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Use of antidepressants and NSAIDs in relation to mortality in long-term breast cancer survivors

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Abstract

Purpose—The aim of this study was to assess the post-diagnosis use of antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs) in relation to all-cause, breast cancer, and cardiovascular disease (CVD) mortality among long-term breast cancer survivors.

Methods—A cohort of 3,058 breast cancer survivors, who previously participated in a series of case-control studies diagnosed between 1988–1999 in Wisconsin. Cancer survivors completed a self-administered mailed follow-up questionnaire in 1998–2001 that addressed use of medications post-diagnosis, including antidepressants and NSAIDs. Vital status information was obtained through the National Death Index through December 31, 2006. We used multivariable Cox proportional hazards modeling to estimate hazard ratios and 95% confidence intervals.

Results—We identified 463 deaths due to all-causes, 163 due to breast cancer, and 93 due to cardiovascular disease during follow-up. Among women who had used any antidepressant after a breast cancer diagnosis, there was an increased risk of all-cause (adjusted HR=1.50, 95% CI 1.12–2.02) and CVD mortality (HR=2.42, 95% CI 1.21–4.83), but not breast cancer mortality (HR=0.93, 95% CI 0.55–1.56). The use of NSAIDs after diagnosis was not associated with all-cause (HR=0.87, 95% CI 0.69–1.18), breast cancer mortality (HR=0.69, 95% CI 0.44–1.10), or CVD (HR=0.97, 95% CI 0.57–1.65)..

Conclusions—The use of antidepressants or NSAIDs were not related to breast cancer mortality in long-term breast cancer survivors. In these women, however, antidepressants may increase the risk of all-cause mortality.

Keywords

antidepressant medication; non-steroidal anti-inflammatory drugs; breast cancer; mortality; survivorship

Key points

- Approximately 15–27% of cancer survivors report using antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs) after diagnosis.
- We observed no association between antidepressant use and breast cancer mortality in long-term survivors of breast cancer, but did observe an increased

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risk of all-cause and cardiovascular disease mortality associated with use of antidepressants. .

- Prior studies have indicated a reduced risk of breast cancer mortality associated with NSAID use. We found a suggestion that NSIADS are associated with reduced mortality, but we had limited power to detect a statistically significant result.
- The results from this study indicate some reassurance to breast cancer survivors that use of antidepressants and NSAIDs after diagnosis might not adversely affect breast cancer survival, but might be relevant to other comorbidities (i.e., cardiovascular disease).

INTRODUCTION

The current number of cancer survivors living in the US is nearly 11.5 million, and women with a diagnosis of breast cancer represent the largest proportion of cancer survivors at more than 2.5 million.¹ As the number of cancer survivors increase, the effects of commonly prescribed and consumed medications on disease prognosis becomes increasingly important, especially for long-term survivors of their disease.

Antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs) are two of the most consumed medications in the US.^{2,3} NSAIDs can also be purchased over-the-counter (OTC). In a recent survey of healthy ambulatory adult women age 18–65+ years, approximately 43–57% of women reported taking at least five medications per week. Among prescriptions consumed in the US, antidepressants and NSAIDs were among the top 40 medications.³ Approximately 15–27% of cancer survivors report using antidepressants and NSAIDs after diagnosis.^{4,5}

It is plausible that the use of either of these medications in women with breast cancer might alter mortality. The use of antidepressants, particularly SSRIs, are shown to increase prolactin levels,^{6,7} which might increase the risk of breast cancer and recurrence.⁸ Prolactin levels also tend to rise in women with distant metastatic breast cancer, even after a decline due to treatment,⁹ and prolactin has been shown to inhibit the effectiveness of chemotherapy.¹⁰ It can be difficult though to tease apart the effects of antidepressants versus underlying health status of depression and pain. The adverse role of inflammation in cancer is well-documented in tumor progression¹¹ and the use of NSAIDs, aspirin specifically, reduces the risk of several cancers (i.e., breast and colorectal).^{12,13} Two previous studies have suggested a reduction in breast cancer mortality in breast cancer survivors associated with NSAID use.^{14,15}

We hypothesized that antidepressants might increase and NSAID use would reduce breast cancer mortality. In a population of breast cancer survivors, we assessed post-diagnosis use of antidepressants and NSAIDs in relation to all-cause, breast cancer-specific, and cardiovascular disease (CVD)-specific mortality in long-term breast cancer survivors. We examined how these commonly consumed medications affected mortality from breast cancer, as well as how mortality differed from the leading cause of death in the general population, cardiovascular disease.¹⁶

MATERIALS AND METHODS

Study Participants

The Collaborative Women's Longevity Study (CWLS) is cohort of breast cancer survivors, aged 25–87 years at enrollment, who were diagnosed with incident breast cancer between 1988–1999 (ICD9 174, ICD10 50).¹⁷ Details of the study have been published elsewhere.¹⁸

Briefly, women with breast cancer had originally participated in a series of three population-based case-control studies [1988–1991 (Phase 1), 1992–1995 (Phase 2), 1997–1999 (Phase 3)] of modifiable risk factors for breast cancer conducted in Wisconsin, Massachusetts (excluding Boston area), and New Hampshire.¹⁹ In the initial case-control studies, women with a diagnosis of breast cancer had completed a standardized telephone questionnaire (n=18,273) within two years of their invasive breast cancer diagnosis. The telephone questionnaire ascertained pre-diagnostic risk factors (e.g., demographics, medical history, and use of medications). Information on tumor staging, histology and treatment was available through state cancer registries.

From 1998–2001, surviving breast cancer cases were asked to participate in the CWLS, which evaluated the association between modifiable risk factors after a breast cancer diagnosis and mortality. Study participants were mailed a questionnaire to self-report information regarding medication history, physical activity,¹⁸ diet, weight gain,²⁰ alternative therapies, quality of life, and other lifestyle factors. Participants who did not return the questionnaire within a timely manner received a reminder telephone call and a second mailing to improve overall response. The median time from diagnosis to completion of the CWLS questionnaire was 5.7 years (range 1.1–14.3 years).

This study is limited to Wisconsin participants due to availability of medication exposure data. A total of 3,245 (36.2%) women completed the questionnaire. There were 8,959 women enrolled in the parent case-control studies who did not participate in CWLS due to death prior to January 1, 1998 (n=1,633), invalid contact information (n=796) and refusal (n=3,285). Further, we excluded women who had distant metastases or unknown stage of disease (n=440) and died within one year of completing the questionnaire (n=40). The final sample includes 3,058 women.

Study protocols were approved by institutional review boards at the University of Wisconsin-Madison and Fred Hutchinson Cancer Research Center.

Exposure assessment

In the follow-up questionnaire, women were asked to report any medication [prescription or OTC] that they had used on a regular basis since the time of their breast cancer diagnosis. The specific wording of question read as; "Please tell us about ANY medications you have used REGULARLY since your breast cancer diagnosis; that is at least twice a week for at least 3 months. DO NOT include cancer chemotherapy or alternative therapies you have already told us about. DO NOT include vitamins. DO include over the counter medicines like aspirin. Please copy the drug name from the container if you have it." Women reported the name of the medication, whether they had taken the medication for two years or more, and whether they were currently taking the medication.

We examined the type of medication for both antidepressants and NSAIDs. For each antidepressant reported by women, the class of antidepressant was also determined.²¹ We evaluated two classes of antidepressants, tricyclic antidepressants (TCA) and selective-serotonin reuptake inhibitors (SSRI). The most commonly used antidepressants included amitriptyline hydrochloride (n=54), fluoxetine hydrochloride (n=51), and paroxetine

hydrochloride (n=40). For NSAIDs, we evaluated both aspirin and ibuprofen-types. Indication for use was not ascertained on the questionnaire.

Outcome Assessment

To ascertain vital status, all breast cancer cases in the parent case-control studies were passively followed for mortality, regardless of participation in the CWLS. Cases were matched through linkages to the National Death Index (NDI) records to obtain date of death and underlying cause of death. We assessed mortality through December 31, 2006. We identified 463 deaths due to all-causes, 163 due to breast cancer (ICD10 C50), and 93 due to cardiovascular disease (ICD 10 I00–99).¹⁷ Other leading causes of death included lung cancer (n=22), chronic obstructive pulmonary disease (n=17), and dementia (n=10).

Statistical Analysis

We estimated hazard ratios using multivariate Cox proportional hazards modeling to assess the relationship between post-diagnostic medication use in relation to all-cause, breast cancer-specific, and CVD-specific mortality. Ever use of an antidepressant or NSAID was defined as use of either medication for at least 3 months and twice per week. Women were classified as never users of either medication if they did not report using either type of medication or use was less than 3 months. Person-time was calculated from date of breast cancer diagnosis until date of censor – the date of death or end of follow-up (December 31, 2006), whichever occurred first, and also from date of diagnosis to CWLS questionnaire return date. Analysis accounted for left truncation by including both time covariates in the Cox models.²² The addition of the time variable from date of diagnosis to the CWLS questionnaire offsets the time at risk for mortality. Women were followed for an average of 7.2 years (range 1.0–8.6 years) from CWLS questionnaire return date until censor date. Initial models were adjusted for age at diagnosis, tumor stage, and treatment. Models were additionally adjusted for potential confounders, including education, cigarette smoking, alcohol consumption, body mass index, menopausal status, and family history of breast cancer ascertained at diagnosis.

We wanted to investigate whether confounding by indication was an issue in the analysis, specifically, whether depression is the mode of action rather than the antidepressant. In sub-analysis, we also adjusted for prior use of antidepressants available from the case-control study interviews. These data were available from only a limited sample (n=1,432). Data on NSAID use prior to breast cancer diagnosis from the case-control studies were not available for evaluation. All analyses were conducted using StataSE version 9.

RESULTS

Sixty-four percent of women reported taking any medication, other than treatment medications, after a diagnosis of breast cancer. Ten percent of women reported taking antidepressants and 17.7% reported taking NSAIDs after diagnosis (data not shown).

Women who had used antidepressants after diagnosis were more likely to be younger, premenopausal, and obese, have few children, and received adjuvant therapy compared to women who had not used antidepressants. Users of NSAIDs were more likely to be older, post-menopausal, obese, and to have received hormone adjuvant therapy compared to non-users of NSAIDs (Table 1).

Among women who had used any antidepressant after diagnosis, the hazard of all-cause mortality was 50% higher compared to non-users of antidepressants (Table 2). Use of SSRIs but not TCAs was also associated with an increased risk of all-cause mortality. There was no association between the use of antidepressants and breast cancer mortality, and risk did not

vary by class of antidepressants. After adjustment in the full model, there was a 2.0-fold increased risk of CVD mortality among any users of antidepressants compared to non-users. Women who had used TCAs had a nearly 2.4-fold increased risk of CVD mortality compared to non-users, though there were few women exposed (Table 2).

In the sub-analysis, we adjusted for use of antidepressants prior to breast cancer diagnosis in the models. The addition of prior use attenuated the results of antidepressant use and all-cause mortality, but still the magnitude of the association was similar to unadjusted model presented (HR 1.39, 95% CI 0.82–2.35) (data not shown).

The use of NSAIDs after diagnosis was not associated with all-cause, breast cancer or CVD mortality (Table 3). Further, the use of aspirin-based NSAIDs nor non-aspirin NSAIDs did not suggest a reduction in mortality.

DISCUSSION

We detected no increased risk of mortality due to breast cancer associated with use of antidepressants, but we did observe an increased risk of all-cause mortality and CVD mortality associated with antidepressant use, specifically TCAs. Use of NSAIDs was not associated with mortality. This is a study of long-term survivors. The majority of women were more than five years from their diagnosis upon entry into this study.

Our findings confirm prior research indicating that there is no association between antidepressant use and breast cancer mortality. Chubak et al reported an adjusted hazard ratio of 0.9 (0.4–1.9) for 5-year breast cancer mortality among any users of antidepressants after breast cancer diagnosis.²³ In their multivariable analysis, the authors included other tumor characteristics (i.e., nodal involvement, tumor size, and ER/PR status), which did not alter the observed unadjusted effect. The authors did not report the risk of death for all-cause or CVD. In our analysis, many women had already survived more than five years before they entered the study, so we could not specifically address five-year mortality in this study.

Despite the posited rationale that antidepressants might hinder breast cancer survival, our result for no association between antidepressant use and breast cancer mortality suggests a few possible conclusions. First, this might be a true association and the effect of an antidepressant in regards to prolactin minimally affects changes of endogenous prolactin in women. Second, we might have assessed the timing of use inappropriately. It is possible that the use of antidepressants after diagnosis is not relevant to those women who have survived the first five years after diagnosis, and the relevant time period might be within the first five years. The results from Chubak et al. suggest that antidepressant use is not associated with five-year survival.²³ Finally, if an effect of antidepressants is only evident in late stage disease, then we would not have seen an effect as we excluded those with metastatic disease in this study.

Most prior research of antidepressant use and CVD mortality has focused on populations of women without breast cancer, not among cancer survivors, which makes our study unique. These prior studies, mainly of persons with prevalent CVD, suggest an increased risk of mortality associated with antidepressant use.^{24,25} In a large cohort of healthy women from the Nurses' Health Study, Whang and colleagues detected that use of antidepressant was associated with a 3.3-fold increased risk of sudden cardiac death (95% CI 2.03–5.50), but there were no elevated risks with other CVD deaths.²⁶ In our analysis, we were unable to determine if results for CVD were due to sudden cardiac death or other death due to CVD. There were few women who subsequently died from CVD during follow-up. There is some biologic rationale that antidepressants might increase CVD mortality. TCAs have been shown to act as potassium channel blockers, which subsequently extends the QT interval of

an electrocardiogram and lead to cardiovascular toxicity.^{27,28} The highest risk of CVD death was among TCA users in our analysis.

We detected no association between the use of any NSAIDs and risk of all-cause, breast-cancer or CVD-specific mortality. Prior studies in women without cancer have suggested a reduction in risk of all-cause and CVD mortality,²⁹ and three studies have explored this association in women with breast cancer.^{14,15,30} In the first, Blair et al from the Iowa Women's Health Study followed 591 breast cancer cases for mortality outcomes.¹⁵ There was a non-statistically significant reduction risk associated with ever use of any NSAID and breast cancer mortality (HR=0.64, 95% CI 0.39–1.05), and a significant reduction in all-cause mortality with use of NSAIDs (HR=0.57, 95% CI 0.40–0.81). Kwan et al investigated the use of aspirin, ibuprofen and other NSAIDs and the risk of breast cancer recurrence in 2,292 early stage breast cancer survivors.¹⁴ The authors detected a 44% reduction in breast cancer recurrences associated with ibuprofen use (RR=0.56, 95% CI 0.32–0.98), but no reduction in risks with aspirin or other NSAIDs. Finally, the largest study to date from the Nurses Health Study, Holmes et al detected a dose-response reduction of breast cancer mortality with increasing days of use of aspirin ($p<0.001$).³⁰ The magnitude of our finding for NSAIDs and breast cancer mortality is also reduced, but we did not reach statistical significance, possibly due to limited power. Another difference between our study and these two prior studies is the timing of follow-up; our study participants had lived longer to enroll in the follow-up study than the populations from the other two studies. The use of NSAIDs might be more relevant in the short-term following diagnosis rather than the long-term. Long-term breast cancer survivors are more likely to report chronic pain, and hence use analgesics, than the general population.³¹

Our study is one of the largest studies of long-term breast cancer survivors to investigate medication use and risk of mortality, but our study is not without its limitations. There is the potential for selection bias, based on those who participated and those who did not in the follow-up study. Non-participants tended to be more likely to have regional involvement of their breast cancer, and were less likely to have a high school education and more likely to be current smokers at their breast cancer diagnosis.¹⁸ Because we suspected that non-participants might have later stage disease than CWLS participants, we restricted the analysis to local and regional disease women to minimize selection bias and confounding. We also did not have data available on tumor marker characteristics. The adjustment for these confounders did not greatly alter the results from Chubak et al,²³ and are unlikely to be strong confounders. Some analyses had few numbers, so these results should be replicated in studies with larger study populations.

One important limitation of our analysis is that we did not assess the indication of use for these two medications, possibly leading to confounding by indication. A history of depression is reported in up to one-quarter of breast cancer patients, and depression has been associated with increased breast cancer^{32–34} and CVD mortality.^{35,36} In a recent meta-analysis, depression was associated with overall mortality but not cancer progression among persons living with cancer.³⁷ We did not assess depression in this population either pre- or post-diagnosis. Breast cancer survivors are prescribed antidepressants for reasons other than depression, including anxiety and for the side effects due to treatment of breast cancer, such as hot flashes, pain and sleep.^{38,39} We attempted to evaluate the role of a depression by adjusting for the use of antidepressants prior to diagnosis in a sub-analysis based on limited data from the study sample. The adjustment of prior antidepressant did not alter our overall interpretation, although the confidence intervals widened. Further, depression was associated with increased CVD events and mortality among women in the Women's Health Initiative.⁴⁰ We were not able to control for prior antidepressant use in the analysis of antidepressant use and CVD mortality due to few numbers.

There is the possibility of misclassification of exposure to antidepressants post-diagnosis. The prevalence of exposure to antidepressants in the study population is lower than other studies.^{4,5} Nearly 94% of women who reported never using an antidepressant prior to their breast cancer diagnosis continued to not use these medications after diagnosis; 56% of women who reported use prior to diagnosis did not report the use of antidepressant after their breast cancer diagnosis. Further, as this study focused on breast cancer, we did not collect all relevant cardiovascular disease risk factors, such as cholesterol or high blood pressure. We were able to adjust the analysis for tobacco smoking and body mass index, and gender is not an issue in the analysis.

The results from this study suggest some reassurance to breast cancer survivors that the use of antidepressants and NSAIDs after diagnosis might not adversely affect breast cancer survival, but might be relevant to other comorbidities in this population.

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TABLE 1

Characteristics of long-term breast cancer survivors in the Collaborative Women's Longevity Study by use of antidepressants and NSAIDs after diagnosis.

CHARACTERISTIC	ANTIDEPRESSANT USE		NSAID USE	
	No (n=2750)	Yes (n=308)	No (n=1095)	Yes (n=1963)
	N (%)	N (%)	N (%)	N (%)
Age at diagnosis, years				
<40	125 (4.6)	12 (3.9)	127 (5.1)	10 (1.9)
40–49	398 (14.5)	73 (23.7)	416 (16.5)	55 (10.2)
50–59	854 (31.1)	109 (35.4)	797 (31.7)	166 (30.7)
60–69	1037 (37.7)	91 (29.6)	893 (35.5)	235 (43.4)
≥70	336 (12.2)	23 (7.5)	284 (11.3)	75 (13.9)
Education				
<High school	256 (9.3)	19 (6.2)	225 (8.9)	50 (9.2)
≥High school	2484 (90.3)	288 (93.5)	2283 (90.7)	489 (90.4)
Parity [/]				
Nulliparous	333 (12.1)	40 (13.0)	306 (12.2)	67 (12.4)
1	243 (8.8)	36 (11.7)	233 (9.3)	46 (8.5)
2	718 (26.1)	79 (23.6)	662 (26.3)	135 (24.9)
3	637 (23.2)	77 (25.0)	595 (23.6)	119 (22.0)
≥4	811 (29.6)	76 (24.7)	713 (28.3)	174 (32.2)
Menopausal status [/]				
Premenopausal	624 (22.7)	86 (27.9)	634 (25.2)	76 (14.1)
Post-menopausal	2010 (73.1)	196 (63.6)	1760 (69.9)	446 (82.4)
Unknown	116 (4.2)	26 (8.4)	123 (4.9)	19 (3.5)
Cigarette smoker [/]				
Never	1405 (51.1)	148 (48.1)	1258 (49.9)	295 (54.5)
Former	890 (32.4)	97 (31.5)	822 (32.7)	165 (30.5)
Current	444 (16.2)	63 (20.5)	427 (17.1)	309 (15.7)
Alcohol consumption [/]				
Non-drinker	399 (14.5)	61 (19.8)	359 (14.4)	101 (18.7)

CHARACTERISTIC	ANTIDEPRESSANT USE		NSAID USE	
	No (n=2750)	Yes (n=308)	No (n=1095)	Yes (n=1963)
	N (%)	N (%)	N (%)	N (%)
<1/day	1,906 (69.3)	194 (63.0)	1,740 (69.3)	360 (66.5)
≥1/day	437 (15.9)	52 (16.9)	409 (16.4)	80 (14.8)
Family History of breast cancer [†]				
No	711 ()	246 (79.9)	1946 (77.3)	422 (78.0)
Yes	582 (21.2)	55 (17.9)	526 (20.9)	111 (20.5)
Unknown	46 (1.7)	7 (2.3)	45 (1.8)	8 (1.5)
Post-diagnosis BMI				
<25	1014 (36.9)	87 (28.3)	948 (37.7)	1153 (28.3)
25–29	908 (33.0)	105 (34.1)	825 (32.8)	188 (34.8)
30+	673 (24.5)	97 (31.5)	605 (24.0)	165 (30.5)
Unknown	155 (5.6)	19 (6.2)	139 (5.5)	35 (6.5)
Years of enrollment				
1988–1991	235 (21.5)	560 (28.5)	639 (25.4)	156 (28.8)
1992–1995	394 (36.0)	812 (41.4)	983 (39.1)	223 (41.2)
1997–1999	466 (42.5)	591 (30.1)	895 (35.6)	162 (29.9)
Stage				
Local	2031 (73.9)	215 (69.8)	1840 (73.1)	406 (75.1)
Regional	719 (26.1)	93 (30.2)	677 (26.9)	135 (24.9)
Treatment				
Surgery	2698 (98.1)	304 (98.7)	2467 (98.0)	535 (98.9)
Radiation	1305 (47.5)	150 (48.7)	1213 (48.2)	242 (44.7)
Adjuvant Therapy				
Chemotherapy	944 (34.3)	129 (41.9)	914 (36.1)	159 (29.4)
Hormone therapy	1615 (58.7)	200 (64.9)	1466 (58.2)	349 (64.5)

[†] at time of diagnosis

TABLE 2

Hazard ratios and 95% confidence intervals for mortality among long-term breast cancer survivors according to use of antidepressants.

ANTIDEPRESSANT USE	ALL-CAUSE MORTALITY			BREAST CANCER MORTALITY			CVD MORTALITY		
	No. Deaths	HR (95% CI) ¹	HR (95% CI) ²	No. Deaths	HR (95% CI) ¹	HR (95% CI) ²	No. Deaths	HR (95% CI) ¹	HR (95% CI) ²
Never use	410	1.00 (Referent)	1.00 (Referent)	145	1.00 (Referent)	1.00 (Referent)	82	1.00 (Referent)	1.00 (Referent)
Any use	53	1.46 (1.10–1.96)	1.50 (1.12–2.02)	18	1.05 (0.64–1.72)	0.93 (0.55–1.56)	11	1.76 (0.92–3.34)	2.42 (1.21–4.83)
Class									
SSRIs	21	1.57 (1.01–2.45)	1.71 (1.09–2.68)	9	1.34 (0.68–2.64)	1.40 (0.51–2.79)	2	0.77 (0.19–3.17)	0.94 (0.22–3.97)
TCA	18	1.32 (0.82–2.12)	1.32 (0.82–2.14)	5	1.12 (0.46–2.75)	1.01 (0.41–2.51)	6	2.22 (0.95–5.18)	2.43 (1.02–5.80)

¹ Cox proportional hazards models account for left truncation by entering the return date of the CWLS questionnaire as the beginning in which the subject comes under observation, and adjusted for age at diagnosis, stage, and treatment.

² Additionally adjusted for education, cigarette smoking, alcohol consumption, body mass index, menopausal status, and family history of breast cancer.

Abbreviations: SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; CVD, cardiovascular disease mortality; HR, hazard ratio; CI, confidence interval.

TABLE 3
Hazard ratios and 95% confidence intervals for mortality among long-term breast cancer survivors according to use of NSAIDs.

NSAID USE	ALL-CAUSE MORTALITY			BREAST CANCER MORTALITY			CVD MORTALITY		
	No. Deaths	HR (95% CI) ¹	HR (95% CI) ²	No. Deaths	HR (95% CI) ¹	HR (95% CI) ²	No. Deaths	HR (95% CI) ¹	HR (95% CI) ²
Never use	383	1.00 (Referent)	1.00 (Referent)	141	1.00 (Referent)	1.00 (Referent)	75	1.00 (Referent)	1.00 (Referent)
Any use	80	0.83 (0.65–1.06)	0.87 (0.69–1.18)	22	0.73 (0.46–1.15)	0.69 (0.44–1.10)	18	0.89 (0.54–1.49)	0.97 (0.57–1.65)
Aspirin	37	0.87 (0.62–1.22)	0.91 (0.65–1.29)	7	0.61 (0.28–1.31)	0.64 (0.27–1.37)	9	0.92 (0.46–1.84)	1.08 (0.53–2.21)
Non-aspirin NSAID	35	0.78 (0.55–1.11)	0.80 (0.56–1.14)	14	0.86 (0.50–1.50)	0.76 (0.43–1.33)	6	0.69 (0.30–1.59)	0.68 (0.29–1.64)

¹ Cox proportional hazards models account for left truncation by entering the return date of the CWLS questionnaire as the beginning in which the subject comes under observation, and adjusted for age at diagnosis, stage, and treatment.

² Additionally adjusted for education, cigarette smoking, alcohol consumption, body mass index, menopausal status, and family history of breast cancer.

Abbreviations: SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants; CVD, cardiovascular disease mortality; HR, hazard ratio; CI, confidence interval.