

Breast Cancer and Nonsteroidal Anti-Inflammatory Drugs: Prospective Results from the Women's Health Initiative¹

Randall E. Harris,² Rowan T. Chlebowski, Rebecca D. Jackson, David J. Frid, Joao L. Ascenseo, Garnet Anderson, Aimee Loar, Rebecca J. Rodabough, Emily White, and Anne McTiernan

The Ohio State University College of Medicine and Public Health, Columbus, Ohio 43210-1240 [R. E. H., R. D. J., D. J. F.]; University of California at Los Angeles (UCLA), Torrance, California 90502 [R. T. C.]; George Washington University Medical Center, Washington, DC 20052 [J. L. A.]; and Fred Hutchinson Cancer Research Center, Seattle, Washington 98109 [G. A., A. L., R. J. R., E. W., A. M.]

ABSTRACT

We analyzed data from the prospective Women's Health Initiative (WHI) Observational Study to examine the effects of regular use of aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs (NSAIDs) on breast cancer risk. We studied a population of 80,741 postmenopausal women between 50 and 79 years of age who reported no history of breast cancer or other cancers (excluding nonmelanoma skin cancer), and we completed a personal baseline interview that elicited comprehensive health information including data on breast cancer risk factors and NSAID use. All of the cases were adjudicated by WHI physicians using pathology reports. Our analysis was based on 1392 confirmed cases of breast cancer. Relative risks (RRs) with 95% confidence intervals (CIs) were estimated with adjustment for age and other breast cancer risk factors. Regular NSAID use (two or more tablets/week) for 5–9 years produced a 21% reduction in the incidence of breast cancer (RR, 0.79; 95% CI, 0.60–1.04); regular NSAID use for 10 or more years produced a 28% reduction (RR, 0.72; CI, 0.56–0.91), and there was a statistically significant inverse linear trend of breast cancer incidence with the duration of NSAID use ($P < 0.01$). The estimated risk reduction for long-term use of ibuprofen (RR, 0.51; CI, 0.28–0.96) was greater than for aspirin (RR, 0.79; CI, 0.60–1.03). Subgroup analysis by breast cancer risk factors did not result in effect modification. Regular use of acetaminophen (an analgesic agent with little or no anti-inflammatory activity) or low-dose aspirin (<100 mg) was unrelated to the incidence of breast cancer. Our results indicate that the regular use of aspirin, ibuprofen, or other NSAIDs may have a significant chemopreventive effect against the development of breast cancer and underscore the need for clinical trials to confirm this effect.

INTRODUCTION

Preclinical studies have consistently shown that NSAIDs³ inhibit mammary carcinogenesis (1–5), and early epidemiological investigations provided support for NSAIDs potentially reducing the risk of human breast cancer (6–9). A recent meta-analysis examined epidemiological studies evaluating NSAID use and breast cancer risk, combining results of six cohort studies and eight case-control studies (10–21). The analysis indicated that NSAID use was associated with a significant decrease (22%) in breast cancer risk, but the data were insufficient to estimate dose-response effects for duration and frequency of use for any particular type of NSAID (22). In addition, differential influence of NSAIDs on breast cancer risk related to family history, HRT, and other breast cancer risk factors, could not be evaluated. To address these issues, we, therefore, estimated the RR of

breast cancer occurrence for selected risk factors according to type and duration of NSAID use in a large cohort of postmenopausal women participating in the WHI.

MATERIALS AND METHODS

The WHI Observational Study Cohort. The WHI includes an ongoing multicenter observational cohort study designed to address some of the major causes of morbidity and mortality in an ethnically and geographically diverse sample of postmenopausal women. Details of the scientific rationale, the eligibility, and other design aspects have been published elsewhere (23). The current report is based on an examination of data from the Observational Study of the WHI.

Participants for the WHI were identified from the general population living in proximity to the 40 participating Clinical Centers, most commonly in response to mass mailings to targeted populations. Women were excluded from the WHI for medical conditions predictive of a survival time <3 years or for conditions (such as dementia) inconsistent with study participation. Women in the Observational Study were either directly recruited or represented women screened for participation in the Clinical Trial components of the WHI but who were ineligible or unwilling to enter and were offered Observational Study participation. All of the participants signed informed consent forms. The Institutional Review Boards at all of the participating institutions, including the clinical coordinating center, subcontractors, and clinical centers, approved all of the protocols and procedures.

Measurement of Exposure. The methods of data collection and validation in the WHI Observational Study have been reported previously (23). Exposures in this analysis were collected at entry (baseline) by using a standardized protocol implemented by centrally trained clinic staff who followed a defined quality assurance program to assure uniform administration of data collection instruments. Cohort members completed self-administered questionnaires to provide information on personal demographics, medical history, reproductive history, smoking and alcohol use, family history, personal habits, thoughts and feelings about their health behavior, and recreational physical activity. Recreational physical activity was assessed by questions on the frequency and duration of several types of recreational activity and metabolic equivalent (MET) scores computed for each activity (24). A family history of breast cancer was quantified as the number of first-degree relatives [mother, sister(s), daughter(s)] who had breast cancer. During the baseline clinic visit, trained and certified Clinical Center staff performed anthropometric measurements following established protocols. BMI was calculated as weight in kilograms divided by the square of height in meters.

Details on medication usage including NSAIDs and the related analgesic, acetaminophen, were collected from an interview-administered questionnaire. Each participant was asked: "Do you take aspirin pills or powders, ibuprofen pills or tablets, other nonsteroidal anti-inflammatory pain pills (prescription drugs), or acetaminophen tablets or capsules?" For those individuals who reported using an NSAID or acetaminophen at least two times in each of the 2 weeks preceding the interview, the type of compound, strength (in milligrams), and duration of use (number of years) were recorded. These medication data were validated by checking pill bottle labels and prescription records during the interview process. Before analysis, it was decided to enroll women reporting 0–11 months of using any of these compounds as the referent category. This assured a large referent sample for statistical comparisons of long- versus short-term or no NSAID use. Each type of NSAID was first considered separately (aspirin, ibuprofen, and prescription NSAIDs such as naproxen, piroxicam, or indomethacin) and these compounds were then com-

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²To whom requests for reprints should be addressed, at College of Medicine and Public Health, The Ohio State University, Columbus, OH 43210-1240. Fax: (614) 293-3903; E-mail: harris.44@osu.edu.

³The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; WHI, Women's Health Initiative; BMI, body mass index; HRT, hormone replacement therapy; RR, relative risk; CI, confidence interval; COX, cyclooxygenase.

bined into a single NSAID variable for an examination of effects. Acetaminophen, a compound with analgesic/antipyretic properties that has relatively weak anti-inflammatory activity, and aspirin dosage less than 100 mg/day (baby aspirin) were examined separately. With respect to HRT, if a woman reported never using any female hormone such as estrogen or progesterone pills or patches for longer than 3 months, she was classified as a never user of HRT. All other women were classified as ever HRT users.

Follow-Up and Ascertainment of Cases. The WHI Observational Study follow-up is conducted using biannual mailed self-administered questionnaires (except for year 3 when a clinic follow-up visit is performed). To ascertain initial self-reports of incident breast tumors for each successive 6-month time period, each participant was asked: "Has a doctor told you for the first time that you have a new cancer or a malignant tumor? What kind of cancer or malignant tumor was it?" Completed questionnaires were mailed to the local Clinical Center for data entry and outcome processing. Potential breast cancer cases were identified through the annual follow-up questionnaires or from nonroutine contacts. Study physicians and cancer coders, blinded to exposure status, reviewed pathology reports, discharge summaries, operative reports, and radiology reports for all biopsies and surgeries, and coded breast cancer cases according to National Cancer Institute Surveillance, Epidemiology, End Results guidelines (SEER; Ref. 25). Follow-up time for each woman was accrued from enrollment to the date of diagnosis of breast cancer, death from a nonbreast cancer cause, loss to follow-up, or the administrative censor date (2/01/01).

Statistical Analyses. Our analyses used the NSAID medication data collected at study baseline. Annual incidence rates of breast cancer for the cohort of postmenopausal women were calculated according to the duration of NSAID intake at baseline (0–11 months, 1–4 years, 5–9 years, and ≥ 10 years). RRs and 95% CIs were estimated and trend tests were performed to examine the dose response of RR with increasing duration of intake. A trend variable was computed for each NSAID/analgesic exposure variable as the

median of the associated duration category for each participant, and Wald χ^2 tests were used to assess statistical significance (26). The reference level for these analyses was 0–11 months of exposure to any NSAID or the related analgesic, acetaminophen.

To evaluate potential confounding and effect modification, we also estimated RR and 95% CI by subgroup of individual breast cancer risk factors (BMI, HRT use, family history of breast cancer, parity under the age of 30, and episodes per week of exercise). For each subgroup, we used Cox multivariate regression to adjust simultaneously for age, ethnicity, education, and main effects of the remaining breast cancer risk factors (26). Participants without complete data for all variables (13,855 participants) were excluded from subgroup analyses.

RESULTS

A total of 93,676 postmenopausal women were enrolled in the WHI Observational Study. To be eligible for inclusion in the analysis, medication usage had to be known from baseline assessment and women must have had follow-up (either a medical outcome or medical update by the time of the analysis) regarding breast cancer status. Women who had a history of cancer (other than nonmelanoma skin cancer) at study enrollment ($n = 12,075$) and women who either had no baseline medication data or had no follow-up time (had no outcome or medical update by the analysis date, $n = 860$) were excluded from the original cohort. The final analysis cohort included 80,741 women with an average follow-up of 43 months, among whom 1,392 adjudicated breast cancers were identified. The annual incidence of breast cancer in the WHI Observational Study (481 cases/100,000) is similar to the incidence of breast cancer estimated for women over the

Table 1 Demographic characteristics and breast cancer risk factors by duration of NSAID exposure in the WHI Observational Study

Characteristic or breast cancer risk factor ^a	Duration of NSAID exposure							
	0–11 mo		1 to <5 yr		>5 yr		Total	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Age at screening, yr								
50–59	18,999	72.0	3,207	12.2	4,176	15.8	26,382	32.7
60–69 ^b	23,586	66.3	5,607	15.8	6,401	18.0	35,594	44.1
70–79 ^b	11,517	61.4	3,433	18.3	3,815	20.3	18,765	23.2
Race/ethnicity								
White	43,723	65.1	10,569	15.7	12,884	19.2	67,176	83.2
Black ^b	4,834	74.3	893	13.7	775	11.9	6,502	8.1
Hispanic ^b	2,404	76.5	390	12.4	347	11.0	3,141	3.9
Native American	246	69.7	45	12.7	62	17.6	353	0.4
Asian/Pacific Islander ^b	2,088	85.8	195	8.0	151	6.2	2,434	3.0
Unknown ^b	807	71.1	155	13.7	173	15.2	1,135	1.4
Education								
\leq HS diploma/GED	11,173	65.2	2,817	16.4	3,143	18.3	17,133	21.4
Some school after HS	19,159	65.7	4,568	15.7	5,418	18.6	29,145	36.4
College degree or higher ^b	23,321	69.0	4,763	14.1	5,725	16.9	33,809	42.2
BMI (kg/m ²)								
<27	31,622	69.2	6,366	13.9	7,710	16.9	45,698	57.3
≥ 27 ^b	21,825	64.0	5,756	16.9	6,520	19.1	34,101	42.7
HRT use (ever)								
No	22,340	70.3	4,514	14.2	4,915	15.5	31,769	39.3
Yes ^b	31,762	64.9	7,733	15.8	9,477	19.4	48,972	60.7
Family history of breast cancer								
No	41,813	67.4	9,347	15.1	10,890	17.6	62,050	81.2
Yes	9,407	65.7	2,203	15.4	2,710	18.9	14,320	18.8
Parous under age 30								
No	11,204	69.3	2,265	14.0	2,688	16.6	16,157	22.3
Yes ^b	37,228	66.0	8,759	15.5	10,406	18.5	56,393	77.7
Episodes/wk of exercise (≥ 20 min)								
<2	27,105	65.8	6,420	15.6	7,649	18.6	41,174	51.6
≥ 2 ^b	26,266	68.1	5,706	14.8	6,623	17.2	38,595	48.4
Total	54,102	67.0	12,247	15.2	14,292	17.8	80,741	100.0

^a NSAID exposure includes aspirin, ibuprofen, prescription NSAIDs, and the related analgesic, acetaminophen. Subgroup comparisons of the distribution of duration of NSAID exposure were assessed using χ^2 tests. Each subgroup is compared with the underlined reference subgroup.

^b Subgroup comparisons with $P < 0.0001$.

^c HS, high school; GED, General Equivalency Diploma.

Table 2 Breast cancer incidence rates, RRs, and 95% CIs by NSAID type and duration in the WHI Observational Study

Type of NSAID	Duration of use at baseline	n	Breast cancer cases	Person-years at risk	Incidence per 100,000 person-years	Age-adjusted RR		Test for linear trend <i>P</i>
						RR	95% CI	
Reference ^a	0–11 mo	54,102	955	194,884	490.04	1.00	N/A ^b	N/A
Any NSAID	1–4 yr	9,000	149	32,127	463.79	0.93	(0.78–1.10)	0.01
	≥5 yr	10,162	148	36,576	404.64	0.81	(0.68–0.97)	
Regular aspirin	1–4 yr	5,124	83	18,231	455.27	0.90	(0.72–1.13)	0.03
	≥5 yr	6,759	99	24,398	405.76	0.81	(0.66–0.99)	
Ibuprofen	1–4 yr	3,469	51	12,553	406.26	0.83	(0.63–1.10)	0.12
	≥5 yr	2,976	42	10,653	394.26	0.82	(0.60–1.12)	
Prescription NSAID	1–4 yr	1,615	31	5,552	558.31	1.14	(0.79–1.62)	0.21
	≥5 yr	947	11	3,388	324.71	0.64	(0.36–1.17)	
Acetaminophen	1–4 yr	2,450	44	8,608	511.18	1.02	(0.75–1.37)	0.71
	≥5 yr	4,675	79	16,698	473.11	0.96	(0.76–1.20)	

^a The reference category includes women who reported 0–11 months of NSAID use (aspirin, ibuprofen, prescription NSAIDs, or the related analgesic, acetaminophen).

^b N/A, not applicable.

age of 50 from 1998 National Cancer Institute Surveillance, Epidemiology, End Results data (478 cases/100,000; Ref. 27).

Demography and Exposure to NSAIDs. Sample characteristics and use of NSAIDs in the analytic cohort derived from the WHI Observational Study are presented in Table 1. The observed profiles of diversity and education were similar to United States women (28): 83.2% were white, 8.1% black, 3.9% Hispanic, 0.4% Native American, and 3.0% Asian/Pacific Islander, and 78.6% had post-high school education or college diplomas.

Estimated NSAID exposure frequencies for ≥5 years increased with age, 15.2% for 50–59 years, 18.0% for 60–69 years, and 20.3% for 70–79 years of age. Exposure frequencies for ≥5 years were highest for HRT users (19.4%), Whites (19.2%), and women with BMI ≥27 (19.1%) and were lowest for Blacks (11.9%), Hispanics (11.0%), and Asian/Pacific Islanders (6.2%). Overall, 67% of women reported NSAID use for 0–11 months, 15.2% reported use for 1–5 years, and 17.8% reported use for ≥5 years.

Age-adjusted Estimates. Incidence rates and age-adjusted RR estimates are presented in Table 2. Use of “Any NSAID” (regular aspirin, ibuprofen, or prescription compounds such as indomethacin, naproxen, piroxicam) for at least five years was associated with a 19% reduction in the RR of breast cancer (RR, 0.81; 95% CI, 0.68–0.97), and there was a statistically significant inverse trend of breast cancer risk with increasing duration of use ($P < 0.01$). Age-adjusted RR estimates for at least 5 years of use were similar for regular aspirin (RR, 0.81), ibuprofen (RR, 0.82), and prescription compounds (RR, 0.64). Trend tests for regular aspirin and ibuprofen also approached statistical significance. Estimates of RR for the analgesic, acetaminophen, were close to unity, irrespective of duration of use. We also examined subjects who reported taking low-dose (81 mg) aspirin, and their risk did not differ significantly from unity.

Multivariate-adjusted Estimates. Multivariate-adjusted RR estimates are presented for “Any NSAID” and the individual compounds, aspirin and ibuprofen, in Fig. 1. Estimates are adjusted for age, ethnicity, education, and potential breast cancer risk factors (BMI, HRT, family history, parity, and exercise). These results reflect significant inverse dose responses of using NSAIDs and breast cancer risk. Compared with the reference category (0–11 months), women who regularly used “Any NSAID” for 5–9 years were 21% less likely to develop breast cancer (RR, 0.79; 95% CI, 0.60–1.04) and women who regularly used “Any NSAID” for 10 or more years were 28% less likely to develop breast cancer (RR, 0.72; 95% CI, 0.56–0.91); and there was a statistically significant inverse linear trend of breast cancer incidence with the duration of NSAID use ($P < 0.01$). The dose response and long-term effects of aspirin use were of marginal

significance (RR, 0.79; CI, 0.60–1.03), whereas ibuprofen produced a significant inverse trend ($P < 0.01$) and was associated with a 49% reduction in the risk of breast cancer (RR, 0.51; CI, 0.28–0.96).

Subgroup Analysis. Results of subgroup analyses of using “Any NSAID” (aspirin, ibuprofen, or prescription compounds) and breast

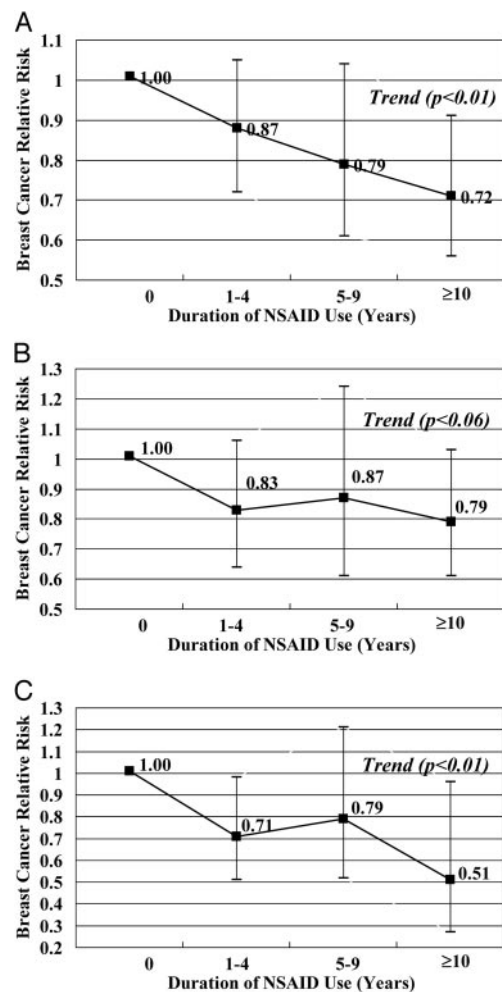


Fig. 1. *a*, RR of breast cancer with duration of NSAID use in the WHI Observational Study (OS). *b*, RR of breast cancer with duration of aspirin use in the WHI OS. *c*, RR of breast cancer with duration of ibuprofen use in the WHI OS. Estimates are adjusted for age, ethnicity, education, BMI, HRT use, family history of breast cancer, parity under age 30, and episodes of exercise per week. OS, observational study.

Table 3 Age- and multivariate-adjusted RRs and 95% CIs relating baseline intake of any NSAID to incident breast cancer in selected strata of women in the WHI Observational Study

Strata and years of use at baseline	n	Breast cancer cases	Person-years at risk	Incidence per 100,000 person-years	Age-adjusted		Multivariate-adjusted ^a		
					RR	95% CI	RR	95% CI	
BMI (kg/m²)									
<i><27</i>									
<1 ^b	31,622	547	115,363	474	1.00		1.00		
1–4	4,510	81	16,372	495	1.02	(0.81–1.29)	0.91	(0.70–1.17)	
≥5	5,529	81	20,150	402	0.83	(0.66–1.05)	0.80	(0.63–1.02)	
<i>≥27</i>									
<1 ^b	21,825	400	77,034	519	1.00		1.00		
1–4	4,399	65	15,421	422	0.80	(0.61–1.04)	0.77	(0.58–1.03)	
≥5	4,519	67	16,006	419	0.79	(0.61–1.03)	0.71	(0.53–0.95)	
HRT use (ever)									
<i>No</i>									
<1 ^b	22,340	323	80,338	402	1.00		1.00		
1–4	3,310	47	11,850	397	0.97	(0.71–1.31)	0.89	(0.64–1.26)	
≥5	3,465	41	12,531	327	0.80	(0.58–1.11)	0.75	(0.52–1.08)	
<i>Yes</i>									
<1 ^b	31,762	632	114,546	552	1.00		1.00		
1–4	5,690	102	20,276	503	0.89	(0.72–1.10)	0.82	(0.65–1.03)	
≥5	6,697	107	24,045	445	0.78	(0.64–0.96)	0.76	(0.61–0.95)	
Family history of breast cancer									
<i>No</i>									
<1 ^b	41,813	669	151,486	442	1.00		1.00		
1–4	6,841	112	24,501	457	1.01	(0.83–1.24)	0.93	(0.75–1.15)	
≥5	7,742	107	27,922	383	0.85	(0.69–1.04)	0.81	(0.66–1.00)	
<i>Yes</i>									
<1 ^b	9,407	237	33,667	704	1.00		1.00		
1–4	1,645	25	5,886	425	0.59	(0.39–0.90)	0.60	(0.38–0.92)	
≥5	1,901	32	6,843	468	0.65	(0.45–0.95)	0.62	(0.41–0.93)	
Parous under age 30									
<i>No</i>									
<1 ^b	11,204	236	40,429	584	1.00		1.00		
1–4	1,677	34	6,095	558	0.93	(0.65–1.33)	0.87	(0.59–1.27)	
≥5	1,937	34	7,068	481	0.81	(0.56–1.16)	0.78	(0.54–1.13)	
<i>Yes</i>									
<1 ^b	37,228	648	134,506	482	1.00		1.00		
1–4	6,463	103	23,022	447	0.91	(0.74–1.12)	0.84	(0.67–1.04)	
≥5	7,335	102	26,297	388	0.79	(0.64–0.98)	0.75	(0.61–0.94)	
Episodes/wk of moderate to strenuous exercise (≥20 min)									
<i><2</i>									
<1 ^b	27,105	457	95,813	477	1.00		1.00		
1–4	4,762	61	16,771	364	0.75	(0.58–0.98)	0.70	(0.52–0.93)	
≥5	5,273	77	18,796	410	0.85	(0.67–1.08)	0.76	(0.59–0.99)	
<i>≥2</i>									
<1 ^b	26,266	475	95,621	497	1.00		1.00		
1–4	4,140	88	14,855	592	1.16	(0.92–1.46)	1.00	(0.77–1.29)	
≥5	4,805	71	17,375	409	0.81	(0.63–1.03)	0.76	(0.58–0.98)	

^a Estimates are adjusted for age, ethnicity, education, and main effects of remaining covariates (BMI, HRT use, family history of breast cancer, parous under age 30, and episodes per week of moderate to strenuous exercise).

^b The reference category is 0–11 months of NSAID use (aspirin, ibuprofen, prescription NSAIDs, or the related analgesic, acetaminophen), within each breast cancer risk factor strata.

cancer are presented in Table 3. Stratification on body mass, HRT, family history of breast cancer, parity under age 30, and exercise did not appreciably modify the observed NSAID effects. Estimates of RR for ≥5 years of NSAID use varied from 0.62 to 0.81 among subgroups with a pooled value of 0.75. A test of heterogeneity did not approach statistical significance ($P < 0.30$). The observed average person-years were also relatively stable for the different NSAID-exposure categories, ranging from 3.72 to 3.81 years.

DISCUSSION

The results of this large prospective cohort study provide evidence of a statistically significant chemopreventive effect of NSAIDs against cancer of the breast. Estimates of RR for regular users of NSAIDs (aspirin, ibuprofen, or prescription compounds) show an inverse trend and internal consistency with adjustment for other factors. Overall, there was a 21% decrease in the risk of breast cancer among women who took NSAIDs at least twice a week for at least 5 years and a 28% decrease in the risk for women who used these compounds for at least 10 years, compared with those who reported either no or minimal use. Regular long-term use of ibuprofen reduced

the risk by 49%, whereas aspirin produced a 21% risk reduction. In contrast, acetaminophen, a compound that has analgesic properties but only weak anti-inflammatory action compared with other NSAIDs, did not produce any detectable effects on breast cancer risk. Aspirin in dosages less than 100 mg/day (baby aspirin) was not associated with reduced breast cancer risk.

It is particularly noteworthy that the effects of NSAIDs were observed to be consistent on stratification for breast cancer risk factors. Risk-reducing NSAID effects were observed for women with high body mass, low exercise, late parity, a positive family history of breast cancer, and for those individuals who reported taking HRT. Thus, our results show internal validity and suggest that women at relatively high risk for the development of breast cancer may receive protection from taking NSAIDs. The data also reflect external validity because the demographic profile of the WHI sample cohort is similar to the general population of postmenopausal American women.

These WHI results are in agreement with a recent meta-analysis of NSAIDs and breast cancer in which the combined estimate of RR across 14 previous studies was 0.78 (22). The majority of these studies focused only on aspirin in geographically specific samples of women,

whereas in the current study, we observed differential effects of individual compounds in a large-population-based cohort of postmenopausal American women, and found that NSAID effects were similar among high-risk groups. Overall, the weight of the combined epidemiological evidence indicates that regular intake of aspirin or other NSAIDs is protective against breast cancer. There is now an urgent need for human clinical trials designed to elucidate dose responses of individual compounds and their biological mechanisms.

The primary mechanism of action of aspirin-like drugs is the inhibition of COX, the rate-limiting enzyme of prostaglandin biosynthesis (29). Two genetic isoforms of COX have been characterized: COX-1, which is constitutively produced in most tissues, and COX-2, which is induced by pro-inflammatory stimuli (30, 31). Recently, genetic expression of COX-2 has been found to be inappropriately induced and up-regulated in human breast cancer (32), and the selective COX-2 blocker, celecoxib, has been observed to have significant chemopreventive effects against breast cancer in animals (33). Furthermore, molecular studies have linked COX-2 overexpression to a number of critical components of mammary carcinogenesis including mutagenesis (34), angiogenesis (35, 36), inhibition of apoptosis (37), and, perhaps most importantly, aromatase-catalyzed estrogen biosynthesis (38, 39). It is also noteworthy that acetaminophen has recently been found to inhibit COX-3, a COX-1 variant, but not COX-2 (40). The lack of acetaminophen effects coupled with the significant effects of COX-2-blocking NSAIDs observed in our study add to the evidence that COX-2 overexpression is an important element of mammary carcinogenesis.

Various mechanisms may be responsible for the observed effects of NSAIDs against breast cancer. The inhibition of COX, particularly the inducible COX-2 isozyme, and blockade of the prostaglandin cascade may impact on neoplastic growth and development by reducing several key features of mammary carcinogenesis including mutagenesis, mitogenesis, angiogenesis, and metastasis, and also by stimulating apoptosis of malignant cells and enhancing immunosurveillance and antineoplastic activity of T and B lymphocytes. It is particularly noteworthy that COX-2 is overexpressed in breast cancer, and the level of COX-2 expression is correlated with the induction of the Promoter II region of the aromatase gene in adjacent adipose (38, 39). Thus, COX-2 induction may promote breast cancer development by enhancing local estrogen biosynthesis, and COX-2 inhibition may reverse the process. Molecular studies have also revealed linkages between overexpression of COX-2 and other oncogenes, such as *HER-2/Neu*, in malignant breast tumors (41). Plausible mechanisms of action and the potential of NSAIDs in the chemoprevention of breast cancer are thoroughly discussed and reviewed elsewhere (42, 43).

Strengths of the current study include the large sample size representative of postmenopausal American women, the prospective nature of the investigation with standardized adjudication of breast cancer diagnoses, and the validation of baseline NSAID data (medical specialists checked pill bottle labels and prescription records at the time of baseline interview). Nevertheless, data on the frequency of NSAID use and compliance information were not collected. Thus, whereas these results reflect a promising lead, we advise caution in advancing guidelines on NSAID use for the chemoprevention of breast cancer until the appropriate clinical trials can be performed and interpreted.

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