

Aspirin and Other Nonsteroidal Anti-inflammatory Drugs and Risk of Colorectal Adenomatous Polyps among Endoscoped Individuals¹

María Elena Martínez,² R. Sue McPherson,³
Bernard Levin, and J. Fred Annegers

The University of Texas-Houston Health Science Center, School of Public Health, Houston, Texas 77225 [M. E. M., R. S. M., J. F. A.], and Division of Cancer Prevention, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030 [B. L.]

Abstract

Most epidemiological evidence supports the inverse association between use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) and colorectal cancer. Few studies have investigated the relation between use of aspirin and other NSAIDs and adenomatous polyps, which are recognized as precursors of colorectal cancer. We examined the association of adenomatous polyps and the dose and duration of use of aspirin and other NSAIDs in a case-control study of dietary risk factors for colorectal adenomatous polyps. The study population comprised 157 case and 480 control individuals who underwent an endoscopy at collaborating gastroenterology clinics in Houston, TX. Face-to-face interviews were conducted to obtain risk factor data that included information on frequency and duration of use of aspirin and other NSAIDs. Compared to the nonusers, the multivariate odds ratios for individuals who took aspirin and other NSAIDs on a weekly basis and for those who took these once/day or more were 0.77 (95% confidence interval, 0.39–1.55) and 0.36 (95% confidence interval, 0.20–0.63), respectively. Compared to nonusers, the odds ratio for individuals who used aspirin and other NSAIDs for <5 years was 0.39 (95% confidence interval, 0.21–0.71), and for those who used these for 5 years or more, the odds ratio was 0.60 (95% confidence interval, 0.32–1.14). The results of this study suggest that aspirin and other NSAIDs are associated with a decreased risk for adenomatous polyps. Limited dose-response analyses found that the point estimate decreased with the frequency but not the duration of use of aspirin and other NSAIDs.

Introduction

In the United States, tumors of the colon and rectum account for approximately 13% of all cancers and for about 11% of all

deaths from cancer (1). There is recent laboratory and population evidence that supports the inverse association between the use of aspirin and other NSAIDs⁴ and the risk of colorectal cancer (2–17). In animals, NSAIDs reduce the number and size of colon adenomas and carcinomas induced by chemical carcinogens (2–5). A reduction in the number and size of polyps associated with the NSAID sulindac has been observed in individuals with familial adenomatous polyposis (6–8). Incidence and mortality rates from gastrointestinal malignancies observed among patients with rheumatoid arthritis, a condition treated primarily with NSAIDs (9–10), are lower than those observed in the general public. Results of several case-control and cohort studies have found an inverse association between use of aspirin and other NSAIDs and risk of colorectal cancer (11–17), although results of one study found no reduction in the incidence of colorectal cancer (18). Adenomatous polyps of the colorectum are widely regarded as precursors of colorectal cancer (19–21). In three observational studies (14, 17, 22) and one intervention study (23), an inverse association between the use of aspirin and other NSAIDs and the risk of adenomatous polyps was shown, although in one study, the inverse association was not statistically significant (14). Because none of these studies was designed as intervention trials of aspirin, adequate data on dosage and duration of use are not available. Until such results are available, emphasis must be focused on data from observational studies.

We conducted a case-control study of dietary risk factors for adenomatous polyps where we collected information on various risk factors. The following report presents findings with respect to the association between aspirin and other NSAIDs use and the presence of colorectal adenomatous polyps.

Materials and Methods

Study Population. The study population comprised white, black, or Hispanic individuals 35–79 years of age who underwent an endoscopy at one of the four collaborating gastrointestinal clinic sites in Houston, TX, between September 1991 and June 1993. Excluded were individuals with a history of colorectal polyps, familial polyposis coli, Gardner's syndrome, hereditary nonpolyposis colorectal cancer, cancer (except for nonmelanoma skin cancer), ulcerative colitis, inflammatory bowel disease and other colitides, HIV infection, chronic renal failure, and those living outside a 30-mile radius of the Texas Medical Center.

Cases were individuals who met the eligibility criteria, had a lower gastrointestinal endoscopy, and had a first-time pathological diagnosis of villous, tubular, or tubulovillous adenomatous polyps. Individuals with both adenomatous and hyperplastic polyps were included in the case group. The control group

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² Present address: Department of Nutrition, Harvard School of Public Health, Boston, MA 02115.

³ To whom requests for reprints should be addressed, at Human Nutrition Center, The University of Texas-Houston School of Public Health, P. O. Box 20186, Houston, TX 77225.

⁴ The abbreviations used are: NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio.

was made up of individuals who met the eligibility criteria but were found to be negative for colorectal polyps. The three primary reasons for ineligibility were history of polyps (37.9%), living outside the study area (32.9%), and history of cancer (25.7%).

Eligible persons were identified by reviewing at each practice site medical records of individuals having had an endoscopy. Four thousand six hundred and ninety-eight medical records were reviewed, and 200 eligible cases and 719 eligible controls were identified. Eligible individuals were contacted by telephone to explain the purpose of the study, request their participation, and schedule a personal interview at the physician's office or at the participant's home or place of employment. Twenty one (10.5%) of eligible cases and 83 (11.5%) of eligible controls could not be contacted due to wrong or disconnected telephone numbers. Among the individuals contacted, 157 (87.7%) of 179 eligible cases participated in the study, and 532 (83.6%) of the 636 eligible controls participated. The sociodemographic characteristics of the eligible individuals who did not participate in the study were not appreciably different from those of the study participants. Excluded from subsequent analyses were five controls with mean caloric intakes >5500 kcal/day and one control whose interview was judged unsatisfactory by the interviewer. In addition, because the youngest case individual was 35 years old, 46 controls <35 years of age were also excluded from the analysis. Thus, the analysis was based on 157 cases of colorectal adenomatous polyps and 480 controls.

Complete ascertainment on indications for endoscopy was not available. According to the information available from the medical record, rectal bleeding was an indicator for endoscopy for 17.2% of the cases and 17.3% of the controls, and occult blood in the stool was an indicator for 12.1% of the cases and 9% of the controls. Likewise, occult blood in the stool was an indicator for endoscopy among 9.9% of the NSAIDs users and 10.3% among the nonusers. The corresponding figures for rectal bleeding were 17.4 and 17.9%, respectively. Because a flexible sigmoidoscopy is the recommended colorectal cancer screening procedure, among the control group 78% of participants only had a sigmoidoscopy exam.

Questionnaire Information. Face-to-face interviews were conducted to obtain information on demographic characteristics, height and current weight, physical activity, family history of colorectal cancer in first-degree relatives, vitamin and mineral supplement use, cigarette smoking habits, frequency and duration of use of prescribed and over-the-counter medications, and dietary intake, which included alcohol consumption. Interviews were conducted within 1 month of the participant's endoscopy.

Information on frequency and duration of use of aspirin and other NSAIDs was obtained from the medications reported by the participant. Frequency of use was recorded as times per week and use of less than once per week was classified as none. Duration of use was recorded as the number of years of regular use with use of <3 months classified as none. Use of nonaspirin and aspirin-containing NSAIDs were combined to increase the precision of the estimates of risk. Among the users, 57% used aspirin-containing NSAIDs, 36% used nonaspirin NSAIDs, and 7% used both.

Dietary intake and alcohol consumption were assessed from a quantified food frequency questionnaire, which elicited the usual frequency of consumption of 138 food items during the month before the day of the interview. Average daily nutrient intakes were computed by using the Food Frequency

Table 1 Risk factor characteristics of study population according to use of aspirin and other NSAIDs

Risk factor	Aspirin and other NSAIDs	
	No (n = 465)	Yes (n = 172)
Dietary variables		
Mean total fat (% energy)	33.3	32.9
Mean dietary fiber (g/1000 kcal)	10.8	10.8
Mean calcium (mg/1000 kcal)	434.2	408.1
Mean alcohol (g/1000 kcal)	2.3	3.2 ^a
Other variables		
Mean age (yr)	54.6	57.7 ^a
Male (%)	50.3	54.1
White (%)	65.0	72.7
Black (%)	25.8	16.3 ^b
Hispanic (%)	9.2	11.0
≥High school education (%)	89.5	82.6 ^b
Mean body mass index (kg/m ²)	27.4	27.2
Mean physical activity (kcal/week)	1485.4	1464.8
Family history ^c (%)	18.1	18.6

^a $P < 0.01$ compared to nonusers.

^b $P < 0.05$ compared to nonusers.

^c History of colorectal cancer in first-degree relatives.

Data Entry and Analysis Program and nutrient and gram weight data from the United States Department of Agriculture Survey Nutrient Database (24, 25).

Data Analysis. With the exception of age and alcohol, continuous scaled variables were categorized based on the quartile distribution among the control group. Age was treated as a continuous variable, and alcohol consumption was categorized into tertiles according to the distribution among the control group.

For the analysis of aspirin and other NSAIDs, the group of nonusers was used as the referent. Frequency of use was categorized as none, less than daily, and greater than or equal to daily use. Duration of use was categorized as none, <5 years, and 5 years or more. Unconditional logistic regression models were used to obtain maximum likelihood estimates and their 95% confidence intervals for the various levels of NSAIDs frequency and duration of use while controlling for confounding factors (26). The final models included the covariates that were significant confounders in the multivariate analyses (27).

Results

The study population includes 157 cases of colorectal adenomatous polyps (98 males and 59 females) and 480 controls (229 males and 251 females). The mean ages of the cases and controls were 57.7 and 54.7 years, respectively. Table 1 presents the risk factor characteristics of the study population by aspirin and other NSAIDs use. Compared to nonusers, users of aspirin and NSAIDs consumed significantly more alcohol, were older, had a lower proportion of blacks, and had less years of education.

The crude and adjusted odds ratios for the association between aspirin and other NSAIDs use and adenomatous polyps is shown in Table 2. Individuals who reported use of aspirin and other NSAIDs had a significantly lower risk of having colorectal adenomatous polyps (OR = 0.59). The association became stronger after adjustment for age, sex, race, cigarette smoking, family history of colorectal cancer, body mass index, dietary fiber, and alcohol consumption (OR = 0.46).

Table 3 presents the crude and adjusted odds ratios for the association between frequency and duration of use of aspirin

Table 2 Crude and adjusted^a ORs for the association between aspirin and other NSAIDs use and colorectal adenomatous polyps

NSAIDs	No. of cases	No. of controls	Crude OR	95% confidence interval	Adjusted OR	95% confidence interval
No	126	339	1.00		1.00	
Yes	31	141	0.59	0.38–0.92	0.46	0.29–0.75

^aAdjusted for age, sex, race, cigarette smoking, family history of colorectal cancer, body mass index, dietary fiber, and alcohol consumption.

and other NSAIDs and adenomatous polyps. In the adjusted model, a decrease in risk was observed for individuals who used aspirin and other NSAIDs on a weekly basis (OR = 0.77), and this risk further decreased and became significant for individuals who used these once per day or more compared to nonusers (OR = 0.36). Individuals who had used aspirin and other NSAIDs for <5 years had the lowest risk of having adenomatous polyps compared to nonusers (OR = 0.39), and an increase in risk was observed from the second to the third category of duration of use (OR = 0.60). As with frequency of use, the inverse association between duration of use and adenomatous polyps became stronger after controlling for the confounding factors.

Discussion

The results of this study suggest that use of aspirin and other NSAIDs is inversely associated with risk of colorectal adenomatous polyps. Individuals who took aspirin and other NSAIDs once per day or more had over a 60% lower risk of having colorectal adenomatous polyps compared to the nonusers. Increased duration of use of aspirin and other NSAIDs was not associated with a decreased risk of adenomatous polyps. Because the number of individuals in the upper category of duration of use was small, it is possible that this finding can be explained by chance.

The results of the present study are consistent with those of two observational studies on aspirin and other NSAIDs and adenomatous polyps. Logan *et al.* (23) reported a 60% decrease in risk of having adenomatous polyps among individuals taking NSAIDs more than 12 times/year compared to nonusers. Giovannucci *et al.* (17) reported a relative risk of 0.77 for adenomatous polyps for individuals who took aspirin two times or more per week compared to nonusers. Furthermore, results from an intervention trial of nutritional supplements found a 48% lower risk of adenoma occurrence among consistent users of aspirin. However, results of two other studies have not provided support for the protective effect of aspirin and other NSAIDs on colorectal adenomas. Suh *et al.* (14) found a lower risk of recurrent polyps among users of aspirin, but these results were not statistically significant, and a dose response was not observed. Most notably, results from the Physician's Health Trial (28) showed that taking 325 mg of aspirin every other day had no significant effect on decreasing the incidence of colorectal adenomas. However, the authors acknowledged the potential limitations of this study, including a short duration of follow-up due to the early termination of the aspirin arm of the trial and a relatively low dosage. Furthermore, the participants were not systematically examined for the presence of colorectal polyps.

The mechanism whereby NSAIDs might prevent the development of colorectal cancer or adenoma remains unclear. NSAIDs appear to reduce concentrations of prostaglandins by

Table 3 Crude and adjusted^a ORs for the association between frequency and duration of aspirin and other NSAIDs use and colorectal adenomatous polyps

NSAIDs	No. of cases	No. of controls	Crude OR	95% confidence interval	Adjusted OR	95% confidence interval
None	126	339	1.00		1.00	
Frequency (times/week)						
1–6	13	47	0.74	0.39–1.42	0.77	0.39–1.55
7–63	18	94	0.52	0.30–0.89	0.36	0.20–0.63
Duration (yr)						
0.3–4.9	16	85	0.51	0.29–0.90	0.39	0.21–0.71
5.0–40.0	15	56	0.72	0.39–1.32	0.60	0.32–1.14

^aAdjusted for age, sex, race, cigarette smoking, family history of colorectal cancer, body mass index, dietary fiber, and alcohol consumption.

inhibiting cyclo-oxygenase, which is the enzyme involved in the biosynthesis of prostaglandins from arachidonic acid (29). This, in turn, may inhibit cell proliferation, tumor initiation, promotion, growth, and spread (30–32). In mouse skin and colon, NSAIDs have been shown to inhibit ornithine decarboxylase activity and cellular proliferation, both of which may be mediated by prostaglandin E₂ (33). There are several strengths to this study. The study population included individuals undergoing a screening lower gastrointestinal endoscopy. Case and control individuals were selected by using the same eligibility criteria and procedures, thus, minimizing the probability of selection bias. We took into account the confounding effect of known or suspected risk factors for colorectal cancer. In all the analyses, the inverse association between aspirin and NSAIDs use and colorectal adenomatous polyps became stronger after adjustment for these factors. Only one published study of aspirin and adenomas has taken into account the confounding effect of lifestyle factors and family history of colorectal cancer (17). The information on prescription and nonprescription drug use was collected as part of an interview mainly pertaining to diet and was administered by an interviewer who was blinded as to the case status of the participant. However, because the participants were aware of their endoscopy results at the time of the interview, we examined the potential for differential over-reporting of medication use. Compared to the case group, we found a slightly higher proportion of use among the control group for over-the-counter medications other than aspirin and other NSAIDs and of vitamin and mineral supplements (63.4 and 57.1%, respectively, for over-the-counter medications and 50.8 and 47.1%, respectively, for vitamin and mineral supplements). Thus, it is unlikely that recall bias was introduced by the method of reporting or interviewing.

Several limitations must be considered in evaluating the results of this study. Because this was a screened population, 78% of the control individuals only had a sigmoidoscopy exam. Thus, we cannot be completely certain that these individuals did not have polyps in the proximal colon. Because it has been reported that 10–20% of individuals who are negative for adenomatous polyps on sigmoidoscopy have proximal adenomas (34, 35), there is the potential for misclassification bias among the control group. However, when an indicator variable for endoscopy type was included in the multivariate models, the overall results of the study remained unchanged. Although we were able to assess both frequency and duration of NSAIDs use, our study is limited by the absence of data on specific dosage. In addition, due to the limited sample size, we were unable to investigate the risk of adenomatous polyps associated with frequency and duration of use of aspirin and NSAIDs by

polyp characteristics, which are known to be associated with increased likelihood for malignancy (*i.e.*, size, histology, etc). Results of the dichotomous analysis (use *versus* nonuse) suggest that there is no difference in risk of adenomatous polyps between individuals with multiple and solitary polyps or those with villous compared to nonvillous histology. There appeared to be a lower risk of adenomas among individuals with polyps <1 cm (OR = 0.40; 95% confidence interval, 0.23–0.69) compared to those with polyps 1 cm or larger (OR = 0.74; 95% confidence interval, 0.32–1.71). However, these results should be interpreted with caution because there is insufficient power for conducting analyses by these polyp characteristics, and the majority of our cases (72%) were made up of small polyps.

Because aspirin users are more likely to have gastrointestinal bleeding than nonusers, aspirin use may influence the diagnosis of colorectal polyps but not their development. As noted earlier, the prevalence of rectal bleeding or fecal occult blood as indicators for endoscopy was not high, and there were no substantial differences between the case and control groups in regard to these indicators. As well, there was no appreciable difference in the prevalence of use of aspirin and other NSAIDs between individuals with and without occult blood in the stool. When we excluded individuals with occult blood in the stool as an indicator for endoscopy from the analysis, this did not change the results for frequency (odds ratio = 0.37; 95% confidence interval, 0.20–0.70 for individuals in the upper category compared to the nonusers) or duration (OR = 0.71; 95% confidence interval, 0.36–1.38 for individuals in the upper category compared to nonusers). In the Health Professionals Follow-Up Study (17), individuals with gastrointestinal bleeding were excluded from the final adenoma analyses. However, including participants with gastrointestinal bleeding did not change the overall results of the reported findings.⁵ Furthermore, it has been suggested that polyps, particularly small ones, do not bleed and the majority are discovered as a result of chance during screening for occult blood in the stool (36).

The results of this study suggest that the use of aspirin and other NSAIDs is associated with a decreased risk for colorectal adenomatous polyps and add to the growing body of evidence that these drugs may protect against colorectal cancer. The mechanism by which aspirin and other NSAIDs might prevent the development of colorectal cancer or adenoma needs additional elucidation. The understanding of this mechanism is complicated by the multistage nature of the carcinogenic process. Intervention studies are needed to confirm the findings of the epidemiological studies, to establish an optimal dose, and to determine the benefits and risks of such therapy. Until such data from intervention trials are available, we must continue to rely on results from informative observational studies. The possibility that the use of aspirin and other NSAIDs might decrease the risk of developing colorectal cancer provides a strong stimulus for additional research in this area.

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