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REGULAR ARTICLE

Depression, antidepressant use, and breast cancer incidence: results from the E3N prospective cohort

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Aim: Depression and antidepressant drugs may both impact breast cancer incidence, potentially in opposite directions. The few epidemiological studies attempting to disentangle their effects have been inconclusive. We aimed to assess within the same prospective cohort the association between depression, antidepressant use, and breast cancer risk, while controlling for potential confounders.

Methods: The study population included 47,791 women from the E3N (Etude Epidémiologique Auprès de Femmes de la Mutuelle Générale de l'Education Nationale) prospective cohort, born between 1925 and 1950 and followed for breast cancer incidence from 2005 to 2014. Depression was defined by a Center for Epidemiologic Studies-Depression Scale (CES-D) score ≥17. Exposure to antidepressants was identified from drug claims data available from 2004 onwards. Hazard ratios (HRs) and 95% confidence intervals (CIs) for invasive breast cancer were calculated using Cox proportional hazards models adjusted for breast cancer risk factors. Antidepressant exposure was time-varying.

Results: During a mean follow-up of 7.2 years, 1365 breast cancers occurred. Depression was associated with a higher incidence of breast cancer (HR, 1.14 [95% CI, 1.01–1.29]), while exposure to antidepressants was associated with a lower risk (HR, 0.85 [95% CI, 0.74–0.98]). No association was observed for treatment durations <6 months (HR, 1.02 [95% CI, 0.79–1.32]), while antidepressant use for at least 24 months was associated with an HR of 0.80 (95% CI, 0.64–0.99).

Conclusion: These findings from a prospective cohort suggest that depression and antidepressant drugs exert opposing effects on breast cancer incidence. While these results require replication in future studies, they could help promote adherence to antidepressant drugs in women with depression.

Keywords: *affective disorders, antidepressive agents, breast cancer, depression, epidemiology and public health.*

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Antidepressant drugs are widely prescribed to women for the treatment of depressive disorders[1,2] and other conditions such as anxiety disorders or chronic pain.[3] In the 2010s, 9.4% of European women reported using antidepressant drugs in the past year[4] and 16.5% of US women reported use in the past month.[5]

Breast cancer is the most common cancer among women, with an estimated 2 million new cases worldwide in 2019.[6] It is also the leading cause of cancer-related mortality and disability-adjusted life-years in women.[6]

Beyond changes in health-related behaviors such as physical activity or alcohol consumption, both depression and antidepressant drugs may influence breast cancer risk through several plausible pathways—for example, involving serotonin transmission or inflammatory processes—that could have opposing effects.[7–12] Investigating the impact of depression on breast cancer incidence therefore requires careful adjustment for the potentially counteracting effects of antidepressants, and vice versa.

The most recent meta-analysis of aggregated data from 10 cohort studies, published in 2020, yielded no significant association between depression and breast cancer risk,[13] while four recent Mendelian randomization studies concluded that genetic liability to depression was associated with an increased risk of breast cancer.[14–17] However, among epidemiological studies evaluating the association of depression and/or antidepressant drugs with the risk of breast cancer,[13,18] only six were based on cohort data and assessed their independent effects. One examined depression while adjusting for antidepressant use,[19] three evaluated antidepressant use while adjusting for depression,[20–22] and two jointly investigated the relationship of depression and antidepressant drugs with breast cancer risk.[23,24] However, of these six studies, three shared a critical limitation: the incomplete capture of antidepressant exposure, which was assessed only at baseline or every 2 to 3 years and only considered current

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antidepressant prescriptions.[19,23,24] In another study, the maximum time elapsed between the initiation of antidepressant use and breast cancer occurrence was 6 years, a period that may have been too short to observe an association.[20] Additionally, one study only considered ever use of tricyclic antidepressants (TCAs),[22] which are now rarely prescribed. None of these studies reported an association between depression and/or antidepressant use and breast cancer incidence. The remaining study, which used data from the General Practice Research Database and identified exposure to antidepressant drugs and depression diagnoses through general practitioners' computerized records, found decreased risks of breast cancer with antidepressant drugs, with a borderline statistical significance for past use of selective serotonin reuptake inhibitors (SSRIs; relative risk [RR], 0.81 [95% confidence interval (CI), 0.67–1.00]) and current use of TCAs (RR, 0.86 [95% CI, 0.73–1.00]).[21]

The limitations of previous epidemiological studies—particularly the inability to simultaneously account for depression and use of antidepressant drugs, exposure misclassification, insufficient follow-up durations, and, in case-control studies, differential recall bias—may have hindered the proper evaluation of the relationship of breast cancer incidence to depression and antidepressant use. Consequently, determining whether depression and antidepressant use are associated with breast cancer risk remains a relevant yet unresolved question. To address this, we investigated the joint association of depression and antidepressant drugs with breast cancer incidence within a large prospective cohort of women. Exposure to antidepressants was identified using drug claims data, enabling updates of exposure during follow-up and allowing us to explore potential effects of antidepressants that may emerge only after extended durations of use. We hypothesized that antidepressants could mitigate an increased risk of breast cancer associated with depression.

Methods

The E3N cohort

The E3N (Etude Epidémiologique Auprès de Femmes de la Mutuelle Générale de l'Education Nationale) study is a prospective cohort initiated in 1990.[25] It includes 98,995 French women born between 1925 and 1950 and insured by a health insurance plan for workers in the national education system. The participants have been followed since 1990 through biennial self-administered questionnaires about their health, reproductive factors, and lifestyle. The average response rate is approximately 80% at each questionnaire. Questionnaire data are linked to a computerized database containing all outpatient healthcare claims issued since 1 January 2004 for each E3N participant, including drug names as well as the dates they were dispensed.

Participants gave their written informed consent. Patient anonymity has been preserved, and the E3N study was approved by the French National Commission for Data Protection and Privacy in conformity to the provisions of the Declaration of Helsinki. It was registered at clinicaltrials.gov as NCT03285230 on September 15, 2017.

Exposures

Depression

The Center for Epidemiologic Studies-Depression Scale (CES-D)[26] was filled in by women of the E3N cohort in a questionnaire sent in July 2005 (baseline). It is a 20-item validated instrument with four graded answers from 0 to 3 for each item, to screen and quantify depressive symptoms (minimal score = 0; maximal score = 60). If a woman answered only 16 to 19 CES-D items, her total score was calculated as the mean score per answered item multiplied by 20. The CES-D score was considered missing for women who answered <16 CES-D items. The presence of depression was defined by a CES-D score ≥17.[26]

Antidepressant drugs

Exposure to antidepressant drugs was determined by using drug claims data available from 1 January 2004 onwards. All antidepressant drugs on the French market between 2004 and 2014 were considered (anatomical therapeutic chemical [ATC] classification: N06A). The following main classes were identified: SSRI (ATC: N06AB), serotonin and norepinephrine reuptake inhibitor (SNRI; ATC: N06AX16, N06AX17, N06AX21, N06AX23), TCA (ATC: N06AA), and others (ATC: N06AF05, N06AG02, N06AX01, N06AX03, N06AX09, N06AX11, N06AX14, N06AX22). The cumulative duration of exposure (in months) was calculated as the number of antidepressant deliveries, assuming that each delivery was for a 1-month treatment (which is the standard rule for drug dispensing in France).

Covariates

Covariates included the following breast cancer risk factors: age at menarche, menopausal status and age at menopause, number of children, breastfeeding, lifetime use of menopausal hormone therapy and lifetime use of oral contraceptives, educational level, family history of breast cancer, personal history of benign breast disease, recent mammogram, current levels of physical activity, body mass index, alcohol consumption, and smoking status. Information on these factors was gathered from the self-administered questionnaires sent between 1990 and 2005, i.e. those available at the start of follow-up of the current study. Furthermore, information on body mass index, menopausal status and age at menopause, personal history of benign breast disease, and whether a mammogram had been performed during the previous follow-up cycle, was updated in subsequent questionnaires (2008 and 2011).

Outcome

The considered end point was the diagnosis of a primary invasive breast cancer, first identified from the self-administered questionnaires, which systematically inquired about any cancer diagnosis (including date and site), close relative spontaneous reports, and the national cause of death registry. Each identified cancer case was then thoroughly investigated, and pathology reports were obtained from the women or their physicians. Only invasive breast cancers confirmed by medical documents were considered for the present study. Of the cases included, 92% were initially identified from self-reports.

Study population and follow-up

Follow-up began 1 year after the responses to the 2005 questionnaire, which assessed depression, and ended at the date of diagnosis of any cancer (other than basal cell skin carcinoma or in situ colorectal cancer), the date when the last information on cancer occurrence was obtained, or 17 November 2014, whichever occurred first.

Of the 98,995 women in E3N, we excluded 27,585 women who did not answer the 2005 questionnaire, 11,385 women with a missing CES-D score, 1202 women with no information on whether a cancer had occurred after the 2005 questionnaire, 2564 women with no file in the health expenditure claim database, 8159 women diagnosed with a cancer before the start of follow-up, and 309 women diagnosed with an incident breast cancer that was either in situ or with an unknown in situ/invasive status, leaving 47,791 women in the study population.

Statistical analysis

Figure S1 shows the directed acyclic graph representing the causal structure we assumed among variables relevant to the assessment of the effects of depression and antidepressant use on breast cancer risk.

Cox proportional hazards regression models with age as the time scale were used to estimate hazard ratios (HRs) and 95% CIs for the associations between depression and/or antidepressant exposure and the risk of invasive breast cancer.

We fitted exposure to antidepressants as time-varying, based on the exact dates of deliveries. This approach allowed participants to

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transition from a period of nonexposure to a period of exposure, and enabled updates to the cumulative duration of use throughout follow-up. A participant was classified as exposed to antidepressants once at least two deliveries of antidepressants had been recorded within a 3-month period. Furthermore, exposure to antidepressants was lagged by 1 year to minimize reverse causation—where undiagnosed breast cancer might cause depression—and to allow for a reasonable induction period for a potential effect of antidepressant use on breast cancer incidence.[27]

Cumulative duration of antidepressant exposure was handled carefully to address challenges posed by prevalent users, i.e. individuals who had a recorded antidepressant delivery in January or February 2004, suggesting that their use had begun before the availability of drug claims data (January 2004). These individuals were initially categorized as having an "unknown" duration of use. Once their observed use during follow-up exceeded 24 months, they were reassigned to the ">24 months" duration category.

Educational level, parity, breastfeeding, age at menarche, family history of breast cancer, level of physical activity, alcohol consumption, smoking status, lifetime use of oral contraceptives, and lifetime use of menopausal hormone therapy were treated as fixed covariates when follow-up started. Other covariates, which were updated in 2008 and/or 2011, were fitted as time-varying variables. Categories used for the analyses are shown in Table 1.

Imputation to the median (for continuous variables) or mode (for discrete variables) was used in case of a missing value for a given covariate, provided it was missing for <5% of participants, since previous analyses in the cohort demonstrated that results were unchanged compared with multiple linear imputation of missing values when <5% missing. Otherwise, a "missing" category was created, which was the case only for alcohol consumption and breastfeeding.

We assessed effect modification of the antidepressant–breast cancer association by baseline depression status by adding cross-product interaction terms in the Cox models. The Wald χ^2 test was used to compare HRs associated with different types of antidepressants obtained from a model where variables corresponding to exposure to each antidepressant type (SSRI/SNRI/TCA/other) were introduced simultaneously.

Supplementary analyses included: (i) lagging exposures by 2 years (with follow-up starting 2 years after the answer to the questionnaire assessing depression, and exposure to antidepressants lagged by 2 years) instead of one; (ii) performing analyses separately among women aged 65 years or younger and those older than 65 years; and (iii) excluding individuals whose depression status at baseline may have been influenced by recent antidepressant use, i.e. those having at least one antidepressant claim between the start of drug claim data availability (January 2004) and the assessment of depression (questionnaire sent in July 2005). All tests of statistical significance were two-sided, and significance was set at the 0.05 level. All analyses were performed using SAS version 9.4 (SAS Institute, Inc.).

Results

Population description

A total of 47,791 women were analyzed, with a mean follow-up of 7.2 years (SD, 1.9 years) starting at a mean age of 64.5 years (SD, 6.0 years). Their main characteristics overall and according to antidepressant exposure at the end of follow-up or according to depression status at baseline are shown in Table 1.

According to their CES-D score, 11,873 (24.8%) women had depression at baseline. A total of 10,821 (22.6%) women had been exposed to antidepressants between 2004 and the end of follow-up. Among them, 69% had been exposed to SSRIs, 21% to SNRIs, 20% to TCAs, and 21% to other antidepressants, with 25% having been exposed to several types of antidepressants. Among women exposed to antidepressants, the mean duration of use during follow-up was 2.9 years (SD, 2.9 years).

During follow-up, 1365 incident invasive breast cancers were diagnosed, at a mean age of 68.1 years (SD, 6.0 years).

Depression and breast cancer incidence

During follow-up, 998 breast cancer cases occurred among women without depression and 367 among women with depression at baseline. A higher incidence of breast cancer was found in women with depression, compared with women without depression, in the age-adjusted model (HR, 1.15 [95% CI, 1.02–1.29]), in the model further adjusted for antidepressant exposure (HR, 1.17 [95% CI, 1.04–1.33]), and in the fully adjusted model (HR, 1.14 [95% CI, 1.01–1.29]).

Antidepressant drugs and breast cancer incidence

Exposure to antidepressants was not significantly associated with breast cancer incidence in the age-adjusted model (HR, 0.94 [95% CI, 0.81–1.08], compared with no exposure) or in the model adjusted for age and breast cancer risk factors (HR, 0.88 [95% CI, 0.76–1.01]). However, the association between exposure to antidepressants and breast cancer incidence became statistically significant when depression was added in the latter model (HR, 0.85 [95% CI, 0.74–0.98]) (Table 2). Of note, there was no heterogeneity of the antidepressant–breast cancer association according to depression status (P for homogeneity = 0.47) (Table 2). Compared with women without depression at baseline and who had not been exposed to antidepressants, those with depression and no exposure to antidepressants had a higher invasive breast cancer risk (HR, 1.17 [95% CI, 1.02–1.35]), those with depression and exposure to antidepressants had an HR of 0.94 (95% CI, 0.77–1.14]), and those with no depression and exposure to antidepressants had an HR of 0.89 (95% CI, 0.74–1.07).

Compared with no antidepressant exposure, in the fully adjusted model, treatment with antidepressants for >24 months was associated with lower breast cancer incidence (HR, 0.80 [95% CI, 0.64–0.99]), whereas antidepressant treatment for ≤6 months was not (HR, 1.02 [95% CI, 0.79–1.32]) (Table 2). The direction of the findings was similar among women with or without depression at baseline (Table 2).

Analyses according to the type of antidepressant yielded no significant heterogeneity of the associations ($P = 0.26$): the multivariable HRs for invasive breast cancer were 0.84 (95% CI, 0.70–0.99) for SSRIs (154 exposed cases), 0.71 (95% CI, 0.50–0.99) for SNRIs (36 exposed cases), 1.09 (95% CI, 0.83–1.45) for TCAs (52 exposed cases), and 0.88 (95% CI, 0.64–1.20) for other types of antidepressants (41 exposed cases), compared with no exposure.

Analyses incorporating a 2-year lag for depression and antidepressant use showed an increased risk of breast cancer associated with depression (HR, 1.17 [95% CI, 1.03–1.34]) and a decreased risk with antidepressant exposure (HR, 0.84 [95% CI, 0.72–0.98]), similar to what we observed in our main analysis incorporating a 1-year lag (Table S1). Excluding individuals with at least one antidepressant claim between January 2004 and the assessment of depression yielded associations for both antidepressant use and baseline depression that closely matched those obtained from our main analysis (Table S1). Finally, age-stratified analyses showed no indication that the associations for antidepressant use or depression with breast cancer risk differed substantially according to age (≤65 years/>65 years) (Table S1).

Discussion

In this large prospective cohort study, we found that depression was associated with a higher incidence of breast cancer, whereas exposure to antidepressants was associated with a lower incidence. The latter association was evident only after adjusting for depression and several potential confounding factors. The observed effect sizes for these associations were modest. We also observed a potential duration effect for antidepressant use, as a significant inverse association emerged only among women with at least 2 years of treatment.

Our findings align with those of four recent Mendelian randomization studies that concluded that genetic liability to depression was

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Table 1. Characteristics of the study population overall and according to their exposure to antidepressants and their depression status

Characteristics[†]	All women (n = 47,791)	Not exposed to antidepressants at the end of follow-up (n = 36,970)	Exposed to antidepressants at the end of follow-up (n = 10,821)	No depression at follow-up start (n = 35,918)	Depression at follow-up start (n = 11,873)
Age, mean (SD), y	64.5 (6.0)	64.5 (6.0)	64.3 (6.0)	64.4 (6.0)	64.7 (6.1)
Physical activity, mean (SD), METs-h/wk	62.0 (50.4)	63.6 (51.0)	56.7 (48.0)	63.5 (50.8)	57.5 (49.0)
Years of schooling, *n* (%)					
<13	4034 (8.4)	3031 (8.2)	1003 (9.2)	2761 (7.7)	1273 (10.7)
13–16	35,159 (73.6)	27,166 (73.5)	7993 (73.9)	26,439 (73.6)	8720 (73.5)
17+	8598 (18.0)	6773 (18.3)	1825 (16.9)	6718 (18.7)	1880 (15.8)
Body mass index at the end of follow-up, mean (SD), kg/m^2	24.0 (4.0)	23.9 (3.9)	24.3 (4.2)	23.9 (3.9)	24.2 (4.3)
Alcohol intake, mean (SD), g/d	12.5 (15.0)	12.5 (14.7)	12.6 (15.9)	12.7 (14.8)	12.2 (15.5)
Smoking status, *n* (%)					
Never smoked	24,957 (52.2)	19,585 (53.0)	5372 (49.6)	18,984 (52.9)	5973 (50.3)
Ever smoked	22,834 (47.8)	17,385 (47.0)	5449 (50.4)	16,934 (47.1)	5900 (49.7)
Age at menarche, *n* (%), y					
<13	21,691 (45.4)	16,722 (45.2)	4969 (45.9)	16,185 (45.1)	5506 (46.4)
≥13	26,100 (54.6)	20,248 (54.8)	5852 (54.1)	19,733 (54.9)	6367 (53.6)
Ever use of oral contraceptives, *n* (%)					
No	16,566 (34.7)	13,136 (35.5)	3430 (31.7)	12,286 (34.2)	4280 (36.0)
Yes	31,225 (65.3)	23,834 (64.5)	7391 (68.3)	23,632 (65.8)	7593 (64.0)
No. of children, *n* (%)					
0	5473 (11.4)	4198 (11.4)	1275 (11.8)	4007 (11.2)	1466 (12.3)
1 or 2	28,620 (59.9)	21,936 (59.3)	6684 (61.8)	21,365 (59.4)	7255 (61.1)
≥3	13,698 (28.7)	10,836 (29.3)	2862 (26.4)	10,546 (29.4)	3152 (26.6)
Breastfeeding, *n* (%)					
No breastfeeding	17,739 (37.1)	13,533 (36.6)	4206 (38.9)	13,119 (36.5)	4620 (38.9)
Yes	27,297 (57.1)	21,357 (57.8)	5940 (54.9)	20,841 (58.0)	6456 (54.4)
Missing	2755 (5.8)	2080 (5.6)	675 (6.2)	1958 (5.5)	797 (6.7)
Age at menopause at the end of follow-up, mean (SD), y	50.7 (3.7)	50.8 (3.7)	50.5 (3.8)	50.8 (3.7)	50.5 (4.0)
Use of menopausal hormone therapy, *n* (%)					
Never	13,463 (28.2)	10,957 (29.6)	2506 (23.2)	10,195 (28.4)	3268 (27.5)
Recent (<1 y since last use)	12,055 (25.2)	9015 (24.4)	3040 (28.1)	9232 (25.7)	2823 (23.8)
Past	22,273 (46.6)	16,998 (46.0)	5275 (48.7)	16,491 (45.9)	5782 (48.7)
Family history of breast cancer in first-degree relatives, *n* (%)					
No	42,406 (88.7)	32,777 (88.7)	9629 (89.0)	31,931 (88.9)	10,475 (88.2)
Yes	5385 (11.3)	4193 (11.3)	1192 (11.0)	3987 (11.1)	1398 (11.8)
History of benign breast disease at the end of follow-up, *n* (%)					
No	29,728 (62.2)	23,405 (63.3)	6323 (58.4)	22,826 (63.6)	6902 (58.1)
Yes	18,063 (37.8)	13,565 (36.7)	4498 (41.6)	13,092 (36.4)	4971 (41.9)
Recent mammogram at the end of follow-up, *n* (%)					
No	6937 (14.5)	5385 (14.6)	1552 (14.3)	5038 (14.0)	1899 (16.0)
Yes	40,854 (85.5)	31,585 (85.4)	9269 (85.7)	30,880 (86.0)	9974 (84.0)
Depression, *n* (%)					
No	35,918 (75.2)	29,848 (80.7)	6070 (56.1)	-	-
Yes	11,873 (24.8)	7122 (19.3)	4751 (43.9)	-	-
Exposure to antidepressant drugs at the end of follow-up					
No	36,970 (77.4)	-	-	29,484 (83.1)	7122 (60.0)
Yes	10,821 (22.6)	-	-	6070 (16.9)	4751 (40.0)

Abbreviation: METs-h/w, metabolic equivalent task-hour per week.

[†]At follow-up start unless otherwise specified.

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Table 2. HRs for invasive breast cancer associated with exposure to antidepressants

	All women ($n = 47,791$)		No depression at baseline ($n = 35,918$)		Depression at baseline ($n = 11,873$)	
	No. cases	HR[†] (95% CI)	No. cases	HR[†] (95% CI)	No. cases	HR[†] (95% CI)
Exposure to antidepressants						
No	1125	1 (reference)	872	1 (reference)	253	1 (reference)
Yes	240	0.85 (0.74–0.98)	126	0.88 (0.73–1.07)	114	0.81 (0.65–1.02)
Cumulative duration of exposure to antidepressant drugs, mo						
Unexposed	1125	1 (reference)	872	1 (reference)	253	1 (reference)
≤6	61	1.02 (0.79–1.32)	34	0.99 (0.70–1.40)	27	1.05 (0.71–1.56)
6–24	56	0.77 (0.59–1.01)	32	0.83 (0.58–1.18)	24	0.70 (0.46–1.07)
≥24	88	0.80 (0.64–0.99)	42	0.85 (0.62–1.15)	46	0.77 (0.56–1.05)
Missing	35	0.87 (0.62–1.23)	18	0.91 (0.57–1.45)	17	0.84 (0.51–1.37)

Abbreviations: CI, confidence interval; HR, hazard ratio.

[†]Adjusted for age (time scale), depression (yes/no), family history of breast cancer, smoking status (baseline), level of physical activity (baseline), body mass index (time-varying), years of schooling (baseline), personal history of benign breast disease (time-varying), ever use of oral contraceptives (baseline), lifetime use of menopausal hormone therapy (baseline), recent mammogram (time-varying), menopausal status and age at menopause (time-varying), breastfeeding (baseline), age at menarche (baseline), parity (baseline), alcohol consumption (baseline). The categories used for the covariates are those displayed in Table 1.

associated with an increased risk of breast cancer.[14–17] These studies provide evidence supporting a causal effect of depression on breast cancer incidence. In contrast, the most recent meta-analysis of 10 cohort studies, published in 2020, found no significant association between depression and breast cancer risk.[13] However, the lack of adjustment for antidepressant use in most previous epidemiological studies may have hindered accurate evaluation of the effect of depression on breast cancer risk: this effect could have been obscured by the protective effect of antidepressant drugs, which were largely unaccounted for in earlier analyses.

Indeed, in our study, antidepressant use was associated with a lower breast cancer incidence. By contrast, a recent meta-analysis of seven cohort studies reported a slightly increased risk of breast cancer associated with antidepressant use (HR, 1.09 [95% CI, 1.01–1.18]).[18] However, in the absence of simultaneous adjustment for depression, a protective effect of antidepressant drugs on breast cancer incidence could have been masked by the effect of depression. In our study, the use of a drug claims database to identify exposure to antidepressants during a 10-year period may also have helped reveal this protective effect by reducing the dilution of any real association due to imprecise assessment of exposure. We observed a statistically significant risk reduction only among women with at least 2 years of antidepressant use, suggesting that an extended duration of treatment may be necessary to observe an effect on breast cancer incidence.

Beyond simultaneously investigating the independent effects of depression and antidepressant use, our study has several notable strengths. First, we lagged exposure to antidepressants by 1 year, discarding any exposure occurring in the year before the attained age, and follow-up started 1 year after the assessment of depressive symptoms. This strategy aimed to minimize the risk of reverse causation, whereby potential symptoms of undiagnosed breast cancer (e.g. fatigue, or anxiety caused by the presence of a lump in the breast) could favor depression. The 1-year lag we implemented is likely sufficient to address this concern, as suggested by Pottegård et al., who investigated patterns of new medication use preceding cancer diagnosis.[28] Their study showed an increase in drug use in the months leading up to cancer diagnosis, with varying patterns by cancer type. For breast cancer specifically, it suggests that a 6-month lag is sufficient to rule out reverse causation, whereas longer lags would be needed for other cancers, such as pancreatic cancer. Moreover, in our study, extending the lag to 2 years did not attenuate associations, further supporting that a 1-year lag was sufficient to minimize potential reverse causation. Second, we used drug claims data to identify exposure to antidepressants, eliminating differential recall bias between cases and noncases. This also enabled us to account for antidepressant exposure during the entire follow-up, reducing exposure misclassification. Third, in order to limit confounding, we adjusted our models for a number of breast cancer risk factors. Fourth, we addressed potential surveillance bias. Women with depression may be less likely to undergo mammograms,[29] whereas women prescribed antidepressants may have more frequent healthcare interactions. To account for these differences, we adjusted our analyses for mammogram receipt during the previous follow-up period as a proxy for gynecologic follow-up. Furthermore, we excluded in situ breast cancers from our analyses, as their diagnosis is more sensitive to breast cancer screening practices. Finally, our results were not affected by immortal time bias[30] since exposure to antidepressants was introduced in our Cox models using time-varying parameters, allowing individuals to move from a period of nonexposure to a period of exposure and to contribute to different durations of use during follow-up.

This study also has some limitations. First, depression was assessed only once, at baseline. Therefore, we were not able to investigate the potential impact of depression duration on breast cancer risk. Furthermore, this may have led to misclassification of depression status during follow-up, potentially diluting the observed associations with breast cancer risk. Indeed, some women may have developed depression after baseline, while others may have recovered during follow-up. This, in turn, could have affected the estimates for antidepressant use, as the underlying indication—depression—was not accurately captured throughout follow-up, potentially resulting in attenuated associations. Accurate estimation of the direct effect of antidepressant use on breast cancer risk would require accounting for the time-varying nature of depression (as illustrated in the directed acyclic graph, Figure S1). In our study, because depression was assessed at baseline only, the estimated HR of breast cancer associated with antidepressant use could reflect both its direct effect and its effect mediated through depression recovery. Second, the use of the CES-D tool does not allow the identification of clinical major depressive disorder. Thus, studies exploring major depressive disorder and its clinical characteristics in relation to breast cancer risk would be valuable. Third, data on antidepressant use before 2004 were not available. Fourth, our assessment of exposure to antidepressants was based on drug claims, which may lead to misclassification of exposure for women who purchased antidepressants without actually

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taking them; however, to limit this bias, we considered as exposed only women who had at least two antidepressant deliveries within any 3-month period. Finally, our study included women born between 1925 and 1950, meaning that all participants were at least 56 years old at the start of follow-up. As a result, our findings may not be generalizable to younger women.

Depression may influence health-related behaviors. Our statistical models included variables related to these behaviors, associated with both depression and breast cancer risk, such as physical activity levels and alcohol consumption. By adjusting for them, our estimates reflect the association between depression (or antidepressant use) and breast cancer risk independently of pathways mediated by these behaviors. Since these covariates were generally measured only at the time of depression assessment, some residual mediating effects of these factors may persist in the association between antidepressant use—updated during follow-up—and breast cancer risk. However, these residual effects are likely limited. Indeed, removing alcohol consumption, physical activity levels, or mammographic surveillance from our models had no impact on the estimated association between depression and breast cancer (data not shown). These findings support the hypothesis that opposing effects of depression and antidepressants on breast cancer incidence driven by mechanisms independent of health-related behaviors may exist. Biological pathways such as serotonin transmission and inflammation, which are implicated in the pathophysiology of both depression and breast cancer, as well as in the mechanisms of action of antidepressants, warrant further investigation.[7,11,12,31] Another possibility regarding depression is that an underlying, unobserved factor could increase an individual's risk for both breast cancer and depression. Therefore, although our study was designed to investigate the independent effects of depression and antidepressant use on breast cancer risk, our results cannot definitely prove causation.

Replication of our findings in independent cohorts is essential to confirm these results. Longer follow-up periods would enable the detection of larger effect sizes associated with extended durations of antidepressant use. Furthermore, potential associations between depression and antidepressant use and other types of cancers should be explored, as these associations may not be specific to breast cancer. Last, studies designed to specifically identify major depressive disorder and its clinical characteristics in relation to breast cancer risk would be valuable.

An implication of our findings is the potential to reassure women about the benefits of long-term antidepressant use. Poor adherence to antidepressant treatment is a well-documented issue among women with depression,[32] and highlighting potential protective effects on breast cancer incidence may help improve adherence.

In conclusion, our study suggests that depression and use of antidepressants may have opposite effects on breast cancer incidence. While depression was associated with a higher risk, antidepressant use appeared to counteract this risk, especially when used for at least 2 years. This study is the first to report both a significantly higher breast cancer incidence associated with depression and a significantly lower incidence associated with antidepressant use. These findings should be replicated in other settings with simultaneous assessment of the independent effects of depression and antidepressants and with extended follow-up durations. If confirmed, these results could support initiatives aimed at improving adherence to antidepressant treatment in women with depression, potentially mitigating their increased breast cancer risk.

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Author contributions

R.C., E.D., A.F., M.C.B., and E.C.: conception and design of the study; acquisition and analysis of data; drafting the manuscript or figures; review and final editing. O.M.: acquisition and analysis of data; review and final editing. G.S. and B.F.: conception and design of the study; review and final editing.

Data availability statement

Data underlying this article are made available under managed access owing to governance constraints and need to protect the privacy of study participants. Data on E3N cohort participants are available to bona fide researchers for all type of health-related research that is in the public interest. Raw data requests should be submitted through the E3N website (www.e3n.fr) or sent to contact@e3n.fr and will be reviewed by the E3N Access Committee. Further information is provided at https://www.e3n.fr/node/78.

References

1. Loosbrock DL, Tomlin ME, Robinson RL, Obenchain RL, Croghan TW. Appropriateness of prescribing practices for serotonergic antidepressants. *Psychiatr. Serv.* 2002; **53**: 179–184.
2. Bahl S, Cotterchio M, Kreiger N. Use of antidepressant medications and the possible association with breast cancer risk. A review. *Psychother. Psychosom.* 2003; **72**: 185–194.
3. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts ACG. Indications for antidepressant drug prescribing in general practice in The Netherlands. *J. Affect. Disord.* 2007; **98**: 109–115.
4. Lewer D, O'Reilly C, Mojtabai R, Evans-Lacko S. Antidepressant use in 27 European countries: Associations with sociodemographic, cultural and economic factors. *Br. J. Psychiatry* 2015; **207**: 221–226.
5. Pratt LA, Brody DJ, Gu Q. Antidepressant use among persons aged 12 and over: United States, 2011–2014. *NCHS Data Brief* 2017; **283**: 1–8.
6. Global Burden of Disease 2019 Cancer Collaboration, Kocarnik JM, Compton K *et al.* Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: A systematic analysis for the global burden of disease study 2019. *JAMA Oncol.* 2022; **8**: 420–444.
7. Gwynne WD, Shakeel MS, Girgis-Gabardo A, Hassell JA. The role of serotonin in breast cancer stem cells. *Molecules* 2021; **26**: 3171.
8. Gururajan A, Clarke G, Dinan TG, Cryan JF. Molecular biomarkers of depression. *Neurosci. Biobehav. Rev.* 2016; **64**: 101–133.

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9. Chen J, Wei Y, Yang W, Huang Q, Chen Y, Zeng K. IL-6: The link between inflammation, immunity and breast cancer. *Front. Oncol.* 2022; **12**: 903800.
10. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: A meta-analysis. *Neuropsychopharmacology* 2011; **36**: 2452–2459.
11. Olfati Z, Rigi G, Vaseghi H, Zamanzadeh Z, Sohrabi M, Hejazi SH. Evaluation of serotonin receptors (5HTR2A and 5HTR3A) mRNA expression changes in tumor of breast cancer patients. *Med. J. Islam Repub. Iran* 2020; **34**: 99.
12. Balakrishna P, George S, Hatoum H, Mukherjee S. Serotonin pathway in cancer. *Int. J. Mol. Sci.* 2021; **22**: 1268.
13. Wang Y-H, Li J-Q, Shi J-F *et al*. Depression and anxiety in relation to cancer incidence and mortality: A systematic review and meta-analysis of cohort studies. *Mol. Psychiatry* 2020; **25**: 1487–1499.
14. Zhu G-L, Xu C, Yang K-B *et al*. Causal relationship between genetically predicted depression and cancer risk: A two-sample bi-directional mendelian randomization. *BMC Cancer* 2022; **22**: 353.
15. Ren Q, Luo F, Ge S, Chen P. Major depression disorder may causally associate with the increased breast cancer risk: Evidence from two-sample mendelian randomization analyses. *Cancer Med.* 2023; **12**: 1984–1996.
16. Ren F, Shang Q, Zhao S *et al*. An exploration of the correlations between seven psychiatric disorders and the risks of breast cancer, breast benign tumors and breast inflammatory diseases: Mendelian randomization analyses. *Front. Psychiatry* 2023; **14**: 1179562.
17. Wu X, Zhang W, Zhao X *et al*. Investigating the relationship between depression and breast cancer: Observational and genetic analyses. *BMC Med.* 2023; **21**: 170.
18. Zhuang Y, Pang X, Qi Y *et al*. The incidence risk of breast and gynecological cancer by antidepressant use: A systematic review and dose-response meta-analysis of epidemiological studies involving 160,727 patients. *Front. Oncol.* 2022; **12**: 939636.
19. Van Tuijl LA, Basten M, Pan K *et al*. Depression, anxiety, and the risk of cancer: An individual participant data meta-analysis. *Cancer* 2023; **129**: 3287–3299.
20. Chen VC-H, Liao Y-T, Yeh D-C, Tseng H-C, Stewart R, Lee CT-C. Relationship between antidepressant prescription and breast cancer: A population based study in Taiwan. *Psychooncology* 2016; **25**: 803–807.
21. Gonzalez-Perez A, Garcia Rodriguez LA. Breast cancer risk among users of antidepressant medications. *Epidemiology* 2005; **16**: 101–105.
22. Walker AJ, Card T, Bates TE, Muir K. Tricyclic antidepressants and the incidence of certain cancers: A study using the GPRD. *Br. J. Cancer* 2011; **104**: 193–197.
23. Reeves KW, Okereke OI, Qian J, Tamimi RM, Eliassen AH, Hankinson SE. Depression, antidepressant use, and breast cancer risk in pre- and postmenopausal women: A prospective cohort study. *Cancer Epidemiol. Biomarkers Prev.* 2018; **27**: 306–314.
24. Brown SB, Hankinson SE, Arcaro KF, Qian J, Reeves KW. Depression, antidepressant use, and postmenopausal breast cancer risk. *Cancer Epidemiol. Biomarkers Prev.* 2016; **25**: 158–164.
25. Clavel-Chapelon F, E3N Study Group. Cohort profile: The French E3N cohort study. *Int. J. Epidemiol.* 2015; **44**: 801–809.
26. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. *Appl. Psychol. Measur.* 1977; **1**: 385–401.
27. Hicks B, Kaye JA, Azoulay L, Kristensen KB, Habel LA, Pottegård A. The application of lag times in cancer pharmacoepidemiology: A narrative review. *Ann. Epidemiol.* 2023; **84**: 25–32.
28. Pottegård A, Hallas J. New use of prescription drugs prior to a cancer diagnosis. *Pharmacoepidemiol. Drug Saf.* 2017; **26**: 223–227.
29. Ludman EJ, Ichikawa LE, Simon GE *et al*. Breast and cervical cancer screening specific effects of depression and obesity. *Am. J. Prev. Med.* 2010; **38**: 303–310.
30. Wallis CJD, Saskin R, Narod SA *et al*. Estimating the effect of immortal-time bias in urological research: A case example of testosterone-replacement therapy. *BJU Int.* 2017; **120**: 584–590.
31. Colle R, Masson P, Verstuyft C *et al*. Peripheral tryptophan, serotonin, kynurenine, and their metabolites in major depression: A case-control study. *Psychiatry Clin. Neurosci.* 2020; **74**: 112–117.
32. Solmi M, Miola A, Croatto G *et al*. How can we improve antidepressant adherence in the management of depression? A targeted review and 10 clinical recommendations. *Braz J. Psychiatry* 2021; **43**: 189–202.

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