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ORIGINAL REPORT

Use of Aspirin, Other Nonsteroidal Anti-Inflammatory Drugs, and Acetaminophen and Postmenopausal Breast Cancer Incidence

Xuehong Zhang, Stephanie A. Smith-Warner, Laura C. Collins, Bernard Rosner, Walter C. Willett, and Susan E. Hankinson

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Xuehong Zhang, Bernard Rosner, Walter C. Willett, and Susan E. Hankinson, Brigham and Women's Hospital and Harvard Medical School; Stephanie A. Smith-Warner, Bernard Rosner, Walter C. Willett, and Susan E. Hankinson, Harvard School of Public Health; Laura C. Collins, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston; and Susan E. Hankinson, University of Massachusetts School of Public Health and Health Sciences, Amherst, MA.

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Corresponding author: Xuehong Zhang, MD, ScD, Brigham and Women's Hospital and Harvard Medical School, Channing Laboratory at Landmark Center (West Wing), 401 Park Dr, Boston, MA 02115; e-mail: xuehong.zhang@channing.harvard.edu.

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ABSTRACT

Purpose
The associations between use of aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen and breast cancer incidence in postmenopausal women are uncertain. We examined these associations with breast cancer, both overall and by molecular subtype.

Patients and Methods
We observed 84,602 postmenopausal women, free of cancer in 1980, until June 2008 and prospectively collected data on analgesic use, reproductive history, and other lifestyle factors using biennial questionnaires. Proportional hazards models were used to estimate multivariable relative risks (RRs) and 95% CIs.

Results
We documented 4,734 cases of incident invasive breast cancer. Compared with nonuse of aspirin, multivariable RRs of regular aspirin use (≥ two tablets per week) for more than 20 years were 0.91 for overall breast cancer (95% CI, 0.81 to 1.01; P_{trend} = 0.16), 0.90 for estrogen receptor (ER) –positive progesterone receptor (PR) –positive breast cancer (95% CI, 0.77 to 1.06; P_{trend} = 0.17), and 0.91 for ER-negative PR-negative breast cancer (95% CI, 0.68 to 1.22; P_{trend} = 0.97). Results did not vary appreciably by past or current use, days per week of use, or dosage of use. Use of other NSAIDs and acetaminophen was largely not significantly associated with breast cancer risk. Additionally, use of higher doses of each analgesic (≥ six tablets per week) for more than 10 years was generally not significantly associated with risk of breast cancer, either overall or by subtype. Furthermore, largely no substantial associations were noted for breast cancer molecular subtypes, including luminal A, luminal B, triple negative, basal-like, human epidermal growth factor receptor 2 positive, cyclooxygenase-2 (COX-2) negative, and COX-2 positive.

Conclusion
Our study suggests that use of aspirin, other NSAIDs, and acetaminophen is not importantly associated with risk of postmenopausal breast cancer, either overall or by specific subtype.

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INTRODUCTION

Breast cancer is the most commonly diagnosed cancer in women in the United States,[1] but few modifiable risk factors have been identified.[2] Given that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) reduce colon cancer risk,[3,4] epidemiologic studies have also been conducted to evaluate these drugs as potential chemopreventive agents for breast cancer. Supportive evidence from laboratory studies has shown that aspirin/NSAIDs might inhibit experimentally induced breast cancer.[5,6] In addition, aspirin/NSAIDs may inhibit cyclooxygenase-2 (COX-2) –mediated prostaglandin E_2 (PGE_2) synthesis,[7,8] and PGE_2 plays an important role in carcinogenesis by influencing cell proliferation, angiogenesis, and apoptosis.[8] Moreover, COX-2 is overexpressed in approximately 30% of mammary tumors but not in normal breast tissue.[9] Furthermore, decreased levels of PGE_2 might result in lower estrogen levels by inhibition of aromatase activity.[10] Endogenous estrogens are well-established risk factors for breast cancer[11]; thus, aspirin/NSAIDs might be associated with lower risk of breast cancer, especially for hormone receptor–positive subtypes.

Despite these potential mechanisms, epidemiologic evidence has been less consistent.[12-15] Although suggestive inverse associations were observed in the majority of case-control studies, results from cohort studies have been mixed.[12-15] In addition, as noted in several meta-analyses,[12,15] important dose-response relationships cannot be evaluated, because most studies lacked information on dose and frequency of use for any type of NSAID. Moreover, although aspirin/NSAIDs may selectively influence certain breast cancer subtypes, limited data exist on breast cancer subtype by hormone receptor status.[16-26] In addition, although differences in clinical behavior and response to therapy have been recognized for other breast cancer subtypes,[27,28] such as luminal A, luminal B, triple negative, basal-like, and human epidermal growth factor 2 (HER2), their risk factor profiles remain largely unknown, and possible associations with analgesic drugs have rarely been examined.[29]

To address these questions, we used the Nurses' Health Study (NHS),[30] a prospective cohort with detailed and updated data on analgesic use. The current study extends our earlier report[31] on aspirin/NSAIDs and overall breast cancer risk. We added 16 more years of follow-up, with 2,000 more cases of incident invasive breast cancer. We included only postmenopausal women in this study, because fewer than 150 cases of premenopausal breast cancer had occurred since our initial report.

PATIENTS AND METHODS

Study Population

The NHS has been described in detail elsewhere.[30] In brief, the NHS involves a prospective cohort of 121,700 registered female nurses in the United States who were age 30 to 55 years at baseline in 1976. These women have been mailed questionnaires every 2 years since 1976 to collect data on demographics, lifestyle factors, medical history, and disease outcomes. The follow-up rate has been greater than 90%. This study has been approved by the institutional review board at the Brigham and Women's Hospital in Boston, Massachusetts.

Assessment of Exposures

Information on aspirin, other NSAIDs, and acetaminophen has been described in detail elsewhere.[32] Briefly, information on aspirin use was first obtained in 1980 and every 2 years thereafter except in 1986. In 1980, participants were asked whether they currently took aspirin in most weeks and, if yes, answered questions on the number of aspirins taken per week and years of aspirin usage. In 1982, 1984, and almost every 2 years thereafter, aspirin dose was asked. Beginning in 1984, the frequency of use was assessed.

Women were classified as current users at each questionnaire in which current use was reported. The women who ceased reporting use were classified as past users, but they were eligible to become current users in subsequent follow-up years. Nonusers were those women who 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 and acetaminophen) to the end of follow-up. 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. In addition, to be consistent with how regular aspirin use was defined in early studies of NSAIDs and breast[31] and colorectal cancers[33,34] in the same cohort, we evaluated the associations with lifetime nonregular and regular use ($\geq$ two tablets per week). The major reasons for taking aspirin included headache, prevention of cardiovascular diseases, arthritis, and other musculoskeletal pain.[35]

Identification of Cases of Breast Cancer

Cases of incident invasive breast cancer were identified on biennial questionnaires. Participants (or next of kin) were contacted to confirm the diagnosis and provide permission to collect relevant medical records. Study investigators, blinded to exposure status, reviewed the medical records and abstracted information on tumor characteristics including hormone receptor status. A diagnosis of breast cancer confirmed by the participant but missing medical record confirmation was included as a case in this analysis, because pathology reports confirmed 99% of the reported cases. Information on collection of breast cancer tissue blocks and tissue microarray construction have been described in detail elsewhere.[36] COX-2 expression was evaluated using tissue microarray for 2,125 women diagnosed with stages I to IV invasive breast cancer between 1976 and 1996. For COX-2 status, cytoplasmic staining for each core was scored as negative, 1+ (weak diffuse cytoplasmic staining), 2+ (moderate to strong cytoplasmic staining), or 3+ (> 90% tumor cell stained with strong intensity).[37] For this analysis, patients scored as negative (0) were considered negative, and those scored as 1+, 2+, or 3+ were considered positive. We used the same criteria described earlier[38] to define other molecular breast cancer subtypes, including luminal A, luminal B, triple negative, basal-like, and HER2 positive.

Assessment of Other Covariates

Information on age at menarche, height, and age at first birth was obtained in 1976. Information on weight at age 18 was assessed in 1980, and information on parity was collected biennially until 1984. History of breast cancer in the participants' mothers and sisters was obtained in 1976, 1982, and every 4 years since 1988. Alcohol consumption was first assessed in 1980, then in 1984 and in 1986 using a validated semiquantitative food frequency questionnaire, and every 4 years thereafter. Data on current weight, diagnosis of benign breast disease, menopausal status, age at menopause, and postmenopausal hormone (PMH) use were collected biennially.

Statistical Analysis

We used different baselines for our analysis of analgesic use depending on the availability of information collected on each drug. We treated 1980 as the baseline for analyses of aspirin use (nonuser, past, current) and dose (tablets per week) and treated 1984 as the baseline for analysis of aspirin frequency (days per week). We treated 1990 as the baseline when analyzing other NSAIDs and acetaminophen use. We excluded participants with a history of cancer (except for nonmelanoma skin cancer) at baseline.

We calculated person-time for each woman from the date of baseline questionnaire return to the date of death, loss to follow-up, breast cancer diagnosis, or end of follow-up (June 1, 2008), whichever came first. We used Cox proportional hazards models[39] to calculate relative risks (RRs) and 95% CIs using SAS software (version 9; SAS Institute, Cary, NC).[40] For each of the medications, we observed no violation of the proportional hazards assumption.

We conducted multivariable analyses and used the most updated information for all covariates, if available, before each follow-up cycle. We conducted trend tests using the Wald test by entering continuous measures (duration) or median values of categories (dose and frequency). To assess whether the associations between each of the drugs and cancer risk varied across levels of other risk factors, we tested interaction terms between duration of drug use and the potential modifier in multivariate models using the Wald test. Additionally, we conducted a lag analysis to evaluate whether timing of use of the drugs was important. All statistical analyses were two sided, with a P value less than .05 indicating significance.

RESULTS

We documented 4,734 cases of incident invasive breast cancer among 84,602 postmenopausal women during 28 years of follow-up. Grouping these patients with breast cancer by estrogen (ER) and progesterone receptor (PR) status, 2,358 had ER-positive PR-positive disease, 648 had ER-positive PR-negative disease, 82 had ER-negative PR-positive disease, and 687 had ER-negative PR-negative disease. As summarized in Table 1, compared with nonusers, analgesic users were slightly more likely to gain weight, have benign breast disease, and use PMH. Furthermore, the prevalence of mammogram screening was

Table 1. Age-Standardized Characteristics of Potential Breast Cancer Risk Factors* by Analgesic Use in the Nurses' Health Study

Characteristic	Aspirin			Nonaspirin NSAIDs			Acetaminophen		
	Nonusers	Past Users	Current Users	Nonusers	Past Users	Current Users	Nonusers	Past Users	Current Users
Mean age, years	60.6	60.5	61.1	61.9	60.8	60.3	61.8	60.5	60.8
Mean age at menarche, years	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.6	12.5
Mean age at first birth, years	25.3	25.3	25.2	25.4	25.3	25.2	25.3	25.3	25.2
Nulliparous, %	5.9	5.6	6.1	6.3	5.6	5.5	6.5	5.6	5.6
Mean height, m	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Mean BMI at age 18 years, kg/m^2†	21.3	21.5	21.4	21.3	21.4	21.6	21.3	21.3	21.5
Mean weight change since age 18 years, kg	9.7	10.6	10.5	9.8	10.8	11.2	10.0	10.1	10.9
Mean physical activity, MET-hours/wk‡	15.7	15.3	16.3	16.1	15.3	15.4	16.6	15.6	15.0
History of breast cancer in parent or sibling, %	12.5	13.2	12.9	12.7	12.8	12.8	12.7	13.0	12.8
History of benign breast disease, %	41.2	42.6	43.3	40.2	43.6	43.8	40.3	42.3	43.5
Mean alcohol consumption, g/d	4.8	4.8	5.2	4.9	4.8	4.9	5.3	4.9	4.5
Ever postmenopausal hormone users, %	58.7	64.4	63.8	59.7	69.1	70.3	62.1	66.5	66.9
Estrogen users only	19.1	22.6	22.1	18.7	24.5	25.6	19.9	23.1	23.5
Estrogen plus progesterone users	13.9	15.4	15.9	13.3	16.4	16.6	15.0	17.0	14.4
Ever smokers, %	42.9	43.0	43.8	44.0	42.0	41.9	43.5	41.2	42.7

Abbreviations: BMI, body mass index; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug.
*Characteristic variables presented in this table were measured in 1992.
†BMI was calculated as weight in kilograms divided by the square of height in meters.
‡MET-hours = sum of the average time per week spent in each activity × MET value of each activity. One MET, the energy spent sitting quietly, is equal to 3.5 mL of oxygen uptake per kilograms of body weight per minute for a 70-kg adult.

similar across analgesic use categories (ie, 89% to 92% among nonusers and past and current aspirin users in 2006).

Because the age-adjusted results were similar to the multivariable-adjusted results, we only present the latter. Compared with nonuse, neither past nor current aspirin use was associated with overall breast cancer risk (Table 2). Similarly, no significant benefit was observed for increasing dose, frequency, or duration of use among past and current aspirin users (all tests for trend P values $\geq .10$). The associations between aspirin use, dose, frequency, and duration and risk of breast cancer by ER/PR status also were largely null, although a modestly lower risk of ER-positive PR-positive breast cancer was observed among women who used six or more tablets per week for at least 10 years (RR, 0.79; 95% CI, 0.66 to 0.95; P value for test for heterogeneity among these three subtypes $> .12$). Associations were similar for 11 to 20 years of use (RR, 0.83; 95% CI, 0.64 to 1.08) and more than 20 years of use (RR, 0.77; 95% CI, 0.63 to 0.96; $P_{trend} = .26$). Results were essentially unchanged after further adjustment for nonaspirin NSAIDs and acetaminophen (data not shown).

For nonaspirin NSAIDs, multivariable RRs were close to 1.0, and in general, no dose-response relationships were observed for increasing dose, frequency, or duration of use among either past or current users either for overall breast cancer or by ER/PR status (Table 3). Furthermore, similar nonsignificant associations were observed for total NSAID use (aspirin and nonaspirin NSAID use combined; data not shown).

Acetaminophen use was generally not associated with overall breast cancer risk or with breast cancer subtype defined by ER/PR status, with a few exceptions. For example, inverse associations were observed between current acetaminophen use and risk of overall, ER-positive PR-positive, and ER-negative PR-negative breast cancer (Table 4). However, when evaluated by frequency or duration of use, nonsignificant trends were observed.

In addition, the associations with each of the drugs and breast cancer risk did not vary by body mass index (< 25 v ≥ 25 kg/m^2), alcohol consumption (nondrinkers v drinkers), postmenopausal hormone use (never v ever), or family history of breast cancer (no v yes; data not shown). Moreover, we conducted sensitivity analyses restricted to women without inflammatory conditions such as myocardial infarction, stroke, coronary artery bypass graft angina, or rheumatoid arthritis, and results were essentially unchanged (data not shown). Furthermore, generally null associations were observed for the 6-year lag analysis, when we analyzed the breast cancer subtypes defined by ER/PR status separately (ie, ER-positive, ER-negative, PR-positive, and PR-negative; data not shown), and when we restricted analysis to women with recent past mammogram examinations (ie, 2000 to 2006) or distant past exams (ie, 1980 to 2000; data not shown).

Use of aspirin, nonaspirin NSAIDs, and acetaminophen was largely unassociated with the risk of luminal A, luminal B, triple-negative, or HER2-positive breast cancer, although an inverse association between long-term acetaminophen use and triple-negative disease was suggested ($P_{trend} = .03$). The associations also did not seem to vary by tumor expression of COX-2 (Table 5). In addition, nonsignificant associations were observed for basal-like breast cancer (data not shown; n = 101 cases).

DISCUSSION

Although modest associations cannot be totally excluded, our study, which involved 4,734 cases of breast cancer among approximately 84,000 postmenopausal women observed for 28 years, found that use of aspirin, other nonaspirin NSAIDs, total NSAIDs, and acetaminophen was not importantly associated with the incidence of breast cancer, either overall or by hormone receptor status. Furthermore, no

Table 2. Multivariable RRs of Postmenopausal Breast Cancer by Hormone Receptor Status According to Aspirin Use in the Nurses' Health Study (1980 to 2008)

Details of Use	Total Breast Cancer			ER Positive PR Positive			ER Positive PR Negative			ER Negative PR Negative		
	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI
Aspirin use												
Nonuser	617	1.0	Reference	263	1.0	Reference	82	1.0	Reference	95	1.0	Reference
Past	1,545	0.97	0.88 to 1.08	840	1.00	0.86 to 1.15	229	1.07	0.82 to 1.40	201	0.88	0.68 to 1.15
Current	2,572	0.96	0.87 to 1.05	1,255	0.95	0.83 to 1.09	337	0.91	0.71 to 1.17	391	1.02	0.81 to 1.29
Dosage, No. of tablets per week												
Nonuser	617	1.0	Reference	263	1.0	Reference	82	1.0	Reference	95	1.0	Reference
Past												
< 2	842	0.96	0.86 to 1.07	436	0.94	0.80 to 1.10	119	1.00	0.74 to 1.34	118	0.89	0.66 to 1.18
2 to 5	357	1.01	0.88 to 1.15	207	1.10	0.91 to 1.33	59	1.24	0.88 to 1.76	43	0.82	0.57 to 1.20
> 5	151	0.90	0.75 to 1.08	86	0.95	0.74 to 1.22	20	0.89	0.54 to 1.47	17	0.71	0.42 to 1.21
P_{trend}		.41			.33			.41			.19	
Current												
< 2	826	1.01	0.91 to 1.13	407	1.03	0.88 to 1.21	117	1.02	0.76 to 1.36	115	0.96	0.72 to 1.27
2 to 5	764	0.95	0.85 to 1.06	397	0.97	0.82 to 1.13	100	0.90	0.66 to 1.21	113	0.95	0.71 to 1.26
6 to 14	628	0.92	0.82 to 1.03	287	0.85	0.72 to 1.01	84	0.91	0.67 to 1.25	101	1.00	0.75 to 1.33
> 14	65	0.94	0.73 to 1.22	24	0.87	0.57 to 1.33	11	1.14	0.60 to 2.15	13	1.34	0.74 to 2.42
P_{trend}		.22			.10			.77			.58	
Frequency, days per week†												
Nonuser	510	1.0	Reference	238	1.0	Reference	77	1.0	Reference	81	1.0	Reference
Past												
< 2	1,058	0.99	0.88 to 1.10	566	1.02	0.87 to 1.19	156	1.07	0.80 to 1.42	150	0.86	0.65 to 1.14
2 to 3	172	1.10	0.92 to 1.31	111	1.35	1.07 to 1.70	14	0.70	0.39 to 1.25	22	0.92	0.57 to 1.48
> 3	107	0.82	0.66 to 1.01	57	0.84	0.62 to 1.12	17	0.97	0.57 to 1.66	16	0.87	0.50 to 1.50
P_{trend}		.31			.78			.35			.68	
Current												
< 2	936	0.99	0.89 to 1.11	453	1.01	0.87 to 1.19	129	0.94	0.71 to 1.25	147	0.97	0.74 to 1.28
2 to 3	529	0.95	0.84 to 1.08	286	1.04	0.87 to 1.24	77	0.98	0.71 to 1.36	65	0.76	0.55 to 1.06
4 to 5	547	0.94	0.83 to 1.06	292	0.97	0.81 to 1.15	62	0.79	0.56 to 1.11	80	0.91	0.66 to 1.25
> 5	363	0.91	0.80 to 1.05	161	0.83	0.68 to 1.02	50	0.89	0.62 to 1.28	51	0.84	0.58 to 1.19
P_{trend}		.48			.22			.51			.48	
Duration, years of use by status												
Nonuser	617	1.0	Reference	263	1.0	Reference	82	1.0	Reference	95	1.0	Reference
Past												
≤ 5	288	1.06	0.91 to 1.22	155	1.10	0.89 to 1.34	45	1.21	0.83 to 1.77	32	0.79	0.52 to 1.20
6 to 10	351	0.96	0.84 to 1.10	188	0.95	0.78 to 1.16	55	1.14	0.79 to 1.62	50	0.96	0.67 to 1.37
11 to 20	275	1.02	0.88 to 1.19	143	0.97	0.78 to 1.20	50	1.46	1.01 to 2.12	33	0.86	0.56 to 1.30
> 20	351	0.89	0.77 to 1.02	210	0.99	0.82 to 1.20	40	0.79	0.53 to 1.17	44	0.75	0.52 to 1.09
P_{trend}		.09			.99			.052			.46	
Current												
≤ 5	351	0.95	0.83 to 1.08	133	0.81	0.66 to 1.01	56	1.06	0.74 to 1.50	53	0.98	0.69 to 1.38
6 to 10	365	0.99	0.87 to 1.13	176	0.98	0.81 to 1.20	42	0.78	0.53 to 1.14	57	1.12	0.80 to 1.57
11 to 20	602	0.97	0.86 to 1.10	319	0.97	0.82 to 1.15	73	0.89	0.64 to 1.25	102	1.13	0.84 to 1.52
> 20	779	0.92	0.82 to 1.03	390	0.91	0.77 to 1.07	119	1.06	0.79 to 1.42	110	0.89	0.67 to 1.19
P_{trend}		.14			.78			.75			.28	
Duration, years of use by dosage												
Nonuser	617	1.0	Reference	263	1.0	Reference	82	1.0	Reference	95	1.0	Reference
Nonregular user (< two tablets per week)‡												
≤ 5	461	1.02	0.90 to 1.16	225	1.01	0.84 to 1.21	71	1.11	0.80 to 1.54	57	0.85	0.61 to 1.20
6 to 10	424	0.97	0.85 to 1.10	204	0.88	0.73 to 1.06	61	1.00	0.70 to 1.41	72	1.18	0.85 to 1.63
11 to 20	277	0.99	0.85 to 1.15	148	0.99	0.80 to 1.22	40	1.09	0.73 to 1.62	40	0.99	0.66 to 1.47
> 20	286	0.95	0.83 to 1.10	155	1.03	0.84 to 1.26	35	0.86	0.57 to 1.29	35	0.81	0.54 to 1.20
P_{trend}		.13			.66			.07			.25	

(continued on following page)

Table 2. Multivariable RRs of Postmenopausal Breast Cancer by Hormone Receptor Status According to Aspirin Use in the Nurses' Health Study (1980 to 2008) (continued)

Details of Use	Total Breast Cancer			ER Positive PR Positive			ER Positive PR Negative			ER Negative PR Negative		
	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI
Regular user (≥ two tablets per week)‡												
≤ 5	110	0.98	0.79 to 1.20	35	0.80	0.56 to 1.15	20	1.33	0.81 to 2.19	17	1.01	0.60 to 1.71
6 to 10	256	1.06	0.92 to 1.24	136	1.16	0.94 to 1.43	32	0.90	0.59 to 1.36	31	0.95	0.63 to 1.45
11 to 20	539	0.97	0.86 to 1.10	280	0.94	0.79 to 1.12	73	0.97	0.69 to 1.34	89	1.14	0.84 to 1.55
> 20	773	0.91	0.81 to 1.01	402	0.90	0.77 to 1.06	117	1.03	0.77 to 1.39	111	0.91	0.68 to 1.22
P_{trend}		.16			.17			.94			.97	
Higher-dose user (≥ six tablets per week)‡												
≤ 10	110	1.07	0.87 to 1.32	46	1.22	0.89 to 1.68	11	0.75	0.39 to 1.41	17	1.19	0.70 to 2.02
> 10	467	0.91	0.80 to 1.03	211	0.79	0.66 to 0.95	74	1.07	0.77 to 1.48	75	1.00	0.73 to 1.37
P_{trend}		.79			.26			.15			.75	

Abbreviations: BMI, body mass index; ER, estrogen receptor; MET, metabolic equivalent of task; PR, progesterone receptor; RR, relative risk.

*Multivariable RRs were adjusted for age (in months), age at menarche (≤ 12, 13, or ≥ 14 years), height (< 1.60, 1.60 to < 1.65, 1.65 to < 1.70, 1.70 to < 1.75, or ≥ 1.75 m), BMI at age 18 years (< 19, 19 to < 21, 21 to < 23, or ≥ 23 kg/m^2), weight change since age 18 years (≤ −2, > −2 to < 2, 2 to < 10, 10 to < 20, or ≥ 20 kg), parity and age at first birth (nulliparous; one to two children, < 25 years; one to two children, 25 to 29 years; one to two children, ≥ 30 years; ≥ three children, < 25; ≥ three children, 25 to 29 years; or ≥ three children, ≥ 30 years), history of breast cancer in parent or sibling (yes or no), history of benign breast disease (yes or no), alcohol consumption (0, > 0 to < 5, 5 to < 15, or ≥ 15 g per day), physical activity (< 3, 3 to < 27, or ≥ 27 MET-hours per week), and postmenopausal hormone use (never; past; current user, < 5 years; or current user, ≥ 5 years).

†No. of nonusers was less, because the information on aspirin frequency (days per week) was not measured until 1984.

‡Regular aspirin user was defined as consumption of ≥ two 325-mg tablets per week. Nonregular user was defined otherwise.

consistent, significant associations were observed with any of several specific tumor molecular subtypes. The associations also did not vary substantially by body mass index, alcohol consumption, PMH use, or family history of breast cancer.

Results from this updated analysis with 16 additional years of follow-up are consistent with those in our earlier report on the NHS.[31] Our findings are in agreement with those reported in some cohort studies of aspirin use and breast cancer[16-21] as well as the only randomized clinical trial, to our knowledge, which evaluated low-dose (100 mg) aspirin.[41] In contrast, one study[42] reported a U-shaped association, one study[43] reported an increased risk, and several cohorts[23,25,26] have reported an approximate 20% reduction in risk with aspirin use. These inconsistencies among cohort studies resulted in significant heterogeneity ($P < .001$) in recent large-scale quantitative meta-analyses.[12,15] Nonetheless, the association with aspirin use, if any, seemed to be modest (19 cohort studies: summary RR, 0.91; 95% CI, 0.84 to 0.98).[15] In contrast to cohort studies, results from case-control studies were more consistent (nine case-control studies: summary RR, 0.79; 95% CI, 0.72 to 0.86; P value for heterogeneity = .12).[12] However, it remains unclear how selection or recall bias might have affected these results. Epidemiologic studies of nonaspirin NSAID use and overall breast cancer have also yielded mixed results.[12] The null results observed in our study were consistent with some[16,17,20,21,44,45] but not with others.[17,22,24,29] We know of no clear reason to explain the inconsistent results. The assessment of aspirin/NSAID use has differed significantly across studies, and direct comparison of our results with others is challenging. Nonetheless, our detailed adult lifetime aspirin/NSAID data covered generally similar ranges of dose and duration of use as other studies reporting null, inverse, or positive associations. Moreover, our null findings did not vary across categories of other factors (eg, body mass index), suggesting different distributions in these factors are unlikely to account for the differences.

Our findings also suggest that aspirin or other NSAID use is not importantly associated with risk of breast cancer defined by hormone receptor status; similar results were reported by the Cancer Prevention Study II Nutrition Cohort[18] and a randomized clinical trial (100 mg aspirin use every other day for 10 years).[20] In contrast, the Long Island Breast Cancer Case-Control Study,[22] Multiethnic Cohort Study,[17] and National Institutes of Health–American Association of Retired Persons study[21] found the inverse associations with nonaspirin NSAIDs to be confined to hormone receptor–positive tumors. In addition, the California Teachers Study[19] observed that at least 5 years of daily aspirin use was not significantly associated with risk of ER-positive PR-positive breast cancer (RR, 0.80; 95% CI, 0.62 to 1.03) but was associated with an increased risk of ER-negative PR-negative breast cancer (RR, 1.81; 95% CI, 1.12 to 2.92).[19] Our study suggests that long-term use of high-dose aspirin but not nonaspirin NSAIDs (ie, ≥ six tablets per week for > 10 years) was inversely associated with the risk of ER-positive PR-positive breast cancer; however, no significant trend with increasing duration of use or significant heterogeneity among the subtypes was observed. It is unclear why the few studies assessing hormone receptor status to date have such inconsistent findings, because exposure assessment and classification, follow-up time, covariate adjustment, and age at data collection seem reasonably similar.

The inconsistent findings for aspirin/NSAID use and breast cancer incidence are in marked contrast to colon cancer where the epidemiologic data consistently showed an inverse association[3,4] and this has been supported by a pooled analysis of randomized trials.[46] Interestingly, despite largely null results observed for postmenopausal breast cancer incidence, a prior study in our cohort found that aspirin use after breast cancer diagnosis was associated with a decreased risk of distant recurrence and breast cancer death.[47] When we examined incidence of fatal breast cancer, a nonsignificant inverse association

Table 3. Multivariable RRs of Postmenopausal Breast Cancer by Hormone Receptor Status According to Nonaspirin NSAID Use in the Nurses' Health Study (1990 to 2008)

	Total Breast Cancer			ER Positive PR Positive			ER Positive PR Negative			ER Negative PR Negative		
Details of Use	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI
Nonaspirin NSAID use												
Nonuser	1,679	1.0	Reference	883	1.0	Reference	237	1.0	Reference	246	1.0	Reference
Past	1,082	0.99	0.91 to 1.07	605	1.01	0.91 to 1.13	136	0.98	0.78 to 1.23	153	0.93	0.75 to 1.16
Current	1,334	0.97	0.90 to 1.04	732	1.00	0.90 to 1.10	193	1.08	0.89 to 1.32	182	0.90	0.74 to 1.10
Frequency, days per week												
Nonuser	1,679	1.0	Reference	883	1.0	Reference	237	1.0	Reference	246	1.0	Reference
Past												
< 2	772	1.02	0.93 to 1.12	418	1.02	0.90 to 1.15	100	1.04	0.81 to 1.33	116	1.01	0.80 to 1.28
2 to 3	85	0.95	0.76 to 1.18	46	0.92	0.68 to 1.25	11	1.01	0.54 to 1.85	12	0.92	0.51 to 1.65
> 3	106	0.92	0.75 to 1.12	69	1.08	0.84 to 1.39	10	0.70	0.37 to 1.32	12	0.73	0.40 to 1.31
P_{trend}		.12			.98			.17			.16	
Current												
< 2	519	0.92	0.83 to 1.02	269	0.90	0.79 to 1.04	78	1.04	0.80 to 1.36	72	0.86	0.66 to 1.13
2 to 3	185	0.94	0.81 to 1.10	108	1.02	0.83 to 1.25	23	0.89	0.57 to 1.37	24	0.85	0.56 to 1.30
4 to 5	222	1.17	1.01 to 1.35	116	1.16	0.95 to 1.41	34	1.44	1.00 to 2.08	31	1.13	0.77 to 1.66
> 5	237	0.95	0.82 to 1.09	135	1.00	0.83 to 1.20	29	0.87	0.59 to 1.28	38	1.04	0.73 to 1.48
P_{trend}		.34			.18			.70			.38	
Duration, years of use by status												
Nonuser	1,679	1.0	Reference	883	1.0	Reference	237	1.0	Reference	246	1.0	Reference
Past												
≤ 5	722	1.05	0.95 to 1.15	407	1.08	0.95 to 1.22	94	1.06	0.82 to 1.36	106	1.00	0.79 to 1.27
6 to 10	286	0.95	0.83 to 1.08	149	0.91	0.76 to 1.09	34	0.90	0.62 to 1.31	39	0.88	0.62 to 1.25
> 10	74	0.73	0.57 to 0.93	49	0.96	0.71 to 1.30	8	0.68	0.33 to 1.40	8	0.59	0.28 to 1.21
P_{trend}		.04			.42			.40			.87	
Current												
≤ 5	586	0.93	0.84 to 1.02	311	0.95	0.83 to 1.08	87	1.00	0.78 to 1.29	78	0.84	0.64 to 1.09
6 to 10	483	0.99	0.89 to 1.10	279	1.02	0.88 to 1.17	74	1.23	0.93 to 1.62	74	0.98	0.74 to 1.29
> 10	264	1.02	0.88 to 1.17	141	1.07	0.88 to 1.30	32	1.01	0.68 to 1.51	30	0.87	0.58 to 1.32
P_{trend}		.04			.08			.97			.29	
Duration, years of use by dosage†												
Nonuser	881	1.0	Reference	463	1.0	Reference	123	1.0	Reference	124	1.0	Reference
Nonregular user (< two tablets per week)‡												
≤ 5	73	0.88	0.69 to 1.12	39	0.92	0.66 to 1.28	6	0.58	0.25 to 1.32	9	0.76	0.38 to 1.51
6 to 10	45	0.77	0.57 to 1.05	22	0.72	0.47 to 1.11	4	0.55	0.20 to 1.49	10	1.12	0.58 to 2.15
> 10	61	1.10	0.84 to 1.43	33	1.18	0.82 to 1.70	6	0.94	0.41 to 2.17	8	1.00	0.48 to 2.08
P_{trend}		.06			.32			.11			.89	
Regular user (≥ two tablets per week)‡												
≤ 5	122	1.06	0.87 to 1.28	68	1.08	0.83 to 1.39	20	1.31	0.81 to 2.12	12	0.75	0.41 to 1.37
6 to 10	210	1.04	0.89 to 1.21	137	1.23	1.01 to 1.50	33	1.28	0.86 to 1.91	20	0.69	0.42 to 1.11
> 10	295	0.93	0.81 to 1.07	165	1.00	0.82 to 1.20	37	0.98	0.67 to 1.45	33	0.76	0.51 to 1.14
P_{trend}		.62			.84			.74			.72	
Higher-dose user (≥ six tablets per week)‡												
≤ 10	163	0.97	0.82 to 1.15	106	1.10	0.89 to 1.37	25	1.11	0.71 to 1.73	16	0.67	0.39 to 1.14
> 10	196	0.99	0.84 to 1.17	109	1.03	0.83 to 1.29	30	1.26	0.83 to 1.92	22	0.81	0.51 to 1.31
P_{trend}		.93			.89			.30			.58	

Abbreviations: BMI, body mass index; ER, estrogen receptor; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug; PR, progesterone receptor; RR, relative risk.

*Multivariable RRs were adjusted for age (in months), age at menarche (≤ 12, 13, or ≥ 14 years), height (< 1.60, 1.60 to < 1.65, 1.65 to < 1.70, 1.70 to < 1.75, or ≥ 1.75 m), BMI at age 18 years (< 19, 19 to < 21, 21 to < 23, or ≥ 23 kg/m^2), weight change since age 18 years (≤ −2, > −2 to < 2, 2 to < 10, 10 to < 20, or ≥ 20 kg), parity and age at first birth (nulliparous; one to two children, < 25 years; one to two children, ≥ 25 years; ≥ three children, < 25; ≥ three children, ≥ 25 years), history of breast cancer in parent or sibling (yes or no), history of benign breast disease (yes or no), alcohol consumption (0, > 0 to < 5, 5 to < 15, or ≥ 15 g per day), physical activity (< 3, 3 to < 27, or ≥ 27 MET-hours per week), and postmenopausal hormone use (never; past; current user, < 5 years; or current user, ≥ 5 years).

†No. of nonusers was less, because the information on dosage (tablets per week) was not measured until 1998.

‡Regular aspirin user was defined as consumption of ≥ two 325-mg tablets per week. Nonregular user was defined otherwise.

Table 4. Multivariable RRs of Postmenopausal Breast Cancer by Hormone Receptor Status According to Acetaminophen Use in the Nurses' Health Study (1990 to 2008)

	Total Breast Cancer			ER Positive PR Positive			ER Positive PR Negative			ER Negative PR Negative		
Details of Use	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI
Acetaminophen use												
Nonuser	1,680	1.0	Reference	924	1.0	Reference	234	1.0	Reference	249	1.0	Reference
Past	1,216	0.93	0.86 to 1.01	673	0.92	0.83 to 1.02	153	0.90	0.73 to 1.12	175	0.88	0.72 to 1.08
Current	1,199	0.89	0.83 to 0.96	623	0.85	0.77 to 0.95	179	1.01	0.83 to .123	157	0.81	0.66 to 1.00
Frequency, days per week												
Nonuser	1,680	1.0	Reference	924	1.0	Reference	234	1.0	Reference	249	1.0	Reference
Past												
< 2	1,068	0.94	0.87 to 1.02	590	0.92	0.83 to 1.03	134	0.90	0.72 to 1.12	153	0.88	0.71 to 1.08
2 to 3	47	0.87	0.65 to 1.16	26	0.86	0.58 to 1.28	6	0.84	0.37 to 1.90	6	0.76	0.34 to 1.72
> 3	40	0.97	0.71 to 1.34	24	1.01	0.67 to 1.51	3	0.56	0.18 to 1.77	5	0.92	0.38 to 2.24
P_{trend}		.46			.80			.68			.38	
Current												
< 2	644	0.90	0.82 to 0.99	315	0.83	0.73 to 0.94	104	1.07	0.85 to 1.35	78	0.76	0.58 to 0.98
2 to 3	186	0.89	0.76 to 1.04	106	0.92	0.75 to 1.13	35	1.27	0.89 to 1.82	21	0.72	0.46 to 1.12
4 to 5	152	0.88	0.74 to 1.04	83	0.88	0.70 to 1.10	14	0.63	0.36 to 1.08	24	1.01	0.66 to 1.54
> 5	128	0.87	0.72 to 1.04	69	0.83	0.64 to 1.06	14	0.74	0.43 to 1.27	18	0.84	0.51 to 1.36
P_{trend}		.54			.95			.11			.86	
Duration, years of use by status												
Nonuser	1,680	1.0	Reference	924	1.0	Reference	234	1.0	Reference	249	1.0	Reference
Past												
≤ 5	829	0.93	0.85 to 1.02	466	0.93	0.83 to 1.04	105	0.89	0.70 to 1.13	118	0.85	0.68 to 1.07
6 to 10	337	0.94	0.84 to 1.07	178	0.89	0.75 to 1.05	41	0.89	0.63 to 1.25	55	1.03	0.76 to 1.40
> 10	49	0.80	0.59 to 1.06	29	0.94	0.64 to 1.37	7	0.99	0.46 to 2.15	2	0.24	0.06 to 0.99
P_{trend}		.75			.94			.28			.33	
Current												
≤ 5	570	0.92	0.83 to 1.02	270	0.83	0.72 to 0.96	94	1.11	0.87 to 1.43	74	0.83	0.63 to 1.09
6 to 10	403	0.85	0.76 to 0.96	248	0.91	0.79 to 1.05	50	0.82	0.60 to 1.13	61	0.86	0.64 to 1.14
> 10	226	0.90	0.78 to 1.04	105	0.78	0.63 to 0.96	35	1.12	0.77 to 1.63	22	0.66	0.42 to 1.04
P_{trend}		.16			.28			.15			.44	
Duration, years of use by dosage†												
Nonuser	1,006	1.0	Reference	566	1.0	Reference	139	1.0	Reference	131	1.0	Reference
Nonregular user (< two tablets per week)‡												
≤ 5	78	0.84	0.66 to 1.06	32	0.65	0.45 to 0.93	13	1.14	0.64 to 2.03	16	1.23	0.72 to 2.11
6 to 10	65	0.86	0.67 to 1.11	39	0.93	0.67 to 1.30	5	0.49	0.20 to 1.20	14	1.43	0.82 to 2.51
> 10	59	0.88	0.68 to 1.15	24	0.68	0.45 to 1.03	8	0.95	0.46 to 1.96	5	0.61	0.25 to 1.50
P_{trend}		.53			.45			.68			.76	
Regular user (≥ two tablets per week)‡												
≤ 5	103	1.00	0.81 to 1.22	63	1.07	0.82 to 1.39	17	1.34	0.80 to 2.22	13	1.03	0.58 to 1.83
6 to 10	114	0.76	0.62 to 0.92	77	0.86	0.67 to 1.09	15	0.75	0.44 to 1.29	8	0.42	0.21 to 0.87
> 10	224	0.87	0.75 to 1.01	113	0.81	0.65 to 0.99	28	0.85	0.56 to 1.30	28	0.90	0.59 to 1.37
P_{trend}		.89			.36			.19			.22	
Higher-dose user (≥ six tablets per week)‡												
≤ 10	104	0.87	0.71 to 1.06	69	0.95	0.74 to 1.23	17	1.05	0.63 to 1.76	7	0.46	0.21 to 0.99
> 10	141	0.89	0.74 to 1.07	74	0.85	0.66 to 1.09	19	0.93	0.57 to 1.53	18	0.93	0.56 to 1.55
P_{trend}		.86			.69			.16			.20	

Abbreviations: BMI, body mass index; ER, estrogen receptor; MET, metabolic equivalent of task; PR, progesterone receptor; RR, relative risk.

*Multivariable RRs were adjusted for age (in months), age at menarche (≤ 12, 13, or ≥ 14 years), height (< 1.60, 1.60 to < 1.65, 1.65 to < 1.70, 1.70 to < 1.75, or ≥ 1.75 m), BMI at age 18 years (< 19, 19 to < 21, 21 to < 23, or ≥ 23 kg/m^2), weight change since age 18 years (≤ −2, > −2 to < 2, 2 to < 10, 10 to < 20, or ≥ 20 kg), parity and age at first birth (nulliparous; one to two children, < 25 years; one to two children, ≥ 25 years; ≥ three children, < 25; ≥ three children, ≥ 25 years), history of breast cancer in parent or sibling (yes or no), history of benign breast disease (yes or no), alcohol consumption (0, > 0 to < 5, 5 to < 15, or ≥ 15 g per day), physical activity (< 3, 3 to < 27, or ≥ 27 MET-hours per week), and postmenopausal hormone use (never; past; current user, < 5 years; or current user, ≥ 5 years).

†No. of nonusers was less, because the information on dosage (tablets per week) was not measured until 1998.

‡Regular aspirin user was defined as consumption of ≥ two standard 325-mg tablets per week. Nonregular user was defined otherwise.

Table 5. Multivariable RRs* of Postmenopausal Breast Cancer Subtypes According to Use of Aspirin, Nonaspirin NSAIDs, and Acetaminophen in the Nurses' Health Study

Details of Use	Luminal A			Luminal B			Triple Negative			HER2 Positive			COX-2 Positive			COX-2 Negative		
	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI	No. of Patients	RR*	95% CI
Duration of aspirin use, years																		
Nonuser	137	1.0	Reference	19	1.0	Reference	38	1.0	Reference	18	1.0	Reference	63	1.0	Reference	155	1.0	Reference
Regular user (≥ two tablets per week)†																		
≤ 10	64	0.66	0.49 to 0.89	19	1.47	0.76 to 2.82	23	1.19	0.70 to 2.02	4	0.41	0.14 to 1.22	40	0.90	0.60 to 1.36	91	0.88	0.67 to 1.14
> 10	140	0.75	0.58 to 0.96	36	1.40	0.79 to 2.51	73	0.83	0.54 to 1.26	50	0.98	0.55 to 1.75	69	0.82	0.57 to 1.18	195	0.97	0.78 to 1.21
P_{trend}		.55			.52			.32			.71			.37			.66	
Duration of nonaspirin NSAID use, years																		
Nonuser	245	1.0	Reference	46	1.0	Reference	104	1.0	Reference	55	1.0	Reference	120	1.0	Reference	291	1.0	Reference
Any use																		
≤ 5	131	0.83	0.66 to 1.03	38	1.33	0.85 to 2.06	67	0.76	0.55 to 1.04	38	0.85	0.56 to 1.30	76	0.98	0.73 to 1.31	173	0.88	0.72 to 1.07
> 5	24	0.91	0.58 to 1.43	11	2.32	1.09 to 4.93	67	0.87	0.61 to 1.22	35	0.73	0.46 to 1.14	13	0.81	0.44 to 1.50	37	1.26	0.86 to 1.84
P_{trend}		.28			.01			.98			.56			.13			.12	
Duration of acetaminophen use, years																		
Nonuser	218	1.0	Reference	42	1.0	Reference	102	1.0	Reference	54	1.0	Reference	93	1.0	Reference	264	1.0	Reference
Any use																		
≤ 5	159	0.87	0.71 to 1.08	46	1.33	0.87 to 2.03	81	0.85	0.63 to 1.14	40	0.77	0.51 to 1.16	102	1.35	1.01 to 1.80	212	0.92	0.77 to 1.11
> 5	23	0.83	0.53 to 1.32	7	1.30	0.55 to 3.09	55	0.75	0.53 to 1.06	34	0.79	0.50 to 1.23	14	1.05	0.58 to 1.91	25	0.75	0.48 to 1.15
P_{trend}		.41			.49			.03			.73			.16			.08	

Abbreviations: BMI, body mass index; COX-2, cyclooxygenase-2; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; MET, metabolic equivalent of task; NSAID, nonsteroidal anti-inflammatory drug; PR, progesterone receptor; RR, relative risk; TMA, tissue microarray.

*Multivariable RRs were adjusted for age (in months), age at menarche (≤ 12, 13, or ≥ 14 years), height (< 1.60, 1.60 to < 1.65, 1.65 to < 1.70, 1.70 to < 1.75, or ≥ 1.75 m), BMI at age 18 years (< 19, 19 to < 21, 21 to < 23, or ≥ 23 kg/m^2), weight change since age 18 years (≤ −2, > −2 to < 2, 2 to < 10, 10 to < 20, or ≥ 20 kg), parity and age at first birth (nulliparous; one to two children, < 25 years; one to two children, 25 to 29 years; one to two children, ≥ 30 years; ≥ three children, < 25; ≥ three children, 25 to 29 years; or ≥ three children, ≥ 30 years), history of breast cancer in parent or sibling (yes or no), history of benign breast disease (yes or no), alcohol consumption (0, > 0 to < 5, 5 to < 15, or ≥ 15 g per day), physical activity (< 3, 3 to < 27, or ≥ 27 MET-hours per week), and postmenopausal hormone use (never; past; current user, < 5 years; or current user, ≥ 5 years). Given that data on dose (tablets per week) of nonaspirin NSAID and acetaminophen use were not queried until 1998, and the TMA data for the molecular subtypes were available up to 2000, we presented total duration of use for these two drugs to have reasonable No. of patients for each subtype.

†One tablet is defined as consumption of one 325-mg standard tablet.

was observed (≥ six tablets per week for at least 10 years *v* nonuse: RR, 0.73; 95% CI, 0.54 to 1.00; P_{trend} = .80). Because pre- and postdiagnostic aspirin use are correlated, it is unclear what time period of use may be most relevant, and we will need to address this issue with further follow-up within the context of a survival analysis. Several animal studies suggested a role of platelet aggregation in cancer metastasis,[48-50] and aspirin may prevent such experimentally induced metastasis in mice,[51] which was also supported by a recent human study of incident cancers across multiple randomized controlled trials (only six cases of breast cancer included).[52] Given the apparent different associations observed for breast cancer risk versus survival, research to identify the potential difference in effect of aspirin use on breast cancer initiation, progression, and metastasis is warranted.

Although suggestive differences in aspirin or NSAID effects on these subtypes of breast cancer were observed in the only prior study to our knowledge,[29] largely no substantial associations were noted for luminal A, luminal B, triple-negative, basal-like, HER2-positive, or COX-2 status in our study. However, because patient numbers were small in a number of these comparisons, only large differences in associations would be detected. In a prior study in our cohort, aspirin use was associated only with colon tumors that expressed COX-2.[53] Given that we observed no variation of the association by COX-2 expression, any influence of aspirin/NSAIDs on risk may not be primarily through a COX-2 pathway; however, data on the correlation between COX-2 expression in normal versus breast tumor tissue are limited,[54] and normal tissue expression may be more important in determining risk. Future studies that examine the correlation of COX-2 expression between normal and malignant breast tissue and also incorporate data on genetic polymorphisms of the *COX-2* gene may provide more insight.

Unlike NSAIDs, acetaminophen has no or little anti-inflammatory effect. However, acetaminophen might decrease estrogen levels.[55] Early epidemiologic studies have been mixed, with suggestive inverse[56-59] or null associations reported[16,19,22-25,43] and no clear patterns emerging by frequency, dose, or duration of use. Similarly, our data suggest no consistent associations, although statistical power was more limited than in our aspirin analyses.

Our study had several limitations. Our study population was registered nurses who were mainly of European origin and more educationally or socioeconomically homogeneous than the general population, which might decrease the generalizability of our results. In addition, some misclassification resulting from the self-reported analgesic use is probable. However, inverse associations between aspirin/NSAID use and colorectal cancer risk[33,34] have been observed in our cohort, as reported in randomized clinical trials.[46] Lastly, although our study was large overall, we had limited patient numbers for several specific molecular subtypes.

Strengths of our study included the prospective design, large size, adult lifetime analgesic use, and long follow-up time with high follow-up rate. Separately collected information on both aspirin and nonaspirin NSAIDs allowed us to evaluate the associations with these drugs separately and combined.

In summary, our large prospective study did not support an important role of aspirin, nonaspirin NSAIDs, or acetaminophen use in breast cancer incidence among postmenopausal women. Additional large prospective studies of specific breast cancer subtypes and studies in premenopausal women and in breast cancer survivors would be informative.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Xuehong Zhang, Stephanie A. Smith-Warner, Walter C. Willett, Susan E. Hankinson
Financial support: Susan E. Hankinson
Collection and assembly of data: Xuehong Zhang, Walter C. Willett, Susan E. Hankinson
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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