Association of Frequency and Duration of Aspirin Use and Hormone Receptor Status With Breast Cancer Risk

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WHILE CANCER EPIDEMIOLogy and prevention have traditionally focused on the identification and modification of lifestyle factors that may increase or decrease the risk of various cancers, much recent attention has been centered on chemoprevention, the use of chemical agents to prevent or inhibit the carcinogenic process. Significant success has been achieved in this area with the use of hormonal therapy, with agents such as tamoxifen, to prevent breast cancer in women at high risk and the use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) to prevent colorectal neoplasia.[1-5]

Over the past decade, numerous studies have suggested that inhibition of prostaglandin synthesis is a rational approach to cancer prevention. Cyclooxygenase (COX) catalyzes the synthesis of prostaglandins. NSAIDs inhibit COX

Context Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with a decrease in the risk of several cancers, including breast cancer. NSAIDs inhibit cyclooxygenase activity and thereby reduce prostaglandin synthesis; prostaglandins stimulate aromatase gene expression and thereby stimulate estrogen biosynthesis. Given the importance of estrogen in the pathogenesis of breast cancer, the ability of aspirin and other NSAIDs to protect against breast cancer could vary according to hormone receptor status.

Objectives To determine the association between the frequency and duration of use of aspirin and other NSAIDs and breast cancer risk and to investigate whether any observed association is more pronounced for women with hormone receptor–positive breast cancers.

Design, Setting, and Patients Population-based case-control study of women with breast cancer, including in-person interviews conducted on Long Island, NY, during 1996-1997 (1442 cases and 1420 controls).

Main Outcome Measure Incident invasive and in situ breast cancer by aspirin and NSAID use and hormone receptor status.

Results Ever use of aspirin or other NSAIDs at least once per week for 6 months or longer was reported in 301 cases (20.9%) and 345 controls (24.3%) (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.66-0.97 for ever vs nonusers). The inverse association was most pronounced among frequent users (≥7 tablets per week) (OR, 0.72; 95% CI, 0.58-0.90). The results for ibuprofen, which was used by fewer women on a regular basis, were generally weaker (OR, 0.78; 95% CI, 0.55-1.10 for <3 times per week vs OR, 0.92; 95% CI, 0.70-1.22 for ≥3 times per week). Use of acetaminophen, an analgesic that does not inhibit prostaglandin synthesis, was not associated with a reduction in the incidence of breast cancer. The reduction in risk with aspirin use was seen among those with hormone receptor–positive tumors (OR, 0.74; 95% CI, 0.60-0.93) but not for women with hormone receptor–negative tumors (OR, 0.97; 95% CI, 0.67-1.40).

Conclusion These data add to the growing evidence that supports the regular use of aspirin and other NSAIDs (which may operate through inhibition of estrogen biosynthesis) as effective chemopreventive agents for breast cancer.

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and thereby prostaglandin production, and they have been shown to protect against cancer in experimental animals.[6,7] Organ site-specific effects, such as modulation of estrogen biosynthesis in breast tissue, might also be relevant.[8] The final step in estrogen biosynthesis is catalyzed by aromatase cytochrome P450 (aromatase gene), the product of cytochrome P19 (CYP19). Prostaglandin E_2 increases aromatase gene expression and thereby estrogen production in cultured cells.[9] Consistent with this, a positive correlation has been observed between the level of COX and expression of CYP19 in human breast cancer.[10] Progesterone synthesis can also be stimulated by PGE_2.[11] Thus, the use of NSAIDs to inhibit prostaglandin-driven production of estrogen or progesterone may be a means to prevent breast cancer. If so, we would predict that the protective effects of NSAIDs would be greater for hormone receptor–positive than for hormone receptor–negative breast cancer.

While most of the epidemiologic studies that have examined the association between aspirin/NSAID use and breast cancer support at least a 20% to 40% reduction in risk,[12-21] prior studies have not explored whether the protective effect of NSAIDs varies as a function of estrogen receptor (ER) or progesterone receptor (PR) status. We examined these issues using data from a large population-based case-control study.

METHODS
Study Population

A population-based case-control study of breast cancer, the Long Island Breast Cancer Study Project was conducted on Long Island, NY, in Nassau and Suffolk counties. Details of the overall study design were published previously and are summarized briefly here.[22] Cases were English-speaking women with newly diagnosed in situ or invasive breast cancer diagnosed between August 1, 1996, and July 31, 1997. There were no age or race restrictions and women ranged in age from 20 to 98 years. The study population was pre-dominantly white (93.8% of cases and 91.8% of controls identified themselves as white, 4.6% of cases and 5.5% as black, and 1.7% of cases and 2.7% of controls as other race).[22] In a separate question on Hispanic ethnicity, 3.8% of cases and 4.0% of controls identified themselves as Hispanic, regardless of race.[22] In-person interviews were completed for 1508 cases (82.1% of eligible cases). Controls were randomly selected through random-digit-dialing methods (for women aged <65 years) and Health Care Financing Administration (HCFA) lists (for women aged ≥65 years), and frequency-matched to cases in 5-year age groups. In-person interviews were completed for 1556 controls (62.8% of eligible controls). Reasons for nonparticipation included subject refusal, 12.4% of cases and 21.6% of controls; too ill, cognitively impaired, or deceased, 4.1% of cases and 7.8% of controls; unlocatable, moved out of area, or other, 1.4% of cases and 7.9% of controls.[22] Of those who participated, 92.2% of the cases and 80% of the controls reported having a mammogram within the past 5 years. A summary of the traditional breast cancer risk factors for this study were published previously and are summarized briefly here.[22] Breast cancer risk factors found to be related to risk in this study population include lower parity, late age at first birth, little or no breastfeeding, and family history of breast cancer. The institutional review boards of all the participating institutions approved the study protocol, and the individual women all signed informed consent forms.

Exposure Assessment

Women were asked to report their intake of aspirin, ibuprofen, and acetaminophen; 1442 cases (96%) and 1420 controls (91%) completed this section of the interviewer-administered, structured questionnaire. Ever use was defined as taking aspirin, ibuprofen, and/or acetaminophen at least once a week for 6 months or longer. The questionnaire also included separate questions on duration and frequency of use.

Information on the calendar years or age at medication use was also collected. We did not specifically ask about dose. Because the interviews took place after the breast cancer was diagnosed, we truncated all exposure information to 12 months prior to the reference age (based on age at diagnosis for the cases and corresponding age for controls).

In addition to separate measures of duration (measured in years) and frequency (measured in tablets per week), we derived composite measures based on duration and frequency to examine the combined effect. We also created a measure of regularity defined as women who used aspirin at least 4 times per week for at least 3 months and initiated use at least 1 year prior to the reference age. This definition was used for comparison with published studies using this definition of regularity. Finally, we assessed the effects of cessation by considering the following categories: current users, former users who stopped using less than 5 years ago, and former users who stopped using 5 or more years ago.

Acetaminophen use was specifically asked for comparison with the NSAIDs. We did not expect there to be any biological basis for an association with acetaminophen use but since other lifestyle factors and also response patterns may be similar between NSAIDs and acetaminophen use, it would provide a worthwhile comparison to see if the association was specific to aspirin and other NSAIDs.

Other Data Collection

We used other data from the main questionnaire including detailed information on medical history, reproductive history, exogenous hormone use, menopausal status, body mass index (BMI), cigarette smoking, alcohol intake, family history of breast cancer, and demographic information (the questionnaire is available at http://epi.grants.cancer.gov/LIBCSP/projects/Questionnaire.html). Information on hormone receptor status (ER and PR) and stage of disease (in situ vs invasive) was obtained from the pathology

reports in the medical records of the breast cancer cases.[22]

Statistical Methods

The potential confounders that we considered fall into 2 groups: those variables that a priori we thought might be related to the exposure and also were risk factors for the disease and those variables that previously published studies had considered as confounders as well as other breast cancer risk factors. Confounders in these 2 groups were group a: age at diagnosis, race, education, use of hormone therapy, oral contraceptive use, hypertension, migraine headache, myocardial infarction, and stroke; group b: age at menarche, menopausal status, age at first birth, active smoking status, alcohol drinking, family history of breast cancer, history of breast biopsy, BMI, change in BMI, prior hysterectomy, lactation history, parity, and incomplete pregnancies.

We assessed confounding by first comparing each potential confounder with exposure among controls and then with breast cancer status among unexposed.[23] Second, we compared the change in estimate for the exposure coefficient between statistical models with and without the potential confounder. Unconditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for potential confounding variables.[24] Variables were kept in the final model if they altered the parameter estimates on the exposure by at least 10%. With our sample size, we had power to detect associations of the following magnitudes for aspirin, ibuprofen, and acetaminophen, respectively: 0.78, 0.73, 0.71.

Effect modification by age, menopausal status, or hormone therapy was first examined through use of stratified analysis, running separate models for each subgroup, and then by comparing the log-likelihood statistic for models that included a multiplicative interaction term in the logistic regression model to those without.[24] Differences in risk estimates by hormone re-

ceptor status and stage of disease were examined using polytomous logistic regression.[24] These models categorized the dependent variable into 5 groups based on ER positivity (ER+) or negativity (ER−) and PR positivity (PR+) or negativity (PR−): ER+PR+, ER+PR−, ER−PR+, ER−PR−, and controls. Finally, we performed sensitivity analyses to evaluate the impact of missing data on the overall conclusions from the study. SAS version 8 (SAS Institute Inc, Cary, NC) was used to analyze the data.

RESULTS

Overall, 301 cases (20.9%) and 345 controls (24.3%) reported ever use of aspirin, defined as at least once per week for 6 months or longer. Ever use of as-

pirin was inversely associated with breast cancer risk (OR, 0.80; 95% CI, 0.66-0.97 for ever vs never use) (TABLE 1). Associations between ever use of aspirin and in situ and invasive cancer were of similar magnitude but only statistically significant among invasive cases (OR, 0.77; 95% CI, 0.63-0.92 for invasive cases vs controls and OR, 0.83; 95% CI, 0.59-1.18 for in situ cases vs controls). Fewer women used ibuprofen (176 cases [12.2%] and 202 controls [14.2%]). Ever use of ibuprofen was not statistically significantly associated with breast cancer risk (OR, 0.91; 95% CI, 0.72-1.16 for ever vs never use). Acetaminophen use was reported by 172 cases (12%) and 184 controls (13%). As expected, there was no

Table 1. Overall Association Between Ever Use of Aspirin, Ibuprofen, or Acetaminophen and Breast Cancer Risk*

	Cases	Controls	OR (95% CI)†	OR (95% CI)‡
All Women				
Aspirin				
Nonusers	1141	1075	1.00	1.00
Ever users	301	345	0.76 (0.65-0.93)	0.80 (0.66-0.97)
Ibuprofen				
Nonusers	1267	1218	1.00	1.00
Ever users	176	202	0.87 (0.70-1.08)	0.91 (0.72-1.16)
Acetaminophen				
Nonusers	1262	1233	1.00	1.00
Ever users	172	184	0.93 (0.75-1.17)	1.02 (0.80-1.31)
Premenopausal Women				
Aspirin				
Nonusers	378	386	1.00	1.00
Ever users	73	79	0.89 (0.62-1.26)	0.83 (0.56-1.22)
Ibuprofen				
Nonusers	376	394	1.00	1.00
Ever users	72	69	1.08 (0.75-1.55)	1.00 (0.66-1.53)
Acetaminophen				
Nonusers	376	406	1.00	1.00
Ever users	68	55	1.32 (0.90-1.94)	1.31 (0.85-2.00)
Postmenopausal Women				
Aspirin				
Nonusers	742	642	1.00	1.00
Ever users	220	253	0.73 (0.59-0.90)	0.77 (0.62-0.97)
Ibuprofen				
Nonusers	872	780	1.00	1.00
Ever users	95	118	0.74 (0.56-0.99)	0.79 (0.58-1.08)
Acetaminophen				
Nonusers	864	784	1.00	1.00
Ever users	97	113	0.79 (0.59-1.05)	0.91 (0.67-1.25)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Ever users and nonusers were defined by status 1 year prior to diagnosis or corresponding reference age for controls.
†Adjusted for age at diagnosis.
‡Adjusted for age at diagnosis, migraine headache, body mass index, and simultaneously adjusted for the other type of medication use.

association with breast cancer risk (OR, 1.02; 95% CI, 0.80-1.31 for ever vs never use).

Table 1 also reports the overall findings stratified by menopausal status. These results support an inverse association between ever use of aspirin and breast cancer risk in both premenopausal and postmenopausal women. The reduced OR is more pronounced among postmenopausal women (OR, 0.77, 95% CI, 0.62-0.97) than for premenopausal women (OR, 0.83; 95% CI, 0.56-1.22). There was some suggestion of an inverse association for ibuprofen use, but only among postmenopausal women (OR, 0.79; 95% CI, 0.58-1.08).

Frequency of aspirin use was associated with breast cancer risk (**TABLE 2**).

Daily use was inversely associated with breast cancer, but not less frequent use (OR, 0.72; 95% CI, 0.58-0.90 for ≥7 times per week vs OR, 0.95; 95% CI, 0.72-1.26 for <7 times per week vs nonusers). Short (<5 years) and long (≥5 years) duration of use had similar associations with breast cancer risk (OR, 0.81; 95% CI, 0.62-1.08 and OR, 0.81; 95% CI, 0.65-1.02, respectively). Composite measures of duration and frequency suggested that the effects for frequency were stronger than they were for duration (OR, 0.74; 95% CI, 0.54-1.01 for frequent but short duration vs OR, 0.77; 95% CI, 0.57-1.04 for frequent but long duration). The inverse association was of borderline statistical significance for current users (OR, 0.81; 95% CI, 0.65-1.00). Regular use

(defined as ≥4 times per week for ≥3 months) was also associated with decreased breast cancer risk (OR, 0.74; 95% CI, 0.59-0.92). While we had information on frequency and duration of use as described, dose information (81 mg vs 325 mg) was not collected.

There were no statistically significant multiplicative interactions for aspirin use by age, menopausal status, or hormone therapy (data not shown). However, the magnitude of the effect for ever use of aspirin was more pronounced among postmenopausal women (OR, 0.73; 95% CI, 0.59-0.90) compared with premenopausal women (OR, 0.89; 95% CI, 0.62-1.26).

Patterns for duration and frequency of ibuprofen use were less clear (**TABLE 3**). Unlike the findings with aspirin, increasing frequency of ibuprofen use was not associated with decreasing risk (OR, 0.78; 95% CI, 0.55-1.10 for <3 times per week vs OR, 0.92; 95% CI, 0.70-1.22 for ≥3 times per week). Measures combining duration and frequency suggested no clear pattern. A combined analysis considering any aspirin and/or ibuprofen use resulted in a statistically significant inverse association for any NSAID use (OR, 0.84; 95% CI, 0.72-0.99) and frequent use (≥7 times per week) (OR, 0.77; 95% CI, 0.63-0.94).

As expected, there was no association between frequency and duration, nor any composite measure of frequency and duration, for acetaminophen use. For example, neither regular use (those who used acetaminophen ≥4 times per week for ≥3 months) nor nonregular use was associated with breast cancer risk (OR, 0.95; 95% CI, 0.65-1.39, and OR, 1.12; 95% CI, 0.80-1.57, respectively).

We examined the association between aspirin use and breast cancer risk by subdividing the cases by hormone receptor status (ER+, ER−, PR+, and PR−). The inverse association between ever use of aspirin and breast cancer risk was evident for every subgroup except ER−PR− (OR, 0.75; 95% CI, 0.58-0.97 for ER+PR+; OR, 0.75; 95% CI, 0.47-1.20 for ER+PR−; OR,

Table 2. Association Between Frequency and Duration of Aspirin Intake and Breast Cancer Risk*

| | No. (%) of Women | | | |
	Cases	Controls	OR (95% CI)†	OR (95% CI)‡
Duration				
Nonusers	1141 (80.6)	1075 (77.7)	1.00	1.00
<5 y	109 (7.7)	122 (8.8)	0.80 (0.61-1.05)	0.81 (0.62-1.08)
≥5 y	166 (11.7)	186 (13.5)	0.80 (0.64-1.00)	0.81 (0.65-1.02)
Frequency				
Nonusers	1141 (79.3)	1075 (75.9)	1.00	1.00
<7 times/wk	110 (7.6)	114 (8.1)	0.92 (0.70-1.21)	0.95 (0.72-1.26)
≥7 times/wk	188 (13.1)	227 (16.0)	0.71 (0.57-0.88)	0.72 (0.58-0.90)
Duration and frequency				
Nonusers	1141 (80.7)	1075 (78.0)	1.00	1.00
Duration <5 y and frequency <7 times/wk	27 (1.9)	24 (1.7)	1.09 (0.62-1.90)	1.13 (0.64-1.99)
Duration <5 y and frequency ≥7 times/wk	81 (5.7)	97 (7.0)	0.72 (0.53-0.99)	0.74 (0.54-1.01)
Duration ≥5 y and frequency <7 times/wk	73 (5.2)	80 (5.8)	0.87 (0.63-1.21)	0.89 (0.64-1.24)
Duration ≥5 y and frequency ≥7 times/wk	92 (6.5)	103 (7.5)	0.76 (0.56-1.02)	0.77 (0.57-1.04)
Regularity§				
Nonusers	1141 (80.7)	1075 (78.0)	1.00	1.00
Regular users	183 (12.9)	218 (15.8)	0.73 (0.58-0.90)	0.74 (0.59-0.92)
Nonregular users	90 (6.4)	86 (6.2)	1.00 (0.73-1.36)	1.03 (0.75-1.41)
Timing‖				
Nonusers	1141 (79.3)	1075 (76.2)	1.00	1.00
Current users	202 (14.0)	222 (15.7)	0.79 (0.64-0.98)	0.81 (0.65-1.00)
Former users <5 y	21 (1.5)	31 (2.2)	0.61 (0.35-1.07)	0.64 (0.36-1.13)
Former users ≥5 y	75 (5.2)	82 (5.8)	0.87 (0.63-1.20)	0.89 (0.64-1.24)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Ever users and nonusers are defined by status 1 year prior to diagnosis or corresponding reference age for controls.
†Adjusted for age at diagnosis.
‡Adjusted for age at diagnosis, migraine headache, and body mass index.
§Regular users are defined as women who take aspirin at least 4 times per week for at least 3 months.
‖Current and former users are defined in terms of status 1 year prior to diagnosis or corresponding reference age for controls.

0.36; 95% CI, 0.14-0.90 for ER–PR+; and OR, 0.93, 95% CI, 0.63-1.38 for ER–PR–). Because effect estimates for ever vs never aspirin use were similar for the 3 subgroups with at least 1 positive hormone receptor, we combined the first 3 groups for added statistical power (**TABLE 4**). The effect of ever use of aspirin and frequency appeared limited to the hormone receptor–positive subgroup. However, effect sizes for duration and regular use followed similar patterns for the hormone receptor–positive and hormone receptor–negative subgroups.

We further examined whether the differences by hormone receptor status were seen among premenopausal and postmenopausal women separately or if they were reflecting differences only in menopausal status because premenopausal women tend to have more hormone receptor–negative tumors. Among postmenopausal women, the inverse association with aspirin use was seen among women with hormone receptor–positive tumors (OR, 0.70; 95% CI, 0.54-0.91) and not among women with hormone receptor–negative tumors (OR, 0.91; 95% CI, 0.58-1.42). Among premenopausal women, there was a more modest inverse association that was not statistically significant (OR, 0.87; 95% CI, 0.56-1.36 for women with hormone receptor–positive tumors vs OR, 1.20; 95% CI, 0.63-2.29 for women with hormone receptor–negative tumors). There was a more marked difference in premenopausal women among regular users (OR, 0.65; 95% CI, 0.35-1.20 for hormone receptor–positive tumors vs OR, 1.33; 95% CI, 0.61-2.89 for hormone receptor–negative tumors). These results suggest that differences by hormone receptor status are not merely reflecting differences in menopausal status.

Because 4% of cases and 9% of controls were missing information on aspirin use, we examined characteristics of those missing data and used this information in sensitivity analyses. Cases with missing aspirin data were younger, less likely to use hormone therapy, less

likely to have hypertension, less likely to report migraine, and less likely to have had a myocardial infarction than were cases with aspirin data available (data not shown). Because all of these factors were inversely associated with aspirin use, the cases with missing data were less likely to have taken aspirin. In contrast, controls with missing aspirin data were older and more likely to have reported hypertension and migraine. Thus, these controls are more likely to have been aspirin users. Sensitivity analyses resulted in statistically significant estimates of ORs ranging from 0.5 to 0.8 for the association between ever aspirin use and breast cancer risk if complete data were available (data not shown). These estimates are consistent with the overall finding of a protective effect, which

demonstrates that our results are unlikely to be substantially biased by the missing information.

All use of aspirin, NSAIDs, and acetaminophen was truncated to 1 year prior to diagnosis (or corresponding reference age for controls) to be consistent with other published studies and also to ensure that medication use started at the time of diagnosis was not counted as contributing to the etiology of the disease. Current use was also defined as use 1 year prior to diagnosis (or corresponding reference age for controls). Although very few cases started aspirin, ibuprofen, and/or acetaminophen use within the same year as diagnosis or corresponding reference age, we performed additional analyses to see how sensitive our results were to the decision we made to truncate all ex-

Table 3. Association Between Ibuprofen Use and Breast Cancer Risk*

| | No. (%) of Women | | | |
	Cases	Controls	OR (95% CI)†	OR (95% CI)‡
Duration				
Nonusers	1267 (89.2)	1218 (86.9)	1.00	1.00
<5 y	76 (5.4)	96 (6.9)	0.78 (0.57-1.06)	0.76 (0.56-1.05)
≥5 y	77 (5.4)	87 (6.2)	0.89 (0.65-1.22)	0.89 (0.64-1.22)
Frequency				
Nonusers	1267 (88.0)	1218 (86.0)	1.00	1.00
<3 times/wk	64 (4.4)	83 (5.9)	0.79 (0.56-1.10)	0.78 (0.55-1.10)
≥3 times/wk	109 (7.6)	115 (8.1)	0.93 (0.71-1.23)	0.92 (0.70-1.22)
Duration and frequency				
Nonusers	1267 (89.3)	1218 (87.1)	1.00	1.00
Duration <5 y and frequency <3 times/wk	19 (1.3)	28 (2.0)	0.68 (0.38-1.22)	0.67 (0.37-1.22)
Duration <5 y and frequency ≥3 times/wk	57 (4.0)	66 (4.7)	0.85 (0.59-1.22)	0.83 (0.57-1.20)
Duration ≥5 y and frequency <3 times/wk	33 (2.3)	47 (3.4)	0.72 (0.46-1.13)	0.71 (0.45-1.12)
Duration ≥5 y and frequency ≥3 times/wk	43 (3.0)	39 (2.8)	1.08 (0.70-1.68)	1.09 (0.70-1.70)
Regularity§				
Nonusers	1267 (89.3)	1218 (87.1)	1.00	1.00
Regular users	79 (5.6)	88 (6.3)	0.87 (0.64-1.20)	0.88 (0.64-1.21)
Nonregular users	73 (5.1)	92 (6.6)	0.81 (0.59-1.11)	0.79 (0.57-1.09)
Timing‖				
Nonusers	1267 (88.0)	1218 (86.0)	1.00	1.00
Current users	141 (9.8)	159 (11.2)	0.89 (0.70-1.13)	0.87 (0.68-1.11)
Former users <5 y	13 (0.9)	18 (1.3)	0.71 (0.35-1.46)	0.71 (0.34-1.45)
Former users ≥5 y	19 (1.3)	21 (1.5)	0.87 (0.46-1.63)	0.92 (0.49-1.73)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Ever users and nonusers are defined by status 1 year prior to diagnosis or corresponding reference age for controls.
†Adjusted for age at diagnosis.
‡Adjusted for age at diagnosis, migraine headache, and body mass index.
§Regular users are defined as women who used ibuprofen at least 4 times per week for at least 3 months.
‖Current and former users are defined in terms of status 1 year prior to diagnosis or corresponding reference age for controls.

Table 4. Association Between Aspirin Intake and Breast Cancer Risk by Hormone Receptor Status*

	Controls (n = 1420)	≥1 Positive Hormone Receptor (n = 755)		No Positive Hormone Receptors (n = 196)	
		No.	OR (95% CI)†	No.	OR (95% CI)†
Aspirin use					
Nonusers	1075	601	1.00	151	1.00
Ever users	345	154	0.74 (0.60-0.93)	45	0.97 (0.67-1.40)
Duration					
Nonusers	1075	601	1.00	151	1.00
<5 y	122	56	0.74 (0.53-1.05)	16	1.00 (0.57-1.73)
≥5 y	186	88	0.80 (0.61-1.06)	20	0.77 (0.46-1.23)
Frequency					
Nonusers	1075	601	1.00	151	1.00
<7 times/wk	114	52	0.87 (0.62-1.24)	17	1.12 (0.65-1.93)
≥7 times/wk	227	100	0.68 (0.52-0.89)	28	0.91 (0.58-1.41)
Regularity‡					
Nonusers	1075	601	1.00	151	1.00
Regular users	218	99	0.71 (0.55-0.93)	25	0.83 (0.52-1.32)
Nonregular users	86	44	0.98 (0.67-1.45)	11	0.96 (0.50-1.85)
Timing§					
Nonusers	1075	601	1.00	151	1.00
Current users	222	103	0.74 (0.57-0.96)	27	0.89 (0.57-1.39)
Former users	113	49	0.79 (0.55-1.13)	18	1.19 (0.70-2.02)

Abbreviations: CI, confidence interval; OR, odds ratio.
*Ever users and nonusers are defined by status 1 year prior to diagnosis or corresponding reference age for controls.
†Adjusted for age at diagnosis, migraine headache, and body mass index.
‡Regular users are defined as women who used aspirin at least 4 times per week for at least 3 months.
§Current and former users are defined in terms of status 1 year prior to diagnosis or corresponding reference age for controls.

posure information, and the overall conclusions do not change. The associations with all reported use, regardless of when it was started, are OR, 0.76 (95% CI, 0.64-0.91) for aspirin; OR, 0.85 (95% CI, 0.69-1.05) for ibuprofen, and OR, 0.97 (95% CI, 0.78-1.19) for acetaminophen. Associations with duration and frequency were also similar whether or not we truncated the exposure information.

COMMENT

We found an overall inverse association of 0.8 between ever use of aspirin and breast cancer risk relative to nonusers, consistent with most of the epidemiologic literature that suggests associations in the range of 0.6 to 0.8.[12-21] Notably, we found the inverse association with aspirin alone or with aspirin and other NSAIDs. We found the association to be strongest among frequent users (≥7 tablets per week) and among current and recent users (<5 years). These findings on the impor-

tance of frequency over duration agree with most,[15,16,19,20] but not all,[14,21] studies. Our data support those of Sharpe and colleagues[18] who conclude that the period within 2 to 5 years of diagnosis is the critical period for an effect. These findings help explain the discrepancy between the few studies[25-27] that reported no association between aspirin use and breast cancer risk, which used different measures of aspirin use.[28] The association between ibuprofen use and breast cancer risk was less clear, but fewer women regularly used ibuprofen than used aspirin in our study. Consistent with the specific pharmacologic effects of NSAIDs, acetaminophen, a non-NSAID analgesic, was not associated with breast cancer risk.

We found that the inverse association with ever aspirin use and with frequent aspirin use was more pronounced for those with hormone receptor–positive cancers. However, analyses of duration and regular use showed similar effect estimates be-

tween the hormone receptor subgroups. The participant numbers were small for these analyses of duration and frequency by hormone receptor status, limiting the statistical power even in this large study. Our study results also suggest that differences by hormone receptor status are not merely reflecting differences in menopausal status. Since this is the first study, to our knowledge, that examined whether the protective effect of aspirin may be limited to hormone receptor–positive breast cancer, our findings need to be replicated before drawing definitive conclusions. The analyses for the 4 hormone receptor groups were preplanned. However, the inverse association between ever use of aspirin and breast cancer risk was evident for every subgroup except ER–PR–. Because effect estimates for ever/never aspirin use were similar for the 3 subgroups with at least 1 positive hormone receptor, we combined the first 3 groups for added statistical power. Furthermore, the idea for carrying out this type of analysis was driven by the extensive preclinical evidence that prostaglandins can regulate the production of both estrogen and progesterone and therefore should have an impact among women with at least estrogen- or progesterone-positive receptors.[9,11]

The inductive effect of COX-derived prostaglandins on aromatase activity occurs rapidly due to enhanced transcription.[9] Because COX is constantly synthesized, frequent use of aspirin should protect against breakthrough synthesis of prostaglandins and thereby suppress aromatase activity. In other words, frequent use would be predicted to lead to a steady-state reduction in intramammary estrogen and thereby reduce the risk of breast cancer. Thus, both our findings on frequent use and on hormone receptor status lend support for this proposed underlying biological mechanism. We did not have data available concerning the dosage of the aspirin tablets. Differences in dose could impact the magnitude of reduction in intramammary

prostaglandin production and thereby estrogen synthesis. Whether the dose of aspirin required for cardiovascular protection will prove to be sufficient for optimal protection against breast cancer remains uncertain.

Our study relied on retrospective reporting of medication use, which is subject to error, particularly underreporting. For recall bias to explain our findings, however, cases would have to underreport more than controls. Our findings, however, agree in magnitude with most of the other observational epidemiologic studies of both cohort[12,16,18,20,21,25,26] and case-control designs.[13-15,17,19,27] Because recall bias is not seen in cohort studies and because effect sizes are similar between the 2 types of studies, it is unlikely that recall bias played a large role in explaining the findings from the case-control studies. However, it is possible that retrospective reporting of medication use may have led to similar estimates by years of duration if women had difficulty assessing when they actually started using medication. This possibility may explain differences with recent large cohort studies like the Women's Health Initiative, which found duration to be important.[21] It is unlikely that missing data could explain our overall findings because our sensitivity analyses indicated that the missing data would not have altered the overall conclusion of a protective effect between aspirin use and breast cancer.

We considered potential confounding by a number of variables, including some medical conditions not considered in other studies, including history of hypertension, migraine headache, and myocardial infarction. Nevertheless, there was little confounding, as the age-adjusted results were very similar to the multivariate-adjusted results. While it is possible that we have not included all of the potential confounders or that our confounders were measured with error, for incomplete adjustment to explain our findings, the unmeasured confounders would have to mimic the patterns

we observed between frequency of aspirin use and breast cancer risk. Furthermore, given that the inverse associations were specific to aspirin and ibuprofen and not to acetaminophen, the likelihood that unmeasured confounding can explain our findings is reduced. If the association were merely reflecting other "lifestyle" factors, we would also expect to see an inverse association between acetaminophen intake and breast cancer risk.

Based on these findings, further studies are warranted to elucidate the mechanisms underlying the protective effect of NSAIDs. It will be important, for example, to determine whether NSAIDs suppress aromatase activity or levels of progesterone in breast tissue. Currently, selective estrogen receptor modifiers (SERMs), such as tamoxifen, are being used to prevent breast cancer. Recently, an aromatase inhibitor was reported to substantially reduce the recurrence of hormone receptor–positive breast cancer.[29] Adverse effects such as osteoporosis sometimes occur in patients treated with aromatase inhibitors. Our results raise the possibility that combining an NSAID with an aromatase inhibitor might permit lower doses of aromatase inhibitor to be used without a loss of efficacy. Because NSAIDs modulate apoptosis, cell proliferation, angiogenesis, and immune surveillance[30] in addition to inhibiting aromatase activity, a combination regimen might result in an overall increase in therapeutic efficacy.

CONCLUSIONS

Our data, supported by other epidemiologic and laboratory evidence, bolster the case for the use of aspirin and NSAIDs as chemopreventive agents against breast cancer, particularly among postmenopausal women. The mechanisms are probably distinct from those that are protective against gastrointestinal tract cancers. There are many attractive features to such a chemopreventive agent, including its ease of use and association with reducing risk of other health outcomes. The poten-

tial benefits need to be balanced against potential harmful effects of long-term aspirin use such as peptic ulcer disease and gastrointestinal bleeding.[31,32] It is also important to study whether these findings are supported in more racially and ethnically diverse populations. Finally, the results of this study support the need for prospective clinical trials to confirm the value of using NSAIDs to prevent breast cancer.

REFERENCES

1. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. *J Natl Cancer Inst*. 2002;94:252-266.
2. Baron JA. Epidemiology of non-steroidal anti-inflammatory drugs and cancer. *Prog Exp Tumor Res*. 2003;37:1-24.
3. Baron JA, Cole BF, Sandler RS, et al. A randomized trial of aspirin to prevent colorectal adenomas. *N Engl J Med*. 2003;348:891-899.
4. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med*. 2003;348:883-890.
5. Farrow DC, Vaughan TL, Hansten PD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev*. 1998;7:97-102.

6. Carter CA, Milholland RJ, Shea W, Ip MM. Effect of the prostaglandin synthetase inhibitor indomethacin on 7,12-dimethylbenz(a)anthracene-induced mammary tumorigenesis in rats fed different levels of fat. *Cancer Res*. 1983;43:3559-3562.

7. Boolbol SK, Dannenberg AJ, Chadburn A, et al. Cyclooxygenase-2 overexpression and tumor formation are blocked by sulindac in a murine model of familial adenomatous polyposis. *Cancer Res*. 1996;56:2556-2560.

8. Howe LR, Subbaramaiah K, Brown AMC, Dannenberg AJ. Cyclooxygenase-2: a target for the prevention and treatment of breast cancer. *Endocrine-Related Cancer*. 2001;8:97-114.

9. Zhao Y, Agarwal VR, Mendelson CR, Simpson ER. Estrogen biosynthesis proximal to a breast tumor is stimulated by PGE2 via cyclic AMP, leading to activation of promoter II of the CYP19 (aromatase) gene. *Endocrinology*. 1996;137:5739-5742.

10. Brueggemeier RW, Quinn AL, Parrett ML, Joarder FS, Harris RE, Robertson FM. Correlation of aromatase and cyclooxygenase gene expression in human breast cancer specimens. *Cancer Lett*. 1999;140:27-35.

11. Elvin JA, Yan C, Matzuk MM. Growth differentiation factor-9 stimulates progesterone synthesis in granulosa cells via a prostaglandin E2/EP2 receptor pathway. *Proc Natl Acad Sci U S A*. 2000;97:10288-10293.

12. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. *Epidemiology*. 1994;5:138-146.

13. Rosenberg L. Nonsteroidal anti-inflammatory drugs and cancer. *Prev Med.* 1995;24:107-109.

14. Harris RE, Namboodiri K, Stellman SD, Wynder EL. Breast cancer and NSAID use: heterogeneity of effect in a case-control study. *Prev Med.* 1995;24:119-120.

15. Harris RE, Namboodiri KK, Farrar WB. Nonsteroidal antiinflammatory drugs and breast cancer. *Epidemiology*. 1996;7:203-205.

16. Harris RE, Kasbari S, Farrar WB. Prospective study of nonsteroidal anti-inflammatory drugs and breast cancer. *Oncol Rep.* 1999;6:71-73.

17. Coogan PF, Rao SR, Rosenberg L, et al. The relationship of nonsteroidal anti-inflammatory drug use to the risk of breast cancer. *Prev Med.* 1999;29:72-76.

18. Sharpe CR, Collet JP, McNutt M, Belzile E, Boivin JF, Hanley JA. Nested case-control study of the effects of non-steroidal anti-inflammatory drugs on breast cancer risk and stage. *Br J Cancer.* 2000;83:112-120.

19. Cotterchio M, Kreiger N, Sloan M, Steingart A. Nonsteroidal anti-inflammatory drug use and breast cancer risk. *Cancer Epidemiol Biomarkers Prev.* 2001;10:1213-1217.

20. Johnson TW, Anderson KE, Lazovich D, Folsom AR. Association of aspirin and nonsteroidal anti-inflammatory drug use with breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2002;11:1586-1591.

21. Harris RE, Chlebowski RT, Jackson RD, et al. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. *Cancer Res*. 2003;63:6096-6101.

22. Gammon MD, Neugut AI, Santella RM, et al. The Long Island Breast Cancer Study Project: description of a multi-institutional collaboration to identify environmental risk factors for breast cancer. *Breast Cancer Res Treat.* 2002;74:235-254.

23. Daniel WW. *Biostatistics: A Foundation for Analysis in the Health Sciences*. New York, NY: John Wiley & Sons; 1991.

24. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons; 1989.

25. Paganini-Hill A, Chao A, Ross RK, Henderson BE. Aspirin use and chronic diseases: a cohort study of the elderly. *BMJ.* 1989;299:1247-1250.

26. Egan KM, Stampfer MJ, Giovannucci E, Rosner BA, Colditz GA. Prospective study of regular aspirin use and the risk of breast cancer. *J Natl Cancer Inst.* 1996;88:988-993.

27. Langman MJ, Cheng KK, Gilman EA, Lancashire RJ. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. *BMJ.* 2000;320:1642-1646.

28. Rosenberg L. Aspirin and breast cancer: no surprises yet. *J Natl Cancer Inst.* 1996;88:941-942.

29. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med.* 2003;349:1793-1802.

30. Subbaramaiah K, Dannenberg AJ. Cyclooxygenase-2: a molecular target for cancer prevention and treatment. *Trends Pharmacol Sci.* 2003;24:96-102.

31. Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. *Heart.* 2001;85:265-271.

32. Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta analysis. *BMJ.* 2000;321:1183-1187.

You gain strength, courage and confidence by every experience in which you really stop to look fear in the face. You are able to say to yourself, "I have lived through this horror. I can take the next thing that comes along." You must do the thing you think you cannot do.

—Eleanor Roosevelt (1884-1962)