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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Use of aspirin, other NSAIDs, and acetaminophen and risk of breast cancer among premenopausal women in the Nurses' Health Study II

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Abstract

Background—The use of aspirin and other non-steroidal 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 little 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, ages 25 to 42 years and free of cancer in 1989, were followed until June 2003. Multivariate relative risks (RRs) and 95% confidence intervals (CIs) were calculated by Cox proportional hazards models, adjusting for age and other important breast cancer risk factors.

Results—Overall, 1,345 cases of invasive premenopausal breast cancer were documented. Regular use of aspirin (≥2 times per week) was not significantly associated with breast cancer risk (RR=1.07, 95% CI=(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/week), dose (tablets/week), or duration of use. Further, associations with each drug category did not vary substantially by estrogen and progesterone receptor status of the tumor.

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

Introduction

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are frequently used for common ailments such as muscular pain, inflammation, and headaches. With consistent data suggesting a reduced risk of cardiovascular disease and colon cancer,

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[1-3] use of these drugs as chemopreventive agents has increased recently. Hopes have been raised that these drugs also might prevent other malignancies, including breast cancer.

NSAIDs act by inhibiting both isoforms of the cyclooxygenase enzyme (COX-1 and -2). COX-1 is constitutively expressed in most tissues while 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.[4, 5] Elevated COX-2 expression has been observed in breast tumor tissue[6] and animal and *in vitro* evidence strongly supports a protective role of aspirin and other NSAIDs against breast cancer.[7-10] 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[11, 12] and COX-2 inhibitors have been shown to decrease aromatase activity in breast cancer cell lines in a dose-dependent manner.[13] Although aromatase in adipose tissue plays an integral role in estrogen levels in postmenopausal women,[14, 15] 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.[16, 17] Thus, while the anti-proliferative and apoptotic mechanisms of NSAIDs may be beneficial in premenopausal breast cancer risk, the potential of NSAIDs to inhibit aromatase suggests the drugs may not reduce 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,[18-26] results from cohort studies are less consistent. Aspirin use was inversely associated with breast cancer risk in six prospective studies,[27-32] but no association was observed in six other studies.[33-39] Similarly, inverse,[27, 29, 31, 40, 41] positive,[36] and null[28, 30, 33, 37, 39] associations have been observed with NSAIDs or non-aspirin NSAIDs. Most prospective studies have included entirely[27, 29, 30, 38, 39] or predominantly[33, 34] 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 (NHSII) cohort to evaluate the associations of aspirin, non-aspirin NSAIDs, and acetaminophen use with breast cancer risk among premenopausal women.

Methods

Study Population

The NHSII began in 1989 when 116,609 female registered nurses, ages 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 excluding women with a history of cancer (except nonmelanoma skin cancer) and those who were postmenopausal at baseline, 112,292 premenopausal women, comprising 1,241,823 person-years, contributed to the analysis. Data up to June 2003 were available for 91% 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 (Boston, Mass).

Exposure and Covariate Assessment

On the baseline questionnaire in 1989, participants were asked if they regularly (≥2 times per week) used acetaminophen, aspirin, or other anti-inflammatory drugs in three separate questions and this was updated biennially from 1993. Women who reported regular use on a questionnaire were considered current users for the subsequent two-year follow-up period (or the four-year follow-up period from 1989−1993). Women who continued to report use on subsequent questionnaires remained classified as current users while those who ceased reporting use became past users, though these women were eligible to become current users on later questionnaires. Non-users during any given follow-up period are 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 days per week or days per month) and updated this every two 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, 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 four years from 1991. Menstrual cycle characteristics between ages 18 and 22, 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 two years women were asked to report whether their periods had ceased permanently and whether they had had hysterectomy and/or oophorectomy. Self-report of natural and surgical menopause has been validated in the NHS cohort.[42] Women were considered premenopausal if they still had periods or had at least one ovary remaining and were <46 (for smokers) or <48 (for nonsmokers) years old.

Case Ascertainment

Cases of invasive breast cancer, diagnosed from the start of follow-up in 1989 until June 2003, were identified on biennial questionnaires; the National Death Index was searched for those who did not respond. Participants, or next of kin for those deceased, were asked for permission to review their medical records. Investigators blinded to exposure status reviewed these records to confirm cancer reports and abstract information on histology and hormone receptor status. Records were unavailable for 138 (10.3%) of 1,345 cases, but the reported diagnoses confirmed by the participants were included as cases in the analysis given the high confirmation rate for self-reported cases.

Statistical Analysis

We calculated person-years from the baseline questionnaire until the first date of dubious or confirmed menopause, diagnosis with 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) and 95% confidence intervals (CIs). The proportional hazards assumptions were tested by including interaction terms

between exposure and time or age and comparing the interaction model to the model without the interaction terms using a likelihood ratio test. In all cases the likelihood ratio tests were not significant, indicating the proportional hazards assumptions were met. Multivariate models controlled for age at menarche, height, body mass index at age 18, weight change since age 18, 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 levels of other risk factors, we tested interaction terms in multivariate models using the likelihood ratio test comparing the model with main effects to the model with cross-classified interaction terms. All analyses were conducted using SAS software, version 9 (SAS Institute Inc., Cary, NC). All p-values were based on two-sided tests and were considered statistically significant at $p<0.05$.

Results

We documented 1,345 cases of invasive breast cancer among premenopausal women during 14 years of follow-up. Compared with non-users at baseline in 1989, women who used aspirin, non-aspirin NSAIDs, or acetaminophen were slightly older, were heavier at age 18, had gained more weight since age 18, 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 non-users of aspirin and non-aspirin NSAIDs, differences were comparable. Throughout follow-up women were more likely to use non-aspirin NSAIDs (22.2% of person-time) than aspirin (9.5%) or acetaminophen (16.3%).

Compared with non-users, current regular users of aspirin were not at a decreased risk of breast cancer, relative risk (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 RR=1.26, 95% CI (0.88−1.80), p-trend=0.55). Frequency of use (days per week) was similarly not associated with breast cancer risk (p-trend=0.39). 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 (RR=1.21, 95% CI (0.78−1.88)). Though 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-trend=0.76).

Current regular use of non-aspirin NSAIDs was associated with a modest increased risk of breast cancer compared with non-users, 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 RR=1.11, 95% CI (0.88−1.39)) (Table 3). Past use of non-aspirin 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=0.06), this may have been driven by a significant increased risk observed for use 2−3 days per week (RR=1.35, 95% CI (1.09−1.67)) since the only point estimate below one was for NSAIDs use 6+ days per week but this was not statistically significant (RR=0.86, 95% CI (0.60−1.24)). The association between regular use of non-aspirin NSAIDs and breast cancer risk did not differ appreciably by ER/PR status (ER+/PR+ RR=1.08, 95% CI (0.89−1.30) and ER-/PR- RR=1.01, 95% CI (0.72−1.43)). With follow-up from 1999 to 2003, when dose data were available, we observed slightly increased risks for low to moderate quantity of use of non-aspirin NSAIDs (1−2 tablets per week RR=1.47, 95% CI (1.02−2.12); 3−5 tablets per week RR=1.45, 95% CI (1.00−2.09)), but with no significant trend (p=0.64) and no significant associations observed with higher intake (6−14 or ≥15 tablets per week) (data not shown).

While acetaminophen is used in similar circumstances as aspirin and other NSAIDs, it is not an anti-inflammatory agent and it does not act on the COX pathway. We investigated the association between acetaminophen use and breast cancer risk as a comparison to ensure that behaviors associated with taking pain-relieving medications did not cause a spurious association between the drugs and breast cancer risk. As expected, acetaminophen was not associated with breast cancer risk by current regular use (RR=0.99, 95% CI (0.84−1.16)), duration (p-trend=0.91), or frequency of use (p-trend=0.60) (Table 4). The association did not differ by ER/PR status (ER+/PR+ RR=0.98, 95% CI (0.78−1.22); ER-/PR- RR=1.00, 95% CI (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-trend=0.94).

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 with 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 (e.g., 25.8% among users vs. 14.5% among non-users at baseline), and this syndrome may be associated with hormonal changes that could impact breast cancer risk, we repeated the analyses excluding these women. Again, results were unchanged (data not shown). Further, 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 three drug categories, nor did adjustment for physical activity (data not shown).

Results for all three drug categories did not substantially vary by oral contraceptive use (never users plus short term (<2 years) users vs. ≥2 years users), weight change since age 18 (<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 non-aspirin 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) and non-aspirin NSAIDs RR=1.16, 95% CI (1.01−1.34)). Use of any NSAIDs (aspirin or non-aspirin) was not significantly associated with breast cancer risk (current use RR=1.11, 95% CI (0.97 −1.28); past use RR=1.05, 95% CI (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 (e.g., 1989 exposure for the 1991−1993 follow-up period). Again, no significant associations were observed.

Discussion

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

Overall, results from studies of aspirin or other NSAIDs use and breast cancer risk have been inconsistent with no clear explanation for the discrepancies. Several case-control studies have reported inverse associations,[18-26] but positive,[36] null,[28, 30, 33-39] and inverse[27-32, 40, 41], associations have been observed for aspirin or other NSAIDs in prospective studies. Although the assessment of aspirin and NSAIDs use is not consistent across prospective studies (e.g., baseline[29, 30, 32, 36, 38, 39] vs. updated[33-35, 37] use, exposure 1 year prior to diagnosis[27, 28] vs. duration ≥5 years[29, 33-37, 39, 40]) the differences in measurement do not correspond with differences in results.

While 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 and postmenopausal women.[16, 17] Evidence among premenopausal women in particular is scarce, with, to our knowledge, no prospective studies of premenopausal women. As with findings regardless of menopausal status, significant[19, 21, 23] or suggestive[18, 22] inverse associations have been observed among premenopausal women in case-control studies. Most prospective studies have included entirely[27, 29, 30, 38, 39] or predominantly[33, 34] postmenopausal populations; among those that have included premenopausal women, none has reported the associations separately by menopausal status. Of five studies that stratified by age 50 or 55 as a surrogate for menopausal status, one smaller study (n=64 cases) found a significant inverse association with aspirin use at baseline among younger women (RR=0.54, 95% CI (0.33−0.89).[32] Although the other studies did not report separate findings, no significant differences were observed by age, with significant inverse[28, 40] or null[36, 37] associations observed overall with aspirin or NSAIDS. In our study, we did not observe an inverse association with either drug and breast cancer risk.

The importance of the modest increased risks we observed with past aspirin and current non-aspirin NSAIDS use is unclear. Although Marshall et al[36] observed increased risks with daily (RR=1.24, 95% CI (1.07−1.44)) and longer-term (≥5 years RR=1.17, 95% CI (1.00−1.36)) use of ibuprofen in their cohort of premenopausal and postmenopausal women, we did not observe significant trends with frequency or duration of NSAIDS use.

A few prospective studies have investigated the association between NSAIDs and breast cancer risk by tumor receptor status with mixed findings.[33, 35, 36, 41] Two studies in which no association was observed overall also found no association among receptor positive subgroups 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 significant increased risk of ER-/PR- breast cancer (RR=1.81, 95% CI (1.12−2.92)), while use was associated with a nonsignificant decreased risk of ER+/PR+ tumors (RR=0.80, 95% CI (0.62−1.03)).[36] In contrast, Gallicchio et al[41] observed a reduction in risk associated with non-aspirin NSAIDs use for both ER+ and ER- tumors. In our population of premenopausal women, we observed no associations with aspirin or other NSAIDs 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 two years throughout follow-up. With aspirin and other NSAIDs data collected separately, we were able to evaluate these two classes of drugs both 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 over the 14-year follow-up, as we lacked information on duration or 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 only be observed after much longer periods of use, such as has been noted in colon cancer.[43] Although the exposure data were self-reported, they are likely to be accurate given our population of registered nurses with a familiarity of health-related exposures and use of drugs. Finally, though we conducted a number of sub-analyses, the results of which should be interpreted with caution, we chose the

comparisons based on biologically motivated hypotheses (e.g., 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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Table 1

Age and age-standardized characteristics (mean (SD) or %) of Nurses' Health Study II participants, categorized by any NSAIDs or acetaminophen use in 1989

	Non-users (N=65,988)	Users (N=46,304)
Age (y)	34.0 (4.6)	34.7 (4.7)
Parity (children)	1.5 (1.2)	1.4 (1.2)
Height (inches)	64.9 (2.6)	64.9 (2.6)
BMI at age 18 years (kg/m^2)	21.1 (3.1)	21.5 (3.6)
Weight change since 18 (kg)	6.9 (9.5)	8.6 (11.5)
Alcohol consumption (g/day)	2.8 (5.2)	3.4 (6.3)
Age at menarche <12 years	23.2%	26.2%
Current oral contraceptive use	12.0%	15.0%
History of benign breast disease	26.9%	30.2%
Family history of breast cancer	6.0%	5.9%

Table 2

Relative risk (95% confidence interval) of invasive breast cancer among premenopausal women according to aspirin use in the Nurses' Health Study II, 1989−2003

	Cases	Simple	MV*
Regular use (≥2 times/week)			
Non-users	863	1.00 (ref)	1.00 (ref)
Past users	227	1.22 (1.05−1.43)	1.21 (1.03−1.41)
Current users	139	1.07 (0.90−1.29)	1.07 (0.89−1.29)
<5 yrs	107	1.03 (0.84−1.26)	1.03 (0.84−1.26)
≥5 yrs	32	1.27 (0.89−1.82)	1.26 (0.88−1.80)
p-trend		0.55	0.55
Frequency of use (follow-up 1993−2003)			
Non-users	610	1.00 (ref)	1.00 (ref)
Past users	191	1.18 (1.00−1.39)	1.15 (0.97−1.36)
Current users			
1 days/wk	67	1.03 (0.80−1.33)	1.01 (0.78−1.30)
2−3 days/wk	46	1.20 (0.89−1.62)	1.18 (0.87−1.60)
4−5 days/wk	11	0.65 (0.36−1.19)	0.64 (0.35−1.16)
6+ days/wk	39	1.02 (0.74−1.42)	1.03 (0.74−1.42)
p-trend		0.24	0.39
Regular use (≥2 times/week)			
ER+/PR+ Non-users	460	1.00 (ref)	1.00 (ref)
Past users	127	1.09 (0.89−1.34)	1.07 (0.87−1.32)
Current users	72	0.98 (0.77−1.26)	0.97 (0.76−1.25)
ER-/PR- Non-users	146	1.00 (ref)	1.00 (ref)
Past users	35	1.29 (0.87−1.91)	1.30 (0.88−1.93)
Current users	24	1.22 (0.79−1.89)	1.21 (0.78−1.88)

* Multivariate model adjusted for age at menarche (<12, 12, 13, ≥14 years, missing), height (<1.6, 1.6-<1.65, 1.65-<1.7, 1.7-<1.75, ≥1.75 m, missing), BMI at age 18 (<19, 19-<21, 21-<23, ≥23 kg/m2, missing), weight change since age 18 (lost ≥2, lost/gained <2, gained 2-<5, 5-<10, 10-<20, 20-<25, ≥25 kg), oral contraceptive use (never, current, past, missing), parity and age at first birth (nulliparous, 1−2 children/<25 years, 1−2 children/25−29 years, 1−2 children/≥30 years, ≥3 children/>25 years, ≥3 children/25−29 years, ≥3 children/≥30 years), alcohol consumption (never, 0−1.4, 1.5-<5, 5-<10, ≥10 g/day, missing), history of benign breast disease (yes, no), family history of breast cancer (yes, no)

Table 3

Relative risk (95% confidence interval) of invasive breast cancer among premenopausal women according to non-aspirin NSAIDs use in the Nurses' Health Study II, 1989−2003

	Cases	Simple	MV
Regular use (≥2 times/week)			
Non-users	586	1.00 (ref)	1.00 (ref)
Past users	320	1.07 (0.92−1.26)	1.06 (0.91−1.24)
Current users	376	1.17 (1.02−1.34)	1.16 (1.01−1.34)
<5 yrs	274	1.19 (1.02−1.37)	1.18 (1.02−1.37)
≥5 yrs	102	1.11 (0.89−1.39)	1.11 (0.88−1.39)
p-trend		0.32	0.23
Frequency of use (follow-up 1995−2003)			
Non-users	183	1.00 (ref)	1.00 (ref)
Past users	209	1.09 (0.88−1.33)	1.08 (0.88−1.32)
Current users			
1 days/wk	200	1.21 (0.99−1.48)	1.20 (0.98−1.47)
2−3 days/wk	166	1.35 (1.09−1.67)	1.35 (1.09−1.67)
4−5 days/wk	40	1.05 (0.74−1.48)	1.05 (0.74−1.48)
6+ days/wk	37	0.86 (0.60−1.22)	0.86 (0.60−1.24)
p-trend		0.06	0.06
Regular use (≥2 times/week)			
ER+/PR+ Non-users	297	1.00 (ref)	1.00 (ref)
Past users	205	0.99 (0.81−1.22)	0.98 (0.79−1.20)
Current users	189	1.10 (0.91−1.32)	1.08 (0.89−1.30)
ER-/PR- Non-users	106	1.00 (ref)	1.00 (ref)
Past users	55	1.14 (0.78−1.66)	1.12 (0.76−1.64)
Current users	53	1.06 (0.76−1.49)	1.01 (0.72−1.43)

*Multivariate model adjusted for factors listed in Table 2 footnote

Table 4

Relative risk (95% confidence interval) of invasive breast cancer among premenopausal women according to acetaminophen use in the Nurses' Health Study II, 1989−2003

	Cases	Simple	MV
Regular use (≥2 times/week)			
Non-users	706	1.00 (ref)	1.00 (ref)
Past users	375	1.00 (0.87−1.16)	1.03 (0.89−1.19)
Current users	185	0.96 (0.82−1.13)	0.99 (0.84−1.16)
<5 yrs	142	0.94 (0.78−1.13)	0.97 (0.81−1.16)
≥5 yrs	43	1.05 (0.76−1.43)	1.07 (0.78−1.47)
p-trend		0.93	0.91
Frequency of use (follow-up 1995−2003)			
Non-users	325	1.00 (ref)	1.00 (ref)
Past users	253	0.94 (0.79−1.12)	0.96 (0.81−1.14)
Current users			
1 days/wk	152	0.91 (0.75−1.11)	0.93 (0.76−1.13)
2−3 days/wk	68	0.90 (0.69−1.17)	0.94 (0.72−1.22)
4−5 days/wk	18	0.94 (0.58−1.51)	1.00 (0.62−1.61)
6+ days/wk	16	1.02 (0.61−1.69)	1.06 (0.64−1.76)
p-trend		0.68	0.60
Regular use (≥2 times/week)			
ER+/PR+ Non-users	362	1.00 (ref)	1.00 (ref)
Past users	224	0.97 (0.81−1.17)	1.00 (0.83−1.20)
Current users	97	0.95 (0.76−1.19)	0.98 (0.78−1.22)
ER-/PR- Non-users	121	1.00 (ref)	1.00 (ref)
Past users	59	1.01 (0.71−1.43)	1.00 (0.70−1.43)
Current users	33	1.03 (0.70−1.51)	1.00 (0.67−1.47)

*Multivariate model adjusted for factors listed in Table 2 footnote