref)	667/587,521	1 (ref)	1 (ref)
SSRI	145/80,001	0.94 (0.79–1.11)	0.83 (0.68–1.02)	115/80,001	0.94 (0.79–1.11)	0.80 (0.64–1.01)	26/80,001	0.98 (0.60–1.58)	0.98 (0.60–1.58)	95/79,872	0.83 (0.65–1.06)	0.83 (0.65–1.06)
Other AD	65/32,774	1.03 (0.80–1.32)	0.92 (0.71–1.20)	57/32,774	1.03 (0.80–1.32)	0.99 (0.75–1.32)	7/32,774	1.07 (0.49–2.38)	1.07 (0.49–2.38)	46/32,741	1.00 (0.73–1.37)	1.00 (0.73–1.37)
SSRI + Other AD	13/8,425	0.80 (0.46–1.38)	0.71 (0.40–1.25)	11/8,425	0.80 (0.46–1.38)	0.72 (0.39–1.34)	1/8,425	0.38 (0.05–2.76)	0.38 (0.05–2.76)	8/8,409	0.66 (0.32–1.35)	0.66 (0.32–1.35)
Pooled (n = 4,014 cases)												
None	3,463/1,315,074	1 (ref)	1 (ref)	2,824/1,315,074	1 (ref)	1 (ref)	477/1,318,074	1 (ref)	1 (ref)	3,004/1,314,163	1 (ref)	1 (ref)
SSRI	339/139,048	0.99 (0.89–1.11)	0.92 (0.77–1.09)	268/139,048	0.99 (0.89–1.11)	0.89 (0.75–1.04)	54/139,048	1.01 (0.73–1.39)	1.01 (0.73–1.39)	288/138,918	0.93 (0.79–1.10)	0.93 (0.79–1.10)
Other AD	158/58,318	1.10 (0.94–1.30)	1.04 (0.85–1.26)	133/58,318	1.10 (0.94–1.30)	1.07 (0.89–1.29)	21/58,318	0.92 (0.49–1.72)	0.92 (0.49–1.72)	139/58,285	1.09 (0.91–1.30)	1.09 (0.91–1.30)
SSRI + Other AD	26/12,905	0.87 (0.59–1.29)	0.81 (0.55–1.21)	19/12,905	0.87 (0.59–1.29)	0.71 (0.45–1.12)	4/12,905	0.98 (0.25–3.81)	0.98 (0.25–3.81)	21/12,889	0.82 (0.53–1.27)	0.82 (0.53–1.27)

<sup>a</sup>Adjusted for age, calendar year, BMI, count of clinical depression, age at menarche, current oral contraceptive use (NHSII only), type of PMH use, age at menopause, age at first birth and parity, history of biopsy-confirmed benign breast disease, family history of breast cancer, mammogram in prior 2 years, smoking status, physical activity, alcohol intake, and AHEI score.

Reeves et al.

and among subgroups of invasive disease defined by ER status and menopausal status at diagnosis.

Most prior studies reported significant positive associations between depression and breast cancer; however, such associations are not supported by our analyses. A meta-analysis of prospective studies reported a statistically nonsignificant 59% increased risk of breast cancer among depressed women compared with non-depressed women (10). Wide variation of results was observed, however, and many studies utilized different assessments and definitions of depression and also included only short follow-up. Two prospective studies (8, 9), both within the Baltimore Epidemiologic Catchment Area sample, included >10 years of follow-up and reported a 3 to 4 times increased risk of breast cancer associated with clinical depression. Yet these studies did not adjust for potentially important confounders, such as antidepressant use, BMI, or exogenous hormone use, and included far fewer breast cancer cases than our analyses [ $n = 203$  (8) and  $n = 343$  (9)]. Our findings agree with those of the WHI, which also reported no association between depression and breast cancer (25).

Antidepressants were linked to increased risk of breast cancer by two recent prospective cohort studies (23, 24), although no association was observed in several retrospective studies (26, 27, 34–37) or within the prospective WHI cohort (25). Our results are consistent with the latter studies, as we observed no associations with either frequency or type of antidepressant use. Concerns regarding antidepressant use have centered around the idea that SSRI use may increase circulating prolactin levels (19), which in turn promotes breast carcinogenesis (20–22). Prior reports of SSRI-related prolactin increases were based primarily on small, highly selected clinical populations. Our recent analysis within the NHS and NHSII cohorts did not observe increased prolactin levels among women using antidepressants or SSRIs, specifically (38), which is consistent with our current report of no relationship between antidepressant use and breast cancer risk. The increased risk of *in situ* disease we observed is intriguing, yet requires confirmation in other prospective cohorts. Although not statistically significant, we noted that HR estimates tended in the direction of protective effects, especially in the case of depressive symptoms. We are unaware of biologic mechanisms that might account for depressive symptoms reducing breast cancer risk. However, women with depression are somewhat less likely to receive mammograms and other health care screenings (39), which might artificially produce a reduced breast cancer risk among women with depressive symptoms. We adjusted for mammogram receipt since previous cycle in our analyses, although the possibility of residual confounding remains. We further adjusted for mammography utilization using inverse probability weighting, whereby analyses were weighted by the inverse probability that a woman received a mammogram (31), and also by repeating among the subgroup of women who had received mammograms since the previous cycle; neither approach substantially altered the estimates, perhaps due to the high prevalence of mammography use (>93% in NHS and >85% in NHSII). Our approach to measuring depressive symptoms may also contribute to the null associations we observed. Depressive symptoms during the previous 4 weeks were assessed once every 4 years; because depression is an episodic condition, this approach may have misclassified women experiencing depressive symptoms outside of this ascertainment window as not depressed.

Our measure of clinical depression has the advantage of high specificity in classifying women with versus without depression; although self-reported, this measure captured all diagnoses occurring since the prior cycle and also includes women with the most persistent and severe depression. An ongoing validation study within NHS found a sensitivity of 56% and a specificity of 95% for self-reported clinical depression compared with diagnosis via a structured clinical interview using DSM-IV guidelines. However, lower sensitivity means that it is possible that some depressed women were classified as nondepressed in our analyses, which may have attenuated a true association. Nevertheless, previous studies within these cohorts have identified important associations with major disease outcomes, supporting the validity of this definition (7, 40, 41). Importantly, clinical diagnosis of depression was not associated with breast cancer risk overall or for any subtype. In addition, some women may have reported prior clinical diagnoses of depression on later questionnaires, as opposed to new diagnoses as was instructed. This potential misclassification, along with the 2-year time between cycles and the lack of information on specific dates of diagnosis, prevents an accurate estimation of the duration of depression. As a result, we have referred to the "intensity" of depression as the number of times each woman reported being diagnosed with the condition. Although this measure provides a reasonable proxy of duration, we could not directly assess effects of duration of depression on breast cancer risk.

Our results must be interpreted within the context of some additional limitations. Antidepressant use also was self-reported; although we have no information on validity of such reports within NHS and NHSII, all participants were registered nurses, supporting their ability to accurately report specific medication use. Furthermore, our results were consistent with those of the WHI, where participants brought medication bottles to clinical visits. However, we lacked information on antidepressant dose; thus, we could not address associations between antidepressant dosage intensity and breast cancer outcomes. Also, we lacked accurate information on duration of antidepressant use, because of the biennial nature of the questionnaires; therefore, we utilized a proxy measure of duration, referred to as "intensity" of use, which captures the number of times each participant reported antidepressant use on a questionnaire and may roughly approximate duration of use. In addition, bias in our results may be possible if women with depression were preferentially lost to follow-up. We believe such bias to be minimal, however, given the high retention rates in the NHS and NHSII cohort (>90%). Also, the intensity of both depression and antidepressant use is constrained by the number of questionnaires each participant completed; therefore, nondifferential misclassification of exposure is possible. However, the categorizations we used (0, 1, 2,  $\geq 3$ ) should have limited such effects, as 99% of women in each cohort returned at least three questionnaires included in our analysis. The NHS and NHSII populations are quite homogeneous with respect to race/ethnicity and socioeconomic status, thus somewhat limiting the generalizability of our results. However, it is unlikely that biological pathways linking depression or antidepressant use to breast cancer would vary substantially by race/ethnicity or socioeconomic status. Many features of the NHS and NHSII cohorts strengthen our analyses, including the large numbers of adjudicated breast cancer cases; with 4,014 incident, invasive breast cancer cases, ours is by far the largest study to date to examine associations between depression and/or antidepressant use and

breast cancer risk. In addition, the prospective nature of the data with repeated measures of depression, antidepressant use, and key covariates, and the extended follow-up with high retention rates are important strengths. We also examined associations separately by invasiveness, ER status, and menopausal status.

Depression is a serious medical condition, with important effects on quality of life as well as obesity and other chronic health conditions. We provide evidence that in the absence of other risk factors, breast cancer should not be a particular concern among women with depression. Importantly, we also observed no increased risk of breast cancer due to antidepressant use overall or by therapeutic class. These results, in particular, should provide reassurance to women and their clinicians that antidepressants can be used to treat depression without concern that such treatment will impact their breast cancer risk.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Disclaimer

The authors assume full responsibility for analyses and interpretation of these data.

#### Authors' Contributions

**Conception and design:** K.W. Reeves, S.E. Hankinson

**Development of methodology:** K.W. Reeves, O.I. Okereke

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**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** K.W. Reeves, O.I. Okereke

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