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ASPIRIN AND THE RISK OF COLORECTAL CANCER IN WOMEN

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Abstract *Background. Most data suggest that the regular use of aspirin reduces the risk of colorectal cancer, but some apparently conflicting evidence exists. The effects of the dose and the duration of aspirin consumption on the risk of colorectal cancer are not well understood.*

Methods. We determined rates of colorectal cancer according to the number of consecutive years of regular aspirin use (defined as two or more tablets per week) among women in the Nurses' Health Study who reported regular aspirin use on three consecutive questionnaires (1980, 1982, and 1984) and compared the rates in this group with the rates among women who said they did not use aspirin. Cases of cancer occurring from 1984 through 1992 (the eight years after the 1984 questionnaire) were included.

Results. From 1984 through 1992, we documented 331 new cases of colorectal cancer during 551,651 person-years of follow-up. Women who consistently took two or more aspirin tablets per week had no appreciable reduction in the risk of colorectal cancer as compared with nonusers after four years (relative risk, 1.06; 95 percent confidence interval, 0.78 to 1.45) or after five to nine years (relative risk, 0.84; 95 percent confidence interval, 0.55 to 1.28). There was a slight reduction in risk among women who took aspirin for 10 to 19 years, but it was not statistically significant (relative risk, 0.70; 95 percent confidence interval, 0.41 to 1.20). However, there was a statistically significant reduction after 20 years of consistent use of aspirin (relative risk, 0.56; 95 percent confidence interval, 0.36 to 0.90; P for trend = 0.008). The maximal reduction in risk was observed among women who took four to six tablets per week; higher doses had a similar apparent benefit. Controlling for risk factors for colorectal cancer, including diet, did not change the results, and the earlier diagnosis and removal of colorectal adenomas among aspirin users did not account for the results.

Conclusions. Regular aspirin use, at doses similar to those recommended for the prevention of cardiovascular disease, substantially reduces the risk of colorectal cancer. However, this benefit may not be evident until after at least a decade of regular aspirin consumption. (N Engl J Med 1995;333:609-14.)

SUBSTANTIAL evidence suggests that the regular use of aspirin and other nonsteroidal antiinflammatory agents (NSAIDs) reduces the risk of colorectal cancer. Case–control studies have consistently found an inverse association between the use of aspirin and the occurrence of colorectal cancer,[1-5] and three prospective studies have found a lower risk of colorectal cancer[6,7] and lower mortality from the disease[8,9] among aspirin users. Patients with rheumatoid arthritis who regularly take aspirin and other NSAIDs have a reduced incidence of gastrointestinal tumors, primarily of the stomach and large bowel,[10-12] and sulfasalazine, an antiinflammatory salicylate, may reduce the risk of colorectal cancer among patients with ulcerative colitis.[13] Regular aspirin use is also associated with a lower than average risk of sporadic colorectal adenomas,[5,7,14,15] the precursors of most nonfamilial cancers.[16] Moreover, sulindac, another antiinflammatory drug, causes the regression of polyps in patients with familial adenomatous polyposis.[17] In rodent models, aspirin[18,19] and other cyclooxygenase inhibitors such as indomethacin,[20,21] piroxicam,[22,23] and sulindac[24] inhibit carcinogenesis in the colon.

One cohort study found no association between aspirin and the incidence of colorectal cancer, however,[25] and in an intervention trial using low-dose aspirin (one tablet on alternate days) there was no reduction in the number of cases of colorectal cancer during the first six years of follow-up.[26] The latter result could mean that an effect on colorectal cancer requires more than six years of regular aspirin consumption or a higher dose of aspirin, or that a causal association does not exist. To help resolve these issues, we undertook an analysis of the relation between the use of aspirin and the risk of colorectal cancer in a large cohort of women enrolled in the Nurses' Health Study.

METHODS

The Nurses' Health Study

The Nurses' Health Study cohort was established in 1976, when 121,701 U.S. female registered nurses between 30 and 55 years of age returned a mailed questionnaire that elicited information about

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known or suspected risk factors for breast cancer and cardiovascular disease.[27] Every two years since then, we have mailed follow-up questionnaires to these women to update information on risk factors and major medical events. In 1980, the questionnaire was expanded to include an assessment of diet and patterns of use of aspirin and other NSAIDs. In total, 89,446 Nurses' Health Study participants completed the sections on medication use in 1980; had no previous diagnosis of cancer (excluding nonmelanoma skin cancer), familial polyposis syndrome, or ulcerative colitis; and completed a food-frequency questionnaire in 1980.

Identification of Cases of Colorectal Cancer and Adenomas

The identification of cases of colorectal cancer has been described previously in detail.[28] Briefly, follow-up questionnaires were mailed to all participants in 1982, 1984, 1986, 1988, 1990, and 1992. We attempted to contact nonrespondents through repeated mailings, including the use of certified mail, and by telephone. Among the 89,446 women, the follow-up rate was 96 percent of the total possible person-years through 1992. Deaths in the cohort were identified on the basis of reports from family members or the Postal Service and by a search of the National Death Index; we estimate that we have identified over 98 percent of the deaths in this cohort through these sources.[29]

When a subject (or her next of kin, in the case of participants who had died) reported a diagnosis of cancer of the colon or rectum on a follow-up questionnaire, we asked for permission to obtain hospital records and pathology reports related to this diagnosis. A study physician blinded to the subjects' exposure status reviewed the medical records to extract information on the histologic type, anatomical location, and stage of the cancer. We included only cases of adenocarcinoma and excluded carcinoma in situ from this analysis. We documented 501 cases of colorectal cancer from June 1, 1980, to May 31, 1992.

We identified cases of adenoma, as reported previously,[30] using methods similar to those described above for cancers. Between 1980 and 1990, we confirmed through histopathological reports 564 cases of adenomatous polyp of the distal colon or rectum (371 colonic and 193 rectal) in the subjects. We obtained information on the size of adenomas from the endoscopy reports (the preferred source) or pathology reports for 479 of the 564 cases.

Assessment of Aspirin Use

The women provided information about regular aspirin use in 1980, 1982, 1984, and 1988. The 1980 questionnaire asked whether the respondents currently took "any of the following vitamins or medications in most weeks," and listed "aspirin (includes Bufferin, Anacin, etc.)" and "other nonsteroidal analgesics (Motrin, Indocin, Tolectin, Clinoril)," among other drugs. 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 she had used the medication. 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 for aspirin, the respondent was then asked how many aspirin tablets or capsules she took per week (1 to 3, 4 to 6, 7 to 14, or 15 or more). In 1984 and 1988, we inquired about the average number of days each month when aspirin was taken (none, 1 to 4, 5 to 14, 15 to 21, or 22 or more) and the number of aspirin tablets usually taken on those days (1, 2, 3 to 4, 5 to 6, or 7 or more). Aspirin use was evaluated in terms of the usual number of pills taken per week. Some regrouping of responses was required to adjust for the differing ways in which aspirin-use habits were recorded from 1980 through 1988. Women who reported taking fewer than two aspirin tablets per week were defined as non-regular users.

Regular aspirin use, defined as the consumption of two or more aspirin tablets per week, was highly prevalent in this cohort; between 41 and 65 percent of the women reported regular aspirin use in the biennial questionnaires. Among women who returned all four questionnaires, 15 percent reported regular aspirin use in each questionnaire, and 15 percent consistently reported no aspirin use over the eight-year period.

The 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 one to six aspirin per week (90 percent response) and 100 women who reported taking seven or more aspirin per week (92 percent response) on the 1980, 1982, or 1984 questionnaire.[31] The major reasons for use among women taking one to six aspirin and seven or more aspirin per week were headache (32 percent and 18 percent, respectively), arthritis or other musculoskeletal pain (30 percent and 50 percent), a combination of headache and musculoskeletal pain (16 percent and 15 percent), the primary prevention of cardiovascular disease (9 percent and 8 percent), and other reasons or "could not recall" (13 percent and 9 percent).

Statistical Analysis

The cohort of 89,446 women contributed person-time from the month of their return of the 1980 questionnaire to the month of diagnosis of colorectal cancer, the month of death from other causes, or the end of the study period (May 31, 1992). We computed rates of incidence by dividing the number of new cases of colorectal cancer by the number of person-years in that aspirin-use category and computed the relative risk by dividing this incidence rate by that of nonusers. We used the Mantel–Haenszel summary estimator and proportional-hazards modeling to adjust for age (in five-year categories) and potentially confounding variables and to calculate 95 percent confidence intervals. All reported P values are two-tailed.

We first examined the association between aspirin use in 1980 and the occurrence of newly diagnosed colorectal cancer up to 1992. Reported regular use of aspirin on any given questionnaire represented a mixture of short-term and long-term users. Thus, to assess long-term, consistent use more accurately, we focused our analyses on women who reported aspirin use on the 1980, 1982, and 1984 questionnaires and their subsequent risk of colorectal cancer from 1984 to 1992. From 1984 to 1992, we documented 331 new cases of colorectal cancer during 551,651 person-years.

We further evaluated relative risk according to the number of years of regular use (1 to 4, 5 to 9, 10 to 19, or ≥20 years), updating this variable every 2 years. For example, if a woman began using aspirin in 1982 and continued aspirin use in 1984 and 1986, she was considered a user of one to four years' duration in 1984 and 1985, and of five to nine years' duration in 1986 and 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 and who continued to report aspirin use in 1982 and 1984 was assumed to have used aspirin for 12 years in 1985. We also conducted analyses to determine whether a higher rate of removal of colorectal adenomas among aspirin users could account for a lower risk of cancer, if any. Because of the small number of women who used NSAIDs, the study had insufficient power to examine NSAIDs separately.

Results

We initially explored the characteristics of women who were regular users of aspirin, defined as those taking two or more aspirin tablets per week, in 1980. The women who took aspirin regularly were approximately equivalent to the nonusers in age (46.7 and 46.5 years, respectively); body-mass index, defined as the weight in kilograms divided by the square of the height in meters (24.6 vs. 24.1); and the proportions of current smokers (30 percent vs. 28 percent) and former smokers (28 percent vs. 27 percent) in the group. Consumption of alcoholic beverages was somewhat higher among aspirin users (7.1 vs. 6.3 g per day). The dietary intake of animal fat was identical in the two groups (52.3 g per day) and that of dietary fiber was very similar (16.5 vs. 16.9 g per day). The intake of other major nutrients was similar among users and nonusers of aspirin. Thus, for a wide range of characteristics, the two groups had only minor differences.

During 12 years of follow-up, we observed a slightly but not significantly lower risk of colorectal cancer among users of aspirin than among those who did not

*Table 1. Relative Risk of Colorectal Cancer According to Aspirin Use as Reported in the Nurses' Health Study.**

Variable	Questionnaire Reporting Aspirin Use		
	1980	1980 and 1982	1980, 1982, and 1984
Follow-up period	1980–1992	1982–1992	1984–1992
No. of cases in nonusers/ no. of person-years	352/680,018	321/570,062	292/456,393
No. of cases in users/ no. of person-years	149/332,241	83/182,630	39/95,258
Age-adjusted RR (95% CI)	0.85 (0.70–1.03)	0.79 (0.62–1.00)	0.62 (0.45–0.86)
Multivariate RR (95% CI)†	0.86 (0.71–1.04)	0.78 (0.61–0.99)	0.62 (0.44–0.86)
P value	0.12	0.05	0.004

*Regular aspirin use was defined as the consumption of two or more tablets per week. Nonusers did not report taking two or more aspirin per week on one or more questionnaires. Relative risks (RRs) are for users as compared with nonusers for each specified period. CI denotes confidence interval.

†Adjusted by proportional-hazards regression for age, family history of colorectal cancer, pack-years of smoking more than 35 years in the past, body-mass index, physical-activity level, and dietary intake of animal fat, dietary fiber, folate, methionine, alcohol, red meat, vitamin D, and calcium in 1980.

use aspirin in 1980 (multivariate relative risk, 0.86; 95 percent confidence interval, 0.71 to 1.04; P = 0.12). The inverse association between the use of aspirin and the risk of colorectal cancer became stronger as aspirin use was reported on subsequent questionnaires (Table 1). Women who reported on three consecutive questionnaires that they took aspirin had a 38 percent lower risk than women who were not using aspirin regularly. Controlling for a family history of colorectal cancer, the number of pack-years of smoking more than 35 years in the past[28] (divided into four categories), body-mass index (in quintiles), physical-activity level (in quintiles), alcohol consumption (in five categories), and quintiles for the dietary intake of red meat, methionine, folate, fiber, calcium, and vitamin D had virtually no effect on the relative risks and confidence intervals (Table 1). Among women who reported consistent use of aspirin from 1980 to 1984, the relative risk of colorectal cancer was 0.72 in 1985 and 1986, 0.62 in 1987 and 1988, 0.61 in 1989 and 1990, and 0.55 in 1991 and 1992. A significant inverse association was evident at a level of four to six aspirin per week (Fig. 1), but no further trend was seen for doses above three aspirin tablets per week (relative risk, 0.99 for each additional aspirin per week above three; 95 percent confidence interval, 0.96 to 1.01; P for trend = 0.35).

We found little reduction in the risk of colorectal cancer during the first 9 years of regular aspirin use, as compared with the risk among nonusers (relative risk, 0.97; 95 percent confidence interval, 0.74 to 1.27), but for 10 or more years of use the relative risk was 0.63 (95 percent confidence interval, 0.42 to 0.94). There was a clear reduction in risk among women who had used aspirin regularly for at least 20 years (Fig. 2). Among women who had used aspirin for 10 to 19 years, we saw a slight reduction in risk, but this effect was not statistically significant. The reduction in risk was similar for cancer of the colon and cancer of the rectum and for colorectal cancers that were metastatic at the time of diagnosis (Table 2). Based on a small number of cases, a similar association with 20 or more years of aspirin use was noted for colorectal cancers that were fatal within the follow-up period (relative risk, 0.59; 95 percent confidence interval, 0.24 to 1.46).

We examined whether a difference in the frequency of endoscopic examination between users and nonusers of aspirin, which could have made a difference in the rate of removal of premalignant adenomas, accounted for our results. Only a small percentage of the women had undergone endoscopy before the study began (Table 3). During the study, endoscopy performed because of the presence of overt or occult fecal blood or for other reasons, including screening, was more frequent among women who took aspirin than among those who did not. However, among women who underwent endoscopy because of fecal blood, adenomas 1 cm or more in diameter were found in 3.2 percent of those who took more than 14 aspirin a week and in 4.0 percent of nonusers (age-standardized percentages). Thus, despite a slightly higher rate of endoscopy, women who took aspirin had fewer large adenomas (0.38 percent of all aspirin users vs. 0.40 percent of nonusers).

Discussion

We found a decreased risk of colorectal cancer among women who took aspirin for 10 or more consecutive years. The full reduction in risk was seen at a level of four to six tablets per week, and higher doses had a similar apparent effect; however, our conclusion about the relation between the dose of aspirin and the reduction in risk is based on relatively few cases and requires confirmation. Controlling for diet, alcohol intake, smoking, body-mass index, physical-activity level, and family history of colorectal cancer did not alter the results. This study was limited to women, but pre-

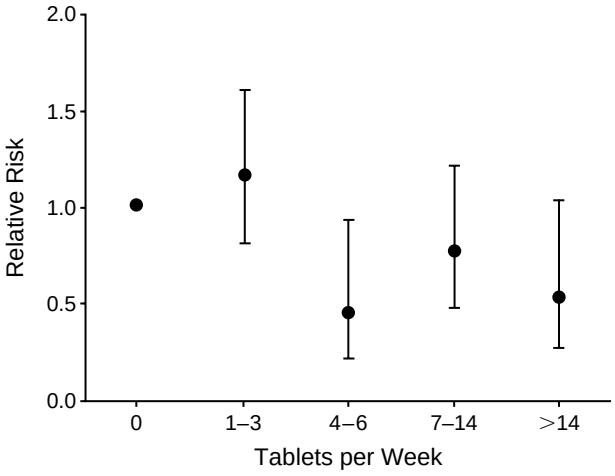

Figure 1. Multivariate Relative Risks of Colorectal Cancer and 95 Percent Confidence Intervals According to the Level of Aspirin Use among Women Who Used Aspirin from 1980 through 1984, as Compared with Nonusers.

Relative risks have been adjusted for age, family history of colorectal cancer, pack-years of smoking more than 35 years in the past, body-mass index, physical-activity level, and dietary intake of animal fat, dietary fiber, folate, methionine, alcohol, red meat, vitamin D, and calcium in 1980.

vious reports[1-15] indicate a similar benefit in men.

Did methodologic biases influence our findings? Women who regularly took aspirin were more likely to have undergone endoscopy than women who took no aspirin, partly because they more often had evidence of occult or overt fecal blood. Bleeding from tumors could have increased the rate of detection of asymptomatic cancer among users of aspirin, thereby causing us to underestimate the protective influence of aspirin. Earlier detection of colorectal cancer may also reduce mortality, which can be an additional benefit of aspirin. And gastrointestinal bleeding due to aspirin could increase the rate of detection of premalignant adenomatous polyps, whose removal could in turn reduce the incidence of cancer. However, in our study fewer adenomas were removed from the women who used aspirin. It is thus unlikely that aspirin-induced gastrointestinal bleeding was responsible for the lower risk of colorectal cancer.

*Table 2. Relative Risk of Colorectal Cancer in 1984 through 1992, According to Number of Consecutive Years of Regular Aspirin Use.**

VARIABLE	YEARS OF USE					P VALUE†
	0	1–4	5–9	10–19	≥20	
No. of person-years	357,905	70,820	42,306	28,709	52,259	—
Colorectal cancer‡						
Total cases	226	48	24	14	19	—
Age-adjusted RR	1.0	1.06	0.84	0.70	0.56	0.008
95% CI	—	0.78–1.45	0.55–1.28	0.41–1.20	0.36–0.90	—
Metastatic cancer§						
Total cases	106	19	11	8	8	—
Age-adjusted RR	1.0	0.89	0.82	0.84	0.51	0.06
95% CI	—	0.55–1.46	0.44–1.52	0.41–1.73	0.25–1.03	—
Colon cancer‡						
Total cases	159	29	17	9	14	—
Age-adjusted RR	1.0	0.91	0.85	0.64	0.59	0.02
95% CI	—	0.61–1.35	0.51–1.40	0.33–1.25	0.34–1.01	—
Rectal cancer‡						
Total cases	43	12	7	3	4	—
Age-adjusted RR	1.0	1.39	1.29	0.81	0.63	0.54
95% CI	—	0.74–2.63	0.58–2.88	0.26–2.56	0.23–1.74	—

*Data are based on the use of aspirin as reported in the Nurses' Health Study questionnaires in 1980, 1982, 1984, and 1988, plus the duration of previous use reported on the 1980 questionnaire. Regular aspirin use was defined as the consumption of two or more tablets per week. Relative risks (RRs) are for users as compared with nonusers. CI denotes confidence interval.

†P value for trend over time.

‡The number of cases of colon and rectal cancer does not equal the number of cases of colorectal cancer because of missing information.

§Cases that were metastatic at diagnosis.

Women with undiagnosed cancer or polyps may have had one or more episodes of gastrointestinal bleeding before 1980, leading them to avoid aspirin. If so, proportionally fewer women who used aspirin in 1980 may have had undetected premalignant or malignant lesions, producing a spurious inverse association between aspirin use and cancer. However, such a source of bias is implausible because the greatest decrease in rates of colorectal cancer among aspirin users appeared only after 10 or more years of use. Even so, a bleeding premalignant adenoma could precede cancer by 10 or more years. Thus, we have to consider the possibility that the lower prevalence of adenomas among regular aspirin users was an artifact of the cessation of aspirin use by women who had bleeding adenomas. However, the vast majority of people who discontinue taking aspirin do so because of abdominal discomfort and upper gastrointestinal bleeding, rather than bleeding from adenomas, which is rare.[32,33] Moreover, among women who underwent endoscopy for reasons related to fecal blood, aspirin users were in fact less likely to have large adenomas than nonusers of aspirin (Table 3).

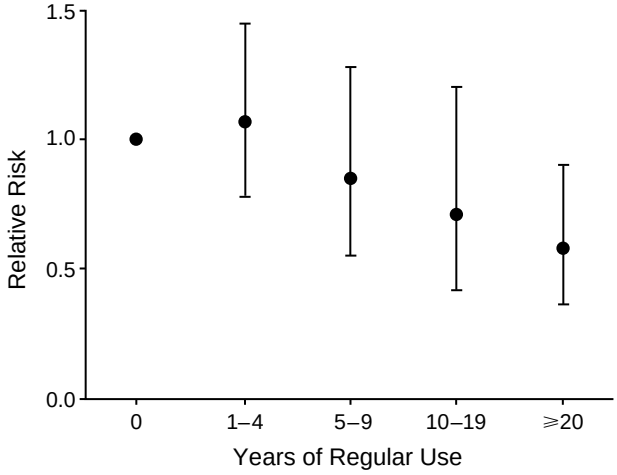

Figure 2. Age-Adjusted Relative Risks of Colorectal Cancer and 95 Percent Confidence Intervals According to the Number of Consecutive Years of Regular Aspirin Use among Users as Compared with Nonusers of Aspirin.

P for trend over time = 0.008. Regular aspirin use was defined as the consumption of two or more tablets per week.

Various mechanisms that might explain the effect of aspirin on colorectal cancer have been discussed in detail by Marnett,[34] though none are established. Aspirin is a potent, irreversible inhibitor of cyclooxygenase, an enzyme necessary for the synthesis of prostaglandins, eicosanoids that may influence tumor growth. Aspirin has also been shown to inhibit phospholipase activity,[35] which is important in various aspects of intracellular signaling.[36]

Participants in a recent interdisciplinary research workshop sponsored by the American Cancer Society concluded that the combined evidence from different research disciplines strongly supports the view that aspirin reduces the incidence of colorectal cancer.[37] Because of the competing risks and benefits of aspirin with respect to cardiovascular disease and gastrointestinal irritation and bleeding,[37,38] we need to understand better the dose and duration of aspirin use required for effective prophylaxis before firm recommendations are made. Unfortunately, the performance of clinical trials with colorectal cancer as the end point is hindered by high costs, the requirement that studies last many years,

Table 3. Frequency of Endoscopy and Detection of Adenomas According to the Level of Aspirin Use as Reported in 1980.

Variable	Tablets per Week				
	0	1–3	4–6	7–14	>14
Endoscopy (% of cohort)*					
Before 1980	4.8	4.9	5.4	5.7	6.7
1980 or later					
Total	17.6	17.7	19.2	18.7	21.5
For fecal blood	4.7	4.6	5.2	5.3	6.6
Adenoma ≥1 cm (% of cohort)					
Total	0.40	0.37	0.42	0.35	0.38
Associated with fecal blood	0.19	0.15	0.19	0.19	0.21
Not associated with fecal blood	0.21	0.22	0.23	0.16	0.17
Adenoma ≥1 cm (% of those undergoing endoscopy)					
Total	2.3	2.1	2.2	1.8	1.8
Endoscopy for fecal blood	4.0	3.3	3.7	3.6	3.2
Endoscopy not for fecal blood	1.6	1.7	1.6	1.2	1.1

*Standardized for age according to the age distribution of the cohort.

and ethical concerns related to the proved cardiovascular benefit of aspirin.[39] For these reasons, the conference participants recommended that intervention trials focus on colorectal adenomas.

Randomized interventional trials of the effect of aspirin on the rate of recurrence of adenomas would be useful in establishing causality, but they would not provide data on dose–response relations and the duration of therapy that would be directly relevant to the prevention of cancer. Observational studies have generally not been designed specifically to obtain information about the amount and duration of aspirin treatment. Our analysis suggests that four to six aspirin tablets per week — doses that may prevent cardiovascular disease — can substantially lower the risk of large-bowel cancer. Whether the very low doses (for example, 80 mg per day) that are probably efficacious in preventing cardiovascular disease are also sufficient for the chemoprevention of colorectal cancer is unclear, but preliminary evidence[40] suggests that 80 mg of aspirin given once a day can significantly modulate rectal epithelial levels of prostaglandin E_2 and prostaglandin $F_{2\alpha}$. Whether this alteration is associated with a reduction in risk remains unknown.

Our results provide direct evidence that the risk of colorectal cancer is reduced only after 10 or more years of aspirin use; these findings may thus explain why a randomized interventional trial[26] of aspirin did not detect any effect on the risk of colorectal cancer during 6 years of follow-up. The epidemiologic findings, the unequivocal effect of NSAIDs in causing the regression of small adenomas related to familial polyposis,[17] and the period of 10 years or more generally required for a small adenoma to become malignant[41] indicate that aspirin may influence only the small-adenoma stage of colonic carcinogenesis. An early influence of aspirin is also supported by some data on animals[18,42] though not all.[19] The potential regular use of aspirin at moderate doses as a means to prevent colorectal cancer certainly requires further evaluation, particularly since aspirin may be effective at the same low doses recommended for the prevention of cardiovascular disease.

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