Aspirin Use and the Risk of Breast Cancer

Kathleen M. Egan, Meir J. Stampfer, Edward Giovannucci, Bernard A. Rosner, Graham A. Colditz*

Background: Evidence suggests that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can inhibit tumor development in the large bowel. An inverse association between the use of NSAIDs and the incidence of breast cancer has been observed, but this association has not been statistically significant in all studies. Purpose: We analyzed data from the prospective Nurses’ Health Study to evaluate the influence of aspirin use on breast cancer risk. Methods: We studied a population of 89,528 female registered nurses who reported no history of breast or other cancers (excluding non-melanoma skin cancer) and who returned a mailed questionnaire in 1980 that elicited information concerning breast cancer risk factors and current and past aspirin use. Follow-up questionnaires were mailed to the participants every 2 years; the women were followed through 1992. Information concerning current aspirin use was obtained from each biennial questionnaire, except in 1986. Cases of breast cancer were identified through questionnaire responses, and permission was sought for a review of medical records to confirm the diagnoses. Our analysis was based on 2,414 cases of invasive breast cancer, which included 2,303 cases confirmed with medical records and 111 cases for which no records were obtained. Relative risks (RRs) with 95% confidence intervals (CIs), adjusted for age or age plus other known or potential breast cancer risk factors (i.e., multivariate), were calculated. Results: Regular aspirin use (two or more tablets per week) in 1980 was unrelated to breast cancer incidence during the succeeding 12-year period (with no regular aspirin use as the referent, multivariate RR = 1.03; 95% CI = 0.95-1.12). The corresponding risk estimate for consistent regular aspirin use during the period from 1980 through 1988 was 1.01 (95% CI = 0.80-1.27). The risks were similar for heavy aspirin use (for more than two tablets per day [i.e., >14 per week] in 1980 and in 1980 through 1988, the multivariate RRs [95% CIs] were 1.05 [0.89-1.23] and 1.09 [0.75-1.60], respectively) and for extended durations of regular use (e.g., for 20 years or more of regular use, multivariate RR = 1.00; 95% CI = 0.71-1.41). Conclusion: Our results indicate that regular aspirin use does not reduce the risk of breast cancer. [J Natl Cancer Inst 1996;88:988-93]

Mounting evidence suggests that non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, can inhibit the development of tumors in the large bowel. In animal models of colon carcinogenesis, certain NSAIDs reduced the incidence of tumors in general, as well as the number of tumors per animal (7-10). In human trials (5,6) and in a series of case reports (7-10), specific NSAIDs were shown to induce the regression of existing adenomatous polyps of the colon and to prevent recurrences in persons genetically at risk. Epidemiologic studies suggest that NSAIDs may also be effective in the prevention of colorectal cancer (11-19). Inverse associations between the use of NSAIDs and the occurrence of sporadic colorectal adenomas (17,19-21) suggest that NSAIDs may inhibit an early event in colon carcinogenesis.

The therapeutic effects of NSAIDs are related to their ability to block the enzyme cyclooxygenase and, in turn, to inhibit prostaglandin biosynthesis. Prostaglandins may serve as cofactors in carcinogenesis (22), with postulated effects ranging from direct mutagenesis (one byproduct of arachidonic acid metabolism is malondialdehyde, a direct-acting mutagen) to tumor promotion, immune suppression, and facilitation of metastasis. However, other evidence suggests that the cancer inhibitory effects of NSAIDs may be independent of their effects on prostaglandin synthesis (23).

Data concerning the possible role of NSAIDs in breast carcinogenesis are limited. In some rodent models, NSAIDs inhibit the formation of chemically induced tumors of the breast (24-27). In some studies (28,29), but not all (30), involving humans, patients with rheumatoid arthritis who use NSAIDs in high doses for symptom relief had fewer than expected occurrences of breast cancer. The association between NSAIDs use and the incidence of breast cancer has been examined in six published epidemiologic studies. In two prospective studies (31,32), aspirin use had a weak but non-significant inverse association with breast cancer risk. In a third study, involving follow-up of the first National Health and Nutrition Examination Survey (15), self-reported aspirin use at baseline (any use in the past month) was associated with a 30% reduction in breast cancer incidence when compared with nonuse. Statistically significant inverse associations for aspirin use also were demonstrated in two (33,34) of three (33-35) case-control studies. To evaluate the potential influence of aspirin use on breast cancer risk, we analyzed data collected in the prospective Nurses’ Health Study.

Methods

Study Cohort

The Nurses’ Health Study cohort was established in 1976, when 121,700 registered nurses between the ages of 30 and 55 years returned a mailed questionnaire that elicited information about known or suspected risk factors for breast cancer, cardiovas-

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See “Notes” section following “References.”
cicular disease, and other illnesses. Every 2 years, follow-up questionnaires are mailed to these women to update information on risk factors and major medical events, including the diagnosis of breast cancer. In 1976, women reported their age at first full-term pregnancy and the number of pregnancies lasting 6 months or more. In 1980, the questionnaire was expanded to include an assessment of diet and patterns of NSAIDs use. Our analysis is based on the 89,528 Nurses' Health Study participants who returned the 1980 questionnaire, completed the section of the questionnaire relating to diet and medication use, and had no previous diagnosis of cancer (excluding nonmelanoma skin cancer).

Breast Cancer Occurrences

Follow-up questionnaires were mailed to all participants in 1982, 1984, 1986, 1988, 1990, and 1992. The corresponding response frequencies were 97%, 90%, 92%, 94%, 95%, and 95%, respectively; among surviving women, the overall follow-up proportion was 96% of the total possible person-years accumulated through 1992. Deaths in the cohort were identified by reports from family members, the Postal Service, and a search of the National Death Index; we estimate that 98% of deaths were ascertained (36). When a case of breast cancer was identified, we asked the participant (or her next of kin if she had died) for permission to review the relevant medical records to confirm the self-reported diagnosis. Medical records were obtained for more than 95% of the women who reported breast cancer, and the diagnosis confirmed was for more than 99% of those who had reported the disease. Pathology reports were obtained for approximately 90% of the cases, and information concerning histologic tumor type, tumor size, and regional lymph node involvement was abstracted by study physicians. We based our analyses on 2414 cases of invasive breast cancer, which included 2303 (95.4%) cases confirmed with medical records and 111 (4.6%) cases for which no records were obtained. We included the latter cases because the accuracy of participant reports was unknowable. The results of analyses limited to confirmed cases only and analyses that included the unconfirmed cases were virtually identical.

Assessment of NSAIDs Use

Information about regular aspirin use was obtained in each biennial questionnaire except in 1986. The 1980 questionnaire included the question: “Do you currently take any of the following vitamins or medications in most weeks?,” and the roster included: “aspirin (includes Bufferin, Anacin, etc.),” and “other nonsteroidal analgesics (Motrin, Indocin, Tolecin, and Clinoril).” If the answer was yes, the participant was asked to record the number of pills or capsules taken each week and the number of years the medication had been used. In 1982, the question was phrased: “Are you currently taking any of the following medications at least once per week?” If the answer was yes to aspirin use, the respondent was then asked how many aspirin per week? “If the answer was yes to aspirin use, the participant was asked to record the number of pills taken in each biennial questionnaire except in 1986. Among women returning all four questionnaires (81%), 15% reported no regular use during the 8-year period; 14% reported being a regular aspirin user in only one questionnaire. Spearmann correlations for the number of aspirin tablets used per day in 1980 versus 1982, 1984, and 1988 were 0.50, 0.40, and 0.26, respectively.

For assessment of the effect of aspirin use in 1980, we allocated follow-up time, equal to the number of months between the return of the 1980 and 1982 questionnaires, to each level of aspirin intake reported in 1980 (regular versus nonregular use and the number of months between the return of the 1980 and 1982 questionnaires). The results of analyses limited to confirmed cases only and analyses that included the unconfirmed cases were virtually identical.

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Statistical Methods

Aspirin use through 1988 was evaluated in terms of the usual number of pills taken per week. Some recoding of responses was necessary to accommodate the differing ways in which the patterns of aspirin use were elicited between 1980 and 1988; recoding was done prior to any analysis.

Following the precedent established in the analysis of aspirin use and colorectal cancer risk in the Nurses' Health Study (18), we defined regular aspirin use as two or more aspirins taken per week. Regular aspirin use was highly prevalent in this cohort; between 41% and 65% of the women reported taking two or more aspirins per week in the four biennial questionnaires, with moderate consistency between 1980 and 1988. Among women returning all four questionnaires (81%), 15% reported regular aspirin use in each questionnaire, and 15% reported no regular use during the 8-year period; 14% reported being a regular aspirin user in only one questionnaire. Spearmann correlations for the number of aspirin tablets used per day in 1980 versus 1982, 1984, and 1988 were 0.50, 0.40, and 0.26, respectively.

For assessment of the effect of aspirin use in 1980, we allocated follow-up time, equal to the number of months between the return of the 1980 and 1982 questionnaires, to each level of aspirin intake reported in 1980 (regular versus nonregular use and the number of months between the return of the 1980 and 1982 questionnaires). Similarly, for each subsequent 2-year interval, additional person-months were allocated according to the 1980 aspirin status. Aspirin use reported in the 1982 questionnaire and in succeeding questionnaires was used to assess the chronicity of regular aspirin use. These analyses were based on the subset of the cohort that returned each of the relevant questionnaires and had not been diagnosed with breast cancer. For example, analyses involving regular aspirin use in 1980 and 1982 were based on women who returned both the 1980 and 1982 questionnaires and were free of breast cancer as of the 1982 questionnaire. We further evaluated the relative risk (RR) according to the years of continuous use (1-4, 5-9, 10-19, and 20 or more years) updating this variable every 2 years. (The results are shown in Fig. 1.) For example, if a woman began using aspirin in 1982 and continued using it in 1984 and 1986, she was considered a user of 1-4 years' duration in 1984-1985 and a user of 5-9 years' duration in 1986-1987. The reported duration of use at base line was used to evaluate previous long-term use. For example, a woman who reported regular use of 7 years' duration in 1980 plus continued use in 1982 and 1984 was assumed to have consumed aspirin for 12 years in 1985.

Follow-up was terminated at the time the last questionnaire was returned, the time an incident cancer (excluding nonmelanoma skin cancer) was diagnosed, or the time of death, whichever came first.

Incidence rates were calculated by dividing the number of events by the number of person-months of follow-up. RRs were calculated by dividing the incidence rates in the aspirin exposure categories by the corresponding rate in the reference category (no regular aspirin use). Age-adjusted rates were calculated by the use of 5-year age categories. Analyses to control for age and other covariates simultaneously were conducted using proportional hazards models (38); in these models, menopausal status and other covariates (Table 1) were updated at 2-year intervals. For all RRs, we calculated 95% confidence intervals (Cls). All P values are two-tailed.

Results

During 12 years of follow-up (1,020,774 person-years), 2414 incident cases of invasive breast cancer were diagnosed. To determine whether known or potential breast cancer risk factors were associated with aspirin intake, we evaluated the age-adjusted distribution of each factor by the category of aspirin use in 1980 (Table 1). For most risk factors, we observed no associations with the level of aspirin use. There was a tendency for higher levels of use among women who were menopausal, had a history of benign breast disease, or were currently taking multivitamins or postmenopausal hormones. For example, benign breast disease was reported by 23.8% of the women taking no aspirin compared with 27.7% of the women taking 15 or more aspirins per week. Multivitamin use was reported by 30.7% and 41% of women in the none and the 15 or more aspirins per week group, respectively.

In Table 2, we present results for regular aspirin use (two or more pills per week) among all women in the cohort after stratifying by age. Regular use in 1980 was unrelated to breast cancer incidence over the succeeding 12-year period (age-adjusted RR = 1.06; 95% Cl = 0.98-1.16). Results were similar after adjusting for breast cancer risk factors (multivariate RR = 1.03; 95% Cl = 0.95-1.12) and in younger (34-49 years of age; age-adjusted RR = 1.11; 95% Cl = 0.95-1.29) as well as older (50-65 years of age; age-adjusted RR = 1.04; 95% Cl = 0.95-1.15) women.
To assess the impact of consistent long-term aspirin use during the period of observation, we examined the RRs among women who reported regular use in successive questionnaires (Table 2). The age-adjusted RR from 1988 to 1992 among women who reported aspirin use in four consecutive questionnaires (1980 through 1988), compared with the risk associated with no regular use during that interval, was 1.02 (95% CI = 0.81-1.28). Results were similar after adjusting for established breast cancer risk factors (multivariate RR = 1.01; 95% CI = 0.80-1.27) and after stratifying by age (Table 2). There was no evidence that aspirin use influenced the stage of breast cancer at diagnosis; the risk estimates were similar for women with node-negative, node-positive, or metastatic disease (data not shown).

Most of the regular aspirin users in 1980 reported relatively long-term aspirin use prior to that year (75% had taken aspirin for 3 or more years). To address the duration of aspirin use further, we studied the effect of long-term regular aspirin use, using the subjects' reported duration of use at base line (in the 1980 questionnaire). The incidence of breast cancer among long-term aspirin users was not materially different from that of nonusers. Age-adjusted RRs for increasing duration of use are shown in Fig. 1, A. Corresponding results from the Nurses' Health Study of colorectal cancer (18) are included (Fig. 1, B) for comparison. The age-adjusted RR for 5 or fewer years of aspirin use by 1984 was 0.89 (95% CI = 0.76-1.05). The estimates were 0.98 (95% CI = 0.81-1.19) for 5-9 years, 1.11 (95% CI = 0.85-1.46) for 10-19 years, and 1.00 (95% CI = 0.71-1.41) for 20 or more years of regular use (P for trend = .90). In contrast to these results, a clear decreasing trend in the rate of colorectal cancer with increasing duration of regular aspirin use has been demonstrated in this cohort (P for trend = .008) (18).

### Table 1. Selected characteristics of study participants by reported aspirin use in 1980

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0</th>
<th>1-3</th>
<th>4-6</th>
<th>7-14</th>
<th>15+</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of women*</td>
<td>53 292</td>
<td>15 653</td>
<td>7320</td>
<td>7719</td>
<td>5544</td>
</tr>
<tr>
<td>Person-years†</td>
<td>607 716</td>
<td>179 078</td>
<td>83 580</td>
<td>87 658</td>
<td>62 742</td>
</tr>
<tr>
<td>Mean age, y</td>
<td>46.4</td>
<td>46.2</td>
<td>46.0</td>
<td>47.4</td>
<td>48.5</td>
</tr>
<tr>
<td>Women with potential risk indicators‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age at menarche</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.5</td>
<td>12.4</td>
</tr>
<tr>
<td>% parous</td>
<td>92.0</td>
<td>92.1</td>
<td>91.9</td>
<td>91.7</td>
<td>91.5</td>
</tr>
<tr>
<td>Mean age at FFTP§ in parous women</td>
<td>24.8</td>
<td>24.8</td>
<td>24.7</td>
<td>24.6</td>
<td>24.5</td>
</tr>
<tr>
<td>% menopausal</td>
<td>43.6</td>
<td>43.8</td>
<td>45.5</td>
<td>47.2</td>
<td>50.9</td>
</tr>
<tr>
<td>Mean age at menopause, y</td>
<td>44.6</td>
<td>44.6</td>
<td>44.5</td>
<td>44.3</td>
<td>44.0</td>
</tr>
<tr>
<td>Mean BMII</td>
<td>24.3</td>
<td>24.3</td>
<td>24.5</td>
<td>24.8</td>
<td>25.4</td>
</tr>
<tr>
<td>% current PMH§ use</td>
<td>7.6</td>
<td>8.2</td>
<td>9.4</td>
<td>10.2</td>
<td>11.6</td>
</tr>
<tr>
<td>Mean alcohol intake, g/day</td>
<td>6.4</td>
<td>6.5</td>
<td>7.0</td>
<td>7.6</td>
<td>6.9</td>
</tr>
<tr>
<td>% family history of breast cancer</td>
<td>6.1</td>
<td>5.9</td>
<td>6.1</td>
<td>6.3</td>
<td>6.2</td>
</tr>
<tr>
<td>% history of benign breast disease</td>
<td>23.8</td>
<td>24.0</td>
<td>25.7</td>
<td>26.2</td>
<td>27.7</td>
</tr>
<tr>
<td>% multivitamin use</td>
<td>30.7</td>
<td>38.9</td>
<td>36.5</td>
<td>39.4</td>
<td>41.0</td>
</tr>
</tbody>
</table>

*Number of women in each aspirin category in 1980.
†Total person-years for each aspirin category during the 12 years of follow-up.
‡Age-standardized by 5-year age categories to the age distribution of the cohort; risk factors were self-reported by questionnaire.
§First full-term pregnancy.
llBody mass index. Weight in kilograms divided by height in meters squared.
§Postmenopausal hormones.

### Table 2. Relative risk (RR) of breast cancer with regular aspirin use in the Nurses' Health Study, 1980 through 1992

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Years regular use:* median (25th-75th percentile)</td>
<td>15 (3-25)</td>
<td>17 (5-27)</td>
<td>19 (8-29)</td>
<td>23 (12-33)</td>
</tr>
<tr>
<td>Total cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonusers, cases/P-Y†</td>
<td>1583/685 450</td>
<td>1101/445 285</td>
<td>843/317 842</td>
<td>415/38 406</td>
</tr>
<tr>
<td>Users, cases/P-Y†</td>
<td>831/335 324</td>
<td>510/184 519</td>
<td>288/96 381</td>
<td>93/29 542</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)§</td>
<td>1.06 (0.98-1.16)</td>
<td>1.09 (0.98-1.21)</td>
<td>1.09 (0.96-1.25)</td>
<td>1.02 (0.81-1.28)</td>
</tr>
<tr>
<td>Multivariate RR§ (95% CI)</td>
<td>1.03 (0.95-1.12)</td>
<td>1.04 (0.93-1.16)</td>
<td>1.07 (0.93-1.22)</td>
<td>1.01 (0.80-1.27)</td>
</tr>
<tr>
<td>Age 34-49 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonusers, cases/P-Y</td>
<td>467/306 878</td>
<td>305/185 435</td>
<td>204/117 853</td>
<td>87/40 232</td>
</tr>
<tr>
<td>Users, cases/P-Y</td>
<td>248/145 709</td>
<td>126/70 855</td>
<td>54/31 818</td>
<td>12/70 004</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.11 (0.95-1.29)</td>
<td>1.07 (0.87-1.31)</td>
<td>0.97 (0.72-1.31)</td>
<td>0.79 (0.43-1.45)</td>
</tr>
<tr>
<td>Age ≥50 y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonusers, cases/P-Y</td>
<td>1116/378 572</td>
<td>796/259 850</td>
<td>639/199 898</td>
<td>32/98 174</td>
</tr>
<tr>
<td>Users, cases/P-Y</td>
<td>583/189 615</td>
<td>384/113 664</td>
<td>234/64 563</td>
<td>81/22 338</td>
</tr>
<tr>
<td>Age-adjusted RR (95% CI)</td>
<td>1.04 (0.95-1.15)</td>
<td>1.10 (0.97-1.24)</td>
<td>1.13 (0.97-1.31)</td>
<td>1.06 (0.83-1.35)</td>
</tr>
</tbody>
</table>

*Years of regular aspirin use (2+/week) as reported in 1980; updated among post-1980 users.
§CI = confidence interval.
§RR adjusted by proportional hazards regression for age and all other factors listed in Table 1.
We found no overall impact of aspirin dose in 1980 on breast cancer incidence rates during the succeeding 12-year follow-up period (Table 3). The adjusted RR (both age-adjusted and multivariate) for women averaging more than two aspirins per day (i.e., >14 per week) in 1980, compared with none, was 1.05 (95% CI = 0.89-1.23). Likewise, there was no evidence that long-term use of higher aspirin doses influenced breast cancer rates (Table 3). Women averaging two or more aspirins per day throughout the period from 1980 through 1988 had breast cancer rates from 1988 to 1992 that were similar to those of consistent nonusers (age-adjusted RR = 1.09; 95% CI = 0.75-1.60). When the data were stratified by age (<50 years versus 50 years and older) and when early and advanced breast cancers were considered separately, the inferences were similar (data not shown).

Questions pertaining to nonaspirin NSAIDs (Motrin, Indocin, Tolectin, and Clinoril) were included in the 1980 questionnaire. Among the 3455 women reporting regular use (two or more per week) of any of these preparations in 1980, 100 developed breast cancer during follow-up. Since these drugs were relatively new to the market in 1980, few women reported long-term use (among users, 75% reported 3 or fewer years of regular use). The multivariate RR for nonaspirin NSAID use for the 12-year follow-up period was 0.95 (95% CI = 0.78-1.17). No trends with increasing nonaspirin NSAID dose were apparent (P for trend = .48); the adjusted RR for more than two pills per day was 1.09 (95% CI = 0.79-1.49). The data were too sparse for examination of the risks associated with individual drug preparations. RRs for combined aspirin and nonaspirin NSAID use in 1980 were similar to those for aspirin alone (data not shown).

In a final series of analyses, we examined possible interactions between NSAIDs (aspirin and nonaspirin preparations) and other breast cancer risk factors. The effects of NSAID use were similar across levels of age at menarche, parity and age at first childbirth, benign breast disease, family history of breast cancer, and all other factors listed in Table 1 (data not shown).

Discussion

Several previous epidemiologic studies have addressed the question of whether aspirin use may affect breast cancer risk, with inconsistent results. In an exploratory hospital-based, case-control study, Rosenberg (35) found a reduced risk associated with aspirin use that was of borderline significance (RR = 0.8; 95% CI = 0.6-1.0); the control subjects were hospitalized for traumatic injuries and infections. Rosenberg et al. (72) had previously evaluated cancer occurrence at multiple sites, and strong (inverse) associations with aspirin use that was of borderline significance (RR = 0.8; 95% CI = 0.6-1.0); the control subjects were hospitalized for traumatic injuries and infections. Rosenberg et al. (72) had previously evaluated cancer occurrence at multiple sites, and strong (inverse) associations with aspirin use were identified only for colorectal cancer. In another hospital-based study, Harris et al. (33) reported a statistically significant 40% reduction in the risk of breast cancer for aspirin use of at least 5 years' duration. However, the control subjects in this study had a higher prevalence of pre-existing medical conditions commonly associated with NSAID use (arthritis, cardiovascular disease, and migraine), which may have accounted for the inverse association. When control subjects with
cancer were used for comparison (excluding those with colorectal cancer), no effect of aspirin could be demonstrated. In a subsequent study, Harris et al. (34) also found statistically significant reductions in RRs associated with the use of both aspirin and other NSAIDs. However, in this latter study, mammography screenings were used as control subjects, thereby casting doubt on the validity of the findings, since health consciousness is likely to be associated with the tendency to use medications.

Two prospective studies (31,32), each based on limited numbers of incident cancers, were essentially null for a breast cancer effect. In contrast, a follow-up study of participants in the first National Health and Nutrition Examination Survey (NHANES I) (15) found substantial reductions in breast cancer incidence rates among women reporting any aspirin use in the month before interview (RR = 0.72; 95% CI = 0.52-1.00). The effect was stronger and statistically significant among women under the age of 50 years (RR = 0.54; 95% CI = 0.33-0.89). However, NHANES I data have several limitations for examining the association. Exposure assessment was based on a single question referring to the 30-day period prior to interview. Furthermore, the analyses were based on only 147 breast cancer cases, and the results may have been confounded by reproductive factors and other covariates. (Only limited data had been collected on these factors.)

Our results provide evidence against an important influence of aspirin use on breast cancer incidence rates. Our study was based on exposure information collected before the onset of disease, thus eliminating the possibility of recall bias. Study participants, all registered nurses, were likely to have reported aspirin exposures with a high degree of accuracy. The quality of the exposure data is supported by the fact that strong inverse associations were demonstrated in this cohort for aspirin use and colorectal cancers (18), consistent with the growing consensus that NSAIDs reduce the occurrence of these cancers (39). Unlike previous studies, information on currency, frequency, and duration of aspirin use were collected, and exposures were updated throughout the follow-up period. Finally, the study was based on 2414 incident cases of invasive breast cancer, and, in most categories of aspirin use, large aspirin effects in either direction could be excluded. Aspirin use was not associated with breast cancer incidence rates overall or in women over and under the age of 50 years (Table 2).

This study was nonrandomized, and we lacked data on the indication for aspirin use. Thus, we were unable to separate the effects of aspirin from the reasons for aspirin use. However, there is no evidence that conditions typically prompting regular aspirin use in women have any association with breast cancer risk. (The most common reason for aspirin use in the cohort, based on a random sample of regular users, was headache and/or musculoskeletal pain [80%].) One other potential limitation of our data is the lack of information on nonaspirin NSAIDs after 1980. Use of these drugs increased markedly in the United States during the 1980s (40). In the Nurses' Health Study, the prevalence of regular nonaspirin NSAID use increased from approximately 4% in 1980 to 19% in 1990 (the next questionnaire in which these data were solicited). Thus, in the present analyses, total NSAID use was underascertained for some women. To the extent that misclassification was nondifferential (e.g., the degree of error was similar in the person-time accumulated for women with and without disease), the RRs would be biased toward the null (41). However, it is unlikely that an important NSAID-breast cancer association, if it existed, would have been missed. Users of nonaspirin NSAIDs in 1980 had similar rates of breast cancer as nonusers, suggesting that NSAIDs, in general, do not influence the pathogenesis of breast carcinomas. Furthermore, misclassification from this source should have been minimal through the early 1980s, and the period-specific RRs for 1980-1982 and 1982-1984 were close to 1.0 and not materially different from those collapsed over all intervals of follow-up (1980-1992).

In summary, these results provide evidence against an important protective influence of aspirin on breast cancer risk. Aspirin has a number of well-established salutary effects, which may include the inhibition of gastrointestinal cancers. However, our data suggest that aspirin does not have a universal anticancer effect, and it is unlikely to alter risk of breast cancer.

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Notes

Supported by Public Health Service grant CA49035 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; and by Special Institution Grant No. 18 from the American Cancer Society. K. M. Eg an is supported by a National Service Award T32 ES 07069. G. A. Colditz is supported by a Faculty Research Award (FRA-398) from the American Cancer Society.

We thank Dr. Dimitrios Trachopoulos for his important comments and suggestions. We also thank Karen Corsano, Barbara Egan, Mark Shneyder, and Stephanie Parker for their expert help.

Representing the Nurses' Health Study investigators (David Hunter, Susan Hankinson, JoAnn Manson, Charles Hennekens, Walter Willett, and Frank Speizer).

Manuscript received November 30, 1995; revised March 21, 1996; accepted May 7, 1996.

Journal of the National Cancer Institute, Vol. 88, No. 14, July 17, 1996

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