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Associations of aspirin and other anti-inflammatory medications with mammographic breast density and breast cancer risk

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Abstract

Purpose: We investigated the associations of aspirin and other non-steroid anti-inflammatory drugs (NSAIDs) with mammographic breast density (MBD) and their interactions in relation to breast cancer risk.

Methods: This study included 3,675 cancer-free women within the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts. Percent breast density (PD), absolute dense area (DA), and non-dense area (NDA) were measured from digitized film mammograms using a computer-assisted thresholding technique; all measures were square root-transformed. Information on medication use was collected in 1980 (NHS) and 1989 (NHSII) and updated biennially. Medication use was defined as none, past or current; average cumulative dose and frequency were calculated for all past or current users from all bi-annual questionnaires preceding the mammogram date. We used generalized linear regression to quantify associations of medications with MBD. Two-way interactions were examined in logistic regression models.

Results: In multivariate analysis, none of the anti-inflammatory medications were associated with PD, DA and NDA. We found no interactions of any of the medications with PD with respect to breast cancer risk (all p-interactions>0.05). However, some of the aspirin variables appeared to have positive associations with breast cancer risk limited only to women with PD 10–24% (past

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Disclosure of potential conflicts of interest

The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. Consent was obtained or implied by return of questionnaires.

aspirin OR=1.56, 95% CI 1.03–2.35; current aspirin with <5 years of use OR=1.82, 95% CI 1.01–3.28; current aspirin with ≥5 years of use OR=1.89, 95% CI 1.26–2.82).

Conclusions: Aspirin and NSAIDs are not associated with breast density measures. We found no interactions of aspirin with MBD in relation to breast cancer risk.

Keywords

aspirin; breast density; breast cancer; interactions

Introduction

Mammographic breast density is a well-established and strong predictor of breast cancer risk (1–4). Appearance of the breast on the mammogram is a reflection of the amount of fat, connective tissue, and epithelial tissue in the breast (3). Light (non-radiolucent) areas on the mammogram represent the connective and epithelial tissues ("mammographically dense"), whereas, the dark (radiolucent) areas represent primarily fat. Women with breasts of 75% or greater percent density (proportion of the total breast area that appears dense on the mammogram) are at 4- to 6-fold greater risk of breast cancer compared to women with more fat tissue in the breasts (3, 5, 6). Absolute dense area of the breast that represents epithelium and connective tissue has been shown to be positively associated with breast cancer risk in both pre- and postmenopausal women (7–13), while non-dense area of the breast (representing fat tissue) has been shown to be inversely associated with breast cancer risk (7, 9, 14, 15).

Epidemiologic studies on the association between aspirin use and breast cancer demonstrated inconsistent findings with some studies reporting an inverse association between aspirin and breast cancer (16–22) and others finding no association (23–26). A meta-analysis of 38 studies found that use of nonsteroidal anti-inflammatory drugs (NSAIDs) was associated with a 12% reduced risk of breast cancer and in the aspirin-specific analysis, a 13% reduction in breast cancer risk (27). The evidence on the association of aspirin use with breast density is extremely limited (28–30). While Wood et al. found an inverse association between aspirin dose and breast density (30), two other studies reported no associations (31, 32).

A potential biological mechanism through which aspirin may reduce breast density and breast cancer risk is includes inhibition of cyclooxygenase-2 (COX-2) enzyme activity (20, 21, 24). Overexpression of COX-2 occurs frequently in women with mammary tumors as compared to women with normal breast tissue (20, 24). COX-2 enzyme mediates the synthesis of prostaglandin E2 (PGE-2) (24), which modulates apoptosis and cell proliferation (20) and may influence endogenous estrogens levels through the stimulation of aromatase (24). Consequently, through the suppression of COX-2, aspirin may lower PGE-2 production, thereby reducing its carcinogenic activity in mammary cells and thus inhibiting tumor growth (20, 24). Finally, a recent study in postmenopausal women suggested that dense breast tissue has a pro-inflammatory microenvironment (33) thus further supporting a potential link between aspirin intake and breast density. To add to the limited evidence on the association between aspirin and mammographic breast density, using Nurses' Health

Study (NHS) and the Nurses' Health Study II (NHS II) cohorts, we examined associations of aspirin and other NSAIDs intake with percent density, absolute dense and non-dense areas overall and by woman's menopausal status. We further examined the interactions between the use of anti-inflammatory drugs and percent breast density in relation to breast cancer risk.

Methods

Study population and design

Women included in this study were selected from participants of the nested case-control study within Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII) cohorts. These prospective cohorts followed registered nurses in the United States who were 30–55 years (NHS) or 25–42 years old (NHSII) at enrollment. After administration of the initial questionnaire, the information on breast cancer risk factors and any diagnoses of cancer or other diseases was updated through biennial questionnaires (3, 34).

A nested case-control approach was originally used as an efficient design to examine the association between selected biomarkers and breast cancer risk within the NHS and NHS II (3, 35). Using incidence density sampling, women without cancer history (other than non-melanoma skin cancer) at the time of the case's cancer diagnosis (controls) were matched 1:1 or 1:2 with women diagnosed with in situ or invasive breast cancer (cases) on age at the time of blood collection, menopausal status and postmenopausal hormone use (current vs. not current) at blood draw, and day/time of blood draw; for NHS II, additional matching included race/ethnicity and day in the luteal phase (36). We attempted to obtain mammograms closest to the time of blood collection (or ~1997 for those who did not provide blood samples). From all eligible women for this nested case-control study, 6,258 women provided consent and had a usable mammogram for density estimation. Of these women, 4,685 (1,519 cases and 3,166 controls) had data on exposures and important covariates and were included in the analysis of interactions between exposures and breast density in relation to breast cancer risk.

Our analysis of anti-inflammatory drugs and breast density included only controls from this nested case-control study as well as additional eligible women within NHSII cohort (without a history of any cancer other than non-melanoma skin) who were not included in the original nested breast cancer case-control study. Of these controls, 3,675 had data on exposures and important covariates.

The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. Consent was obtained or implied by return of questionnaires.

Assessment of aspirin intake and NSAIDs

The methods of assessing exposure to aspirin and other NSAIDs have been described in detail elsewhere (26). Briefly, information on aspirin use in NHSI was first obtained in 1980 and biennially thereafter except in 1986. In 1980, participants were asked whether they

currently took aspirin in most weeks and, if yes, what was the weekly amount and years of aspirin use. Information on aspirin dose and frequency of use was also collected beginning in 1982 and 1984, respectively. In NHSII, on the baseline questionnaire in 1989, participants were asked if they regularly (≥2 times per week) used aspirin, or other anti-inflammatory drugs in three separate questions and this was updated biennially from 1993. Beginning in 1993 (for aspirin) or 1995 (for other anti-inflammatory drugs), women were asked to report frequency of use (categorized as either days per week or days per month). Beginning in 1999, participants were additionally asked about quantity used (tablets per week) in each category.

Women were classified as current users at each questionnaire in which current use was reported and were considered current users for the subsequent two-year follow-up period (or the four-year follow-up period from 1989−1993). For participants who missed a questionnaire, drug use information was carried forward from the previous cycle. The women who ceased reporting use were classified as past users, but they were eligible to become current users in subsequent follow-up years. Women were classified as nonusers if they did not report analgesic use at baseline or on any of their follow-up questionnaires. Duration of use of each drug was calculated from baseline (1980 for aspirin, 1990 for other NSAIDs for NHSI and 1989 for NHSII) to the reference date (date of the mammogram) (26). To better represent long-term use, we calculated the cumulative average dose (standard 325-mg tablet) and frequency (days per week) for each woman who was classified as a past or current user as the average of current use and all previous follow-up cycles. Status, quantity and frequency of use were carried forward one cycle to replace missing data and cumulative average quantity, cumulative average frequency and duration of use were calculated from these variables with the carried-forward data.

Assessment of Mammographic Breast Density

To quantify mammographic density, the craniocaudal views of both breasts for all mammograms in the NHS and for the first two batches of mammograms in the NHSII were digitized at 261 μm per pixel with a Lumisys 85 laser film scanner (Lumisys, Sunnyvale, California). The third batch of NHSII mammograms was digitized using a VIDAR CAD PRO Advantage scanner (VIDAR Systems Corporation; Herndon, VA) and comparable resolution of 150 dots per inch and 12 bit depth). The Cumulus software (University of Toronto, Toronto, Canada) was used for computer-assisted determination of the absolute dense area, non-dense area, and percent mammographic density on all mammograms (3, 37). As reported previously, the measure of breast density from NHS mammograms was highly reproducible (within-person intraclass correlation coefficient=0.93) (3). All NHSII images were read by a single reader. Although within batch reproducibility was high (intraclass correlation coefficient ≥0.90) (7), density measures varied across the NHSII batches. We included a small subset of identical mammograms in all batches to account for batch drift in density measurement readings. The density measures from the second and third batches of NHSII mammograms were adjusted to account for the batch effect (whether due to intra-reader variability or scanner), as previously described (38). Additionally, to assess the potential variability in percent density by scanner, we conducted a pilot study of 50 mammograms. These mammograms were scanned using both the Lumysis 85 laser scanner

and the VIDAR CAD PRO Advantage scanner; percent density was measured by the same observer using Cumulus. The correlation between percent density as measured by the two scanners was 0.88; the mean difference was 2.3% points (39).

Percent breast density was measured as percentage of the total area occupied by epithelial/stromal tissue (absolute dense area) divided by the total breast area. Because breast densities of the right and left breast for an individual woman are strongly correlated (37), the average density of both breasts was used in this analysis.

Covariate Information

Information on breast cancer risk factors was obtained from the biennial questionnaires closest to the date of the mammogram. Women were considered to be postmenopausal if they reported: 1) no menstrual periods within the 12 months before blood collection with natural menopause, 2) bilateral oophorectomy, or 3) hysterectomy with one or both ovaries retained, and were 54 years or older for ever smokers or 56 years or older for never smokers (40, 41).

Statistical analysis

We used generalized linear regression to examine the associations of anti-inflammatory drug use with percent density, absolute dense and non-dense areas. Because density measures were non-normally distributed, we used square root transformation to improve normality in all the regression analyses. The regression estimates were adjusted for age (continuous), body mass index (continuous), age at menarche (<12, 12–13, >13 years), parity and age at first child's birth (nulliparous, parous with age at first birth <25 years, or parous with age at first birth of ≥25 years), a confirmed history of benign breast disease (yes, no), a family history of breast cancer (yes, no), study cohort, alcohol use (0, <5, ≥5 g/day), and age at menopause (<46, 46-<50, 50-<55, ≥55, unknown). To assess the overall trend for exposure, we used respective medians within each category, where appropriate. The overall analysis was followed by stratified analysis by women's menopausal status.

We used unconditional logistic regression to assess interactions of exposures with percent breast density in relation to breast cancer risk by including an interaction term in the logistic regression models. The regression estimates were adjusted for all covariates listed above. Differences in the associations of breast density with breast cancer risk by the level of exposures was tested with two-way interactions and using Wald Chi-square test. In modeling these interactions, we first determined the median percent density within each category and respective medians within each category of exposure among controls which were then used to model interactions. Next, we described associations of exposures with breast cancer risk stratified by the category of percent density (<10%, 10–24%, 25–49%, and ≥50%), consistently used in previous studies (42–47).

Statistical significance in all the analyses was assessed at 0.05 level. The analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

Association of anti-inflammatory medication use with breast density

In this study of 3,675 cancer-free women, the average age at the mammogram was 53 years (range 30–84). Of these women, 1,693 were premenopausal and 1,982 were postmenopausal. Among premenopausal women, 51.2% never used aspirin, 21.4% were past users and 27.3% were currently using aspirin while 30.0% never used other NSAIDs and 23.0% and 47.0% were past or current users, respectively. Among postmenopausal women, 24.3% never used aspirin, 30.4% used it in the past and 45.4% were current users while 44.4% never used other NSAIDs and 16.7% and 38.9% were past or current users, respectively. Distribution of breast cancer risk factors by aspirin intake categories in pre- and postmenopausal women are presented in Table 1. In premenopausal women, current aspirin users as compared to non-users had a slightly greater percent breast density (40.1% vs. 38.9%), a greater absolute dense area (48.9 vs. 43.9 cm^2) and a greater non-dense breast area (84.2 vs. 78.5 cm^2). Current aspirin users were also on average older at the time of the mammogram as compared to non-users (47.5 vs. 44.8 years), consumed greater amount of alcohol (5.7 vs. 4.1 g/day), were less likely to be nulliparous (10% vs. 15%), and less likely to have a history of confirmed benign breast disease (17% vs. 19%). In postmenopausal women, current aspirin users had a slightly larger absolute dense area (37.3 vs. 35.3 cm^2) and a larger non-dense area (133.1 vs. 123.1 cm^2). As compared to non-user, current aspirin users were older at the time of the mammogram (59.3 vs. 54.6 years), consumed greater amount of alcohol (5.7 vs. 4.8 g/day), and were less likely to be nulliparous (8% vs. 10%). Distributions of other risk factors were similar across aspirin intake categories in both pre- and postmenopausal women.

In the multivariate regression analysis, we did not find any consistent patterns in associations of aspirin and other NSAIDs with percent breast density in overall as well as stratified analysis by menopausal status (Table 2). None of these medications were associated with absolute dense area in the overall analysis and among postmenopausal women (Supplementary table 1). In premenopausal women, current use of aspiring for less than 5 years was positively associated with absolute dense area (β=0.51, 95% CI 0.20, 0.82), however, the overall trend did not reach statistical significance (p-trend=0.11) and was lacking a clear pattern. Similarly, the suggestive decrease in absolute dense area change with increasing dosage of aspirin use among past users was only marginally significant (p-trend=0.09). Use of aspirin and other NSAIDs were not associated with non-dense area neither in overall nor in stratified analysis by menopausal status (Supplemental table 2).

Interactions of anti-inflammatory medications use with percent breast density in relation to breast cancer risk

The analysis of interactions included 4,685 women (1,519 cases and 3,166 controls). We found no significant interactions between anti-inflammatory medications and percent breast density in relation to breast cancer risk with exemption of any use of anti-inflammatory medication (p-interaction<0.0001; all other p-values>0.05). There were also marginally significant interactions between breast density and dosage of past aspirin use (p-interaction=0.08) and between breast density and frequency of NSAIDs use (p-

interaction=0.08). No clear differences were observed in the magnitude of the risk estimates for anti-inflammatory drugs in relation to breast cancer risk across percent breast density strata.

In a stratified analysis by the degree of percent breast density, positive associations with breast cancer risk were found among women with 10–24% breast density for regular aspirin use: (past use: OR=1.56, 95% CI 1.03–2.35; current aspirin use <5 years: OR=1.82, 95% CI 1.01–3.28); current aspirin use ≥5 years: OR=1.89, 95% CI 1.26– 2.82), dosage of past aspirin use (use of 5 or more tablets per week: OR=2.55, 95% CI 1.18–5.54), duration of current aspirin use (use for 2–5 years: OR=1.97, 95% CI 1.02–3.82); use for >5 years: OR=1.84, 95% CI 1.22–2.77), and current use of any NSAIDs for 5 or more years (OR=1.67, 95% CI 1.06–2.65) (Table 3). In stratified analysis, it also appeared that some of the associations might be in opposite directions in women with 10–24% breast density vs. dense breasts (≥50%) (Table 3).

Discussion

In this study of associations of anti-inflammatory drug use, mammographic breast density and interactions of breast density with medications in relation to breast cancer risk, we found no associations of aspirin or NSAIDs with percent density, absolute dense and non-dense areas, overall and by woman's menopausal status. Positive associations of regular aspirin use, dosage of past aspirin use, and duration of current aspirin with breast cancer risk were limited to women with percent density 10–24%. Our findings contribute to the very limited evidence on the association of anti-inflammatory drug use and breast density.

Some previous studies have suggested that aspirin intake may be associated with a reduced risk of breast cancer and breast cancer-specific mortality after primary breast cancer diagnosis (16–22); others found no associations (23–26). The existing evidence on these associations has recently been summarized by a meta-analysis of 38 studies (27). The authors found that use of any NSAIDs was associated with a 12% reduced risk of breast cancer (relative risk [RR]=0.88, 95% confidence interval [CI] 0.84– 0.93). In medication-specific analysis, aspirin use was associated with a 13% reduction in breast cancer risk (RR=0.87, 95% CI 0.82–0.92) and use of ibuprofen with 21% risk reduction (RR=0.79, 95% CI 0.64–0.97) (27). Two studies of associations between anti-inflammatory medication and breast cancer in NHS and NHSII found no associations in both pre- and postmenopausal women (26, 48). No differences were noted in associations for specific breast cancer subtypes (48).

Several biological mechanisms were suggested as a possible explanation for potential effects of aspirin and other anti-inflammatory medications on breast cancer risk, including inhibition of COX-2 enzyme activity (20, 21, 24) that could subsequently lead to changes in apoptosis, cellular proliferation and aromatase activity (20, 24) However, very limited data exists on associations of anti-inflammatory medications with breast density (28–30). A recent study of 26,000 women undergoing screening mammography found an inverse association between aspirin use (within the year preceding the mammogram) and breast density defined using Breast Imaging-Reporting and Data System (BI-RADS) density (p-

trend< 0.001). Women with extremely dense breasts (BI-RADS IV) were less likely to have used aspirin as compared to women with scattered fibroglandular density (BI-RADS II, OR 0.73; 95% CI 0.57–0.93), with an apparent dose-response pattern (p-trend=0.007) (30). In contrast to this study, due to prospective data collection in NHS and NHSII, we were able to examine the associations of cumulative, long-term exposures with breast density. In addition, we used continuous breast density measures from computerized breast density estimation in our analyses. Unlike Woods et al., we did not find any associations of any of the medications with percent breast density, absolute dense and non-dense areas. Differences in breast density assessment approaches, study size (3,675 in our study vs. 26,000 in Woods et al.), and exposure assessment could potentially explain these differences in study findings. Consistent with our findings, two other studies (a cross-sectional analysis by Stone et al. within Australian Mammographic Density Twins and Sisters Study [AMDTSS] and the Genes Behind Endometriosis Study [3,286 women] and a randomized controlled trial by McTiernan et al.[143 postmenopausal women]) found no associations of aspirin and NSAIDs with breast density (31, 32).

We did not observe any clear differences in associations of anti-inflammatory drugs with breast cancer risk across percent breast density strata, though it appeared that some of the associations might be in opposite directions in women with 10–24% breast density vs. dense breasts (≥50%). However, we cannot rule out completely that this is a chance finding. As NSAIDs reduce aromatase activity (49) and as dense breast tissue appears to have greater activity of aromatase as compared to non-dense area (50) it is possible that the effect of aspirin on breast cancer risk may be modified by the degree of breast density. However, we were unable to find any significant interactions between anti-inflammatory drugs and breast density and further studies are warranted to examine these suggestive association patterns in a larger study sample.

Our study used data from the NHS and NHSII cohorts with more than 25 years of follow-up, ascertainment of disease status, and comprehensive information on breast cancer risk factors and breast density. Our study has a few limitations. The examined associations are based on the density measures from a single mammogram which might not be reflective of the woman’s life-long density pattern, however studies have suggested that a single measure can predict breast cancer risk for up to 10 years in both pre- and postmenopausal women (6, 51). Despite the prospective nature of the cohort, potential errors in recall of aspirin and other medication use are possible. However, given our population of registered nurses with a familiarity of health-related exposures and use of drugs as well as prospective data collection, the medication use data are likely to be accurate.

In conclusion, we investigated the associations of aspirin and NSAIDs use with mammographic breast density. Our findings suggested that anti-inflammatory medications are not associated with percent breast density, absolute dense and non-dense breast area. Even though we found no interactions of aspirin with MBD in relation to breast cancer risk, in women with percent density 10–24%, regular aspirin use, dosage of past aspirin use and duration of current aspirin use appear to be positively associated with breast cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Age-adjusted characteristics of women in the study (NHS and NHSII) at the time of the mammogram, by aspirin intake

Characteristic	Premenopausal women			Postmenopausal women		
	Non-users (n=867)	Past users (n=363)	Current users (n=463)	Non-users (n=481)	Past users (n=602)	Current users (n=899)
Mean (SD)						
Percent mammographic density	38.9 (18.2)	39.4 (19.3)	40.1 (19.3)	25.7 (18.1)	26.2 (17.9)	25.3 (17.7)
Dense area (cm^2)	43.9 (25.7)	45.2 (26.3)	48.9 (30.6)	35.3 (26.4)	37.4 (27.8)	37.3 (28.5)
Non-dense area (cm^2)	78.5 (50.5)	82.1 (59.2)	84.2 (57.6)	123.1 (71.1)	128.6 (79.2)	133.1 (80.7)
Age (years)*	44.8 (4.4)	46.7 (4.1)	47.5 (4.2)	54.6 (8.2)	58.8 (7.4)	59.3 (7.6)
Age at menarche (years)	12.5 (1.4)	12.2 (1.3)	12.5 (1.4)	12.5 (1.4)	12.5 (1.5)	12.4 (1.4)
Age at menopause (years)	-	-	-	47.4 (5.9)	47.6 (5.9)	47.4 (6.2)
Body Mass Index (kg/m^2)	25.7 (5.4)	25.6 (6.2)	25.6 (5.2)	26.4 (5.6)	26.2 (5.2)	26.0 (5.2)
Alcohol consumption, g/day	4.1 (7.1)	4.1 (6.2)	5.7 (9.3)	4.8 (8.8)	4.8 (8.2)	5.7 (8.7)
Percentages						
Parity/age at first birth	26.2 (4.3)	26.1 (4.3)	25.9 (4.2)	25.0 (3.5)	25.1 (3.6)	25.0 (3.2)
Nulliparous	15	15	10	10	9	8
Parous, age<25 years	32	34	36	44	46	49
Parous, age≥25 years	52	51	53	44	44	43
Family history of breast cancer	10	7	9	13	12	12
Benign breast disease	19	16	17	21	23	22
Never used HT	-	-	-	38	35	36
Past HT use	-	-	-	18	19	19
Current HT use	-	-	-	44	45	45

Abbreviations: SD – standard deviation; HT – postmenopausal hormone therapy

*Value not age adjusted

Table 2.

Associations of aspirin and other NSAIDs with mammographic percent breast density (square root-transformed), by menopausal status

Intake category	All women		Premenopausal		Postmenopausal	
	N	Full Models, β and 95% CI[a]	N	Full Models, β and 95% CI[b]	N	Full Models, β and 95% CI[c]
ASPIRIN USE						
Regular use (≥2 times/week)						
Non-users	1348	Reference	867	Reference	481	Reference
Past users	965		363	0.10 (−0.07, 0.28)	602	0.12 (−0.07, 0.32)
Current users						
<5 yrs	339	0.28 (0.11, 0.46)	177	0.43 (0.20, 0.65)	162	0.09 (−0.19, 0.37)
≥5 yrs	1023	0.06 (−0.08, 0.20)	286	0.02 (−0.19, 0.23)	737	0.03 (−0.16, 0.22)
p-trend		0.25		0.11		0.88
Frequency of use						
Non-users	1343	Reference	862	Reference	481	Reference
Past users	1072	0.14 (0.01, 0.27)	389	0.15 (−0.03, 0.33)	683	0.12 (−0.07, 0.31)
Current users						
1 day/wk	632	0.21 (0.05, 0.36)	264	0.31 (0.09, 0.52)	368	0.09 (−0.14, 0.31)
2–3 days/wk	310	0.08 (−0.11, 0.28)	114	0.06 (−0.22, 0.34)	196	0.05 (−0.22, 0.31)
4–5 days/wk	142	0.10 (−0.16, 0.37)	37	0.16 (−0.31, 0.63)	105	0.01 (−0.33,0.34)
6+ days/wk	457	0.10 (−0.07, 0.27)	107	0.13 (−0.16, 0.42)	350	0.04 (−0.18, 0.27)
p-trend		0.61		0.68		0.84
Dosage (number of tablets per week)						
Non-users	759	Reference	390	Reference	369	Reference
Past users						
<2	410	0.23 (0.02, 0.43)	108	0.22 (−0.14, 0.59)	302	0.22 (−0.03, 0.46)
2–5	124	0.35 (0.05, 0.66)	24	0.30 (−0.34, 0.94)	100	0.33 (−0.02, 0.69)
>5	87	−0.07 (−0.42, 0.29)	13	−0.86 (−1.71, −0.01)	74	0.07 (−0.32, 0.47)
p-trend		0.54		0.08		0.75
Current users						
<2	450	0.25 (0.05, 0.44)	154	0.42 (0.11, 0.73)	296	0.13 (−0.12, 0.37)

Intake category	All women		Premenopausal		Postmenopausal	
	N	Full Models, β and 95% CI[a]	N	Full Models, β and 95% CI[b]	N	Full Models, β and 95% CI[c]
2–5	332	0.20 (−0.01, 0.42)	65	−0.02 (−0.44, 0.40)	267	0.22 (−0.04, 0.48)
>5	379	0.01 (−0.19, 0.21)	100	0.23 (−0.12, 0.58)	279	−0.13 (−0.38, 0.12)
p-trend		0.48		0.62		0.16
Duration (years of use by status)						
Non-users	1348	Reference	867	Reference	481	Reference
Past users						
<2	36	−0.03 (−0.51, 0.46)	17	0.02 (−0.65, 0.68)	19	−0.09 (−0.80, 0.62)
2–5	433	0.19 (0.03, 0.35)	215	0.20 (−0.01, 0.41)	218	0.16 (−0.09, 0.40)
>5	496	0.08 (−0.09, 0.25)	131	−0.06 (−0.34, 0.21)	365	0.12 (−0.10, 0.35)
p-trend		0.55		0.85		0.54
Current users						
<2	142	0.15 (−0.10, 0.41)	81	0.35 (0.03, 0.66)	61	−0.14 (−0.55, 0.27)
2–5	253	0.29 (0.09, 0.49)	126	0.37 (0.11, 0.64)	127	0.15 (−0.15, 0.46)
>5	967	0.06 (−0.08, 0.20)	256	0.01 (−0.21, 0.23)	711	0.04 (−0.15, 0.24)
p-trend		0.48		0.91		0.47
NSAIDs						
Regular use (≥2 times/week)						
Non-users	1310	Reference	479	Reference	831	Reference
Past users	680	0.05 (−0.09, 0.19)	367	−0.07 (−0.26, 0.13)	313	0.14 (−0.07, 0.35)
Current users						
<5 yrs	877	0.03 (−0.10, 0.15)	436	−0.04 (−0.22, 0.13)	441	0.06 (−0.12, 0.24)
≥5 yrs	599	0.03 (−0.12, 0.18)	313	−0.10 (−0.30, 0.11)	286	0.14 (−0.09, 0.36)
p-trend		0.71		0.41		0.29
Frequency of use						
Non-users	1301	Reference	471	Reference	830	Reference
Past users	678	0.06 (−0.09, 0.20)	365	−0.05 (−0.24, 0.15)	313	0.13 (−0.08, 0.34)
Current users						
1 day/wk	566	0.12 (−0.03, 0.27)	337	−0.00 (−0.20, 0.19)	229	0.20 (−0.03, 0.43)
2–3 days/wk	429	0.02 (−0.15, 0.18)	255	0.01 (−0.20, 0.22)	174	−0.02 (−0.28, 0.23)
4–5 days/wk	131	0.00 (−0.26, 0.27)	59	−0.15 (−0.53, 0.22)	72	0.12 (−0.25, 0.50)

Intake category	All women		Premenopausal		Postmenopausal	
	N	Full Models, β and 95% CI[a]	N	Full Models, β and 95% CI[b]	N	Full Models, β and 95% CI[c]
6+ days/wk	274	−0.07 (−0.27, 0.12)	74	−0.31 (−0.65, 0.03)	200	0.02 (−0.22, 0.27)
p-trend		0.50		0.21		0.98
ANY NSAIDs use						
Regular use (≥2 times/week)						
Non-users	602	Reference	287	Reference	315	Reference
Past users	892	0.01 (−0.15, 0.16)	432	−0.09 (−0.31, 0.12)	460	0.11 (−0.11, 0.33)
Current users						
<5 yrs	895	0.05 (−0.10, 0.21)	466	0.01 (−0.20, 0.22)	429	0.09 (−0.13, 0.32)
≥5 yrs	1528	0.00 (−0.14, 0.14)	569	−0.08 (−0.28, 0.13)	959	0.06 (−0.14, 0.26)
p-trend		0.93		0.73		0.84

Abbreviations: CI- confidence interval; NSAIDs-non-steroid anti-inflammatory drugs

[a]Adjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, >13), menopausal status/postmenopausal hormone use (premenopausal, postmenopausal/no hormones, postmenopausal/ past hormones, postmenopausal/current hormones, postmenopausal/past/ unknown current), a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort (NHSI, NHSII), alcohol use (none, >0-<5, ≥5 g/day), and parity and age at first child's birth (nulliparous, parous with age at first birth <25, parous with age at first birth ≥25)

[b]Adjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, >13), a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort (NHSI, NHSII), alcohol use (none, >0-<5, ≥5 g/day), and parity and age at first child's birth (nulliparous, parous with age at first birth <25, parous with age at first birth ≥25)

[c]Adjusted for age (continuous), BMI (continuous), , age at menarche (<12, 12, 13, >13), a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort (NHSI, NHSII), alcohol use (none, >0-<5, ≥5 g/day), hormone therapy (none, past, current, past/unknown current), age at menopause (<46, 46-<50, 50-<55, ≥55, unknown), and parity and age at first child's birth (nulliparous, parous with age at first birth <25, parous with age at first birth ≥25)

Table 3.

Associations of aspirin and other NSAIDs with breast cancer risk, stratified by percent density[a]

Intake category	<10		10–24		25–49		≥ 50	
	N (Cases/ Controls)	Full Models, OR and 95% CI[a]	N (Cases/ Controls)	Full Models, OR and 95% CI[b]	N (Cases/ Controls)	Full Models, OR and 95% CI[c]	N (Cases/ Controls)	Full Models, OR and 95% CI[d]
ASPIRIN USE								
Regular use (≥2 times/week)								
Non-users	18/95	Reference	53/274	Reference	193/477	Reference	153/256	Reference
Past users	64/175	1.57 (0.85, 2.91)	112/284	1.56 (1.03, 2.35)	213/332	1.12 (0.85, 1.48)	129/155	1.09 (0.77, 1.53)
Current users								
<5 yrs	8/24	1.56 (0.57, 4.23)	23/57	1.82 (1.01, 3.28)	39/90	0.96 (0.63, 1.46)	28/57	0.82 (0.49, 1.38)
≥5 yrs	50/196	1.06 (0.56, 2.00)	147/298	1.89 (1.26, 2.82)	191/279	1.05 (0.78, 1.42)	98/117	0.93 (0. 62, 1.38)
p-trend		0.40		0.00		1.00		0.49
Frequency of use								
Non-users	18/94	Reference	53/261	Reference	193/443	Reference	152/240	Reference
Past users	73/193	1.70 (0.93, 3.12)	133/321	1.56 (1.05, 2.34)	256/371	1.11 (0.85, 1.45)	144/172	1.00 (0.71, 1.41)
Current users								
1 day/wk	16/56	1.37 (0.62, 3.04)	37/71	2.16 (1.27, 3.68)	60/95	1.09 (0.73, 1.62)	36/55	0.73 (0.43, 1.23)
2–3 days/wk	12/28	1.83 (0.75, 4.47)	31/53	2.36 (1.34, 4.16)	54/86	1.06 (0.70, 1.59)	24/39	0.68 (0.38, 1.23)
4–5 days/wk	6/39	0.70 (0.25, 1.97)	23/55	1.71 (0.93, 3.13)	25/41	0.91 (0.52, 1.60)	19/24	1.00 (0.51, 1.96)
6+ days/wk	41/128	1.35 (0.70, 2.62)	95/217	1.52 (1.00, 2.32)	121/187	0.89 (0.64, 1.24)	65/66	1.13 (0.72, 1.77)
p-trend		0.54		0.56		0.21		0.35
Dosage (number of tablets per week)								
Non-users	18/85	Reference	49/205	Reference	178/327	Reference	127/181	Reference
Past users								
<2	35/82	1.78 (0.89, 3.58)	57/165	1.28 (0.79, 2.08)	105/142	1.02 (0.71, 1.47)	58/48	1.31 (0.76, 2.26)
2–5	11/44	0.86 (0.35, 2.09)	27/52	1.82 (0.99, 3.35)	27/47	0.76 (0.44, 1.32)	16/21	0.88 (0.40, 1.91)
>5	11/23	1.94 (0.75, 4.98)	16/22	2.55 (1.18, 5.54)	24/30	1.02 (0.55, 1.90)	8/9	0.80 (0.28, 2.33)
p-trend		0.70		0.01		0.91		0.27
Current users								
<2	22/60	1.53 (0.72, 3.26)	58/105	2.05 (1.27, 3.30)	75/118	0.94 (0.64, 1.37)	51/67	0.92 (0.57, 1.48)

Intake category	<10		10–24		25–49		≥ 50	
	N (Cases/ Controls)	Full Models, OR and 95% CI[a]	N (Cases/ Controls)	Full Models, OR and 95% CI[b]	N (Cases/ Controls)	Full Models, OR and 95% CI[c]	N (Cases/ Controls)	Full Models, OR and 95% CI[d]
2–5	11/71	0.58 (0.24, 1.37)	45/118	1.30 (0.78, 2.16)	81/100	1.06 (0.71, 1.58)	27/41	0.63 (0.34, 1.16)
>5	25/80	1.17 (0.56, 2.44)	62/112	2.02 (1.25, 3.28)	66/110	0.80 (0.54, 1.18)	35/41	0.81 (0.46, 1.44)
p-trend		0.87		0.07		0.32		0.54
Duration (years of use by status)								
Non-users	18/95	Reference	53/274	Reference	193/477	Reference	153/256	Reference
Past users								
<2	2/3	3.01 (0.43, 20.92)	4/10	1.74 (0.51, 5.97)	10/7	2.93 (1.07, 8.02)	9/3	5.90 (1.50, 23.18)
2–5	15/53	1.47 (0.66, 3.25)	30/79	1.60 (0.94, 2.74)	79/141	1.12 (0.80, 1.57)	48/82	0.86 (0.56, 1.32)
>5	47/119	1.58 (0.82, 3.04)	78/195	1.51 (0.96, 2.37)	124/184	1.02 (0.73, 1.43)	72/70	1.13 (0.71, 1.78)
p-trend		0.26		0.26		0.84		0.77
Current users								
<2	2/13	0.78 (0.15, 3.90)	9/23	1.92 (0.82, 4.53)	17/44	0.91 (0.50, 1.66)	11/25	0.87 (0.41, 1.85)
2–5	7/14	2.44 (0.81, 7.34)	18/38	1.97 (1.02, 3.82)	30/56	1.11 (0.68, 1.82)	24/38	0.95 (0.54, 1.69)
>5	49/193	1.04 (0.55, 1.98)	143/294	1.84 (1.22, 2.77)	183/269	1.00 (0.73, 1.36)	91/111	0.87 (0.57, 1.32)
p-trend		0.57		0.02		0.55		0.83
NSAIDs								
Regular use (≥2 times/week) Non-users	65/214	Reference	124/344	Reference	241/431	Reference	145/188	Reference
Past users	44/126	1.15 (0.72, 1.84)	111/250	1.19 (0.86, 1.65)	203/315	1.17 (0.91, 1.51)	134/165	1.10 (0.79, 1.54)
Current users								
<5 yrs	23/97	0.85 (0.49, 1.48)	47/158	1.01 (0.67, 1.52)	114/234	0.98 (0.73, 1.30)	67/116	0.75 (0.50, 1.10)
≥5 yrs	33/101	1.32 (0.78, 2.25)	93/244	1.16 (0.81, 1.65)	153/297	0.98 (0.75, 1.29)	98/146	0.86 (0.59, 1.25)
p-trend		0.56		0.57		0.68		0.16
Frequency of use								
Non-users	65/211	Reference	124/331	Reference	241/379	Reference	144/171	Reference
Past users	44/126	1.16 (0.72, 1.84)	111/248	1.14 (0.82, 1.57)	206/315	1.07 (0.83, 1.38)	134/162	1.02 (0.72, 1.43)
Current users								
1 day/wk	9/49	0.71 (0.32, 1.56)	30/107	0.91 (0.56, 1.49)	84/167	0.96 (0.69, 1.32)	62/104	0.73 (0.48, 1.10)
2–3 days/wk	11/44	1.10 (0.52, 2.34)	25/113	0.67 (0.40, 1.13)	73/172	0.76 (0.55, 1.07)	63/75	1.02 (0.66, 1.57)

Intake category	<10		10–24		25–49		≥ 50	
	N (Cases/ Controls)	Full Models, OR and 95% CI[a]	N (Cases/ Controls)	Full Models, OR and 95% CI[b]	N (Cases/ Controls)	Full Models, OR and 95% CI[c]	N (Cases/ Controls)	Full Models, OR and 95% CI[d]
4–5 days/wk	6/12	2.26 (0.78, 6.57)	19/35	1.70 (0.90, 3.21)	25/44	0.90 (0.53, 1.53)	17/25	0.81 (0.41, 1.60)
6+ days/wk	26/65	1.41 (0.79, 2.50)	44/87	1.32 (0.84, 2.05)	56/77	1.05 (0.71, 1.56)	17/29	0.54 (0.27, 1.05)
p-trend		0.12		0.13		0.82		0.25
ANY NSAIDs use								
Regular use (≥2 times/week)								
Non-users	16/64	Reference	28/129	Reference	102/199	Reference	67/89	Reference
Past users	52/130	1.41 (0.72, 2.75)	93/245	1.45 (0.89, 2.36)	196/332	1.03 (0.76, 1.40)	131/161	1.04 (0.69, 1.58)
Current users								
<5 yrs	21/82	0.96 (0.45, 2.07)	48/148	1.49 (0.87, 2.57)	104/238	0.88 (0.62, 1.24)	72/128	0.74 (0.47, 1.16)
≥5 yrs	76/267	1.05 (0.55, 1.99)	208/478	1.67 (1.06, 2.65)	313/512	0.98 (0.73, 1.31)	176/240	0.78 (0.52, 1.16)
p-trend		0.46		0.04		0.68		0.06

Abbreviations: CI –confidence interval; OR-odds ratio; NSAIDs – non-steroid anti-inflammatory drugs

[a]Adjusted for age (continuous), BMI (continuous), age at menarche (<12, 12, 13, >13), a family history of breast cancer (Yes/No), a history of benign breast disease (Yes/No), NHS cohort (NHSI, NHSII), alcohol use (none, >0-<5, ≥5 g/day), menopausal status/postmenopausal hormone use (premenopausal, postmenopausal/no hormones, postmenopausal/past hormones, postmenopausal/current hormones, postmenopausal/past/ unknown current) and parity and age at first child's birth (nulliparous, parous with age at first birth <25, parous with age at first birth ≥25)

NOTE: Interaction of percent breast density with: regular aspirin use p=0.26; frequency of aspirin use p=0.67; dosage of past aspirin use p=0.08; dosage of current aspirin use p=0.30; duration of past aspirin use p=0.19; duration of current aspirin use p=0.37; regular NSAID use p=0.39; frequency of NSAIDs use p=0.08; regular use of any anti-inflammatory medications p<0.0001