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Non-steroidal anti-inflammatory drug (NSAID) use and breast cancer risk in the Western New York Exposures and Breast Cancer (WEB) Study

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Abstract

Objective—Chronic inflammation is suspected to have a role in breast carcinogenesis. Results of studies of non-steroidal anti-inflammatory drugs (NSAIDs) and breast cancer have been inconsistent. Timing of exposure and analysis of individual NSAIDs should be considered.

Methods—We conducted a population-based case-control study in western New York State between 1996 and 2001. Cases, 35-79yrs, had incident, primary, histologically confirmed breast cancer (n=1170). Controls (n=2115) were randomly selected from NY Department of Motor Vehicles records (<65yrs) or Medicare rolls (≥65yrs). Participants were queried on use of aspirin, ibuprofen, and acetaminophen in the year prior and on aspirin during adulthood. Unconditional logistic regression was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (95% CI).

Results—Recent aspirin use was inversely associated with breast cancer risk (adjusted OR 0.80, 95% CI: 0.68-0.94); the strongest reduction in risk was observed among those who took ≥2 pills/day on days that aspirin was taken (OR 0.74, 95% CI: 0.61-0.90). Adult lifetime use was also associated with breast cancer risk (>10 days/month, adjusted OR 0.68, 95% CI: 0.46-1.00). Use of ibuprofen or acetaminophen was not associated with breast cancer.

Conclusions—This is the first study to investigate the association of adult lifetime aspirin intake with breast cancer risk. Our findings provide evidence that aspirin use throughout a woman's life may confer some benefit.

Keywords

Aspirin; Breast Cancer; Ibuprofen; Inflammation; Non-steroidal Anti-inflammatory Drugs

Introduction

Among women in the United States, breast cancer is the most common incident cancer and the second largest cause of cancer mortality. While risk factors for breast cancer have been identified, unexplained variation remains. Inflammation may account for some of this variation. Chronic inflammation is suspected to have a role in carcinogenesis at several sites, including the breast [1]. Non-steroidal anti-inflammatory drugs (NSAIDs) are currently thought to exhibit chemopreventive effects through the inhibition of cyclooxygenase-2 (COX-2, EC 1.14.99.1) and its prostaglandin products, particularly prostaglandin E₂ (PGE₂), a strong mitogen [2,3]. In addition, COX-2 expression has been associated with increased aromatase expression and estrogen synthesis in breast epithelia [4]. Inhibition of inflammation through the use of NSAIDs has been inversely associated with cancers of several sites including the colon, lung, and prostate [2].

Results of observational studies on the association of NSAID use and risk of breast cancer have not been consistent [5-33]; however, results of a recent meta-analysis of observational studies showed modest reductions in risk with NSAID use with stronger associations reported for case-control studies [34]. Inconsistencies of study results may be further explained, in part, by limitations in the measures of NSAID use including differences in NSAID dose and differences in how 'regular use' is defined. In a controlled trial of 39,876 women randomized to low-dose aspirin (100mg) or placebo every other day for ten years, aspirin did not affect breast cancer incidence [35]. The lack of effect in this study may be related to the low albeit consistent dose [35]. In a few studies, the use of several different agents was combined under the assumption that different NSAIDs are homogenous in their effects [5,6,8,11], although they differ chemically and in their affinity to bind to COX-2 [36]. In most studies, only recent, short-term use is measured and this measure has been defined differently across studies.

To better understand the relation, if any, between NSAID use and breast cancer risk, it may be that examination of long-term use will provide more insight. We report here on the association of recent and adult lifetime use of aspirin, as well as an examination of recent use of ibuprofen and acetaminophen, with the risk of breast cancer in the Western New York Exposures and Breast Cancer (WEB) Study.

Materials and Methods

The WEB study is a population-based case-control study of women living in Erie or Niagara counties of Western New York, which has been described in detail elsewhere [37-40]. Briefly, eligible participants were English-speaking women, age 35-79 yrs, who were current residents of Erie or Niagara counties, with no previous history of malignancy other than non-melanoma skin cancer.

Subject Selection

Cases were women with incident, first primary, histologically confirmed breast cancer, diagnosed between 1996 and 2001. Nurse case-finders who visited pathology departments of area hospitals identified potential cases. Patients' physicians were contacted to verify the diagnosis and to obtain permission to contact them. Once permission was granted, cases were interviewed within one year of diagnosis; most were interviewed within six months (median 5.43 months). Controls were randomly selected from Department of Motor Vehicles records (<65yrs) or from Medicare rolls (≥65yrs) and frequency matched to cases on age and race. Seventy-two percent (n=1170) of eligible cases and 63% (n=2115) of eligible controls were interviewed. All participants provided informed consent; study

protocols were approved by the Institutional Review Boards of the University at Buffalo and of participating hospitals.

Data Collection

Information on demographics and breast cancer risk factors were collected. Included were questions regarding analgesic use: the average monthly frequency of use for aspirin, ibuprofen, and acetaminophen in the 12-24 months prior to interview, and the average number of pills taken per day that each medication was used during that time period (“intensity”). Additionally, participants were asked about their average monthly frequency of aspirin use for each decade of adult life. We did not collect data on adult lifetime use of ibuprofen, which was not made available over the counter until 1984 [41].

Statistical Analysis

We compared characteristics of cases and controls with *t*-tests and χ^2 tests for continuous and categorical variables, respectively. Unconditional logistic regression was used to estimate multivariable-adjusted odds ratios (OR) and 95% confidence intervals (95% CI). Exposure-response trends (*p*-trend) were calculated in multivariable logistic regression models from beta-coefficients of NSAID frequency or intensity using the continuous variables from which the data were categorized. We additionally calculated *p*-trend by removing non-users from the analysis. All reported *p*-values are two-tailed.

For the analysis of recent NSAID use, frequency of use for each respective NSAID was categorized into non-users (0 days/month), infrequent users (≤ 14 days/month), and regular users (> 14 days/month). NSAID intensity was categorized into non-users (0 pills/day), low (< 2 pills/day) and high (≥ 2 pills/day). For the analysis of aspirin use per decade of adult life, we were unable to use the same category cut-points as for recent frequency of use. Therefore, categories of frequency of aspirin use per decade of adult life were determined by the median aspirin use among controls. Cut-points for the analysis by decade of life were non-users, < 2 , ≥ 2 days per month. Cumulative adult lifetime aspirin usage was estimated as the sum of average annual aspirin frequency for each decade of life. From this data, participants were classified based upon their average monthly aspirin use throughout their adult lifetime; adult lifetime aspirin non-users (0 days/month), irregular users (≤ 10 days/month), and regular users (> 10 days/month).

Risk factors for breast cancer (age at menarche, age at first birth, parity, body mass index [measured, kg/m²], lifetime physical activity [sports or exercise; hrs/wk], menopausal status, postmenopausal hormone use, family history of breast cancer, and history of benign breast disease), as well as correlates of NSAID use (history of diabetes, hypertension, coronary heart disease, cerebrovascular disease, and arthritis) were considered as potential confounders in multivariable modeling. We forced the matching variables, age and race, into multivariable models. Final logistic regression models of recent NSAID use were further adjusted for years of education, age at menarche, age at menopause (categorized: premenopausal women, quartiles of age at menopause), number of full-term births, use of postmenopausal hormone therapy (yes/no), personal history of benign breast disease (yes/no), family history of breast cancer (yes/no), and simultaneously adjusted for use of the other two NSAIDs. For the analysis of aspirin use per decade of adult life, we adjusted for the same variables, but replaced adjustment of the other two NSAIDs (for which we did not have lifetime data) with adjustment of aspirin use during other decades of life. Missing values were recoded as zero for women that were not of an age to contribute to a given decade analysis for adjustment variables of aspirin use during other decades. Because adjustment for arthritis and cerebrovascular disease did not alter our findings, we chose not to retain them in our final models.

Because body mass index is associated with greater inflammation and estrogen production in postmenopausal women [42], we hypothesized the effect of NSAIDs may be stronger in postmenopausal, overweight women. We analyzed the association of recent NSAID use with breast cancer risk by menopausal status and BMI (<25 , ≥ 25). As alcohol consumption is hypothesized to be associated with greater inflammation [43], we additionally hypothesized a stronger association of NSAIDs with breast cancer among those who consumed greater amounts of alcohol over their lifetime; we examined associations of NSAID use within strata of alcohol consumption.

Results

Characteristics of WEB study participants are presented in Table 1. In addition to differences by established risk factors, cases were somewhat more likely than controls to have ever had arthritis. Cases and controls were similar with respect to other diseases that might affect their use of NSAIDs, including history of hypertension and cerebrovascular disease.

Multivariable-adjusted odds ratios and 95% confidence intervals for the association of recent NSAID use with risk are presented in Table 2. In this study population, there was a decrease in breast cancer risk among those reporting ever using aspirin in the year prior to interview (OR 0.80, 95% CI: 0.68-0.94). We did not observe an exposure-response gradient when the data were analyzed by categories of aspirin use: infrequent & regular users had similar reductions in risk (p -trend = 0.23). Intensity of aspirin use was also associated with risk. Those who used ≥ 2 pills/day on days that aspirin was taken were at reduced risk of breast cancer (OR 0.74, 95% CI: 0.61-0.90). Although the test for trend was statistically significant when we included non-users in the calculation of the test for trend, it did not persist when non-users were excluded (p -trend = 0.18). Recent use of ibuprofen (OR 1.15, 95% CI: 0.97-1.36) and acetaminophen (OR 0.97, 95% CI: 0.83-1.15) were not associated with breast cancer risk. Results were unchanged when the analyses were repeated using a referent group composed of women who were non-users of both aspirin and ibuprofen. When users of aspirin and ibuprofen (any NSAID) were compared to non-users of both agents, we observed no association with risk (OR 0.98, 95% CI: 0.83-1.17; data not shown).

When we compared recent aspirin and ibuprofen users to non-users, stratified by menopausal status, we observed no differences in the associations with breast cancer (Table 3). The p -interaction for aspirin and ibuprofen with menopausal status in relation to breast cancer risk was 0.64 and 0.78, respectively. We additionally observed no interaction of aspirin or ibuprofen use with menopausal status and BMI, or alcohol consumption (data not shown).

To test whether our findings of no association with ibuprofen use might be the result of reverse-causality bias, we analyzed the data cases whose breast cancer was identified by mammographic screening. No differences were found (data not shown).

The association of average monthly frequency of aspirin use by decade of adult life is presented in Table 4. For each of the decades of life, we observed a mostly uniform reduction in breast cancer risk associated with reported frequency of use of ≥ 2 days per month compared to non-users. We did not observe a reduction in risk for women who used aspirin < 2 days per month. Aspirin use during the seventh decade of life was associated with the greatest reduction in breast cancer risk (OR 0.73, 95% CI: 0.51-1.03). When categories of average monthly adult lifetime aspirin use were compared to adult lifetime non-users, women who used aspirin > 10 days/month across their adult lifetime were at a reduced risk of breast cancer, although this finding was of borderline statistical significance (OR 0.69,

95% CI: 0.49-1.00). The test for trend was statistically significant when we included and excluded lifetime aspirin non-users from the analysis (p -trend < 0.01).

We additionally examined lifetime aspirin use by recency of use (1-40 years) prior to diagnosis. Similar to our findings by decade of life, we observed modest reductions in risk regardless of the time period prior to diagnosis (data not shown).

Discussion

In this study of women living in Western New York, we found that recent and adult lifetime aspirin use were inversely associated with breast cancer risk. Recent use of ibuprofen and acetaminophen were not associated with risk.

NSAIDs are thought to exert anti-inflammatory effects by binding with the inducible isoform of the COX enzyme, COX-2. COX-2 catalyzes the synthesis of prostaglandins in response to cytokines, oncogenes, and growth factors [44]. In transgenic and knockout animal models, COX-2 and its prostaglandin products play important roles in carcinogenesis [45-48]. There is evidence that COX-2 affects mutagenesis, mitogenesis, anti-apoptosis, angiogenesis, immunosuppression, and metastasis [2,49]. The COX-2 product, PGE₂, is hypothesized also to promote tumorigenesis in the breast through induction of increased estrogen biosynthesis in breast epithelia and stromal cells [4].

Our findings on recent aspirin use are similar to several other case-control [7,12-17] and cohort studies [20-23], which generally showed small inverse associations with breast cancer risk and use of this agent. However, several prospective studies [19,26,28,30-33] did not show a reduction in breast cancer risk with aspirin use. In addition, there was no change in breast cancer incidence in a clinical trial of low dose (100mg) aspirin [35]. We observed inverse associations of aspirin use for both irregular and regular users of recent aspirin. Though we did not collect information on dose during the time periods studied, we were able to collect information, including dose, on medications taken in the past 30 days. A quarter of women who reported using aspirin during that time period used low-dose aspirin (80-100mg); the remaining women reported taking regular strength (325mg) aspirin. A handful of studies have investigated the association of NSAIDs with breast cancer by specific dose [12,14,19,20,29,33,35]; the majority of which have separated only aspirin into low and regular dose. Among them, low-dose aspirin was not associated with breast cancer risk. It may be that our findings with aspirin differ from the null result reported from the clinical trial due to differences in dosage. It is unclear why our finding is in agreement with some [20-23], but not other cohort studies [19,26,28,30-33]. Results of a recent meta-analysis showed modest reductions in breast cancer risk for aspirin (RR 0.87, 95% CI: 0.82-0.92) [34], consistent with our findings. Findings were stronger for case-control studies (RR 0.79, 95% CI: 0.72-0.86) than cohorts (RR 0.92, 95% CI: 0.86-0.97) [34].

Our finding of no reduction in risk among ibuprofen users is consistent with findings from several recent prospective cohort studies that analyzed non-aspirin NSAIDs [12,22,24,27,30,32,33], though few analyzed ibuprofen separately. Use of ibuprofen has also been reported to be associated with increased risk of breast cancer in some prospective studies [28,30,31,33], though the exact mechanism for this association is not clear. In contrast to our results, ibuprofen use was associated with reduced risk in the meta-analysis (RR 0.79, 95% CI: 0.64-0.97) [34]. As with aspirin, findings were stronger among case-control studies (RR 0.68, 95% CI: 0.48-0.98) as compared to cohorts (RR 0.86, 95% CI: 0.66-1.12) [34]. However, the findings of the meta-analysis with respect to ibuprofen-specific analyses were based upon few studies and the reported difference between study designs may have been influenced by two case-control studies, one of which was hospital-

based, which reported very protective point-estimates [7,17]. Among the case-control studies included in the meta-analysis, Terry et al [13], whose population-based study population was most similar to our own, reported no association with ibuprofen use.

Differences in findings between case-control and cohort studies may be further explained by selection or differential information biases, of which case-control studies, including this one, are susceptible. Additional differences may be explained by the limitation of prospective studies to analyze exposures in the few years prior to diagnosis. Only four cohorts updated their NSAID exposure data prospectively [18,26,30,32].

As expected, we observed no association between acetaminophen use and breast cancer risk. Acetaminophen is an analgesic that has very little anti-inflammatory properties; despite this, it is colloquially referred to as an NSAID. Like ours, other studies have not found it to be associated with risk [13,14,17,20,²¹,25,26,28,31].

We observed no association with risk when we analyzed aspirin and ibuprofen together (either NSAID vs. none). In contrast, most studies that combined analyses of aspirin with non-aspirin NSAIDs, either exclusively [5,6,8,11] or in tandem with agent-specific analyses [9,14,16,20-22,26], showed inverse associations with risk. One reason for this difference may be the inclusion of other NSAID classes (e.g., naproxen) in other studies that were not queried in this study.

Carcinogenesis is a multi-step process that can take decades to develop into an identifiable tumor. If NSAIDs reduce cancer risk because of their anti-inflammatory properties, it, too, is likely that the process is one that takes decades. Recent NSAID use may be a surrogate for use during other periods of life. Recent aspirin use was positively correlated with use during each decade of life ($r=0.21-0.75$). Our findings may be indicative of the association of use during earlier time periods with breast cancer. However, as inflammation is associated with promotion and progression of carcinogenesis [2,49], recent use may be of importance.

We know of little reason for the differences in our findings regarding aspirin and ibuprofen use. Aspirin has a longer plasma half-life (12hrs) than ibuprofen (2hrs) and it binds irreversibly to COX-2 [36]. It is not clear whether this would translate into greater anti-cancer effect, especially as others have observed inverse associations with non-aspirin NSAIDs [34].

In this study, aspirin users were older than ibuprofen users, and more likely to have a history of hypertension or cerebrovascular disease. Ibuprofen users were more likely to have a history of arthritis compared to aspirin users, but users of each drug were generally similar with regard to breast cancer risk factors (data not shown). With adjustment for these factors our findings were essentially unchanged. It is possible that additional differences in mechanism of action between aspirin and ibuprofen exist and have not yet been elucidated. As ibuprofen is a better-tolerated anti-inflammatory drug than aspirin, it is also possible that higher frequency of use may be an indicator of greater inflammation such that a protective effect of the drug was obscured by greater inflammation among the cases. As we assessed only recent use of ibuprofen, it is also possible that our analysis is susceptible to reverse-causality bias, in which recent use of ibuprofen is a consequence of symptoms associated with early disease; however, if this were the case, we would have expected to observe similar findings with aspirin and acetaminophen. Further arguing against this bias, we did not observe differences in the association when we restricted our analysis to cases identified from mammography.

We observed reductions in the risk of breast cancer across each decade of adult life. Our findings suggest a stronger reduction in risk for women who used aspirin during their 60's,

however, reported aspirin use for a given decade was highly correlated ($r=0.61-0.74$) with the reported use for an adjacent decade.

To our knowledge, there are no other studies examining adult lifetime aspirin use in relation to breast cancer risk. Results of studies in which long-term duration has been assessed have not been clear. Sharpe et al. [8] investigated the association of breast cancer risk with any NSAID use 1-6m, 7-12m, 2-5yrs, 6-10yrs, and 11-15yrs prior to cancer development in a prescription linkage study in Saskatchewan, Canada. They found no clear benefit of NSAID use in all but the time period 2-5yrs prior to diagnosis, however, the authors were unable to account for over-the-counter NSAID use [8]. We observed modest decreased risks of breast cancer regardless of the decade of life in which aspirin was taken. When we examined recency of use, we observed modest reductions in risk regardless of the time period (1-40yrs) prior to diagnosis. We were not able to look at periods as recent as 1-6 months, as was done in the Saskatchewan study. Zhang et al. [16] assessed long-term duration of regular aspirin use with breast cancer risk in a hospital-based case-control study of women in four US cities. They similarly observed no clear association between increasing duration of use with risk, however prevalence of regular aspirin use was very low beyond 5-10 years [16]. In contrast, we found that average adult lifetime use was associated with modest reductions in breast cancer risk.

There are a number of pertinent limitations that need to be considered in evaluation of our findings. Because we were able to recruit 72% and 63% of eligible cases and controls, respectively, it is possible that there was bias based on self-selection of participating subjects, and that there may have been differences in participation associated with NSAID use. Given the relatively small reduction in risk that was observed for recent and lifetime aspirin use, we cannot rule out selection bias as an explanation of our finding.

In this study, recent NSAID and adult lifetime aspirin use were self-reported and are likely subject to error. It is unclear whether recall bias might explain our findings. As aspirin is considered by some to be a more serious medication than other NSAIDs, it is possible that cases could have more accurately recalled their exposure to aspirin as compared to controls. If this were to have happened, the modest reduction in risk observed with aspirin use may be explained. This hypothesis is supported as some cohort studies, which are not prone to such bias, have not observed a reduction in risk with aspirin use. On the other hand, our finding is consistent with the hypothesized biologic mechanism and the findings of several studies, including some cohort studies, and a recent meta-analysis, which found reductions in breast cancer risk for both case-control and prospective studies [34].

As there is some variation in currently available doses of aspirin and ibuprofen, it is possible that this misclassification, likely non-differential, may partly explain the lack of an exposure-response gradient in our study. Low-dose aspirin has not been associated with breast cancer risk [12,14,19,20,29,33,35], therefore, the lack of exposure-response gradient with increasing frequency of use may be explained, in part, if a substantial proportion of frequent aspirin users in this study were taking low-dose aspirin. In addition, we did not have data on the indication for NSAID use in this study. Adjustment for a history of arthritis, cerebrovascular disease, or restriction of the data to a sub-sample of women who reported no history of such conditions, however, did not affect point estimates.

A major strength of this study is its large sample size. Another strength is that we had data regarding the frequency and intensity of use of individual NSAIDs, and the frequency of aspirin use throughout a woman's adult lifetime. We did not, however, ascertain information on the dose or duration of use for each NSAID taken, adding to possible misclassification.

In conclusion, we observed a significant reduction in breast cancer risk with recent and adult lifetime aspirin use. Our findings suggest the strongest reduction in risk occurred during the decade 61-70yrs; however, use over a woman's lifetime was inversely associated with risk. We observed no reduction in risk with use of ibuprofen. These findings further support existing evidence that aspirin reduces the risk of breast cancer. Further research may be warranted to elucidate possible differences in mechanisms of effect between aspirin and other NSAIDs.

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Table 1

Characteristics of WEB study participants, by disease status.

Characteristic	Cases n = 1170	Controls n = 2115	p-value
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	
Age (y)	57.97 (11.13)	57.84 (11.82)	0.77
Education (y)	13.50 (2.58)	13.32 (2.38)	0.06
Age at Menarche (y)	12.57 (1.59)	12.70 (1.65)	0.03
Age at Menopause (y) ^a	48.28 (5.41)	47.41 (6.30)	<0.001
Age at 1 st Pregnancy (y) ^b	23.81 (4.84)	23.74 (4.46)	0.71
Number of Births ^b	2.84 (1.44)	3.09 (1.59)	<0.0001
Body Mass Index (kg/m ²)	28.46 (6.35)	28.27 (6.39)	0.43
	<i>n (%)</i>	<i>n (%)</i>	
Race			0.10
Nonwhite	93 (7.95)	205 (9.69)	
White	1077 (92.05)	1910 (90.31)	
Menopausal Status			0.51
Pre-menopausal	326 (27.86)	612 (28.94)	
Post-menopausal	844 (72.14)	1503 (71.06)	
HRT Use			0.08
Never	707 (61.11)	1299 (64.21)	
Ever	450 (38.89)	724 (35.79)	
History of BBD			<0.0001
No	744 (65.09)	1636 (78.17)	
Yes	399 (34.91)	457 (21.83)	
Family History of Breast Cancer			<0.0001
No	856 (79.41)	1712 (87.17)	
Yes	222 (20.59)	252 (12.83)	
Ever Hypertension			0.28
No	752 (64.66)	1399 (66.52)	
Yes	411 (35.34)	704 (33.48)	
Ever CVD			0.06
No	865 (76.01)	1628 (78.88)	
Yes	273 (23.99)	436 (21.12)	
Ever Arthritis			0.04
No	997 (93.35)	1813 (95.17)	
Yes	71 (6.65)	92 (4.83)	

^a Among postmenopausal women^b Among gravid women

Table 2

Association of recent NSAID use with breast cancer among WEB study participants

NSAID Use	Cases n = 1170	Controls n = 2115	OR (95% CI) ^{a,b}
	<i>n (%)</i>	<i>n (%)</i>	
Aspirin			
Non-Users	678 (58.60)	1137 (54.30)	1.00 referent
Users	479 (41.40)	957 (45.70)	0.80 (0.68-0.94)
<i>Frequency</i>			
Non-Users	678 (58.60)	1137 (54.30)	1.00 referent
Infrequent Users (≤14 days/month)	325 (28.09)	665 (31.76)	0.80 (0.67-0.95)
Regular Users (>14 days/month)	154 (13.31)	292 (13.94)	0.80 (0.62-1.03)
		<i>p</i> -trend	0.23
<i>Intensity^c</i>			
Non-Users	678 (58.30)	1137 (54.25)	1.00 referent
Low (<2 pills/day)	238 (20.46)	247 (21.24)	0.94 (0.75-1.16)
High (≥2 pills/day)	247 (21.24)	545 (26.00)	0.74 (0.61-0.90)
		<i>p</i> -trend	<0.01
Ibuprofen			
Non-Users	501 (43.45)	953 (45.62)	1.00 referent
Users	652 (56.55)	1136 (54.38)	1.15 (0.97-1.36)
<i>Frequency</i>			
Non-Users	501 (43.45)	953 (45.62)	1.00 referent
Infrequent Users (≤14 days/month)	565 (49.00)	963 (46.10)	1.18 (0.99-1.41)
Regular Users (>14 days/month)	87 (7.55)	173 (8.28)	1.00 (0.73-1.36)
		<i>p</i> -trend	0.82
<i>Intensity^c</i>			
Non-Users	501 (43.41)	953 (45.45)	1.00 referent
Low (<2 pills/day)	171 (14.82)	284 (13.54)	1.20 (0.93-1.53)
High (≥2 pills/day)	482 (41.77)	860 (41.01)	1.12 (0.94-1.34)
		<i>p</i> -trend	0.74
Acetaminophen			
Non-Users	449 (38.98)	833 (39.86)	1.00 referent
Users	703 (61.02)	1257 (60.14)	0.97 (0.83-1.15)
<i>Frequency</i>			
Non-Users	449 (38.98)	833 (39.86)	1.00 referent
Infrequent Users (≤14 days/month)	649 (56.34)	1162 (55.60)	0.96 (0.81-1.14)
Regular Users (>14 days/month)	54 (4.69)	95 (4.55)	0.98 (0.66-1.46)
		<i>p</i> -trend	0.99
<i>Intensity^c</i>			
Non-Users	449 (38.81)	833 (39.76)	1.00 referent
Low (<2 pills/day)	145 (12.53)	275 (13.13)	0.86 (0.66-1.13)

NSAID Use	Cases n = 1170	Controls n = 2115	OR (95% CI) ^{a,b}
High (≥2 pills/day)	563 (48.66)	987 (47.11)	1.01 (0.85-1.20)
		<i>p</i> -trend	<i>0.64</i>

^a Odds Ratios & 95% Confidence Intervals

^b Adjusted for age, race, education, age at menarche, age at menopause, parity, use of hormone therapy, benign breast disease, family history of breast cancer, and other NSAID use

^c Average number of pills taken on days the medication was used

Table 3

Association of recent aspirin and ibuprofen use with breast cancer, stratified by menopausal status among WEB study participants

NSAID Use	Cases n = 1170	Controls n = 2115	OR (95% CI) ^{a,b}
Aspirin	<i>n (%)</i>	<i>n (%)</i>	
<i>Premenopausal</i>			
Non-Users	222 (68.73)	393 (64.53)	1.00 referent
Users	101 (31.27)	216 (35.47)	0.71 (0.52-0.98)
<i>Postmenopausal</i>			
Non-Users	456 (54.68)	744 (50.10)	1.00 referent
Users	378 (45.32)	741 (49.90)	0.83 (0.69-1.01)
<i>p</i> -interaction			0.64
Ibuprofen			
<i>Premenopausal</i>			
Non-Users	90 (28.04)	177 (29.16)	1.00 referent
Users	231 (71.96)	430 (70.84)	1.17 (0.83-1.64)
<i>Postmenopausal</i>			
Non-Users	411 (49.40)	776 (52.36)	1.00 referent
Users	421 (50.60)	706 (47.64)	1.14 (0.94-1.39)
<i>p</i> -interaction			0.78

^a Odds Ratios & 95% Confidence Intervals

^b Adjusted for age, race, education, age at menarche, age at menopause, parity, use of hormone therapy, benign breast disease, family history of breast cancer, and other NSAID use

Table 4

Association of lifetime average monthly aspirin use by decade of life with breast cancer among WEB study participants

Lifetime Aspirin Use	Cases n = 1170	Controls n = 2115	OR (95% CI)^{a,b}
<i>Average Monthly Frequency During Decades of Life</i>	<i>n (%)</i>	<i>n (%)</i>	
21-30 years			
Non-Users	305 (26.71)	551 (26.50)	1.00 referent
<2	726 (63.57)	1274 (61.28)	0.96 (0.80-1.16)
≥2	111 (9.72)	254 (12.22)	0.85 (0.62-1.16)
<i>p</i> -trend			0.06
31-40 years			
Non-Users	369 (31.98)	627 (30.19)	1.00 referent
<2	653 (56.59)	1151 (55.42)	0.91 (0.76-1.08)
≥2	132 (11.44)	299 (14.40)	0.79 (0.58-1.07)
<i>p</i> -trend			0.94
41-50 years			
Non-Users	406 (37.08)	665 (34.76)	1.00 referent
<2	542 (49.50)	954 (49.87)	0.94 (0.78-1.12)
≥2	147 (13.42)	294 (15.37)	0.88 (0.65-1.19)
<i>p</i> -trend			0.27
51-60 years			
Non-Users	303 (37.50)	454 (32.85)	1.00 referent
<2	384 (47.52)	668 (48.34)	0.86 (0.69-1.06)
≥2	121 (14.98)	260 (18.81)	0.79 (0.57-1.09)
<i>p</i> -trend			0.98
61-70 years			
Non-Users	181 (37.71)	301 (34.09)	1.00 referent
<2	192 (40.00)	337 (38.17)	0.91 (0.69-1.21)
≥2	107 (22.29)	245 (27.75)	0.73 (0.51-1.03)
<i>p</i> -trend			0.70
71-80 years			
Non-Users	73 (38.02)	134 (41.36)	1.00 referent
<2	52 (27.08)	76 (23.46)	1.19 (0.72-1.98)
≥2	67 (34.90)	114 (35.19)	1.10 (0.67-1.81)
<i>p</i> -trend			0.13
<i>Average Monthly Lifetime Aspirin</i>			
Non-Users	212 (18.83)	369 (17.90)	1.00 referent
≤10 days/month	855 (75.93)	1554 (75.40)	0.95 (0.77-1.18)
>10 days/month	59 (5.24)	138 (6.70)	0.68 (0.46-1.00)
<i>p</i> -trend			<0.01

^aOdds Ratios & 95% Confidence Intervals

^b Adjusted for age, race, education, age at menarche, age at menopause, parity, use of hormone therapy, benign breast disease, family history of breast cancer, and aspirin use during other decades