Use of Aspirin, Other Nonsteroidal Anti-inflammatory Drugs, and Acetaminophen and Risk of Breast Cancer Among Premenopausal Women in the Nurses’ Health Study II

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Background: The use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) is widespread for treatment of common symptoms such as headaches, muscular pain, and inflammation. In addition, the chemopreventive use of NSAIDs is increasingly common for heart disease and colon cancer. Evidence of a protective association with breast cancer risk has been inconsistent, and few data exist for premenopausal women.

Methods: We assessed the associations for use of aspirin, other NSAIDs, and acetaminophen with breast cancer risk among premenopausal women in the prospective Nurses’ Health Study II. In total, 112,292 women, aged 25 to 42 years and free of cancer in 1989, were followed up until June 2003. Multivariate relative risks and 95% confidence intervals were calculated by Cox proportional hazards models, adjusting for age and other important breast cancer risk factors.

Results: Overall, 1345 cases of invasive premenopausal breast cancer were documented. Regular use of aspirin (≥2 times per week) was not significantly associated with breast cancer risk (relative risk, 1.07; 95% confidence interval, 0.89-1.29). Regular use of either non-aspirin NSAIDs or acetaminophen also was not consistently associated with breast cancer risk. Results did not vary by frequency (days per week), dose (tablets per week), or duration of use. Furthermore, associations with each drug category did not vary substantially by estrogen and progesterone receptor status of the tumor.

Conclusion: These data suggest that the use of aspirin, other NSAIDs, and acetaminophen is not associated with a reduced risk of breast cancer among premenopausal women.

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See Invited Commentary at end of article

The NSAIDs act by inhibiting both isozymes of the cyclo-oxygenase enzyme (COX-1 and -2); COX-1 is constitutively expressed in most tissues, whereas COX-2 is induced as part of the inflammatory pathway, synthesizing prostaglandins from arachidonic acid. The inhibition of COX-2 may decrease carcinogenesis by decreasing cell proliferation, angiogenesis, and metastasis and increasing apoptosis. Elevated COX-2 expression has been observed in breast tumor tissue, and animal and in vitro evidence strongly supports a protective role of aspirin and other NSAIDs against breast cancer. In addition, COX-2 may play a specific role in breast cancer etiology because prostaglandins have been shown to induce the expression of aromatase, which converts androgens to estrogens, in breast tissue, and animal and in vitro evidence strongly supports a protective role of aspirin and other NSAIDs against breast cancer. Although aromatase in adipose tissue plays an integral role in estrogen levels in postmenopausal women, aromatase inhibitors may increase ovarian estradiol production in premenopausal women via a feedback loop whereby lower estrogen levels trigger increased pituitary gonadotropin secretion, which then stimulates ovarian synthesis of estrogen. Thus, while the antiproliferative and apoptotic mechanisms of NSAIDs may be
beneficial in premenopausal breast cancer risk, the potential of NSAIDs to inhibit aromatase suggests that the drugs may not reduce the risk of breast cancer in premenopausal women.

Despite strong experimental evidence of an inverse association between aspirin or other NSAIDs and breast cancer risk, epidemiologic data to date have produced mixed results. Although inverse associations between either aspirin or NSAIDs and breast cancer have been reported in most case-control studies, results from cohort studies are less consistent. Aspirin use was inversely associated with breast cancer risk in 6 prospective studies, but no association was observed in 6 other studies. Similarly, inverse, positive, and null associations have been observed with NSAIDs or nonaspirin NSAIDs. Most prospective studies have included entirely or predominantly postmenopausal populations. To our knowledge, there has not been a thorough exploration of these associations among premenopausal women in prospective studies.

We conducted an analysis within the prospective Nurses' Health Study II cohort to evaluate the associations of aspirin, nonaspirin NSAIDs, and acetaminophen use with breast cancer risk among premenopausal women.

STUDY POPULATION

The Nurses' Health Study II began in 1989, when 116,609 female registered nurses, aged 25 to 42 years, completed a mailed questionnaire. Information on lifestyle factors, including many breast cancer risk factors, and new disease diagnoses has been collected on biennial mailed questionnaires. After exclusion of women with a history of cancer (except nonmelanoma skin cancer) and those who were postmenopausal at baseline, 112,292 premenopausal women, composing 1,241,823 person-years, contributed to the analysis. Data up to June 2003 were available for 91.2% of the potential person-years of follow-up. This study was approved by the Committee on the Use of Human Subjects in Research at Harvard School of Public Health and the Brigham and Women's Hospital.

EXPOSURE AND COVARIATE ASSESSMENT

On the baseline questionnaire in 1989, participants were asked in 3 separate questions whether they regularly (≥2 times per week) used acetaminophen, aspirin, or other anti-inflammatory drugs, and this was updated biennially from 1993. Women who reported regular use on a questionnaire were considered current users for the subsequent 2-year follow-up period (or the 4-year follow-up period from 1989 through 1993). Women who continued to report use on subsequent questionnaires remained classified as current users, whereas those who ceased reporting use became past users, although these women were eligible to become current users on later questionnaires. Nonusers during any given follow-up period were women who had not reported use on the current or any prior questionnaire. Beginning in 1993 (for aspirin) or 1995 (for acetaminophen and other anti-inflammatory drugs), we first asked about frequency (categorized as either daily or weekly) and updated this every 2 years. Beginning in 1999, with biennial updates, participants were additionally asked about quantity used (tablets per week) in each category. Duration of regular use was calculated from baseline in 1989 to the end of follow-up. For participants who missed a questionnaire, drug use information was carried forward from the previous cycle.

Age (in months) was calculated at each follow-up cycle by the difference between the date of the questionnaire return and the participant's date of birth. Age at menarche, height, and weight at age 18 years were assessed on the 1989 questionnaire. Age at first birth, parity, oral contraceptive use, current weight, and history of benign breast disease were assessed biennially. Family history of breast cancer in the participant's sisters or mother was assessed in 1989 and 1997. Alcohol consumption was assessed in 1989 and every 4 years from 1991. Menstrual cycle characteristics between ages 18 and 22 years, including cycle pattern and length, were assessed in 1989. Physical activity was assessed in 1991 and 1999. Diagnoses of cardiovascular disease and rheumatoid arthritis were assessed biennially and confirmed by medical record review. Diagnosis of premenstrual syndrome was assessed on every questionnaire except 1991 and 1999.

Every 2 years, women were asked to report whether their periods had ceased permanently and whether they had had a hysterectomy and/or oophorectomy. Self-report of natural and surgical menopause has been validated in the Nurses' Health Study cohort.

We calculated person-years from the baseline questionnaire until the first date of dubious or confirmed menopause, diagnosis as having breast or other cancer (except nonmelanoma skin cancer), death, or June 1, 2003. Cox proportional hazards models, stratified jointly by age in months and calendar year of follow-up at the beginning of each 2-year questionnaire cycle, were used to calculate adjusted hazard ratios (relative risks [RRs]) and 95% confidence intervals (CIs). The proportional hazards assumptions were tested by including interaction terms between exposure and time or age and comparing the interactions terms by means of a likelihood ratio test. In all cases the likelihood ratio tests were not significant, indicating that the proportional hazards assumptions were met. Multivariate models controlled for age at menarche, height, body mass index at age 18 years, weight change since age 18 years, oral contraceptive use, parity, age at first birth, alcohol consumption, history of benign breast disease, and family history of breast cancer. Tests for trend were calculated by the Wald test using continuous measures (for duration) or the midpoints of categories modeled continuously (for frequency). To assess whether the associations between drug use and breast cancer varied across lev-
We documented 1345 cases of invasive breast cancer among premenopausal women during 14 years of follow-up. Compared with nonusers at baseline in 1989, women who used aspirin, nonaspirin NSAIDs, or acetaminophen were slightly older, were heavier at age 18 years, had gained more weight since age 18 years, and consumed more alcohol (Table 1). Users also had a higher prevalence of early menarche, current oral contraceptive use, and history of benign breast disease. In a comparison of users and nonusers of aspirin and nonaspirin NSAIDs, differences were comparable. Throughout follow-up, women were more likely to use nonaspirin NSAIDs (22.2% of person-time) than aspirin (9.5%) or acetaminophen (16.3%).

Compared with nonusers, current regular users of aspirin were not at a decreased risk of breast cancer (RR, 1.07; 95% CI, 0.89-1.29) (Table 2). Risk among past users was slightly elevated (RR, 1.21; 95% CI, 1.03-1.41). Duration of use was not associated with risk among current users (<5 years: RR, 1.03; 95% CI, 0.84-1.26; ≥5 years: 1.26; 0.88-1.80; P for trend = .55). Frequency of use (days per week) was similarly not associated with breast cancer risk (P for trend = .39). When we examined regular use of aspirin by estrogen and progesterone receptor (ER/PR) status of the tumor, no associations with current use were apparent among either ER+/PR+ cases (RR, 0.97; 95% CI, 0.76-1.25) or ER−/PR− cases (1.21; 0.78-1.88). Although follow-up was limited with our assessment of quantity (tablets per week), which began in 1999, we did not observe any relation with breast cancer risk (P for trend = .76) (data not shown).

Current regular use of nonaspirin NSAIDs was associated with a modestly increased risk of breast cancer compared with nonusers (RR, 1.16; 95% CI, 1.01-1.34), although there was no evidence of a trend in risk with increasing duration of use (<5 years: RR, 1.18; 95% CI, 1.02-1.37; ≥5 years: 1.11; 0.88-1.39) (Table 3). Past use of nonaspirin NSAIDs was not associated with breast cancer risk (RR, 1.06; 95% CI, 0.91-1.24). Although there was a suggestive inverse trend with frequency of use (P = .06), this may have been driven by a significant increased risk observed for use 2 or 3 days per week (RR, 1.35; 95% CI, 1.09-1.67) because the only point estimate below 1 was for NSAID use 6 or more days per week, but this was not statistically significant (RR, 0.86; 95% CI, 0.60-1.24). The association between regular use of nonaspirin NSAIDs and breast cancer risk did not differ appreciably by ER/PR status (ER+/PR+: RR, 1.08; 95% CI, 0.89-1.30; ER−/PR−: 1.01; 0.72-1.43). With follow-up from 1999 to 2003, when dose data were available, we observed slightly increased risks for...

**Table 1. Age and Age-Standardized Characteristics of Nurses’ Health Study II Participants, Categorized by Any NSAID or Acetaminophen Use in 1989**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonusers (n=65 988)</th>
<th>Users (n=46 304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>34.0 (4.6)</td>
<td>34.7 (4.7)</td>
</tr>
<tr>
<td>Parity, mean (SD), No. of children</td>
<td>1.5 (1.2)</td>
<td>1.4 (1.2)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>164.8 (6.6)</td>
<td>164.8 (6.6)</td>
</tr>
<tr>
<td>BMI at age 18 y, mean (SD)</td>
<td>21.3 (3.1)</td>
<td>21.3 (3.6)</td>
</tr>
<tr>
<td>Weight change since age 18 y, mean (SD), kg</td>
<td>6.1 (9.5)</td>
<td>8.6 (11.5)</td>
</tr>
<tr>
<td>Alcohol consumption, mean (SD), g/d</td>
<td>2.8 (5.2)</td>
<td>3.4 (6.3)</td>
</tr>
<tr>
<td>Age at menarche &lt;12 y, No. (%)</td>
<td>15 309 (23.2)</td>
<td>12 132 (26.2)</td>
</tr>
<tr>
<td>Current oral contraceptive use, No. (%)</td>
<td>7919 (12.0)</td>
<td>6946 (15.0)</td>
</tr>
<tr>
<td>History of benign breast disease, No. (%)</td>
<td>17 751 (26.9)</td>
<td>13 984 (30.2)</td>
</tr>
<tr>
<td>Family history of breast cancer, No. (%)</td>
<td>3959 (6.0)</td>
<td>2732 (5.9)</td>
</tr>
</tbody>
</table>

**Table 2. Relative Risk of Invasive Breast Cancer Among Premenopausal Women According to Aspirin Use in the Nurses’ Health Study II, 1989-2003**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nonusers (≥2 times/wk)</th>
<th>Users (≥2 times/wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>34.0 (4.6)</td>
<td>34.7 (4.7)</td>
</tr>
<tr>
<td>Parity, mean (SD), No. of children</td>
<td>1.5 (1.2)</td>
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<td>8.6 (11.5)</td>
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<tr>
<td>Alcohol consumption, mean (SD), g/d</td>
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<td>Age at menarche &lt;12 y, No. (%)</td>
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<td>Family history of breast cancer, No. (%)</td>
<td>3959 (6.0)</td>
<td>2732 (5.9)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NSAID, nonsteroidal anti-inflammatory drug.
low to moderate quantity of use of nonaspirin NSAIDs (1–2 tablets per week: RR, 1.47; 95% CI, 1.02–2.12; 3–5 tablets per week: 1.45; 1.00–2.09), but with no significant trend for trend (.60) (Table 4). The association did not differ by ER/PR status (ER+/PR+: RR, 0.98; 95% CI, 0.78–1.22; ER−/PR−: 1.00; 0.67–1.47). Quantity of use (tablets per week) also was not associated with risk, although follow-up (1999–2003), and hence statistical power, was limited in these analyses (P for trend = .94) (data not shown).

To exclude the possibility that the associations were confounded by other reasons for taking the drugs, we conducted a sensitivity analysis restricted to women who were not diagnosed as having inflammatory conditions, such as myocardial infarction, stroke, coronary artery bypass graft, angina, or rheumatoid arthritis; results were unchanged (data not shown). Given that women who used NSAIDs were more likely to report a diagnosis of premenstrual syndrome (eg, 25.8% among users vs 14.5% among nonusers at baseline), and this syndrome may be associated with hormonal changes that could affect breast cancer risk, we repeated the analyses excluding these women. Again, results were unchanged (data not shown). Furthermore, adjustment for menstrual cycle characteristics, including years from menarche to the onset of regular cycles, cycle pattern between ages 18 and 22 years, and cycle length between ages 18 and 22 years, did not substantially alter results for any of the 3 drug categories, nor did adjustment for physical activity (data not shown).

Results for all 3 drug categories did not substantially vary by oral contraceptive use (never-users plus short-term [<2 years] users vs users for ≥2 years), weight change since age 18 years (<10 kg vs ≥10 kg), family history of breast cancer (yes vs no), or age (<40 years vs ≥40 years) (data not shown). Results were also similar when in situ cases were included (data not shown). When aspirin and nonaspirin NSAIDs were included in the same statistical model, results for both were essentially unchanged (current use of aspirin: RR, 1.05; 95% CI, 0.88–1.27; current use of nonaspirin NSAIDs: 1.16; 1.01–1.34). Use of any NSAIDs (aspirin or nonaspirin)


<table>
<thead>
<tr>
<th>Frequency of use</th>
<th>No. of Cases</th>
<th>Simple MVa</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+/PR+</td>
<td>Nonusers 297</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Past users 205</td>
<td>0.99 (0.81-1.22)</td>
<td>0.98 (0.79-1.20)</td>
<td></td>
</tr>
<tr>
<td>Current users 189</td>
<td>1.10 (0.91-1.32)</td>
<td>1.08 (0.89-1.30)</td>
<td></td>
</tr>
<tr>
<td>ER−/PR−</td>
<td>Nonusers 106</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Past users 55</td>
<td>1.14 (0.78-1.66)</td>
<td>1.12 (0.76-1.64)</td>
<td></td>
</tr>
<tr>
<td>Current users 53</td>
<td>1.08 (0.76-1.49)</td>
<td>1.01 (0.72-1.43)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ER, estrogen receptor; MV, multivariate analysis; NSAID, nonsteroidal anti-inflammatory drug; PR, progesterone receptor.

Table 4. Relative Risk of Invasive Breast Cancer Among Premenopausal Women According to Acetaminophen Use in the Nurses’ Health Study II, 1989–2003

<table>
<thead>
<tr>
<th>Frequency of use</th>
<th>No. of Cases</th>
<th>Simple MVa</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular use (&gt;2 times/wk)</td>
<td>Nonusers 183</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Past users 209</td>
<td>1.09 (0.88-1.33)</td>
<td>1.08 (0.88-1.32)</td>
<td></td>
</tr>
<tr>
<td>Current users, d/wk</td>
<td>1</td>
<td>200</td>
<td>1.21 (0.99-1.48)</td>
</tr>
<tr>
<td>2-3</td>
<td>168</td>
<td>1.35 (1.09-1.67)</td>
<td>1.35 (1.09-1.67)</td>
</tr>
<tr>
<td>4-5</td>
<td>40</td>
<td>1.05 (0.74-1.48)</td>
<td>1.05 (0.74-1.48)</td>
</tr>
<tr>
<td>≥6</td>
<td>37</td>
<td>0.86 (0.60-1.22)</td>
<td>0.86 (0.60-1.24)</td>
</tr>
<tr>
<td>P value for trend</td>
<td>.06</td>
<td>.06</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ER, estrogen receptor; MV, multivariate analysis; PR, progesterone receptor.

a Multivariate model adjusted for factors listed in Table 2 footnote.
was not significantly associated with breast cancer risk (current use: RR, 1.11; 95% CI, 0.97-1.28; past use: 1.05; 0.89-1.23). To examine the importance of the timing of exposure, we conducted a lagged analysis using exposure from 2 years prior to the follow-up period (eg, 1989 exposure for the 1991-1993 follow-up period). Again, no significant associations were observed.

In this large, prospective analysis of premenopausal women, we did not observe an inverse association between aspirin, nonaspirin NSAID, or acetaminophen use and breast cancer risk. Although there was a modestly increased risk associated with NSAID use, we did not observe significant trends by duration or frequency of use.

Overall, results from studies of aspirin or other NSAID use and breast cancer risk have been inconsistent, with no clear explanation for the discrepancies. Several case-control studies have reported inverse associations,16-26 but positive,27-30 null,31,32,33,39 and inverse37-40,41 associations have been observed for aspirin or other NSAIDs in prospective studies. Although the assessment of aspirin and NSAID use is not consistent across prospective studies (eg, baseline,29,30,32,36,38,39 vs updated33-35,37 use, exposure 1 year prior to diagnosis27,28 vs duration ≥ 5 years29,30,32,37,39,40), the differences in measurement do not correspond with differences in results.

Although NSAIDs may inhibit proliferation and angiogenesis, given the possibility that they also inhibit aromatase, which may potentially increase estrogen levels in premenopausal women, it is crucial to investigate the associations with aspirin and NSAIDs separately among premenopausal women, given the possibility that they also inhibit aromatase, which may potentially increase estrogen levels.18,22 Invasive5,30,31,37 groups but did not report findings for ER−/PR− tumors.33,35 In the California Teachers' Study, long-term (≥ 5 years) daily use of aspirin was associated with a significantly increased risk of ER−/PR− breast cancer (RR, 1.81; 95% CI, 1.12-2.92), whereas use was associated with a nonsignificantly decreased risk of ER+/PR+ tumors (0.80; CI, 0.62-1.03).36 In contrast, Gallicchio et al41 observed a reduction in risk associated with nonaspirin NSAID use for both ER+ and ER− tumors. In our population of premenopausal women, we observed no associations with aspirin or other NSAID use among any ER/PR subtypes.

One of the main strengths of our large prospective cohort study is the focus on premenopausal women, an area that most studies are underpowered to evaluate. In addition, our data were collected prospectively, with exposure information and detailed covariate information updated every 2 years throughout follow-up. With aspirin and other NSAID data collected separately, we were able to evaluate these 2 classes of drugs separately and combined. In addition, we had information on acetaminophen use as a comparison to evaluate whether the behavior of taking pain medication affects risk. We were also able to examine the associations by ER/PR status of the tumor.

Although we have fairly thorough and updated data on regular use of the drugs of interest, we were limited by the lack of information on dose. In addition, frequency data were not available for the early years of follow-up. We also were restricted to examining exposure during the 14-year follow-up because we lacked information on duration of frequency of use before baseline in 1989. Thus, our findings are applicable to relatively recent use of these drugs, and it is possible that any protective effect of aspirin or other NSAIDs would be observed only after much longer periods of use, such as has been noted in colon cancer.31 Although the exposure data were self-reported, they are likely to be accurate given our population of registered nurses familiar with health-related exposures and use of drugs. Finally, although we conducted a number of subanalyses, the results of which should be interpreted with caution, we chose the comparisons on the basis of biologically motivated hypotheses (eg, hormonally driven comparison groups).

In summary, we did not observe any strong associations between aspirin, NSAIDs, or acetaminophen and breast cancer risk in this large, prospective cohort of premenopausal women with 14 years of exposure information and follow-up. Although animal and in vitro data suggest that NSAIDs may inhibit breast cancer growth, strong evidence is not apparent in epidemiologic data. Thus, chemopreventive use of aspirin or other NSAIDs for breast cancer among premenopausal women is not warranted.

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Author Contributions: Dr Eliassen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. 

Study concept and design: Eliassen, Spiegelman, Willett, and Hankinson. Acquisition of data: Spiegelman, Willett, Hunter, and Hankinson. Analysis and interpretation of data: Eliassen, Chen, Spiegelman, Willett, and Hankinson. Drafting of the manuscript: Eliassen. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: Eliassen, Spiegelman, Willett, and Hunter. Obtained funding: Willett. Administrative, technical, and material support: Eliassen and Willett. Study supervision: Hankinson.

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Additional Contributions: We are grateful to the Nurses’ Health Study II participants for their ongoing contributions to this study.

Apirin and other NSAIDs, such as ibuprofen, have been found in preclinical in vitro, in vivo, and epidemiologic studies to have potential utility in breast and colon cancer risk reduction by several mechanisms. These mechanisms include inhibition of COX-2, cell proliferation, angiogenesis, and metastasis and induction of apoptosis. However, for breast cancer chemoprevention (cancer risk reduction), COX-2 inhibition may specifically decrease progesterin induction of aromatase, the enzyme responsible for converting androgens to estrogen in breast tissue. Aspirin and other NSAIDs may, therefore, reduce risk of ER+ breast cancer, as suggested by epidemiologic observational data to date, but not ER- breast cancer.

Eliassen et al, using the prospective Nurses' Health Study II data, examined the relative risk of invasive breast cancer in premenopausal women and concluded that there is no cancer risk reduction with regular use of aspirin or other NSAIDs. However, several design factors may contribute to a negative result in this study. First, the relative risk of invasive breast cancer in premenopausal women is lower than in postmenopausal women, so it is more difficult to demonstrate efficacy in a low-risk group. Second, a significant proportion of breast cancer in premenopausal women is ER- and would not be expected to be prevented by manipulation of prostaglandins and aromatase. Third, carcinogenesis is a process that involves decades, and chronicity of use of cancer risk-reductive agents may be required to intervene in this process. Observations from the Nurses' Health Study that aspirin reduces colon cancer risk in women if taken for a prolonged period (>7 years) established the concept of chronicity as an important variable.

Furthermore, regular use of aspirin or other NSAIDs was defined by Eliassen et al as 2 or more times per week. While the irreversible binding of aspirin to COX makes this definition of consistent effect on COX viable, the reversible binding, pharmacokinetics, and relative potencies of nonaspirin NSAIDs differ, possibly producing only intermittent effects on COX and aromatase at twice-per-week dosing. The participants who used NSAIDs were slightly older and heavier and consumed more alcohol than non-NSAID users. These are all established risk factors for breast cancer and potential confounders in assessing relative NSAID efficacy as a cancer risk-reductive intervention.


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