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Nonsteroidal Anti-Inflammatory Drug Use and Breast Cancer Risk by Stage and Hormone Receptor Status

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Background: **Epidemiologic studies of the association between nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, and breast cancer risk have yielded inconsistent results. We investigated the association of NSAID use with risk of breast cancer in the California Teachers Study cohort, with special attention to risk of specific breast cancer subtypes and to type of NSAID used.** ***Methods:*** **We analyzed data on 114 460 women in the California Teachers Study cohort who were aged 22 to 85 years and free of breast cancer at baseline in 1995 to 1996. Information on frequency and duration of NSAID use was collected through a self-administered questionnaire. A total of 2391 women were diagnosed with breast cancer during the follow-up period from 1995 to 2001. We used Cox proportional hazards regression to estimate relative risks (RR) and 95% confidence intervals (CI) of breast cancer subtypes with NSAID use.** ***Results:*** **Neither regular use (more than once a week) of any NSAID (aspirin and ibuprofen combined) nor regular use of aspirin was associated with breast cancer risk (RR = 1.09, 95% CI = 0.97 to 1.21 for daily versus no regular use of NSAIDs and RR = 0.98, 95% CI = 0.86 to 1.13 for daily versus no regular use of aspirin). However, long-term (≥5 years) daily aspirin users had a non–statistically significant decreased risk of estrogen receptor and progesterone receptor (ER/PR)–positive breast cancer (RR = 0.80, 95% CI = 0.62 to 1.03). In contrast, we observed a statistically significantly increased risk of ER/PR-negative breast cancer with long-term daily use of aspirin (RR = 1.81, 95% CI = 1.12 to 2.92). In this population, 11 fewer ER/PR-positive breast cancer cases and seven excess ER/PR-negative breast cancer cases may be due to daily long-term aspirin use among 2391 breast cancer cases observed over 6 years if the association were proven to be causal. Long-term daily use of ibuprofen was also associated with an increased risk of breast cancer (RR = 1.51, 95% CI = 1.17 to 1.95), particularly of nonlocalized tumors (RR = 1.92, 95% CI = 1.24 to 2.97). If causality were subsequently proven, 16 of the observed 2391 breast cancer cases and 8 of the 713 non-localized breast cancer cases would be attributable to long-term daily use of ibuprofen.** ***Conclusions:*** **Long-term daily use of NSAIDs was not associated with breast cancer risk overall. Ibuprofen use was associated with an increased risk of breast cancer, and long-term daily aspirin use was associated with an increased risk of ER/PR-negative breast cancer. However, it is not clear if the observed association is causal. [J Natl Cancer Inst 2005;97:805–12]**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used for common ailments such as headaches, muscular pain, inflammation, and fever and are prescribed to alleviate chronic conditions such as arthritis. NSAIDs may also be used prophylactically to reduce the risk of heart attack, stroke, or blood clot formation *(1)*. In addition, the role of NSAIDs as potential chemopreventive agents in cancer has been explored. Although a consistent inverse association between NSAID use and colorectal cancer has been observed *(1,2)*, whether NSAIDs are associated with reduced breast cancer risk is unclear. Clarifying this association is important, because a chemopreventive strategy as inexpensive and readily available as NSAIDs would be highly desirable.

Aspirin and other NSAIDs inhibit the expression of the cyclooxygenase 2 (COX-2) gene, which encodes one of two cyclooxygenase enzymes that catalyzes the synthesis of prostaglandins from the dietary fatty acid arachidonic acid. COX-2 gene expression is induced in wounded or inflamed tissue, and increased COX-2 levels are associated with increased angiogenesis, increased estrogen synthesis, and reduced apoptosis, all of which may stimulate cancer growth. Indeed, COX-2 expression is highly elevated in more aggressive, metastatic, and larger breast tumors that are estrogen receptor (ER) or progesterone receptor (PR) negative *(3,4)*.

Data from cohort studies of aspirin use and breast cancer risk have been inconsistent. Four studies, including the largest *(5)*, did not find an association between aspirin use and breast cancer *(5–8)*; however, four others found that recent *(9,10)* or regular *(11,12)* aspirin use was inversely associated with breast cancer risk. Some case-control studies have found less regular use of aspirin by women with breast cancer compared with cancer-free subjects *(13–17)*, but others have not observed this association *(18,19)*. Similarly, studies assessing use of nonaspirin NSAIDs and breast cancer risk have been equivocal. Four studies reported an inverse association with breast cancer risk *(10,11,13,15)*, but four studies reported no association with breast cancer risk *(6,8,12,17)*.

In an attempt to resolve these inconsistent findings, a few studies have explored whether the inverse association of NSAID

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use is restricted to certain breast cancer subtypes. One study investigated whether ER or PR status may modify this association *(17)*. The authors concluded that use of aspirin is inversely associated with risk of breast cancer that is either ER- or PR-positive but is not associated with risk of breast cancer that is both ER- and PR-negative *(17)*. Three studies have also assessed the association between NSAID use and stage of breast cancer; two studies found no differential association by stage *(6,12)* and one found that NSAID exposure 2 to 10 years preceding diagnosis was inversely associated with risk of distant, but not regional, lymph node–positive disease *(15)*.

Given the widespread use of over-the-counter pain relievers, such as acetaminophen, understanding the relationship between these drugs and breast cancer risk is of particular public health importance. The primary purpose of this study was to examine the association between use of NSAIDs and breast cancer risk in a large prospective study of California educators with a high incidence of breast cancer *(20)*. Our secondary aims were to investigate whether the association between use of NSAIDs and breast cancer risk was modified by ER/PR status or by whether the disease was localized at diagnosis and to determine whether associations with breast cancer risk differed by type of pain relief medication.

Subjects and Methods

Study Population

The California Teachers Study is a prospective cohort of 133 479 teachers and school administrators established from the rolls of the California State Teachers Retirement System. It was created specifically to investigate risk factors for breast cancer, as described elsewhere *(20)*.

Calculation of Follow-up

The cohort was followed from the date of completion of the baseline questionnaire, which was distributed by mail in 1995 and returned by participants in 1995 to 1996, until the earliest of the following events: the date of first in situ or invasive breast cancer diagnosis, date of death, date of move outside of California, or December 31, 2001. Continued California residence was self-reported on three questionnaires (mailed in 1995, 1997, and 2000) and was supplemented by information obtained from the U.S. Postal Service National Change of Address database and the California Department of Motor Vehicles. Censoring at the time of a move out of California was imposed because the California Cancer Registry records only cancers diagnosed among state residents. Deaths were identified by family report and annual probabilistic record linkage to the California state mortality file and the nationwide Social Security Administration death master file.

Outcome Assessment

An annual probabilistic record linkage to the statewide population-based California Cancer Registry by name, date of birth, Social Security number, sex, and address was used to identify cohort members residing in California with newly diagnosed cancer. Cancer reporting to the California Cancer Registry through its 10 regional registries is mandated by state law and is 99% complete for all cancers *(21)*. Dates of birth were recorded for all California Teachers Study members and were verified by comparisons with California Department of Motor Vehicles and California State Teachers Retirement System records.

We defined a case subject as any woman living in California at the start of follow-up, who was diagnosed with invasive breast cancer after the date she completed her baseline questionnaire (n = 2391). We excluded women who were living out of state at baseline or who were diagnosed with invasive or in situ breast cancer before joining the cohort. Women who were diagnosed with in situ breast cancer during follow-up were censored at the time of diagnosis.

We categorized breast cancer cases into two groups, localized and nonlocalized, using the Surveillance, Epidemiology and End Results (SEER) summary stages *(22)*. Localized cancers included those that were SEER summary stage 1 and confined to the breast at the time of diagnosis; nonlocalized cancers were defined as breast cancer with SEER summary stages 2 through 7 and had spread to regional or distant lymph nodes or had metastasized. In separate analyses, we also categorized breast cancer cases according to their ER and PR status. Hormone receptor status was determined using immunohistochemistry; the exact methodology varied according to the individual laboratory or hospital submitting the cancer report. Two categories were used: ER/PR-positive includes tumors that were ER or PR receptor–positive at diagnosis, and ER/PR-negative includes tumors that were negative for both receptors. These categories were chosen to match and therefore be comparable with the only existing analysis of NSAIDs by breast cancer hormone receptor type *(17)*. We obtained information on hormone receptor and localized/nonlocalized tumor status at diagnosis from the California Cancer Registry files. Information on whether the tumor was localized or nonlocalized was missing for 22 (0.9%) patients, and information on hormone receptor status was missing for 385 (16.1%). These patients were excluded from the relevant analyses.

Exposure Assessment

The baseline questionnaire included the question, "Have you taken any of the following medications regularly (at least once a week)? Aspirin (Anacin, Bufferin, Excedrin), Acetaminophen (Tylenol, Anacin-3, Panadol, Aspirin Free Excedrin, etc.), Ibuprofen (Advil, Motrin, Nuprin)." If the answer was yes, participants were asked to indicate for how many total years (<1, 1, 2, 3–4, 5–9, or ≥10), and how many days per week (1–3, 4–6, or 7), on average, they took each type of medication. "Any NSAID" combines use of aspirin and ibuprofen. Acetaminophen is not an NSAID and does not inhibit COX-2 gene expression, but it was included in these analyses for comparison and to check that any observed associations were specific to NSAIDs and not attributable to any pain medication.

We created a priori categories for frequency of use (no regular use, 1–6 times per week, and daily), and for duration of use (no regular use, <5 years, and ≥5 years). We combined duration and frequency of use for some of the analyses described in the statistical analysis section (not regular user, <5 years and 1–6 days per week of use, ≥5 years and 1–6 days per week of use, <5 years and daily use, and ≥5 years and daily use).

Risk Factors

With the exception of socioeconomic status (described below), all risk factors included in the analyses as potential confounders are based on self-reported data from the baseline questionnaire.

Personal Risk Factors. Race was divided into five categories: white; African-American; Hispanic; Asian/Pacific Islander; and other/mixed/not specified. Family history of breast cancer was defined as breast cancer in one first-degree relative and was categorized as yes, no, and unknown. Body mass index (BMI) was calculated from self-reported height and weight and was categorized into underweight or normal weight (<27 kg/m^2), overweight or obese (≥27 kg/m^2), and unknown.

Lifestyle Factors. Smoking history was divided into four categories: never smoker, former smoker, current smoker, and unknown. Average alcohol consumption was measured in grams per day and daily intake was divided into less than 20 g (including nondrinkers), 20 g or more, and unknown. Alcohol intake categories were chosen based on previous findings from this cohort *(23)*. Physical activity, defined as the average lifetime (high school through current age or age 54 years, if 55 years or older) strenuous activity per week, was grouped into: less than 4 hours; 4 hours or more; and unknown. Neighborhood socioeconomic status was obtained by linking the residential street addresses of cohort members at baseline to U.S. Census neighborhood (block group) data *(24)*. A summary index of socioeconomic status for each participant was calculated as previously described *(25,26)*. The categories used were low, medium, high, and unknown socioeconomic status.

Reproductive Factors. Pregnancy history incorporated responses to questions on the number of births and the age at first full-term pregnancy and was summarized as parous before age 30 years, nulliparous before age 30 years, and unknown. Menopausal status and use of hormone therapy (estrogen or estrogen with progesterone) were combined into one variable, which was categorized in five groups: premenopausal; perimenopausal; postmenopausal and never hormone therapy user; postmenopausal and hormone therapy user; and unknown. Menopausal status was defined by combining information collected on age, age at last menstrual period, reason for cessation of menstrual periods, and oophorectomy status. Perimenopausal women were defined as women who had stopped menstruating within 6 months of completing the baseline questionnaire. Women who reported that their menstrual periods had stopped more than 6 months before completing the baseline questionnaire or who had had a bilateral oophorectomy were defined as postmenopausal. In addition, all women 55 years of age or older who were not already classified as perimenopausal were considered to be postmenopausal.

Screening. To adjust for recent breast cancer screening, we included a measure of breast biopsy history (ever or never/unknown) and mammography during the 2 years before cohort entry (yes or no/unknown).

Statistical Analysis

We obtained information for women who were living in California at baseline and who had no prior breast cancer (n = 118 339). The results shown include the 114 640 women remaining after excluding those who were 85 years or older at baseline (n = 1910) and those whose history of pain medication use was unknown (n = 1789).

Multivariable Cox proportional hazards regression methods were used to assess the association of NSAID use with the risk of invasive breast cancer, using ages at start and end of follow-up (in months) to define time on study. Models were adjusted for the risk factors described above and were stratified by age at baseline (in single years of age). Hazard rate ratios, presented as relative risks (RR) with 95% confidence intervals (CI), were estimated and tested for linear trend across exposure categories. Several approaches were used to check the proportional hazards assumption for each medication variable. We visually examined Kaplan–Meier survivor curves and plotted scaled Schoenfeld residuals, for which parallel lines indicated proportionality of hazards *(27)*. We also assessed the correlation of the scaled Schoenfeld residuals with time on study. P values ranged from .16 to .92, consistent with hazards that are proportional.

Analyses were performed for all women and then repeated, stratified by age group (younger than 50 years or 50 years or older) and by menopausal status (premenopausal, perimenopausal, or postmenopausal). We examined risks of localized versus nonlocalized and of ER/PR-negative versus ER/PR-positive breast cancer with use of NSAIDs and acetaminophen compounds.

We used a likelihood ratio test to evaluate homogeneity of the relative risk estimates when we compared women who used only ibuprofen with women who used aspirin infrequently (with ibuprofen) and with women who used aspirin daily (with ibuprofen) (2 df). We also used a likelihood ratio test to evaluate effect modification by age and menopausal status. We did not adjust the P values for multiple comparisons. All analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC).

Results

Of the 114 640 women included in the analyses, 40 122 (35.0%) reported regular use of an NSAID (Table 1). Among regular users of NSAIDs, 10 835 participants (27.0%) used both an NSAID and acetaminophen and 8836 women (22.0%) used both aspirin and ibuprofen. In addition to the women using both aspirin and ibuprofen regularly, 16 895 women used only aspirin and 14 391 used only ibuprofen, totaling 25 731 (22.5%) regular aspirin users and 23 227 (20.3%) regular ibuprofen users in the analyses. In our study, 8341 (7.3%) women took aspirin daily and 15 590 (13.6%) had taken it for at least 5 years. A similar proportion of women took ibuprofen daily; however, fewer participants took ibuprofen for 5 or more years (n = 7852 or 6.9%) than took aspirin for that time, a difference that is consistent with the more limited period of ibuprofen availability in the United States [licensed for over-the-counter use in 1984 *(28)*]. Most users of both NSAIDs either took aspirin and ibuprofen at equal frequencies (48.5%) or took aspirin more frequently (40.8%).

Daily NSAID use was more common in older women than in younger women. At baseline, the mean age of long-term daily users of NSAIDs was 60.7 years, whereas that of women who did not report using NSAIDs regularly was 51.2 years (Table 2). We examined the distribution of risk factors according to NSAID exposure after age-standardizing the proportions exposed in 10-year age groups to the age distribution of the entire cohort

Table 1. Prevalence of regular NSAID and acetaminophen use in the California Teachers Study, 1995 to 1996*

Frequency and duration of medication use	Aspirin	Ibuprofen	Any NSAID	Acetaminophen
Regular use	25 731 (22.5%)	23 227 (20.3%)	40 122 (35.0%)	15 323 (13.4%)
Frequency of use among regular users				
1–6 days/wk	17 390 (15.2%)	17 235 (15.0%)	25 532 (22.3%)	13 477 (11.8%)
Daily	8341 (7.3%)	5992 (5.2%)	14 590 (12.7%)	1846 (1.6%)
Duration of use among regular users				
<5 y	10 141 (8.9%)	15 375 (13.4%)	19 338 (16.9%)	5860 (5.1%)
≥5 y	15 590 (13.6%)	7852 (6.9%)	20 784 (18.1%)	9463 (8.3%)
No regular use	88 909 (77.6%)	91 413 (79.7%)	74 518 (65.0%)	99 317 (86.6%)

*Regular use is defined as at least once a week. NSAID = nonsteroidal anti-inflammatory drugs.

(Table 2). After accounting for age, regular NSAID users were more likely to be white, to be overweight or obese, to be current or former smokers, to have had a mammogram in the last 2 years, and to have used postmenopausal hormone therapy than nonregular NSAID users. For example, 41.6% of long-term daily NSAID users were postmenopausal and were taking hormone therapy, compared with 35.8% of those who did not use NSAIDs regularly. Overall, aspirin and ibuprofen users shared similar characteristics. However, aspirin users were, on average, 5 years older (in each category of use) than ibuprofen users, and ibuprofen users had higher BMI than aspirin users.

During follow-up, 2391 participants were diagnosed with invasive breast cancer. Regular use of aspirin, ibuprofen, any NSAID (aspirin and ibuprofen use combined), or acetaminophen was not associated with reduced risk of breast cancer (Table 3). In a multivariable analysis, the relative risk was 0.98 (95% CI = 0.86 to 1.13) for invasive breast cancer among daily users of aspirin and 1.07 (95% CI = 0.96 to 1.20) among women who had used aspirin for 5 or more years, both compared with women who did not take aspirin regularly. There was no apparent trend in the relative risks for invasive breast cancer by either duration (P_{trend} = .21) or frequency (P_{trend} = .59) of aspirin use.

In contrast with the lack of association with breast cancer risk observed with aspirin use, both daily and long-term uses of ibuprofen were associated with increased risk of breast cancer (Table 3). The greatest risk increase was seen in daily long-term users; compared with nonusers, women who took ibuprofen daily for 5 years or longer had a relative risk for breast cancer of 1.51 (95% CI = 1.17 to 1.95). If there was a causal relationship between long-term daily use of ibuprofen and breast cancer, we estimate that 16 (95% CI = 5 to 29) of the observed 2391 breast cancer cases in this population over 6 years of follow-up may be attributable to this exposure. This positive association with daily long-term ibuprofen use was stronger among those diagnosed 4 or more years since baseline (RR = 1.79, 95% CI =1.28 to 2.48) than among those diagnosed during the first 3 years of follow-up (RR = 1.22, 95% CI = 0.81 to 1.83). When we stratified the association between ibuprofen use and breast cancer risk by frequency of aspirin use, the relative risks did not differ statistically by stratum (likelihood ratio test P>.60).

We also assessed whether the associations between breast cancer and use of aspirin, of any NSAID, or of acetaminophen might be modified by localization of disease. We did not observe any consistent patterns in risk with aspirin, any NSAID, or acetaminophen use by localization of disease (Table 4). In contrast, we observed that the increase in breast cancer risk associated with daily long-term use of ibuprofen was stronger for nonlocalized disease (RR = 1.92, 95% CI = 1.24 to 2.97) than for localized breast cancer (RR = 1.33, 95% CI = 0.97 to 1.84). In this cohort, eight (95% CI = 2 to 18) of the 713 non-localized incident breast cancers observed over 6 years of follow-up may be attributable to daily long-term use of ibuprofen.

Lastly, we evaluated the risk of breast cancer associated with aspirin, ibuprofen, any NSAID, and acetaminophen stratified

Table 2. Selected characteristics of study participants by reported regular NSAID and acetaminophen use, age-standardized by 10-year age categories to the age distribution of the cohort*

	Regular use of any NSAID					Regular use of acetaminophen				
Variable	No regular use	<5 y, 1–6 days/wk	≥5 y, 1–6 days/wk	<5 y daily	≥5 y daily	No regular use	<5 y, 1–6 days/wk	≥5 y, 1–6 days/wk	<5 y daily	≥5 y daily
Mean age, y	51.2	50.4	51.2	59.2	60.7	52.5	49.5	49.0	60.0	60.6
% white	85.2	86.2†	89.8†	88.6†	90.8†	86.3	84.5†	87.6	88.3†	87.0
% overweight or obese	16.8	21.3†	20.9†	26.1†	29.1†	18.1	23.8†	24.2†	30.2†	29.6†
% family history of breast cancer	12.0	12.8	12.4	11.7	12.6	12.1	12.2	12.6	13.2†	14.2
% postmenopausal and hormone therapy use	35.8	37.7†	39.5†	39.4†	41.6†	36.6	38.8†	39.6	40.6†	45.3†
% current/former smokers	30.6	33.7†	35.6†	34.3†	37.1†	31.7	34.3†	35.3†	36.4†	35.5†
% high alcohol intake	7.1	8.4†	9.9†	8.5†	10.4†	7.8	7.6	8.3	7.1	6.5
% high physical activity	16.5	16.8	17.3	15.6	17.4	16.7	14.9†	16.5	16.7	20.1†
% ever breast biopsy	15.0	16.2†	16.1	16.8†	17.4†	15.2	17.1†	14.8	18.2†	16.8
% mammogram in last 2 y	73.6	75.1†	76.8†	75.3†	77.0†	74.1	75.6	76.2	75.9†	77.6†
% parous before age 30 y	56.0	57.3	56.1	55.1	55.8	55.9	57.7†	59.3	52.8†	57.3
% high neighborhood socioeconomic status	45.1	43.9	44.7	43.2†	41.3†	45.1	42.0†	42.0	43.3†	36.1†

*Regular use is defined as at least once a week. NSAID = nonsteroidal anti-inflammatory drugs.

†Proportion for women with this level of drug use is statistically different from women with no regular use.

Table 3. Multivariable-adjusted relative risks (95% confidence intervals) for invasive breast cancer according to self-reported frequency and duration of regular NSAID and acetaminophen use in the California Teachers Study, 1995 to 1996*

Frequency and duration of medication use	RR (95% CI)			
	Aspirin	Ibuprofen	Any NSAID	Acetaminophen
Frequency				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use†				
1–6 days/wk	1.09 (0.98 to 1.22)	1.00 (0.89 to 1.13)	1.06 (0.96 to 1.17)	1.08 (0.95 to 1.23)
Daily	0.98 (0.86 to 1.13)	1.24 (1.07 to 1.44)	1.09 (0.97 to 1.21)	0.99 (0.74 to 1.31)
P_{trend}	.59	.022	.10	.44
Duration				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use				
<5 y	1.02 (0.90 to 1.17)	1.04 (0.92 to 1.17)	1.02 (0.92 to 1.14)	1.01 (0.83 to 1.21)
≥5 y	1.07 (0.96 to 1.20)	1.17 (1.00 to 1.36)	1.11 (1.01 to 1.23)	1.10 (0.95 to 1.27)
P_{trend}	.21	.058	.044	.23
Duration and frequency				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use				
<5 y, 1–6 days/wk	1.05 (0.87 to 1.25)	0.98 (0.85 to 1.14)	0.98 (0.85 to 1.13)	1.00 (0.81 to 1.24)
≥5 y, 1–6 days/wk	1.12 (0.99 to 1.26)	1.04 (0.86 to 1.26)	1.12 (0.99 to 1.26)	1.12 (0.96 to 1.31)
<5 y daily	1.00 (0.84 to 1.20)	1.14 (0.95 to 1.37)	1.06 (0.92 to 1.23)	1.01 (0.68 to 1.48)
≥5 y daily	0.96 (0.79 to 1.18)	1.51 (1.17 to 1.95)	1.11 (0.96 to 1.30)	0.96 (0.63 to 1.47)
P_{trend}	.56	.007	.057	.37

*Adjusted for race, body mass index, first-degree family history of breast cancer, menopausal and hormone therapy use status, smoking, alcohol intake, physical activity, mammography history, breast biopsy history, parity status before age 30, and neighborhood socioeconomic status. NSAID = nonsteroidal anti-inflammatory drug; RR = relative risk; CI = confidence interval.

†Regular use is defined as at least once a week.

by ER/PR status. Daily long-term use of aspirin was associated with an 81% increased risk (95% CI = 1.12 to 2.92) of ER/PR-negative breast cancer. By contrast, no association was observed for ER/PR-positive breast cancer (RR = 0.80, 95% CI = 0.62 to 1.03) (Table 5). In this population, seven excess ER/PR-negative breast cancer cases and 11 fewer ER/PR-positive breast cancer cases may possibly be due to daily long-term aspirin use among the 2391 breast cancer cases observed over 6 years. Unlike the association observed with aspirin use, daily ibuprofen use was positively associated with both ER/PR-positive and ER/PR-negative breast cancers. In particular, among long-term daily ibuprofen users, a statistically significant association with ER/PR-positive breast cancer was observed (RR = 1.50, 95% CI = 1.11 to 2.03). Similar associations were observed when ER-negative, PR-negative, ER-positive, and PR-positive cancers were modeled separately (data not shown).

Discussion

NSAIDs, such as aspirin and ibuprofen, are potential chemopreventive agents that suppress COX-2 expression and may, as a result, prevent or reduce the rate of tumor growth. However, we observed a statistically significant increased risk of breast cancer, especially nonlocalized breast cancer, in long-term daily users of ibuprofen. The association with long-term daily use of ibuprofen was also statistically significant among women with ER/PR-positive tumors. In contrast, aspirin use was not associated with overall breast cancer risk, which is consistent with results from the Nurses' Health Study *(6)*. In addition, we observed a nonstatistically significantly reduced risk of ER/PR-positive breast cancer risk and a statistically significantly increased risk of ER/PR-negative breast cancer risk among long-term daily users of aspirin.

In previous case–control and cohort studies, the observed relationships between regular use of aspirin, ibuprofen, or any NSAID and breast cancer risk have been inconsistent *(1,4)*. The conflicting results may indicate that any associations are limited to certain subtypes of tumors. Indeed, COX-2 is expressed in only 40% of breast carcinomas. Furthermore, elevated COX-2 expression is more commonly observed in women with poorer-prognosis breast cancers, such as those with nonlocalized disease or ER/PR-negative tumors *(3)*. The only other study, to our knowledge, that investigated risk of breast cancer by hormone receptor status also reported inverse associations with aspirin use *(17)*, which is consistent with COX-2 expression patterns. That case–control study, unlike ours, did not report an increased risk of ER/PR-negative tumors with aspirin use; however, small numbers precluded examination of the highest category of use *(17)*.

We also examined whether risk of breast cancer differed by the type of NSAID used. The results suggest that long-term daily use of ibuprofen is associated with increased breast cancer risk, particularly of nonlocalized tumors. Few previous studies have assessed the association between ibuprofen use and breast cancer risk. Harris et al. *(11,13)* reported an inverse association between ibuprofen use and breast cancer among attendees at a mammogram screening program. The only other studies to present ibuprofen results separately from those for other nonaspirin NSAIDs either found no association *(8)* or found that the risk of breast cancer increased in the highest category of use *(17)*; the latter result is consistent with our finding. Our finding of increased risk among users of ibuprofen irrespective of their use of aspirin raises the possibility that ibuprofen may differ from aspirin in the degree to which it inhibits COX-2 expression in breast tissue. There was no association with acetaminophen in our study, which is consistent with its lack of nonsteroidal anti-inflammatory properties.

Table 4. Multivariable-adjusted relative risks (95% confidence intervals) for localized and nonlocalized breast cancer according to frequency and duration of regular NSAID and acetaminophen use in the California Teachers Study, 1995 to 1996*

Frequency and duration of medication use	RR (95% CI)			
	Aspirin	Ibuprofen	Any NSAID	Acetaminophen
Localized (n = 1656)†				
Frequency				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use‡				
1–6 days/wk	1.16 (1.02 to 1.31)	1.02 (0.88 to 1.18)	1.10 (0.98 to 1.24)	1.09 (0.93 to 1.27)
Daily	0.99 (0.84 to 1.17)	1.15 (0.95 to 1.38)	1.07 (0.94 to 1.22)	0.99 (0.71 to 1.39)
P_{trend}	.36	.18	.17	.46
Duration and frequency				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use				
<5 y, 1–6 days/wk	1.12 (0.90 to 1.38)	1.02 (0.85 to 1.22)	1.01 (0.85 to 1.20)	0.99 (0.76 to 1.28)
≥5 y, 1–6 days/wk	1.18 (1.02 to 1.36)	1.03 (0.81 to 1.30)	1.17 (1.02 to 1.36)	1.14 (0.95 to 1.38)
<5 y daily	1.09 (0.89 to 1.34)	1.08 (0.87 to 1.34)	1.09 (0.93 to 1.29)	1.07 (0.68 to 1.66)
≥5 y daily	0.88 (0.68 to 1.12)	1.33 (0.97 to 1.84)	1.04 (0.87 to 1.25)	0.91 (0.55 to 1.52)
P_{trend}	.45	.13	.14	.39
Nonlocalized (n = 713)				
Frequency				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use				
1–6 days/wk	0.98 (0.80 to 1.19)	0.95 (0.77 to 1.19)	0.97 (0.81 to 1.17)	1.07 (0.85 to 1.35)
Daily	0.94 (0.71 to 1.23)	1.46 (1.12 to 1.90)	1.13 (0.92 to 1.39)	0.93 (0.52 to 1.64)
P_{trend}	.62	.043	.36	.77
Duration and frequency				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use				
<5 y, 1–6 days/wk	0.91 (0.64 to 1.30)	0.91 (0.69 to 1.19)	0.95 (0.73 to 1.24)	1.06 (0.73 to 1.55)
≥5 y, 1–6 days/wk	1.01 (0.80 to 1.27)	1.04 (0.74 to 1.45)	0.99 (0.79 to 1.24)	1.08 (0.82 to 1.43)
<5 y daily	0.75 (0.51 to 1.10)	1.30 (0.95 to 1.79)	0.98 (0.75 to 1.30)	0.88 (0.39 to 1.97)
≥5 y daily	1.17 (0.82 to 1.66)	1.92 (1.24 to 2.97)	1.31 (1.00 to 1.70)	0.97 (0.44 to 2.18)
P_{trend}	.86	.013	.23	.77

*Adjusted for race, body mass index, first-degree family history of breast cancer, menopausal and hormone therapy use status, smoking, alcohol intake, physical activity, mammography history, breast biopsy history, parity status before age 30, and neighborhood socioeconomic status. NSAID = nonsteroidal anti-inflammatory drugs; RR = relative risk; CI = confidence interval.

†Localized cancers were confined to the breast at the time of diagnosis; nonlocalized cancers had spread to regional or distant lymph nodes or had metastasized.

‡Regular use is defined as at least once a week.

The reasons for the statistically significantly increased risks of nonlocalized and ER/PR-positive tumors associated with long-term daily use of ibuprofen requires additional exploration, as does the increased risk of ER/PR-negative tumors associated with long-term daily use of aspirin. One explanation may be that certain health conditions leading to regular NSAID use may result in frequent doctor visits, which increase the chances of cancer detection. Indeed, rates of recent mammography were slightly higher among daily long-term NSAID users than among nonregular users in our study. Another possible explanation for these associations could be that women with early symptoms of undiagnosed breast cancer take pain relief medication to relieve these symptoms. However, this scenario is unlikely because early-stage breast cancer is generally asymptomatic. If either of these explanations for the associations were correct, we would expect to observe a reduction in risk over calendar time since baseline. However, stratification by calendar year of diagnosis had the opposite effect. In fact, an increased risk was apparent only for breast cancers diagnosed some years after long-term NSAID use was already achieved. Indeed, calendar effects have been proposed as a reason for differing results between studies; although our results do not confirm a reduced risk at any time, two of the studies that reported a reduced risk of breast cancer with aspirin use measured only recent use *(9,10)*. It has also been suggested that protective effects of NSAIDs are limited to certain populations. For example, there are some reports of a differential effect of age on the association between NSAIDs and breast cancer *(9)*. Again, we did not observe such effects, but we were unable to thoroughly assess modification by age given the small numbers of younger women with frequent and regular NSAID use.

One of the strengths of our study is its prospective design and the large number of incident breast cancers, which gave us substantial statistical power to detect any associations. Recall bias was also minimized by the assessment of NSAID use before cancer diagnosis. Furthermore, with the use of the California Cancer Registry we have virtually complete cancer case ascertainment, accurate diagnoses of cancer, and access to detailed information about stage and ER and PR status of tumors. Nevertheless, our study has several limitations. One of the inaccuracies is quantification of NSAID use. The list of anti-inflammatory medications in our questionnaire covers the more common brand names, but it is not comprehensive. Moreover, we do not know precisely during what period during a woman's lifetime that these medicines were taken. In addition, information on dose was not collected, so amount of cumulative exposure could only be approximated using measures of frequency and duration. Some study participants also reported using both aspirin and ibuprofen or both NSAIDs with acetaminophen, and use of these combinations may have limited our ability to assess the effect of each type of drug. Nevertheless, the prevalence of pain medication use in

Table 5. Multivariable-adjusted relative risks (95% confidence interval) for invasive breast cancer by estrogen and progesterone-receptor status according to frequency and duration of regular NSAID and acetaminophen use in the California Teachers Study*

Frequency and duration of medication use	RR (95% CI)			
	Aspirin	Ibuprofen	Any NSAID	Acetaminophen
ER/PR-positive (n = 1727)†				
Frequency				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use‡				
1–6 days/wk	1.05 (0.93 to 1.20)	1.00 (0.87 to 1.16)	1.04 (0.92 to 1.17)	1.07 (0.92 to 1.25)
Daily	0.89 (0.75 to 1.05)	1.25 (1.05 to 1.49)	1.03 (0.90 to 1.17)	1.02 (0.73 to 1.42)
P_{trend}	.43	.040	.57	.46
Duration and frequency				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use				
<5 y, 1–6 days/wk	1.03 (0.83 to 1.28)	0.96 (0.81 to 1.15)	0.99 (0.84 to 1.17)	0.99 (0.77 to 1.27)
≥5 y, 1–6 days/wk	1.06 (0.92 to 1.23)	1.08 (0.87 to 1.35)	1.07 (0.93 to 1.24)	1.12 (0.94 to 1.35)
<5 y daily	0.96 (0.78 to 1.19)	1.16 (0.94 to 1.43)	1.04 (0.87 to 1.22)	1.12 (0.73 to 1.72)
≥5 y daily	0.80 (0.62 to 1.03)	1.50 (1.11 to 2.03)	1.02 (0.85 to 1.23)	0.91 (0.55 to 1.52)
P_{trend}	.37	.013	.51	.41
ER/PR-negative (n = 279)				
Frequency				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use				
1–6 days/wk	1.31 (0.97 to 1.77)	1.29 (0.94 to 1.78)	1.21 (0.91 to 1.62)	1.38 (0.98 to 1.93)
Daily	1.40 (0.96 to 2.05)	1.26 (0.80 to 1.98)	1.38 (1.01 to 1.89)	1.36 (0.63 to 2.88)
P_{trend}	.026	.11	.031	.063
Duration and frequency				
No regular use	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Regular use				
<5 y, 1–6 days/wk	1.46 (0.91 to 2.35)	1.42 (0.98 to 2.06)	1.21 (0.82 to 1.80)	1.37 (0.80 to 2.35)
≥5 y, 1–6 days/wk	1.25 (0.87 to 1.78)	1.07 (0.62 to 1.84)	1.21 (0.85 to 1.73)	1.38 (0.92 to 2.08)
<5 y daily	1.08 (0.62 to 1.86)	1.31 (0.78 to 2.18)	1.14 (0.74 to 1.76)	1.86 (0.77 to 4.54)
≥5 y daily	1.81 (1.12 to 2.92)	1.14 (0.47 to 2.78)	1.67 (1.12 to 2.48)	0.80 (0.20 to 3.23)
P_{trend}	.022	.21	.021	.094

*Adjusted for, race, body mass index, first-degree family history of breast cancer, menopausal and hormone therapy use status, smoking, alcohol intake, physical activity, mammography history, breast biopsy history, parity status before age 30, and neighborhood socioeconomic status. NSAID = non-steroidal anti-inflammatory drug; RR = relative risk; CI = confidence interval.

†ER/PR-positive breast cancers are estrogen or progesterone receptor–positive and ER/PR-negative breast cancers are estrogen and progesterone receptor–negative.

‡Regular use is defined as at least once a week.

our cohort did not appear to be over-reported. The prevalence of recent regular use of ibuprofen (20%) was generally consistent with what has been seen in other studies (range 13% to 24%), but aspirin use was low (23% compared with a range of 23% to 44%) *(6,12,17)*.

In summary, long-term daily use of NSAIDs, in general, was not associated with breast cancer risk. However, daily long-term use of ibuprofen was associated with an increased risk of breast cancer, and use of aspirin and ibuprofen was associated with risks of particular tumor subtypes. These observations warrant further exploration because of the public health impact such readily available NSAIDs may have on breast cancer. Additional large-scale prospective epidemiologic studies may help clarify the findings by further examining the long-term effects of aspirin and ibuprofen, especially with regard to ER/PR-negative and nonlocalized breast cancer. A more detailed understanding of the tissue-specific effects of NSAIDs, particularly in the context of the complex biological mechanisms involved in the development of different cancers, is also needed.

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Notes

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