Short Communication

Aspirin and Other Nonsteroidal Anti-inflammatory Drugs and Breast Cancer Incidence in a Large U.S. Cohort

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Abstract

Use of nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin, has consistently been associated with reduced risk of breast cancer in case-control studies. However, results from prospective studies have been less consistent. We examined the association between NSAID use and breast cancer incidence, adjusting for multiple breast cancer risk factors among 77,413 women in the Cancer Prevention Study II Nutrition Cohort. During follow-up from 1992 to 2001, we observed 3,008 cases of incident breast cancer. Information on NSAID use was obtained from a questionnaire completed at enrollment in 1992 or 1993 and was updated using follow-up questionnaires in 1997 and 1999. NSAID use was modeled using time-dependent variables to update exposure status. Neither current total NSAID use (aspirin and other NSAIDs combined) nor current aspirin use were associated with breast cancer incidence even at relatively high levels of use [rate ratio (RR), 1.07; 95% confidence interval (95% CI), 0.96-1.21 for ≥60 NSAID pills per month compared with no reported use of NSAIDs; RR, 1.01; 95% CI, 0.84-1.20 for ≥60 aspirin per month compared with no reported use of aspirin]. Even long-duration regular use (≥30 pills per month for ≥5 years) was not associated with breast cancer incidence (RR, 1.05; 95% CI, 0.88-1.26 for total NSAIDs; RR, 0.88; 95% CI, 0.69-1.12 for aspirin). Although we cannot exclude a small reduction in breast cancer risk associated with NSAID use, the results of this study provide evidence against a large reduction in risk. (Cancer Epidemiol Biomarkers Prev 2005;14(1):261–4)

Introduction

Use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) has been consistently associated with reduced risk of colon cancer in epidemiologic studies (1). NSAIDs might plausibly also reduce risk of breast cancer given that several NSAIDs inhibit breast cancer in rodent models (2, 3).

At least 19 previous epidemiologic studies have examined the association between use of aspirin or total NSAIDs and breast cancer risk (4-22). Of these, eight are U.S. or Canadian case-control studies (4-11), four are analyses using prospectively collected NSAID data from pharmacy databases in Canada or Europe (12-15), and seven are U.S. cohort studies (16-22). All eight case-control studies (4-11) found aspirin or total NSAID use to be associated with lower risk of breast cancer, with most finding reductions in risk of between ~20% and ~40%. The largest pharmacy database study reported ~20% lower breast cancer incidence associated with NSAID use during an interval of 2 to 5 years before diagnosis but no apparent association with NSAID use during other time intervals (13), whereas the other three pharmacy database studies found no association (12, 14, 15). Results from cohort studies have been inconsistent, with four studies finding either aspirin or total NSAID use to be associated with lower risk of breast cancer (17, 19-21) and three, including the largest study (18), finding no association (16, 18, 22).

Despite the number of studies of NSAID use and breast cancer incidence, it remains unclear whether NSAID use is associated with a lower risk of developing breast cancer and, if so, whether this association varies by frequency or duration of NSAID use. We examined the association between NSAID use and breast cancer incidence in the Cancer Prevention Study II (CPS-II) Nutrition Cohort using detailed information collected at several time points to examine NSAID use according to frequency of current use and duration of regular use.

Materials and Methods

Study Cohort. Women in this analysis were drawn from the 97,786 female participants in the CPS-II Nutrition Cohort, a prospective study of cancer incidence and mortality in the United States established in 1992 (described in detail in ref. 23). The Nutrition Cohort is a subgroup of the larger CPS-II cohort, a prospective study of cancer mortality established in 1982. The Emory University Institutional Review Board approves all aspects of the CPS-II Nutrition Cohort. At enrollment in 1992 or 1993, participants completed a mailed self-administered questionnaire, including information on demographic, medical, and lifestyle factors. Follow-up questionnaires to update exposure information and to ascertain newly diagnosed cancers were sent in 1997, 1999, and 2001. The response rate for each follow-up questionnaire was at least 90%.

We excluded from this analysis participants who were lost to follow-up from enrollment in 1992 or 1993 to August 31, 2001 (n = 3,456). In addition, we excluded participants with a history of cancer, other than nonmelanoma skin cancer (n = 13,055), or with missing information on NSAID use at enrollment (n = 3,839) or year of breast cancer diagnosis (n = 23).

Case Ascertainment. We documented 3,008 incident cases of breast cancer between enrollment in 1992 or 1993 and August 31, 2001. Of these, 2,623 were initially identified by self-report on the 1997, 1999, or 2001 follow-up questionnaires

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and were subsequently verified by obtaining medical records or through linkage with state registries when complete medical records could not be obtained (23). A total of 277 self-reported cases for which medical verification could not be obtained were also included because previous work linking cohort members to state cancer registries indicated that our participants can accurately self-report breast cancer diagnoses (sensitivity = 0.91, positive predictive value = 0.85; ref. 24). An additional 79 cases of fatal breast cancer among women who did not report breast cancer were identified through linkage with the National Death Index (25). Finally, 29 women who did not report breast cancer were identified as breast cancer cases during the process of verifying a different cancer.

Ascertainment of NSAID Use. NSAID use was reported on questionnaires in 1982 (at the time of enrollment into the larger CPS-II mortality cohort), 1992 or 1993 (at enrollment into the Nutrition Cohort), 1997, and 1999. The 1982 questionnaire asked for ''times per month'' of aspirin use in the last month but did not ask about aspirin dose or about use of NSAIDs other than aspirin, which was the only NSAID available over-the-counter at that time. The questionnaire completed at enrollment in 1992 or 1993 (hereafter called the 1992 questionnaire) asked about use during the past year of three types of NSAIDs, aspirin, ibuprofen, and ''other nonsteroidal analgesics.'' For each type of NSAID, participants were asked for average days per month of use, average number of pills taken on days used, and number of years used. Follow-up questionnaires in 1997 and 1999 included similar questions but asked separately about use of low-dose ''baby'' aspirin and regular-dose aspirin.

Statistical Analysis. For each type of NSAID, we calculated pills per month by multiplying days used per month by pills used per day. We counted each low-dose aspirin pill (typically 80 mg) as one quarter of a regular-dose aspirin pill (typically 325 mg). Participants who reported days per month they used a particular NSAID but did not report pills per day were assigned a value of one pill per day. Total NSAID pills per month was calculated by summing pills per month of aspirin, ibuprofen, and other NSAIDs.

We used Cox proportional hazards modeling (26) to calculate rate ratios for breast cancer incidence. We examined two measures of NSAID use, frequency of current NSAID use and duration of regular NSAID use. Frequency of current NSAID use was examined using a time-dependent variable initially defined by pills per month reported at enrollment and then updated by pills per month reported on each follow-up questionnaire.

Analyses of duration of regular NSAID use were designed specifically to examine risk among women we hypothesized would be at the lowest risk, those who were both currently

Table 1. Breast cancer risk factors by NSAID use at enrollment of the CPS-II Nutrition Cohort in 1992-1993

	No NSAID use (n = 34,933)	1-29 NSAID pills per month (n = 20,084)	≥30 NSAID pills per month (n = 22,396)
Age (y)			
40-49	2.2	2.8	1.9
50-59	33.3	38.9	31.6
60-69	49.8	46.5	49.6
70-79	14.7	11.8	16.8
≥80	0.1	0.0	0.1
Menopausal status			
Premenopausal	4.4	5.0	4.0
Perimenopausal	1.1	1.2	1.0
Postmenopausal	93.7	93.2	94.4
Unknown	0.7	0.7	0.7
Race			
White	96.8	97.4	98.0
Black	1.7	1.4	1.2
Other	1.4	1.2	0.8
Body mass index (kg/m^2)			
<22	25.7	23.1	18.9
22 to <25	30.3	30.0	26.7
25 to <27	15.3	16.0	16.0
27 to <30	14.2	15.4	16.8
≥30	12.9	14.0	20.0
Unknown	1.5	1.4	1.6
Weight gain or loss since age 18 (lb)			
>5 loss	5.9	4.8	4.5
5 loss-5 gain	11.5	10.1	8.9
6-15 gain	17.6	16.6	14.2
16-25 gain	17.8	18.2	16.9
26-35 gain	15.6	15.6	15.3
>35 gain	29.5	32.6	38.3
Unknown	2.1	1.9	1.9
Hormone replacement therapy			
Never	53.0	48.7	43.3
Current	30.2	33.8	38.7
Former	13.0	13.5	14.8
Ever, recency unknown	1.7	2.1	1.8
Unknown	2.0	1.9	1.4
Most recent mammogram			
Never	8.4	7.5	6.0
Within the past year	64.0	65.2	67.5
1-3 y ago	20.4	20.5	20.4
>3 y ago	6.4	5.9	5.2
Unknown	0.9	0.9	0.8

NOTE: Data are percentages adjusted to the age distribution of the entire study population.

regular NSAID users and had used NSAIDs regularly over several years. We created a time-dependent variable for duration of regular NSAID use with four categories: (*a*) never use, (*b*) past or less than regular use only, (*c*) current regular use of <5 years, and (*d*) current regular use of ≥5 years. We defined regular use as ≥30 NSAID pills per month. During the follow-up interval between completion of the 1992 and 1997 questionnaires, participants were categorized as having ≥5 years of regular use if they reported at least 5 years of NSAID use on their 1992 questionnaire and also reported regular NSAID use on both the 1982 and 1992 questionnaires. During the 1997 to 1999 follow-up interval, participants were categorized as having ≥5 years of regular NSAID use if they reported regular NSAID use on both the 1992 and 1997 questionnaires. During the 1999 to 2001 follow-up interval, participants were categorized as having ≥5 years of regular NSAID use if they reported regular aspirin use on the 1992, 1997, and 1999 questionnaires. In each follow-up interval, participants who had not reported NSAID use on any previous questionnaire were categorized as never users, whereas participants who were neither never users nor current regular users were categorized as ''past or less than regular use only.''

When examining each individual type of NSAID (aspirin, ibuprofen, or other NSAIDs), we calculated frequency of current use and duration of regular use as described above. However, duration of regular use of ibuprofen or other NSAIDs could not be calculated during the 1992 to 1997 interval because the 1982 questionnaire asked only about aspirin.

Analyses of each individual type of NSAID were adjusted for use of other NSAID types. Specifically, frequency of current use of each NSAID type was adjusted for frequency of current use of other NSAID types, and duration of regular use of each NSAID type was adjusted for duration of regular use of other NSAID types. During the 1992 to 1997 interval, we adjusted duration of regular aspirin use for current frequency of ibuprofen and other NSAIDs because duration of use of NSAIDs other than aspirin could not be calculated.

Potential confounders included in all models were age at menarche (<12, 12, 13, ≥14, unknown), age at menopause (<45, 45 to <50, 50 to <55, ≥55, unknown), number of live births (0, 1, 2-3, >4, unknown), years of oral contraceptive use (never, <5, 5 to <10, ≥10, unknown), family history of breast cancer in mother or sister (yes, no), history of breast cysts (yes, no), mammography history (never, within the last year, not within the last year, unknown), use of hormone replacement therapy (never, current, former, ever not otherwise specified, unknown), adult weight gain in pounds (lost >5, lost 5 to gained 5, gained 6-15, gained 16-25, gained 26-35, gained >35, unknown), body mass index (<22, 22 to <25, 25 to <27, 27 to <30, ≥30, unknown), education (high school or less, some college, college graduate, unknown), alcohol use (none, <1, 1, ≥2 drinks per day, unknown), and race (White, Black, other/unknown). These covariates were based on information reported on the 1992 enrollment questionnaire, except mammography history, which was a time-dependent variable. All covariates, except age, were modeled using the categories shown above. We adjusted for age using the stratified Cox procedure with 1-year age strata.

Results

The great majority of participants, regardless of NSAID use, were White and postmenopausal (Table 1). Regular NSAID users (≥30 pills per month) were more likely than nonusers to be obese, to have had a large weight gain since age 18, to use hormone replacement therapy, and to have had a recent mammogram.

Frequency of total NSAID use and aspirin use were not associated with breast cancer incidence [rate ratio (RR), 1.07; 95% confidence interval (95% CI), 0.96-1.21 for ≥60 total NSAID pills per month; Table 2]. Long-duration regular use of NSAIDs was also not associated with breast cancer incidence (RR, 1.05; 95% CI, 0.88-1.26; Table 3). There were small increases in breast cancer risk among women reporting either past or less than regular use (RR, 1.15; 95% CI, 1.03-1.29) or current regular use of short duration (RR, 1.16; 95% CI, 1.02-1.31) compared with women who had never reported NSAID use. Results for long-duration regular aspirin use were not inconsistent with a small reduction in risk (RR, 0.88; 95% CI, 0.69-1.12). The associations between breast cancer incidence and duration of regular total NSAID use and duration of regular aspirin use did not appear to differ by stage at diagnosis, body mass index, or use of hormone replacement therapy (data not shown).

Table 2. Breast cancer incidence by frequency of current NSAID use, CPS-II Nutrition Cohort, 1992-2001

NSAID pills per month	Cases/person-years	Multivariate-adjusted rate ratios (95% CI)*
Total NSAIDs		
None	1,207/234,783	1.00 (reference)
1-14	684/113,575	1.11 (1.01-1.22)
15-29	283/52,557	1.02 (0.89-1.16)
30-59	444/80,688	1.02 (0.91-1.14)
≥60	340/67,441	1.07 (0.96-1.21)
Aspirin		
None	1,759/328,703	1.00 (reference)
1-14	625/98,030	1.14 (1.04-1.25)
15-29	180/38,209	0.89 (0.76-1.03)
30-59	314/59,328	0.96 (0.85-1.09)
≥60	130/24,775	1.01 (0.84-1.20)
Ibuprofen		
None	2,262/418,105	1.00 (reference)
1-14	388/68,184	1.04 (0.93-1.16)
15-29	116/20,954	1.04 (0.86-1.25)
30-59	106/18,640	1.04 (0.86-1.26)
≥60	136/23,162	1.06 (0.89-1.26)
Other NSAIDs		
None	2,692/498,123	1.00 (reference)
1-14	84/14,888	0.95 (0.76-1.18)
15-29	22/5,329	0.71 (0.46-1.07)
30-59	95/13,693	1.20 (0.98-1.48)
≥60	115/17,012	1.16 (0.96-1.40)

NOTE: Current NSAID use is defined as use reported on the last completed questionnaire (as reported in 1992 for follow-up through 1997, as reported in 1997 for follow-up through 1999, and as reported in 1999 for follow-up through 2001).
*Adjusted for age, race, education, family history of breast cancer, personal history of breast cysts, history of mammography, age at menarche, duration of oral contraceptive use, parity, age at menopause, use of hormone replacement therapy, weight change since age 18, body mass index, and alcohol consumption. Rate ratios for individual NSAID types are also adjusted for use of other types of NSAIDs.

It has been recently hypothesized that NSAIDs could influence breast cancer risk by reducing synthesis of both estrogen and progesterone and therefore that NSAIDs might have a stronger protective effect against hormone receptor–positive breast cancers than against hormone receptor–negative breast cancers (11). Complete information on both estrogen and progesterone receptor status was available on 1,351 cases of which 957 were positive for both estrogen receptor and progesterone receptor status. We examined the association between long-duration regular NSAID use and breast cancer that was both estrogen receptor positive and progesterone receptor positive but found no suggestion of reduced risk (RR, 1.15; 95% CI, 0.85-1.56).

Discussion

In this large prospective study, we found no association between NSAID use, even long-duration regular use, and breast cancer risk. This result is consistent with those from

Table 3. Breast cancer incidence by duration of regular NSAID use, CPS-II Nutrition Cohort, 1992-2001

	Cases/ person-years	Multivariate-adjusted rate ratios (95% CI)*
Total NSAIDs		
No reported use	393/84,814	1.00 (reference)
Past or less than regular use only	1,781/316,101	1.15 (1.03-1.29)
Current regular use, <5-y duration	656/118,157	1.16 (1.02-1.31)
Current regular use, ≥5-y duration	178/29,972	1.05 (0.88-1.26)
Aspirin		
No reported use	565/114,586	1.00 (reference)
Past or less than regular use only	1,999/350,356	1.11 (1.01-1.22)
Current regular use, <5-y duration	370/68,940	1.08 (0.94-1.23)
Current regular use, ≥5-y duration	74/15,162	0.88 (0.69-1.12)
Ibuprofen†		
No reported use	681/113,472	1.00 (reference)
Past or less than regular use only	365/58,949	0.99 (0.87-1.13)
Current regular use, <5-y duration	61/9,486	1.02 (0.79-1.33)
Current regular use, ≥5-y duration	35/4,260	1.29 (0.92-1.82)
Other NSAIDs†		
No reported use	931/153,882	1.00 (reference)
Past or less than regular use only	135/21,503	0.97 (0.81-1.17)
Current regular use, <5-y duration	55/7,290	1.17 (0.89-1.53)
Current regular use, ≥5-y duration	21/3,492	0.90 (0.58-1.40)

NOTE: Regular use is defined as ≥30 pills per month.

*Rate ratios adjusted for age, race, education, family history of breast cancer, personal history of breast cysts, history of mammography, age at menarche, duration of oral contraceptive use, parity, age at menopause, use of hormone replacement therapy, weight change, body mass index, and alcohol consumption. Rate ratios for duration of each type of NSAID are also adjusted for duration of use of other NSAID types.

†Includes only follow-up from 1997-2001 because duration of use of this NSAID could not be estimated until 1997.

three previous cohort studies on NSAID use (16, 18, 22). However, other cohort studies (17, 19-21) as well as many case-control studies (4-10) have found overall NSAID or aspirin use to be associated with reduced breast cancer risk. We know of no clear reason for these differing results, although the overall pattern of results across studies seems compatible with NSAID use being associated with a small reduction in breast cancer risk.

Important strengths of this study include its large size and detailed updated information on NSAID use, which enabled us to examine long-duration regular use. A limitation of this study is that confounding by factors associated with both NSAID use and breast cancer cannot be ruled out. In conclusion, our results do not support the hypothesis that NSAID use substantially reduces breast cancer risk, although a small reduction in risk cannot be excluded.

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