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## Long-term Use of Aspirin and Nonsteroidal Anti-inflammatory Drugs and Risk of Colorectal Cancer

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### Abstract

**Context**—Randomized trials of short-term aspirin use for prevention of recurrent colorectal adenoma have provided compelling evidence of a causal relationship between aspirin and colorectal neoplasia. However, data on long-term risk of colorectal cancer according to dose, timing, or duration of therapy with aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) remain limited.

**Objective**—To examine the influence of aspirin and NSAIDs in prevention of colorectal cancer.

**Design, Setting, and Participants**—Prospective cohort study of 82 911 women enrolled in the Nurses' Health Study providing data on medication use biennially since 1980 and followed up through June 1, 2000.

**Main Outcome Measure**—Incident colorectal cancer.

**Results**—Over a 20-year period, we documented 962 cases of colorectal cancer. Among women who regularly used aspirin ( $\geq 2$  standard [325-mg] tablets per week), the multivariate relative risk (RR) for colorectal cancer was 0.77 (95% confidence interval [CI], 0.67–0.88) compared with

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nonregular users. However, significant risk reduction was not observed until more than 10 years of use ( $P \leq .001$  for trend). The benefit appeared related to dose: compared with women who reported no use, the multivariate RRs for cancer were 1.10 (95% CI, 0.92–1.31) for women who used 0.5 to 1.5 standard aspirin tablets per week, 0.89 (95% CI, 0.73–1.10) for 2 to 5 aspirin per week, 0.78 (95% CI, 0.62–0.97) for 6 to 14 aspirin per week, and 0.68 (95% CI, 0.49–0.95) for more than 14 aspirin per week ( $P < .001$  for trend). Notably, women who used more than 14 aspirin per week for longer than 10 years in the past had a multivariate RR for cancer of 0.47 (95% CI, 0.31–0.71). A similar dose-response relationship was found for nonaspirin NSAIDs ( $P = .007$  for trend). The incidence of reported major gastrointestinal bleeding events per 1000 person-years also appeared to be dose-related: 0.77 among women who denied any aspirin use; 1.07 for 0.5 to 1.5 standard aspirin tablets per week; 1.07 for 2 to 5 aspirin per week; 1.40 for 6 to 14 aspirin per week; and 1.57 for more than 14 aspirin per week.

**Conclusions**—Regular, long-term aspirin use reduces risk of colorectal cancer. Non-aspirin NSAIDs appear to have a similar effect. However, a significant benefit of aspirin is not apparent until more than a decade of use, with maximal risk reduction at doses greater than 14 tablets per week. These results suggest that optimal chemoprevention for colorectal cancer requires long-term use of aspirin doses substantially higher than those recommended for prevention of cardiovascular disease, but the dose-related risk of gastrointestinal bleeding must also be considered.

RECENT RANDOMIZED INTERVENTION trials have demonstrated that regular use of aspirin in patients with a history of colorectal adenoma or cancer reduces the risk of recurrent adenoma within 1 to 3 years.<sup>1–3</sup> However, whether aspirin similarly reduces risk of colorectal cancer and, if so, the necessary dose and duration of use, remain unclear. Although short-term aspirin use appears effective in reducing risk of adenoma, 2 randomized trials of aspirin that have specifically examined colorectal cancer as an outcome did not demonstrate a benefit after 5 or 10 years.<sup>4,5</sup> Moreover, intervention trials of adenoma or cancer have provided only limited and conflicting data on the optimal dose of aspirin.<sup>1–5</sup> Finally, it remains uncertain whether nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), which share several underlying mechanisms with aspirin, exert a similar antineoplastic benefit.

Thus, we prospectively examined the influence of aspirin and NSAIDs on the risk of colorectal cancer in a large cohort of women enrolled in the Nurses' Health Study. This cohort, which provides detailed and updated information on aspirin use, permitted a more comprehensive examination of the effect of long-term aspirin use at a wide range of doses on the primary prevention of sporadic colorectal cancer than would be feasible in a placebo-controlled trial. An earlier examination of aspirin use and colorectal cancer in this cohort did not observe a strong dose relationship; however, that analysis was limited by the number of overall cases ( $n = 331$ ), short follow-up (8 years), and few participants in the higher-dose categories.<sup>6</sup> In the present study, we offer results that encompass 20 years of follow-up and 962 documented cases of colorectal cancer.

## METHODS

### Study Population

The Nurses' Health Study was established in 1976, when 121 701 US female registered nurses aged 30 to 55 years completed a mailed questionnaire. With a follow-up rate exceeding 90%, every 2 years we have mailed questionnaires to update information and identify newly diagnosed cases of cancer. In 1980, the questionnaire was expanded to include a validated assessment of diet and patterns of aspirin and NSAID use.<sup>7</sup> In 1992, to assess the racial/ethnic composition of the cohort, we asked participants to self-classify their race using investigator-defined classification options. The institutional review board at the Brigham and Women's

Hospital, Boston, Mass, approved this study; completion of the questionnaire was considered to imply informed consent.

### Assessment of Medication Use

Since 1980, we assessed intake of aspirin biennially except in 1986. In 1980, we asked women if they used “any of the following vitamins or medicines in most weeks,” and listed “aspirin (includes Bufferin, Anacin, etc)” and “other non-steroidal analgesics (Motrin, Indocin, Tolectin, Clinoril).” For each medication, participants were asked to record the number of pills or capsules taken each week and the number of years of use. In 1982, we inquired if they currently took aspirin at least once a week and, if so, how many aspirin tablets per week (1–3, 4–6, 7–14, or  $\geq 15$ ). In 1984 and 1988, we queried the average number of days per month of aspirin use (none, 1–4, 5–14, 15–21, or  $\geq 22$ ) and the number of aspirin tablets usually taken (1, 2, 3–4, 5–6, or  $\geq 7$ ). In 1990 and 1992, we asked women about the number of days per month of use (none, 1–4, 5–14, 15–21, or  $\geq 22$ ) in separate questions for aspirin, “other anti-inflammatory drugs (eg, Ibuprofen, Naprosyn, Advil),” and “acetaminophen (eg, Tylenol).” Although we did not query the number of tablets used per day in 1990 and 1992, we sent a detailed supplementary questionnaire of current and lifetime analgesic use to 4238 participants (91% response) in 1999. The median number of aspirin tablets typically consumed was 1 standard (325-mg) tablet per day and the median number of NSAID or acetaminophen tablets was 2 per day.<sup>8</sup>

In 1994 and 1996, we asked women about the frequency of aspirin use (<1 day per month, 1–3 days per month, 1–2 days per week, 3–4 days per week, 5–6 days per week, or daily), the number of aspirin tablets per week (0, 0.5–2, 3–5, 6–14, or  $\geq 15$ ), if they used acetaminophen “ $\geq 2$  times per week (eg, Tylenol)” and if they used other anti-inflammatory medications “(eg, Advil, Motrin, Indocin).” In 1998, we asked women on average how frequently they took aspirin (0 days per month, 1–3 days per month, 1–2 days per week, 3–4 days per week, 5–6 days per week, or daily) and how many aspirin tablets were taken per week (0, 0.5–2, 3–5, 6–14, or  $\geq 15$ ). Women were also asked, in separate questions, if they regularly used acetaminophen “(eg, Tylenol),” or an NSAID “(eg, Advil, Motrin, Indocin),” the days used per week (1, 2–3, 4–5, or  $\geq 6$  days), and the tablets taken per week (1–2, 3–5, 6–14, or  $\geq 15$ ).

Early in the study, most women used standard-dose aspirin tablets of 325 mg<sup>8</sup>; however, to reflect overall secular trends in consumption of low-dose (baby) aspirin, questionnaires after 1992 asked participants to convert intake of 4 baby aspirin to 1 adult standard-dose tablet. As previously described, some regrouping of responses was required to adjust for the differing ways in which aspirin-use habits were recorded.<sup>6,9</sup> Cyclooxygenase 2 (COX-2) inhibitors were not introduced in the United States until 1999; hence, we did not collect information on their use in the present study. In 2004, we also asked participants to report any major episodes of gastrointestinal bleeding that required either hospitalization or a blood transfusion, and when they occurred. For the present analysis, we included episodes of gastrointestinal bleeding through June 1, 2000. We did not specifically inquire about minor episodes of gastrointestinal bleeding.

Reasons for aspirin use were not assessed for the entire cohort, but a questionnaire was sent in 1990 to a sample of 100 women who reported taking 1 to 6 aspirin per week (90% response) and 100 women who reported taking 7 or more aspirin per week (92% response) on the 1980, 1982, or 1984 questionnaire. The major reasons for use among women taking 1 to 6 aspirin and 7 or more aspirin per week, respectively, were headache (32% and 18%, respectively), arthritis and other musculoskeletal pain (30% and 50%), a combination of headache and musculoskeletal pain (16% and 15%), cardiovascular disease prevention (9% and 8%), and other reasons (13% and 9%).<sup>10</sup>

## Ascertainment of Cases

We requested written permission to acquire medical records and pathology reports from women who reported colorectal cancer on our biennial questionnaires. We identified deaths through the National Death Index and next of kin.<sup>11</sup> For all deaths attributable to colorectal cancer, we requested permission from next of kin to review medical records. A study physician, blinded to exposure information, reviewed records to extract information on histological type and anatomic location of the cancer.

Proximal colon cancers were defined as those from the cecum to and including the splenic flexure; distal colon cancers were defined as those in the descending and sigmoid colon. Rectal cancers were defined as those in the rectosigmoid or rectum. We classified stage of cancer according to the sixth edition of the American Joint Committee on Cancer's cancer staging handbook.<sup>12</sup> According to stage, the distribution of cases and 5-year overall survival were 21% and 92%, respectively, for stage I, 24% and 85% for stage II, 25% and 63% for stage III, 19% and 7% for stage IV, and 11% and 50% for cases of unknown stage. As a validation of our staging procedures, we found our distribution of cases and survival rates to be comparable with the National Cancer Data Base<sup>13</sup> and the Surveillance, Epidemiology, and End Results database, respectively.<sup>14</sup>

## Statistical Analysis

At baseline, we excluded women who did not complete the dietary questionnaire or medication questions, recorded implausible dietary or aspirin data (eg, responded "yes" to use but then recorded zero aspirin tablets per week), or reported a history of cancer (except nonmelanoma skin cancer), inflammatory bowel disease, a familial polyposis syndrome, or hereditary non-polyposis colorectal cancer. After these exclusions, 82 911 women were eligible for analysis and accrued follow-up time beginning on the month of return of the baseline 1980 questionnaire and ending on the month of diagnosis of colorectal cancer, month of death from other causes, or June 1, 2000, whichever came first.

As previously described,<sup>15</sup> to reduce within-person variation and to better estimate long-term intake, we used the cumulative average intake of aspirin as reported on all available questionnaires up to the start of each 2-year follow-up interval. Consistent with previous analyses of this cohort, women who reported taking 2 or more standard aspirin tablets per week were defined as regular users, whereas those who reported less aspirin use were defined as nonregular users.<sup>6,9</sup> Based on our prior analyses, we also examined duration of aspirin use by the number of years of use reported in 1980 with updating of this variable every 2 years<sup>6,9</sup> and estimated long-term, consistent use more accurately by restricting some analyses to women who reported regular aspirin use on consecutive biennial questionnaires and comparing their incidence with that of women who were nonusers on consecutive questionnaires. We also grouped women according to previously described categories of number of tablets used per week to estimate dosage of aspirin.<sup>16</sup>

We calculated incidence rates of colorectal cancer for women in a specific category of aspirin use by dividing the number of incident cases by the number of person-years. We computed relative risks (RRs) by dividing the incidence rate of disease in one category divided by the incidence rate in the reference category. We used Cox proportional hazards modeling to control for multiple variables simultaneously and to compute 95% confidence intervals (CIs). We used the most updated information for all covariates prior to each 2-year interval. We used SAS, version 8.2 (SAS Institute Inc, Cary, NC) for all analyses. All *P* values are 2-sided, and *P* < .05 was considered statistically significant.

## RESULTS

Among the 82 911 eligible women, we documented 962 cases of colorectal cancer during 1 592 017 person-years. Compared with participants who reported no aspirin use, women reporting the highest levels of use were older, slightly less apt to exercise regularly, and more likely to smoke and regularly use multivitamins, postmenopausal hormones, and NSAIDs. In addition, women who reported higher aspirin intake consumed slightly more alcohol and folate (TABLE 1).

We observed a significantly lower risk of colorectal cancer among regular aspirin users ( $\geq 2$  standard aspirin tablets per week) compared with non-regular users (multivariate RR, 0.77; 95% CI, 0.67–0.88), even after controlling for other known or suspected risk factors (TABLE 2). The effect was similar for both distal and proximal colon cancers; however, aspirin did not appear effective against rectal cancers (multivariate RR, 0.94; 95% CI, 0.72–1.23). In addition, regular use of aspirin appeared to offer a significant reduction in risk of early (stages I and II) cancers (multivariate RR, 0.67; 95% CI, 0.55–0.82) but not advanced (stages III and IV) cancers (multivariate RR, 0.86, 0.71–1.05).

To assess long-term, consistent aspirin use more accurately, we focused our analyses on women who reported regular aspirin use on the initial 3 consecutive biennial questionnaires and compared their incidence with women who were nonregular users on consecutive questionnaires (TABLE 3). The inverse association between aspirin and colorectal cancer risk became stronger as aspirin use was reported on subsequent questionnaires.

We also assessed the effect of duration of regular aspirin use on colorectal cancer risk (TABLE 4). During the first 5 years of use, we did not observe any reduction in risk (multivariate RR, 1.04; 95% CI, 0.88–1.24) compared with nonusers. Beyond 5 years, we found progressively greater reduction in risk, although a significant benefit was not evident until more than 10 years of use (multivariate RR, 0.67; 95% CI, 0.54–0.85;  $P < .001$  for trend). It did not appear that use beyond 20 years conferred any additional decrease in risk (multivariate RR, 0.68; 95% CI, 0.54–0.85).

The apparent benefit associated with aspirin use was substantially greater with increasing dose (TABLE 5). Compared with participants who took no aspirin, women who used the equivalent of 2 to 5 standard aspirin tablets per week experienced a modestly lower risk of colorectal cancer (multivariate RR, 0.89; 95% CI, 0.73–1.10), whereas women who used more than 14 tablets per week experienced the greatest risk reduction (multivariate RR, 0.68; 95% CI, 0.49–0.95;  $P < .001$  for trend). This dose-relationship was observed for colon cancers ( $P < .001$  for trend); however, for rectal cancer, even higher doses did not significantly influence risk ( $P = .26$  for trend). Moreover, we observed a significant reduction in the risk for early (stages I and II) colorectal cancers among participants who reported use of 6 or more tablets per week (multivariate RR, 0.58; 95% CI, 0.41–0.84). However, for advanced (stages III and IV) colorectal cancer, a nonsignificant reduction in risk was confined to women using more than 14 tablets per week (multivariate RR, 0.72; 95% CI, 0.43–1.20). Similarly, 6 or more tablets per week offered a significant reduction in the risk of relatively low-grade (well- or moderately differentiated) tumors (multivariate RR, 0.72; 95% CI, 0.55–0.94), whereas any appreciable, although statistically non-significant, reduction in the risk of high-grade (poorly differentiated) lesions was observed only among participants who consumed more than 14 tablets per week (multivariate RR, 0.49; 95% CI, 0.19–1.27).

We considered the possibility that the influence of aspirin dose was due to more consistent long-term aspirin use among women taking higher doses. We therefore repeated our analysis after restricting the cohort to participants who reported consistent aspirin use on the initial 3 consecutive questionnaires (1980, 1982, and 1984) and those who reported no use on those 3



consecutive questionnaires. Among women who reported consistent aspirin use across 6 years, we continued to observe a significant reduction in cancer risk with increasing aspirin dose ( $P<.001$  for trend).

We further examined whether the influence of aspirin dose differed according to duration of use. We therefore evaluated the influence of cumulative average aspirin dose consumed within the immediately preceding 10 years and that consumed more than 10 years in the past (Table 5). Updating data biennially, increasing aspirin dose within the immediately preceding 10 years was not associated with lower risk of colorectal cancer after controlling for aspirin intake more than 10 years in the past ( $P=.40$  for trend). However, increasing aspirin dose greater than 10 years in the past was associated with progressively lower risk of colorectal cancer, even after adjusting for aspirin intake within the immediately preceding 10 years ( $P<.001$  for trend).

We also evaluated the influence of NSAIDs on colorectal cancer risk (TABLE 6). Compared with nonregular users, women who regularly used NSAIDs ( $\geq 2$  tablets per week) had a multivariate RR for colorectal cancer of 0.79 (95% CI, 0.64–0.97). As with regular aspirin use, it appeared that the effect of regular NSAID use was confined to cancers of the colon (multivariate RR, 0.71; 95% CI, 0.56–0.91); women who used NSAIDs regularly did not appear to have a significant benefit against rectal cancer (multivariate RR, 1.04; 95% CI, 0.72–1.52). Moreover, consistent with aspirin, the influence of NSAIDs on colorectal cancer also appeared to be strongly dose-dependent ( $P<.001$  for trend).

We considered the possibility that concurrent use of NSAIDs and aspirin may have influenced our findings. However, analyses mutually adjusting for use of the other agent did not materially alter the observed RRs associated with each dose category for aspirin ( $P\leq.001$  for trend) or for NSAIDs ( $P=.01$  for trend). Moreover, the influence of aspirin or NSAIDs did not appear to differ when we limited our analyses to participants who reported regular use of one but not both medications. The multivariate RRs for regular aspirin use ( $\geq 2$  standard tablets per week) was 0.79 (95% CI, 0.68–0.91) among women who did not use NSAIDs regularly. Similarly, the multivariate RRs for regular NSAID use ( $\geq 2$  tablets per week) was 0.83 (95% CI, 0.62–1.10) among women who did not use aspirin regularly. Finally, compared with women who did not use either NSAIDs or aspirin, regular users of either drug had a multivariate RR of 0.77 (95% CI, 0.68–0.88).

To assess whether these associations reflected a nonspecific analgesic effect, we examined the influence of regular acetaminophen use on colorectal cancer risk. Because data on acetaminophen were not collected until 1990, we limited the cohort to follow-up after 1990. We did not observe an association between regular use of acetaminophen ( $\geq 2$  tablets per week) and colorectal cancer risk (multivariate RR, 0.95; 95% CI, 0.67–1.34). Moreover, increasing acetaminophen dose was not associated with lower risk ( $P=.83$  for trend). In contrast, the multivariate RRs were 0.80 (95% CI, 0.65–1.00) for regular use of aspirin ( $\geq 2$  standard tablets per week) and 0.69 (95% CI, 0.50–0.96) for regular use of NSAIDs ( $\geq 2$  tablets per week); increasing dose of either aspirin ( $P=.003$  for trend) or NSAIDs ( $P=.008$  for trend) was also consistent with our findings among the larger cohort.

Data in our cohort as well as a randomized controlled trial demonstrate an inverse association between use of post-menopausal hormones and colorectal cancer risk.<sup>17,18</sup> Although we controlled for the use of current and past hormone use in all of our multivariate analyses, we also considered the possibility that the benefit we observed with aspirin was due to residual confounding by the duration of hormone use. However, the addition of duration of either past or current hormone use to our multivariate models did not change our results (RR for regular aspirin use=0.77; 95% CI, 0.67–0.88;  $P<.001$  for trend).

Aspirin-associated gastrointestinal bleeding may have also influenced the likelihood of participants having a positive fecal occult blood test result or undergoing endoscopy. Although we controlled for use of screening endoscopy in all of our multivariate analyses, we also evaluated the influence of aspirin among women who did not report having a positive fecal occult blood test result or did not undergo screening endoscopy. Among such women, the influence of aspirin was not materially altered (multivariate RR for regular aspirin use, 0.78; 95% CI, 0.68–0.90;  $P < .001$  for trend).

The effect of aspirin use was not modified by the presence of a family history ( $\geq 1$  first-degree relative) of colorectal cancer. Regular aspirin use was associated with a multivariate RR for colorectal cancer of 0.76 (95% CI, 0.57–1.02) among women with a family history of colorectal cancer and 0.78 (95% CI, 0.67–0.90) for those without a family history.

We also assessed the incidence of reported gastrointestinal bleeding according to intake of aspirin and NSAIDs. Over follow-up, there were 1687 reports of gastrointestinal bleeding requiring either a blood transfusion or hospitalization. The incidence of events per 1000 person-years was 0.77 among women who denied any aspirin use; 1.07 for 0.5 to 1.5 standard aspirin tablets per week; 1.07 for 2 to 5 aspirin per week; 1.40 for 6 to 14 aspirin per week; and 1.57 for more than 14 aspirin per week. Similarly, the incidence of events per 1000 person-years was 1.01 among women who denied any NSAID use; 0.99 for 0.5 to 1.5 NSAID tablets per week; 1.30 for 2 to 5 NSAID tablets per week; 1.71 for 6 to 14 NSAID tablets per week; and 1.91 for more than 14 NSAID tablets per week.

In our analyses, participants who died were censored at the date of their death. In a preliminary analysis, we also evaluated the relationship between aspirin use and death. Throughout follow-up, we confirmed 6974 deaths from any cause. The age-standardized incidence of death per 1000 person-years was 3.86 among women who denied any aspirin use; 2.70 for 0.5 to 1.5 standard aspirin tablets per week; 3.05 for 2 to 5 aspirin per week; 3.36 for 6 to 14 aspirin per week; and 4.20 for more than 14 aspirin per week.

## COMMENT

Long-term, regular aspirin use ( $\geq 2$  standard tablets per week) was associated with a significant reduction in the risk of colorectal cancer in an average-risk population. Notably, the greatest reduction in risk was observed at cumulative doses of more than 14 standard tablets per week and a statistically significant benefit was not evident until use was sustained for more than 10 years. Regular use of nonaspirin NSAIDs was also associated with comparable risk reduction, with a similar dose-response relationship. Although our study was limited to women, previous reports have also demonstrated a protective effect for aspirin in men.<sup>19</sup> The magnitude of the potential risk reduction is within the range demonstrated in trials of aspirin, calcium, and postmenopausal hormones in the prevention of adenoma or cancer.<sup>1–3,18,20</sup>

Results from 3 intervention trials of patients with prior colorectal adenoma or cancer have demonstrated a benefit to aspirin use on the subsequent risk of adenoma.<sup>1–3</sup> Although these studies have established causality, they were only able to examine limited doses over short-term follow-up and yielded conflicting results. One trial demonstrated that both 160 mg and 300 mg of soluble aspirin daily was effective<sup>3</sup>; a second trial, which examined only 1 dose, showed that standard-dose aspirin reduced risk<sup>2</sup>; on the other hand, a third trial did not observe any reduction in adenoma recurrence in a group randomized to receive standard-dose aspirin but did observe a moderate benefit in a group randomized to receive low-dose aspirin.<sup>1</sup>

Several lines of evidence support our findings that the anticancer benefit of aspirin is highly dose-dependent. First, although 81 mg of aspirin daily may be sufficient to inhibit colonic prostaglandins,<sup>21</sup> higher doses are needed to inhibit the COX-2 isoenzyme,<sup>22</sup> which appears

to be directly relevant to colorectal neoplasia.<sup>23</sup> Second, experimental data suggest that aspirin may also work through non-COX mechanisms that are maximized at higher doses.<sup>24–29</sup> Finally, a randomized trial of the COX-2 inhibitor celecoxib demonstrated that high but not standard doses significantly reduced adenoma burden in patients with familial polyposis,<sup>30</sup> and a prior prospective study in this cohort demonstrated that the strongest reduction in risk of sporadic adenoma was also with more than 14 aspirin tablets per week.<sup>9</sup> Other epidemiological studies have found consistent dose relationships for both adenoma<sup>31–34</sup> and cancer.<sup>31,35–38</sup>

Our findings might appear to conflict with the recent observations from the Women's Health Study, a large placebo-controlled trial of low-dose aspirin use with an average follow-up of 10 years. In this trial, participants randomized to receive aspirin at a dose of 100 mg every other day experienced no reduction in risk of colorectal cancer. However, in our cohort, a similar low dose of aspirin also had no effect on the risk of colorectal cancer (multivariate RR, 1.10; 95% CI, 0.92–1.31), although higher doses did confer progressively greater reductions in cancer risk. Thus, in both our study and the Women's Health Study, aspirin at a dose equivalent to 50 mg/d appears to be inadequate for prevention of colorectal cancer.<sup>5</sup>

Although short-term use of aspirin appears to reduce risk of adenoma,<sup>1–3,9</sup> our present study suggests that a statistically significant benefit against cancer is evident only after a decade of use, consistent with other studies.<sup>6,39,40</sup> Moreover, we also show that the most relevant period of use is greater than 10 years in the past. Taken together, these data are consistent with our present understanding of the latency underlying the adenoma-carcinoma pathway and suggest that aspirin may have a greater influence on tumor initiation rather than progression.

The short-term follow-up in the adenoma recurrence trials permitted only an assessment of adenoma as a surrogate end point for cancer. However, most adenomas do not progress to cancers,<sup>41</sup> and a previous randomized trial of aspirin examining colorectal cancer as an end point, the Physicians' Health Study, had null results.<sup>4</sup> However, our data suggest that the low dose (325 mg every other day) and short (5-year) duration of randomized aspirin treatment in the Physicians' Health Study was insufficient to influence cancer risk.

Our study suggests that nonaspirin NSAIDs also reduce risk of colorectal cancer in a dose-dependent manner. Other studies generally support our results, although they have been limited by their retrospective design,<sup>42–47</sup> did not separately analyze aspirin and nonaspirin NSAIDs,<sup>40,44,47,48</sup> or relied primarily on prescription data with limited information on potentially confounding risk factors.<sup>31,35,37,38,40,48–50</sup>

Although we observed that regular aspirin use was not associated with substantially reduced risk of advanced (stage III or IV) cancers, there was a suggestion that higher doses may be more effective. Previous prospective studies have had limited ability to evaluate cancer risk according to contemporary staging criteria.<sup>6,19,51</sup> Although our findings may be related to the latency of neoplasia and/or a delay in diagnosis in cases of advanced cancer, it is possible that advanced tumors represent a more aggressive form of the disease requiring higher aspirin doses. In support of this hypothesis, we observed that participants with tumors with high-grade histology, which correlates independently with poorer survival,<sup>14</sup> may also require higher doses of aspirin to achieve comparable benefit. Similarly, advanced tumors may express progressively greater levels of COX-2,<sup>52</sup> which is associated with a more invasive phenotype that is reversible with NSAIDs in a dose-dependent fashion.<sup>53</sup> Notably, we also did not observe a significant risk reduction with aspirin for rectal cancer. However, these findings should be interpreted with caution given the limited number of cases of rectal cancer. Further investigation is required to evaluate a range of tumor characteristics, including tumor site and molecular markers, which may influence differential response to chemopreventive agents.



Although previous studies have demonstrated an inverse relationship between aspirin and colorectal cancer,<sup>\*</sup> the present study differs in several important ways. First, because we collected detailed, updated information on aspirin during 20 years of follow-up, we were able to evaluate long-term use across a broad range of intake. Second, we were able to estimate several distinct measures of aspirin use, including dose, duration, consistency, and timing of use. Thus, our findings are less prone to internal confounding because of correlations between these parameters (eg, use at higher doses may reflect more consistent use). Third, we obtained aspirin data prospectively, prior to diagnosis. Thus, any errors in recall would have tended to attenuate rather than exaggerate true associations, and biases related to incomplete data collection from participants with fatal diagnoses were minimized. Fourth, since participants were all nurses, the accuracy of self-reported aspirin use is likely to be high and more likely to reflect actual consumption of these largely over-the-counter medications. Fifth, we also collected detailed data on potential confounders and had a high follow-up response rate. Finally, we were able to individually examine aspirin and nonaspirin NSAIDs.

Several limitations of our study deserve comment. Our study was observational and aspirin and NSAID use was self-selected. However, these agents were primarily used for analgesia, particularly in the high-dose categories, and the effect of acetaminophen, an analgesic used for similar maladies, but with a distinct mechanism of action, was null for colorectal cancer. Moreover, adjustment for a wide range of potential factors had minimal influence on our findings, suggesting little potential for residual or uncontrolled confounding. Finally, our findings have strong biological plausibility, and causality for the cancer precursor has been demonstrated in 3 intervention trials.

Our results are not as definitive as would be those of a randomized intervention trial designed to evaluate the effect of various doses of aspirin on colorectal cancer risk. However, such a trial is not likely to be feasible, given the need for a large number of participants and prolonged follow-up, as well as ethical concerns, given the efficacy of currently accepted endoscopic screening practices.

Consistent with other studies, we did observe an increase in the incidence of reported major gastrointestinal bleeding with increasing aspirin dose.<sup>58–61</sup> Based on the incidence of colorectal cancer within this cohort, our results, if proven causal, suggest that use of aspirin at the highest-dose category compared with no use of aspirin would prevent 1 to 2 cases of colorectal cancer with an excess of 8 episodes of major gastrointestinal bleeding for every 10 000 person-years. Further studies are warranted to thoroughly address this risk-benefit profile in the context of other potential benefits and hazards of long-term aspirin use.

In our preliminary analysis, we did not note a substantial difference in the age-standardized mortality rate within the various aspirin subgroups. However, because aspirin may play a role in the prevention and treatment of other chronic conditions (eg, cardiovascular disease), a more detailed analysis accounting for potential biases introduced by the effects of incident disease on mortality are needed.

Although selective COX-2 inhibitors are currently under investigation in the prevention of colorectal neoplasia, their potential cardiovascular risk, particularly with long-term use, may preclude their use in chemoprevention.<sup>62,63</sup> Our study supports a possible role for aspirin in cancer prevention, which has been demonstrated by prior adenoma recurrence trials. However, any substantial impact of aspirin on cancer necessitates early initiation and prolonged, consistent use. Moreover, optimal chemoprevention may require substantially higher doses of aspirin than currently recommended for the prevention of cardiovascular disease.<sup>64</sup> Many

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\*References 6, 19, 31, 36–40, 43–48, 51, 54–57.

toxicities of aspirin, including gastrointestinal bleeding, are dose-dependent.<sup>58–61,65,66</sup> Thus, future studies will need to thoroughly consider the risk-benefit profile for aspirin/NSAID chemoprevention among various risk groups and compare such a strategy with other potential prevention efforts.

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Table 1

## Baseline Characteristics of the Study Cohort\*

Characteristics	No. of 325-mg Aspirin Tablets per Week				
	0 (n = 47 114)	0.5–1.5 (n = 6713)	2–5 (n = 13 710)	6–14 (n = 9982)	>14 (n = 5392)
Age, median (interquartile range), y	46 (40–53)	47 (41–53)	45 (40–52)	47 (41–53)	49 (43–54)
Race, %					
Nonwhite	3	2	2	1	1
White	97	98	98	99	99
Former or current smoker, %	56	54	58	59	59
Pack-years, mean (SD), No. †	20.4 (16.5)	19.9 (16.5)	20.4 (16.0)	20.5 (16.9)	22.0 (17.9)
Body mass index, mean (SD) ‡	24.1 (4.7)	24.2 (4.7)	24.2 (4.6)	24.6 (4.9)	25.2 (5.6)
Regular vigorous exercise, % §	44	48	45	43	41
Postmenopausal, % ¶	43	43	44	47	50
Never use of hormones	64	61	62	58	55
Past use of hormones	18	17	18	19	22
Current use of hormones	18	22	19	23	23
Current multivitamin use, %	30	41	37	39	41
Current NSAID use, % ¶¶	4	2	2	4	8
Colorectal cancer in a parent or sibling, %	15	15	15	15	15
Dietary intake, mean (SD)					
Beef, pork, or lamb as a main dish, servings/wk	2.5 (2.0)	2.5 (2.0)	2.6 (2.0)	2.6 (2.0)	2.6 (2.0)
Folate, µg/d ††	357 (281)	386 (303)	363 (259)	374 (249)	387 (278)
Alcohol, g/d	6.2 (10)	5.9 (10)	6.6 (10)	7.3 (11)	6.7 (11)
Calcium, mg/d †††	735 (321)	738 (321)	720 (297)	722 (300)	741 (325)

\* Characteristics as recorded on baseline questionnaire in 1980. All values other than for age have been directly standardized according to the age distribution of the cohort.

† Pack-years were calculated for former and current smokers only.

‡ Body mass index was calculated as weight in kilograms divided by the square of height in meters.

§ Regular vigorous exercise was defined as vigorous physical activity (enough to work up a sweat) on at least 1 day per week.

¶ Hormone use was defined as postmenopausal estrogen or estrogen-progesterone preparations. The percentage of never, past, and current use was calculated among postmenopausal women only. Percentages do not sum to 100% because of rounding.

¶¶ Current nonaspirin nonsteroidal anti-inflammatory drug (NSAID) use was defined as intake of at least 2 tablets per week.

†† Nutrient values for folate and calcium represent the mean of energy-adjusted intake.

Table 2

## Relative Risk of Colorectal Cancer According to Regular Aspirin Use\*

	Nonregular Users	Regular Users
All women with colorectal cancer		
No. of cases/total No. of person-years	607/953 712	355/638 305
Age-adjusted RR (95% CI)	1.0	0.77 (0.67–0.87)
Multivariate RR (95% CI) <sup>†</sup>	1.0	0.77 (0.67–0.88)
Women with any colon cancer <sup>‡</sup>		
No. of cases/total No. of person-years	460/953 837	252/638 384
Age-adjusted RR (95% CI)	1.0	0.71 (0.61–0.83)
Multivariate RR (95% CI) <sup>†</sup>	1.0	0.71 (0.61–0.83)
Women with proximal colon cancer <sup>‡</sup>		
No. of cases/total No. of person-years	246/954 024	148/638 484
Age-adjusted RR (95% CI)	1.0	0.77 (0.63–0.94)
Multivariate RR (95% CI) <sup>†</sup>	1.0	0.77 (0.62–0.94)
Women with distal colon cancer <sup>‡</sup>		
No. of cases/total No. of person-years	214/954 046	104/638 502
Age-adjusted RR (95% CI)	1.0	0.65 (0.51–0.82)
Multivariate RR (95% CI) <sup>†</sup>	1.0	0.64 (0.51–0.81)
Women with rectal cancer <sup>‡</sup>		
No. of cases/total No. of person-years	136/954 113	94/638 526
Age-adjusted RR (95% CI)	1.0	0.92 (0.71–1.20)
Multivariate RR (95% CI) <sup>†</sup>	1.0	0.94 (0.72–1.23)
Women with stage I or II colorectal cancer <sup>§</sup>		
No. of cases/total No. of person-years	290/953 954	152/638 458
Age-adjusted RR (95% CI)	1.0	0.68 (0.56–0.82)
Multivariate RR (95% CI) <sup>†</sup>	1.0	0.67 (0.55–0.82)
Women with stage III or IV colorectal cancer <sup>§</sup>		
No. of cases/total No. of person-years	260/954 039	167/638 477
Age-adjusted RR (95% CI)	1.0	0.85 (0.70–1.03)
Multivariate RR (95% CI) <sup>†</sup>	1.0	0.86 (0.71–1.05)

Abbreviations: CI, confidence interval; RR, relative risk.

\* Regular aspirin use was defined as consumption of 2 or more standard tablets per week. Nonregular use was defined as the consumption of fewer than 2 tablets per week. Relative risks are for regular users compared with nonregular users.

<sup>†</sup> Multivariate RRs are adjusted for age (5-year categories), smoking before age 30 years (0, 1–4, 5–10, 11–15, or > 15 pack-years), body mass index (in quintiles), regular vigorous exercise (in quintiles of metabolic equivalent task score per week), colorectal cancer in a parent or sibling (yes or no), history of endoscopy (yes or no), history of polyp (yes or no), postmenopausal hormone use (premenopausal, never, past, or current), current multivitamin use (yes or no), beef, pork, or lamb as a main dish (0–3 per month, 1 per week, 2–4 per week, or ≥5 per week), alcohol consumption (0, 0.1–4.9, 5.0–14.9, or ≥15 g/d), and energy-adjusted quintiles of folate and calcium intake.

<sup>‡</sup> Women with colon cancer include women with cancers of the proximal colon (proximal to the splenic flexure) and cancers of the distal colon (distal to the splenic flexure and proximal to the rectum). Women with rectal cancer include women with cancers of the rectum. Information on the specific site of cancer was missing for 20 women.

<sup>§</sup> Information on stage of cancer was missing for 73 women.

Relative Risk of Colorectal Cancer According to Consecutive Biennial Questionnaires Reporting Regular Aspirin Use\*

	1980	1980 and 1982	1980, 1982, and 1984
No. of cases in nonusers/total No. of person-years	607/953 712	425/770 262	319/678 170
No. of cases in users/total No. of person-years	355/638 305	204/481 877	125/381 318
Age-adjusted RR (95% CI)	0.77 (0.67-0.87)	0.68 (0.57-0.80)	0.63 (0.51-0.77)
Multivariate RR (95% CI) <sup>†</sup>	0.77 (0.67-0.88)	0.69 (0.58-0.82)	0.64 (0.52-0.79)

Abbreviations: CI, confidence interval; RR, relative risk.

\* See Table 2 footnote for definitions of regular and nonregular aspirin use. Relative risks are for regular users compared with nonregular users.

<sup>†</sup> See Table 2 footnote for definition of multivariate adjustment.

**Table 4**

Relative Risk of Colorectal Cancer According to Duration of Regular Aspirin Use\*

	Years of Regular Aspirin Use					Pfor Trend
	0	1-5	6-10	11-20	>20	
No. of cases/total No. of person-years	396/665 129	213/297 733	157/224 518	95/175 419	101/229 218	
Age-adjusted RR (95% CI)	1.0	1.04 (0.88-1.23)	0.88 (0.73-1.07)	0.67 (0.53-0.84)	0.68 (0.54-0.85)	<.001
Multivariate RR (95% CI) <sup>†</sup>	1.0	1.04 (0.88-1.24)	0.89 (0.74-1.08)	0.67 (0.54-0.85)	0.68 (0.54-0.85)	<.001

Abbreviations: CI, confidence interval; RR, relative risk.

\* See Table 2 footnote for definitions of regular and nonregular aspirin use. Relative risks are for regular users compared with nonregular users.

<sup>†</sup> See Table 2 footnote for definition of multivariate adjustment.

Table 5

Relative Risk of Colorectal Cancer According to Aspirin Dose\*

	No. of 325-mg Aspirin Tablets per Week					Pfor Trend
	0	0.5-1.5	2-5	6-14	>14	
All women with colorectal cancer	219/412 064	388/541 648	186/314 888	127/231 663	42/91 753	
No. of cases/total No. of person-years						
Age-adjusted RR (95% CI)	1.0	1.10 (0.92-1.31)	0.89 (0.73-1.09)	0.77 (0.62-0.97)	0.67 (0.48-0.93)	<.001
Multivariate RR (95% CI) <sup>†</sup>	1.0	1.10 (0.92-1.31)	0.89 (0.73-1.10)	0.78 (0.62-0.97)	0.68 (0.49-0.95)	<.001
Women with colon cancer <sup>‡</sup>						
No. of cases/total No. of person-years	165/412 110	295/541 727	130/314 928	92/231 696	30/91 760	
Age-adjusted RR (95% CI)	1.0	1.11 (0.91-1.36)	0.82 (0.65-1.04)	0.74 (0.57-0.96)	0.64 (0.43-0.94)	<.001
Multivariate RR (95% CI) <sup>†</sup>	1.0	1.12 (0.92-1.38)	0.83 (0.65-1.05)	0.73 (0.56-0.95)	0.64 (0.43-0.95)	<.001
Women with rectal cancer <sup>‡</sup>						
No. of cases/total No. of person-years	47/412 204	89/541 908	53/315 001	30/231 744	11/91 781	
Age-adjusted RR (95% CI)	1.0	1.16 (0.80-1.68)	1.18 (0.79-1.77)	0.88 (0.55-1.40)	0.80 (0.41-1.55)	.19
Multivariate RR (95% CI) <sup>†</sup>	1.0	1.10 (0.75-1.60)	1.15 (0.77-1.73)	0.86 (0.54-1.38)	0.81 (0.41-1.58)	.26
Women with stage I or II colorectal cancer <sup>§</sup>						
No. of cases/Total No. of person-years	97/412 158	193/541 797	85/314 958	47/231 730	20/91 770	
Age-adjusted RR (95% CI)	1.0	1.17 (0.91-1.52)	0.88 (0.65-1.18)	0.62 (0.44-0.88)	0.68 (0.42-1.11)	.005
Multivariate RR (95% CI) <sup>†</sup>	1.0	1.09 (0.84-1.42)	0.96 (0.70-1.29)	0.58 (0.41-0.84)	0.67 (0.41-1.09)	.006
Women with stage III or IV colorectal cancer <sup>§</sup>						
No. of cases/total No. of person-years	96/412 175	164/541 864	82/314 979	67/231 724	18/91 774	
Age-adjusted RR (95% CI)	1.0	1.15 (0.88-1.50)	0.96 (0.70-1.29)	0.99 (0.72-1.36)	0.68 (0.41-1.13)	.04
Multivariate RR (95% CI) <sup>†</sup>	1.0	1.23 (0.94-1.62)	1.01 (0.75-1.38)	1.05 (0.76-1.45)	0.72 (0.43-1.20)	.05
Aspirin use in the preceding 10 y <sup>  </sup>						
No. of cases/total No. of person-years	277/460 134	366/558 777	156/283 363	129/215 099	34/74 144	
Age-adjusted RR (95% CI)	1.0	0.96 (0.82-1.13)	0.75 (0.62-0.92)	0.77 (0.63-0.96)	0.63 (0.44-0.90)	.003
Multivariate RR (95% CI) <sup>†</sup>	1.0	0.96 (0.81-1.13)	0.75 (0.62-0.92)	0.78 (0.62-0.96)	0.63 (0.44-0.91)	.004
Multivariate RR adjusted for aspirin dose ≥10 y in the past (95% CI) <sup>†</sup>	1.0	0.97 (0.83-1.14)	0.79 (0.65-0.97)	0.89 (0.71-1.11)	0.88 (0.60-1.31)	.40
Aspirin use ≥10 y in the past <sup>  </sup>						
No. of cases/total No. of person-years	524/903 329	225/284 703	101/202 648	87/141 747	25/59 591	
Age-adjusted RR (95% CI)	1.0	0.94 (0.78-1.12)	0.72 (0.58-0.90)	0.78 (0.62-0.99)	0.47 (0.31-0.70)	<.001
Multivariate RR (95% CI) <sup>†</sup>	1.0	0.94 (0.78-1.12)	0.73 (0.58-0.91)	0.78 (0.62-0.99)	0.47 (0.31-0.71)	<.001
Multivariate RR adjusted for aspirin dose in preceding 10 y (95% CI) <sup>†</sup>	1.0	0.94 (0.79-1.13)	0.74 (0.59-0.93)	0.81 (0.63-1.05)	0.51 (0.33-0.80)	<.001

Abbreviations: CI, confidence interval; RR, relative risk.

\* Relative risks are for women in each dose category compared with women in the reference category of 0 aspirin per week.

<sup>†</sup> See Table 2 footnote for definition of multivariate adjustment.



‡ Women with colon cancer include women with cancers of the proximal colon (proximal to the splenic flexure) and cancers of the distal colon (distal to the splenic flexure and proximal to the rectum). Women with rectal cancer include women with cancers of the rectum. Information on the specific site of cancer was missing in 20 women.

§ Information on stage of cancer was missing in 73 women.

// Aspirin use in the preceding 10 years was calculated as the cumulative average number of standard aspirin tablets used within the last 10 years. Aspirin use more than 10 years in the past was calculated as the cumulative average number of standard aspirin tablets used between 11 and 20 years in the past.

¶ Multivariate-adjusted RRs additionally adjusted for aspirin dose more than 10 years in the past are adjusted for all covariates in the multivariate models as well as cumulative average number of standard aspirin tablets used between 11 and 20 years in the past. Multivariate-adjusted RRs additionally adjusted for aspirin dose in the preceding 10 years are adjusted for all covariates in the multivariate models as well as cumulative average number of standard aspirin tablets used within the last 10 years.

Relative Risk of Colorectal Cancer According to NSAID Dose\*

**Table 6**

	No. of NSAID Tablets per Week					P for Trend
	0	0.5-1.5	2-5	6-14	>14	
No. of cases/total No. of women	694/1187 944	151/207 216	66/93 446	44/79 882	5/14 592	
Age-adjusted RR (95% CI)	1.0	0.99 (0.82-1.20)	0.90 (0.69-1.17)	0.66 (0.48-0.90)	0.52 (0.22-1.27)	.003
Multivariate RR (95% CI) <sup>†</sup>	1.0	1.00 (0.82-1.21)	0.91 (0.69-1.19)	0.69 (0.51-0.95)	0.54 (0.22-1.30)	.007

Abbreviations: CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk.

\* Relative risks (RRs) are for women in each dose category compared with women in the reference category of 0 tablets of NSAIDs per week.

<sup>†</sup> See Table 2 footnote for definition of multivariate adjustment.