

Association of Aspirin and Nonsteroidal Anti-inflammatory Drug Use with Breast Cancer¹

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Abstract

Objective: Previous epidemiological studies have suggested that use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) may be associated with reduced risk of breast cancer, but some studies have been limited in their ability to separate the effects of aspirin from other NSAIDs or to account for breast cancer risk factors.

Methods: We examined the incidence of breast cancer in association with self-reported aspirin, as well as other nonaspirin NSAID use in a large prospective cohort of postmenopausal women ($n = 27,616$). Over 6 years of follow-up, 938 incident breast cancers were identified.

Results: After adjustment for other breast cancer risk factors, any current use of aspirin or other NSAIDs compared with no use was associated with a reduction in risk of breast cancer [relative risk (RR) = 0.80, 95% confidence interval (CI) 0.67–0.95]. There was a trend of decreasing risk of incident breast cancer with increasing frequency of aspirin use ($P_{\text{trend}} = 0.0011$). The multivariate-adjusted RR of breast cancer was 0.71 (95% CI 0.58–0.87) for women who reported using aspirin six or more times per week compared with women who reported no use. These results did not depend on whether women had early or late stage breast cancer. No association was found between nonaspirin NSAID use and incident breast cancer. The adjusted RR of using other NSAIDs six or more times per week compared with no use was 1.01 (95% CI 0.83–1.25).

Conclusion: This prospective study corroborates other reports that use of aspirin might reduce risk of breast cancer.

Introduction

NSAIDs,³ widely used for pain relief, include many over-the-counter drugs, such as aspirin and ibuprofen, as well as pre-

scription drugs, such as celecoxib. These drugs, particularly aspirin, have been reported in a number of observational epidemiological studies to be associated with reduced risk of coronary heart disease and colorectal cancer (1, 2). Fewer studies have been conducted to assess the association between NSAIDs and breast cancer.

One action common to NSAIDs is the inhibition of COX-1 and -2, the rate-limiting enzymes in the conversion of arachidonic acid to prostaglandins (3). Prostaglandins are important mediators of signal transduction pathways, which in turn modify cellular adhesion, growth, and differentiation (3). Elevated prostaglandin synthesis may promote carcinogenesis through mechanisms ranging from direct mutagenesis (one byproduct of arachidonic acid metabolism is malondialdehyde, a direct-acting mutagen) to increased cell proliferation, immune suppression, tumor promotion, and facilitation of metastasis (4–7). The chemopreventive potential of NSAIDs is thought to be through COX inhibition; however, NSAIDs comprise many compounds, and other mechanisms of action are not fully understood.

An inhibitory effect of various NSAIDs on mammary tumor development has been shown in rodents (8, 9). Cellular and animal data have shown that levels of prostaglandins are high in breast and colon cancer cells. In human studies, elevated levels of prostaglandins have been linked to metastatic potential and poorer survival of patients (10, 11). The COX-2 gene is overexpressed in breast tumors and cancer cell lines but not in normal breast tissue (12–14). Moreover, the level of COX-2 enzyme present in the tumor tissue is directly proportional to the density of cancer cells (14). Changes in COX-1 expression are not consistently observed in breast cancer cells, *e.g.*, estrogen-dependent MCF-7 breast cancer cells have a high expression of COX-1, whereas estrogen-independent, highly invasive, and metastatic MDA-MB-231 breast cancer cells showed a low expression of COX-1 (3).

Epidemiological data have shown either no association or inverse associations of breast cancer with NSAID or aspirin use (Table 1). Three prospective studies (15–17) and two case-control studies (18, 19) reported no statistically significant association between the use of NSAIDs and risk of breast cancer. In contrast, two prospective studies (20, 21) and four case-control studies (5, 22–24) found a significant inverse association between risk of breast cancer and NSAID use. The RRs ranged from 0.6 to 1.1 in the case-control studies and from 0.6 to 1 in the cohort studies for women who regularly used aspirin or NSAIDs compared with those who did not. Some of these studies have been limited in their ability to separate the effects of aspirin from other NSAIDs or account for breast cancer risk factors.

We report here on the association between NSAID use and incidence of postmenopausal breast cancer in a large cohort. In this study, information was collected about known risk factors for breast cancer, as well as current use of aspirin and other

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³ The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; COX, cyclo-oxygenase; RR, relative risk; CI, confidence interval; BMI, body mass index.

Table 1 Previous studies on the association between NSAID use and breast cancer

Study	Type	Cases	Population	RR	95% CI	Contrast ^a	Adjustment
Schreinemachers, <i>et al.</i> (21) (NHANES)	Cohort	147	12,688	0.70	0.50–0.96	Any use of aspirin in last 30 days	Age
Thun, <i>et al.</i> (17) (ACS)	Cohort (mortality)	Not given	638,031	0.98	0.76–1.26	1–15 aspirin per month	Age
Harris, <i>et al.</i> (20)	Cohort	393	32,505	0.88	0.62–1.24	16+ aspirin per month	Age
				0.57	0.44–0.74	4+ aspirin/NSAIDs per week	Multivariate
				0.64	0.45–0.90	4+ aspirin per week	Multivariate
Paganini-Hill, <i>et al.</i> (16)	Cohort	214	8,881	0.49	0.30–0.80	4+ ibuprofen per week	Multivariate
				0.96	nonsignificant	Daily aspirin use	Age
Egan, <i>et al.</i> (15) (Nurses Health Study)	Cohort	2414	89,528	1.03	0.95–1.12	2+ aspirin per week	Multivariate
Harris, <i>et al.</i> (5)	Case control	303	906	0.64	0.47–0.89	3+ aspirin/NSAIDs per week for 1+ yrs	Multivariate
				0.60	0.37–0.96	7+ aspirin/NSAIDs per week for 5+ yrs	Multivariate
Harris, <i>et al.</i> (23)	Case control	511	1,534	0.66	0.52–0.83	3+ aspirin/NSAIDs per week for 1+ yrs	Multivariate
Harris, <i>et al.</i> (24)	Case control	744	767	0.63	0.46–0.87	5+ aspirin/NSAIDs use	Multivariate
				0.80	0.7–1.0	Cancer controls, aspirin/NSAIDs regular use 1+ yrs	Multivariate
Coogan, <i>et al.</i> (22)	Case control	6558	3,296	0.70	0.6–0.9	Noncancer controls, aspirin/NSAIDs regular use	Multivariate
			2,925	0.70	0.6–0.9	Noncancer controls, aspirin/NSAIDs regular use	Multivariate
Rosenberg (18)	Case control	4485	1,181	0.90	0.6–1.2	Cancer controls, aspirin/NSAIDs generally	Multivariate
			4,906	0.80	0.6–1.0	Noncancer controls, aspirin/NSAIDs generally	Multivariate
Langman, <i>et al.</i> (19)	Case control	3105	9,272	1.12	0.90–1.40	≥7 NSAID prescriptions 25–36 months before dx	Age, gender

^a Reference group for RR estimates was nonuse.

types of NSAIDs; thus, we were able to overcome some of the limitations of previous research.

Materials and Methods

Study Population and Follow-Up for Cancer Outcomes. In 1986, a random sample of 99,826 women who had a valid Iowa driver's license and were between the ages of 55 and 69 years was conducted. A detailed mailed questionnaire was completed by 41,836 women, corresponding to a response rate of 42%. These women constituted the Iowa Women's Health Study cohort. Nonrespondents have been characterized and found to have breast cancer rates virtually identical to respondents (25). Follow-up questionnaires were sent in 1987 (91% response rate of the original cohort), 1989 (89% response), 1992 (83% response), and 1997 (79% response) to update exposure information, residence, and vital status. Deaths in nonrespondents and emigrants from Iowa were found through the National Death Index. Breast cancer incidence was ascertained by linkage to the State Health Registry of Iowa, which is part of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program. Linkage used name, address, maiden name, birth date, and social security number. Incident breast cancer included *in situ* breast cancer, as well as localized and distant disease.

Exposure Assessment. NSAID and aspirin use was collected from this cohort only in 1992. The respondents were asked how often they currently took aspirin in the first of two questions pertaining to NSAID use. The question included examples of aspirin-containing products: Bufferin, Anacin, enteric-coated aspirin, Ecotrin, and Excedrin. The second question asked about use of other NSAIDs or arthritis medicines and included examples: (a) ibuprofen; (b) Advil; (c) Nuprin; (d) Motrin; (e) Naprosyn; (f) Feldene; and (g) Clinoril. Both questions specifically directed respondents to exclude use of acetaminophen or Tylenol. The categories for frequency of use for both questions were: (a) current nonusers or (b) current users with a frequency of less than once per week; (c) once per week; (d) two to five times per week; and (e) six or more times per week.

Current weight (to calculate BMI), current use of estrogen

replacement, current alcohol intake, current smoking status, and any diagnoses of arthritis and migraines were assessed from the 1992 follow-up survey data. Other variables were obtained from the 1986 baseline questionnaire. These included sociodemographic information, height, waist:hip ratio, age at menarche, parity, age at first live birth, age at menopause, history of benign breast disease, and use of multivitamins. History of mammography screening was available from the 1989 follow-up questionnaire. To assess overall family history of breast cancer in a first-degree relative and personal history of cardiovascular disease before 1992, a combination of baseline and follow-up surveys was used.

Data Analysis. We excluded women who reported at baseline in 1986 that they were premenopausal ($n = 569$), had a cancer other than skin cancer ($n = 2,293$), or had a previous total or partial mastectomy ($n = 1,870$). Women with incident cancer between the 1986 questionnaire and the follow-up questionnaire in 1992 were also excluded ($n = 2,512$). Women who developed lobular carcinoma *in situ* breast cancer ($n = 10$) between 1992 and 1999 were excluded from the analysis, but women with ductal carcinoma *in situ* were included. Further exclusion of women who did not complete the 1992 follow-up questions regarding aspirin and NSAID use ($n = 6,970$) left 27,616 women who were followed for incident breast cancer. A total of 938 cases of breast cancer were ascertained from the time of the questionnaire in 1992 until December 31, 1999.

The length of follow-up time for each woman was calculated from the date of completion of the 1992 follow-up questionnaire to one of the following events, listed in descending order of priority: (a) the date of diagnosis of breast cancer, (b) the date of death (if the death occurred in Iowa); (c) the date the woman moved out of Iowa (if known); (d) the midpoint of the interval between the last follow-up contact and December 31, 1999 (if the date of the woman's departure from Iowa was unknown); or (e) the midpoint of the interval between the date of last contact and the date of death (for deaths in women who had moved from Iowa). Women for whom these criteria did not apply were assumed to be living in Iowa and contributed follow-up data until December 31, 1999.

Table 2 Prevalence (%) of participant characteristics by frequency of aspirin or other NSAID use

Times per week Characteristic	Aspirin					NSAIDs				
	0 n = 7752	<1 n = 7608	1 n = 1515	2-5 n = 4860	6+ n = 5876	0 n = 16622	<1 n = 4215	1 n = 836	2-5 n = 2253	6+ n = 3595
Age (years) ^a										
61-65	35	40	35	38	34	35	42	36	39	37
66-70	36	35	36	35	35	36	35	38	34	36
71+	29	24	29	27	31	29	23	25	26	28
BMI \geq 30 kg/m ^{2a}	26	22	23	23	27	21	24	27	28	37
Waist:hip ratio \geq 0.8278 ^a	52	46	51	49	54	49	48	51	51	56
Benign breast disease ^a	19	20	19	19	21	19	21	19	21	21
Family history of breast cancer ^a	12	12	12	12	12	12	12	10	12	12
Current estrogen replacement ^b	16	16	18	18	19	15	19	18	19	23
Current multivitamin use ^a	31	31	34	35	37	32	34	37	37	38
History of arthritis ^b	27	17	19	21	33	17	19	22	34	59
History of migraines ^b	9	7	8	11	13	8	10	11	13	14
History of cardiovascular disease ^b	12	7	9	10	22	12	10	11	12	16
History of mammography ^b	64	64	65	67	69	63	68	68	69	71

^a Reported at baseline.^b Reported before 1992.

Person-years were calculated for individuals in each aspirin and NSAID exposure category. Incidence of breast cancer was calculated by dividing the number of new cases by the number of person-years of follow-up for each exposure category. Analyses were first performed to assess the association between any NSAID (aspirin and other NSAIDs) use and breast cancer, relative to nonusers. Subsequent analyses were conducted to assess the independent effects of any aspirin use or any nonaspirin NSAID use, compared with nonusers. In these analyses, nonusers of aspirin or NSAIDs comprised the reference group, depending on which exposure was being assessed, with adjustment for the other type of NSAIDs. Age-adjusted and multivariate-adjusted RRs and 95% CIs were calculated using proportional hazards regression models (SAS Institute, Inc.; Ref. 26). The trend test option in the proportional hazards regression model was used to test for trend in RRs using ordinal categories of increasing frequency of aspirin or other nonaspirin NSAID use. To examine a potential interaction of the combined use of aspirin and other NSAIDs on risk of breast cancer, nine categories combining the frequency of aspirin and NSAID use were created ranging from no reported current use of either drug (reference) to high frequency of reported use of both aspirin and other NSAIDs. Results were also stratified by stage of breast cancer, *i.e.*, ductal carcinoma *in situ*, local, or regional/distant disease.

Results

In this cohort, 28% of respondents reported no current use of aspirin, 28% reported using aspirin less than once per week, 5% reported using aspirin once per week, 18% reported using aspirin two to five times per week, and 21% reported using aspirin six or more times per week. The corresponding frequencies for other nonaspirin NSAID agents were 61, 15, 3, 8, and 13%. Current aspirin users were just as likely as aspirin nonusers to report use of other NSAIDs.

Women reporting arthritis, migraines, or a history of cardiovascular disease were more likely to use aspirin or other NSAIDs (Table 2) than women without these conditions, *e.g.*, 17% of women taking no NSAIDs reported having arthritis compared with 59% of women taking six or more NSAIDs per week. There was a tendency for women with a BMI \geq 30 kg/m² compared with those with a BMI < 30 kg/m² to use nonaspirin

NSAIDs more frequently. Women using aspirin or other NSAIDs frequently were also somewhat more likely to be using postmenopausal estrogen and multivitamins and have had a previous screening mammography. The distribution of other known breast cancer risk factors did not differ between aspirin and nonaspirin NSAID users, nor were they associated with frequency of aspirin or other nonaspirin NSAID use (data not shown).

From 1992 to 1999 (~190,000 person-years), 938 incident cases of breast cancer were identified. Risk factors for breast cancer among these women included age, BMI (RR = 1.32, 95% CI 1.15-1.52 for \geq 30 kg/m² versus <30 kg/m²), waist:hip ratio (RR = 1.14, 95% CI 1-1.29 for \geq 0.8278 versus <0.8278, the median value), history of benign breast disease (RR = 1.41, 95% CI 1.22-1.63), family history of breast cancer in a first degree relative (RR = 1.51, 95% CI 1.28-1.79), current estrogen replacement use (RR = 1.35, 95% CI 1.15-1.58), and baseline multivitamin use (inversely, RR = 0.87, 95% CI 0.76-1). Age at menarche, age at menopause, parity, age at first live birth, and current alcohol use were reported previously to be associated with breast cancer incidence in this cohort, but these relationships did not hold for women diagnosed with breast cancer since 1992.

After accounting for age, or for age and other breast cancer risk factors, any current use of aspirin or other NSAIDs relative to no users (Table 3) was 0.8 (95% CI 0.67-0.95). This reduction in risk appeared to be confined to aspirin users. The multivariate-adjusted RR of any current use of aspirin compared with no use of aspirin, adjusted for use of nonaspirin NSAIDs, was 0.82 (95% CI 0.71-0.95). Compared with nonusers of aspirin, the RRs of breast cancer for women who reported using two to five aspirin per week or six or more aspirin per week were 0.8 (95% CI 0.65-0.99) and 0.71 (95% CI 0.58-0.87), respectively. In contrast, current use of nonaspirin NSAIDs, adjusted for current aspirin use (Table 3), was not associated with breast cancer incidence ($P_{\text{trend}} = 0.63$).

The association of current aspirin use with breast cancer occurrence was not modified nor appreciably confounded by other NSAID use. Women who used both aspirin and other NSAIDs six or more times per week had an RR of 0.6 (95% CI 0.39-0.97) for breast cancer compared with women who reported no use of either aspirin or other NSAIDs. Among

Table 3 Association between aspirin and NSAID use and incident breast cancer

	No. of cases	Total person-years	Age-adjusted RR	95% CI	Multivariate-adjusted RR ^a	95% CI
Aspirin or NSAID use ^b						
Nonusers	180	32,179	1.00		1.00	
Any use	749	156,082	0.86	0.73–1.02	0.80	0.67–0.95
Aspirin use						
Nonusers	300	52,622	1.00		1.00	
Any use	638	137,232	0.82	0.71–0.94	0.82	0.71–0.95
NSAID use						
Nonusers	554	114,172	1.00		1.00	
Any use	383	75,041	1.06	0.93–1.21	0.98	0.85–1.14
Aspirin use						
Nonusers	300	52,622	1.00		1.00	
<1 per week	256	52,956	0.85	0.72–1.03	0.87	0.72–1.04
1 per week	60	10,458	1.01	0.76–1.33	1.09	0.81–1.46
2–5 per week	155	33,743	0.81	0.67–0.98	0.80	0.65–0.99
6+ per week	167	40,075	0.73	0.60–0.88	0.71	0.58–0.87
			<i>P</i> trend = 0.0016		<i>P</i> trend = 0.0011	
NSAID use						
Nonusers	554	114,172	1.00		1.00	
<1 per week	151	29,128	1.08	0.90–1.29	1.08	0.89–1.31
1 per week	15	5,978	0.52	0.31–0.87	0.47	0.26–0.83
2–5 per week	79	15,507	1.06	0.84–1.34	0.93	0.71–1.21
6+ per week	138	189,213	1.17	0.97–1.41	1.01	0.83–1.25
			<i>P</i> trend = 0.22		<i>P</i> trend = 0.63	

^a Adjusted for age (continuous), BMI (continuous), estrogen use (current or not current), family history of breast cancer (yes or no), benign breast disease (yes or no), multivitamin use (yes or no), NSAID use five categories), mammography (yes or no), and waist:hip ratio (continuous).

^b Aspirin analyses are adjusted for NSAIDs, and NSAID analyses are adjusted for aspirin use.

Table 4 Joint association of aspirin and NSAID use and breast cancer incidence^a

	Aspirin ^b		
	Nonusers	<1–5 per week	6+ per week
Nonusers	1 (Referent)	0.79 (0.65–0.97)	0.74 (0.57–0.95)
NSAID			
<1–5 per week	0.69 (0.48–0.98)	0.92 (0.73–1.15)	0.57 (0.39–0.85)
6+ per week	1.11 (0.83–1.50)	0.76 (0.54–1.08)	0.6 (0.38–0.97)

^a Adjusted for age (continuous), BMI (continuous), estrogen use (current or not current), family history of breast cancer (yes or no), benign breast disease (yes or no), multivitamin use (yes or no), mammography (yes or no), and waist:hip ratio (continuous).

^b Aspirin analyses are adjusted for NSAIDs, and NSAID analyses are adjusted for aspirin use.

women who reported no use of nonaspirin NSAIDs, risk estimates for the associations between aspirin use and breast cancer were similar to those reported in Table 4. Likewise, there was little change in the RRs for nonaspirin NSAIDs users compared with women who used neither drug.

We examined the association between aspirin use and breast cancer stratified by early or late stage breast cancer. The dose-response trend in breast cancer incidence associated with increasing use of aspirin was significant among women diagnosed with *in situ* breast cancer or late stage disease. The strongest inverse associations were observed among the heaviest aspirin users, regardless of stage of disease (Table 5). The RR of breast cancer associated with current use of aspirin six or more times per week, *versus* no use, was 0.52 (95% CI 0.3–0.9) for *in situ* disease, 0.8 (95% CI 0.63–1.03) for localized disease, and 0.5 (95% CI 0.29–0.88) for late stage disease.

Discussion

Results from this study provide evidence that aspirin use, but not other NSAIDs, may be associated with lower breast cancer risk among postmenopausal women. A clear dose-response trend of decreasing risk of breast cancer incidence with increasing intake of aspirin was observed. The inverse association appears to be limited to some minimum frequency of aspirin use of at least several times per week. This trend remained after adjustment for nonaspirin NSAID use, as well as for other breast cancer risk factors, including age, BMI, estrogen use, family history of breast cancer, history of benign breast disease, multivitamin use, previous mammography, and waist:hip ratio. Reported intake of aspirin six or more times per week compared with no current use was inversely associated with *in situ*, localized, and late stage breast cancer.

Five prospective studies examined the relationship between aspirin or NSAID use and breast cancer (20, 21); three reported null results, and two reported statistically significantly reduced risks of breast cancer. Three of the five studies adjusted only for age (16, 17, 21), whereas two adjusted for other breast cancer risk factors (15, 20). Frequency of aspirin or nonaspirin NSAID use was not measured consistently across these studies, and only one reported on the effect of aspirin use separately from other NSAIDs (20).

The three prospective studies that found no association of NSAID use with breast cancer (15–17) differed from our study in that breast cancer mortality was the end point in one study (17), a much older population (mean age of 73) of limited size ($n = 214$ cases) was studied in another (16), and premenopausal women were included in the third (15). The American Cancer Society study found use of aspirin was associated with a significantly reduced mortality from colon and digestive cancers but only a slightly and nonsignificantly reduced risk of breast cancer mortality (17). The Nurses' Health Study found no association between frequency of aspirin use (two or more

Table 5 Association between aspirin and NSAIDs and incident breast cancer by extent of disease^a

	<i>In situ</i> disease <i>n</i> = 130 cases <i>n</i> = 26,663 noncases		Local disease <i>n</i> = 629 cases <i>n</i> = 26,663 noncases		Regional or distant disease <i>n</i> = 171 cases <i>n</i> = 26,663	
	Multivariate-adjusted RR	95% CI	Multivariate-adjusted RR	95% CI	Multivariate-adjusted RR	95% CI
Aspirin use						
Nonuse	1.00		1.00		1.00	
<1 per week	0.57	0.35–0.94	0.90	0.72–1.12	1.10	0.72–1.67
1 per week	1.22	0.61–2.44	0.93	0.63–1.37	1.71	0.93–3.13
2–5 per week	0.52	0.28–0.95	0.85	0.65–1.09	0.97	0.59–1.58
6+ per week	0.52	0.30–0.90	0.80	0.63–1.03	0.50	0.29–0.88
	<i>P</i> trend = 0.03		<i>P</i> trend = 0.077		<i>P</i> trend = 0.016	
NSAID use						
Nonuse	1.00		1.00		1.00	
<1 per week	1.35	0.83–2.21	1.05	0.83–1.33	1.03	0.66–1.61
1 per week			0.52	0.27–1.01	0.58	0.18–1.84
2–5 per week	0.67	0.29–1.56	0.95	0.69–1.31	0.95	0.52–1.74
6+ per week	1.28	0.77–2.13	1.03	0.80–1.32	0.76	0.45–1.30
	<i>P</i> trend = 0.77		<i>P</i> trend = 0.90		<i>P</i> trend = 0.34	

^a Adjusted for age (continuous), BMI (continuous), estrogen use (current or not current), family history of breast cancer (yes or no), benign breast disease (yes or no), multivitamin use (yes or no), mammography (yes or no), and waist:hip ratio (continuous). Aspirin analyses are adjusted for NSAIDs, and NSAID analyses are adjusted for aspirin use.

aspirin per week) or extended duration of aspirin use (defined as ≥ 20 years of regular use) and breast cancer incidence (15). A study conducted in an elderly community in California found no association between daily use of aspirin and breast cancer (16).

In contrast to the prospective cohort studies, most case-control studies have reported a reduction in breast cancer risk among NSAID users. However, none of these studies distinguished aspirin from other NSAIDs in the analyses. Our study is only the second to examine nonaspirin NSAIDs separately from aspirin in relation to breast cancer, and our results for nonaspirin NSAIDs were opposite to those reported previously (20).

The fact that the degree of inhibition of COX-1 and -2 varies between different types of NSAIDs provides some biological plausibility for our findings, *e.g.*, aspirin is the only compound that covalently modifies and permanently disables COX; all other NSAIDs bind tightly but reversibly (27). Such differences might account, in part, for the differences we observed between aspirin and nonaspirin NSAIDs.

A number of studies conducted on the relationship between aspirin and nonaspirin NSAID use and colorectal cancer has found significant reduction in risk among individuals who use some type of NSAID consistently (1, 2). If a mechanism of action of NSAIDs on cancer is thought to be similar between colorectal and breast cancer, we would not expect to see a difference in results between aspirin and other NSAIDs. One possible explanation is a difference in the duration of use of aspirin *versus* other NSAIDs. Although aspirin has been available for many years, most other NSAIDs were not available over the counter before 1992 and may not have been taken for long enough to result in a detectable reduction in cancer risk.

The mechanism by which aspirin and other NSAIDs may lower the risk of incident breast cancer is not established but has been investigated in cellular and animal studies (6, 13, 14, 28, 29). Aside from the reduction of prostaglandins in response to NSAIDs, one study found that an NSAID (a sulfone metabolite of sulindac) inhibited mammary carcinogenesis in rats through a mechanism that did not involve prostaglandins (6, 30). Regardless of the mechanism, NSAIDs have shown anti-tumor effects in animal studies and have reduced both the

number and size of tumors in rodents, even when the NSAIDs are given after the exposure to a carcinogen and after microscopic tumors are present (17).

An important limitation of this study was the brief assessment of exposure to aspirin and other NSAIDs. No information was obtained on dose or duration of aspirin or nonaspirin NSAID use. Subjects' recall of use may be error prone, because these drugs are often taken sporadically. In addition, participants may have inaccurately recalled use of combination medications that contain aspirin, such as Alka-Seltzer (31). Although our results remain unchanged after adjustment for stage of disease and mammography history, there may be unmeasured lifestyle characteristics that have confounded the association. Furthermore, we had no information on osteoporosis, which has been reported recently to be associated with reduced risk of breast cancer (32). If osteoporosis were also associated with greater aspirin use, to relieve bone pain, the observed RR for aspirin could have been biased away from the null.

If use of aspirin is truly associated with reduced incidence of both localized and distant breast cancer, use of aspirin-containing compounds could have a significant public health impact. Although clinical trials to test the efficacy of aspirin to prevent breast cancer may be logical, it would be difficult to implement such trials given the widespread use of these drugs. Thus, additional observational studies with better measures of NSAID use and laboratory experiments to elucidate biological mechanisms of NSAIDs on breast carcinogenesis will be needed before concluding that NSAIDs prevent breast cancer.

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