CLINICAL–ALIMENTARY TRACT

Aspirin Dose and Duration of Use and Risk of Colorectal Cancer in Men

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Background & Aims: **Long-term data on the risk of colorectal cancer according to dose, duration, and consistency of aspirin therapy are limited.** ***Methods:*** **We conducted a prospective study of 47,363 male health professionals who were ages 40–75 years at enrollment in 1986. Biennially, we collected data on aspirin use, other risk factors, and diagnoses of colorectal cancer. We confirmed all reports of colorectal cancer through 2004 by review of medical records.** ***Results:*** **During 18 years of follow-up, we documented 975 cases of colorectal cancer over 761,757 person-years. After adjustment for risk factors, men who regularly used aspirin (≥2 times per week) had a multivariate relative risk (RR) for colorectal cancer of 0.79 (95% confidence interval, [CI], 0.69–0.90) compared with nonregular users. However, significant risk reduction required at least 6–10 years of use (*P* for trend = .008) and was no longer evident within 4 years of discontinuing use (multivariate RR, 1.00; CI, 0.72–1.39). The benefit appeared related to increasing cumulative average dose: compared with men who denied any aspirin use, the multivariate RRs for cancer were 0.94 (CI, 0.75–1.18) for men who used 0.5–1.5 standard aspirin tablets per week, 0.80 (CI, 0.63–1.01) for 2–5 aspirin tablets per week, 0.72 (CI, 0.56–0.92) for 6–14 aspirin tablets per week, and 0.30 (CI, 0.11–0.81) for >14 aspirin tablets per week (*P* for trend = .004).** ***Conclusions:*** **Regular, long-term aspirin use reduces risk of colorectal cancer among men. However, the benefit of aspirin necessitates at least 6 years of consistent use, with maximal risk reduction at doses greater than 14 tablets per week. The potential hazards associated with long-term use of such doses should be carefully considered.**

Three randomized, placebo-controlled trials have demonstrated that short-term aspirin use reduces the risk of adenoma recurrence in patients with a prior history of colorectal neoplasia.[1–3] However, the influence of aspirin on cancer risk is less certain. Two large randomized trials, the Physicians' Health Study and the Women's Health Study, failed to show a protective benefit of low-dose aspirin on risk of colorectal cancer in men and women, respectively.[4,5] As noted by a recent systematic review for the US Preventive Services Task Force,[6] the failure of aspirin in the latter two trials may reflect the low doses of aspirin used or insufficient duration of treatment or follow-up. In support of this explanation, a recent secondary analysis of data pooled from two other randomized trials of higher doses of aspirin did observe a protective benefit for colorectal cancer with long-term use.[7] Identification of well-designed studies examining the optimal dose of aspirin for chemoprevention has been deemed a high priority.[6]

Thus, we examined the influence of aspirin on the risk of colorectal cancer among men enrolled in a large prospective cohort study that provides detailed and updated information on aspirin use (the Health Professionals Follow-up Study). This population 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 observe an inverse association; however, that analysis was limited by the number of overall cases (251), short follow-up (6 years), and the lack of information on aspirin dose.[8] In the current study, we offer results that

Abbreviations used in this paper: CI, confidence interval; HPFS, Health Professionals Follow-up Study; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk.

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encompass 18 years of follow-up with 975 documented cases of colorectal cancer and include data on aspirin dose.

Materials and Methods

Study Population

The Health Professionals Follow-up Study (HPFS) is a cohort of 51,529 US male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians who returned a mailed health questionnaire in 1986. Participants were 40–75 years of age at entry. The questionnaire included a validated assessment of diet,[9] aspirin use, and medical diagnoses, including cancer. With a follow-up rate exceeding 90%, we have mailed biennial questionnaires to update information and identify newly diagnosed cases of cancer. The institutional review board at the Harvard School of Public Health approved the study.

Assessment of Medication Use

In the 1986 questionnaire and every 2 years thereafter, we inquired whether men used aspirin 2 or more times per week (eg, Anacin, Bufferin, Alka-Seltzer), acetaminophen 2 or more times per week (eg, Tylenol), and other anti-inflammatory medications (eg, Motrin, Indocin, Naprosyn, Dolobid). We did not collect information on individual nonsteroidal anti-inflammatory drugs (NSAID). Beginning in 1992, we also asked men the average number of aspirin tablets used per week (in categories). Early in the study, most men used standard-dose aspirin tablets of 325 mg[8]; however, to reflect overall secular trends in consumption of low-dose, or baby aspirin, questionnaires after 1992 asked participants to convert intake of 4 baby aspirin to 1 adult tablet. The reasons for aspirin use were not assessed for the entire cohort, but a supplementary questionnaire was sent in 1993 to a sample of 211 men who reported aspirin use from 1986 to 1990 (88% response). The major reasons for use were cardiovascular disease, 25.4%; to decrease risk for cardiovascular disease, 58.4%; headaches, 25.4%; joint or musculoskeletal pain, 33.0%; and other reasons, 7.0%.[8]

Ascertainment of Cases

We requested written permission to acquire medical records and pathology reports from men who reported colorectal cancer on our biennial questionnaire. We identified deaths with over 96% sensitivity through the National Death Index and next of kin.[10] 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 histologic type, anatomical location, and stage of the cancer. We classified stage of cancer according to the sixth version of the American Joint Committee on Cancer.[11]

Statistical Analysis

At baseline, we excluded men with a history of cancer (except nonmelanoma skin cancer), inflammatory bowel disease, a familial polyposis syndrome, or recorded implausible dietary data (outside the range of 800–4200 kcal per day). After these exclusions, 47,363 men were deemed eligible for analysis and accrued follow-up time beginning on the month of return of the baseline 1986 questionnaire and ending on the month of diagnosis of colorectal cancer, month of death from other causes, or January 1, 2004, whichever came first. We recognized that participants may have varied their use of aspirin over the 18-year study period. Thus, we used time-varying covariates such that each individual participant contributed person-time according to the aspirin data they provided on each biennial questionnaire. Consistent with previous analyses of this cohort, men who reported using aspirin 2 or more times per week were defined as regular users, whereas those who reported less aspirin use were defined as nonregular users.[8,12] As previously described,[12,13] for our dose analyses, we calculated a cumulative average

Table 1. Baseline Characteristics of the Study Cohort in 1986[a]

	Nonregular user	Regular user
Characteristic	(N = 33441)	(N = 13922)
Median age (*y*)	53	56
Race		
Nonwhite (%)	6	4
White (%)	94	96
Former or current smoker (%)	49	58
Pack-year[b]	24.2	25.6
Body mass index (kg/m^2)[c]	25.5	25.7
Physical activity, METS/wk[d]	21.0	20.8
Current multivitamin use (%)	39	49
Prior lower endoscopy (%)	25	27
Prior polyp (%)	4	4
Colorectal cancer in a parent or sibling (%)	9	8
Alcohol (*g per day*)	10.8	12.6
Dietary intake[e]		
Beef, pork, or lamb as a main dish (*servings per week*)	1.8	1.8
Folate (*μg per day*)	473	498
Calcium (*mg per day*)	890	917

[a]Characteristics at baseline in 1986 for men enrolled in the Health Professionals Follow-up Study (HPFS). Regular aspirin use was defined according to previously described categorization as the consumption of aspirin at least 2 times per week. Nonregular use was defined as the consumption of aspirin less than 2 times per week. All values, other than age, have been directly standardized according to the age distribution of the cohort.

[b]Pack-years were calculated for former and current smokers only.

[c]The body mass index is the weight in kilograms divided by the square of the height in meters.

[d]METS are metabolic equivalents. This was calculated on the basis of the frequency of a range of physical activities (eg, jogging).

[e]Nutrient values (folate and calcium) represent the mean of energy-adjusted intake.

intake of aspirin as reported on all available questionnaires up to the start of each 2-year follow-up interval to reduce in-person variation and better estimate long-term intake. We examined duration of aspirin use by calculating the number of years of use according to response to all biennial questionnaires before each 2-year follow-up interval.[13,14] We calculated incidence rates of colorectal cancer for men in a specific category of aspirin use by dividing the number of incident cases by the number of person-years. We computed relative risk (RR) by dividing the incidence rate of disease in one category by the incidence rate in the reference category. We used Cox proportional hazards modeling to control for multiple variables to compute 95% confidence intervals (CI). Age was controlled using 1-year categories and calendar time in 2-year intervals as stratified variables in the Cox models. Consistent with our prior studies,[13] all multivariate relative risks were adjusted for risk factors previously shown to be associated with colorectal cancer risk in this cohort.[15–18] We used the most updated information for all covariates before each 2-year interval. We used SAS version 9.1.3 (Cary, NC) for all analyses. All *P* values are two-sided.

Results

Among the 47,363 eligible men, we documented 975 cases of colorectal cancer over 761,757 person-years. At baseline, compared with participants who denied aspirin use, men reporting regular use (≥2 times per week) were older, more likely to have previously smoked, and more likely to regularly use multivitamins. In addition, men who reported regular aspirin intake consumed slightly more alcohol and folate (Table 1).

Compared with men who denied regular aspirin use, participants reporting regular aspirin use experienced a significantly lower risk of colorectal cancer (multivariate RR, 0.79; 95% CI, 0.69–0.90), even after controlling for other colorectal cancer risk factors (Table 2). The effect

Table 2. Relative Risk of Colorectal Cancer According to Regular Use of Aspirin[a]

	Nonregular users	Regular users
All men with colorectal cancer		
No. of cases/total no. of person-years	557/428,244	418/333,513
Age-adjusted RR (95% CI)	1.0	0.79 (0.70–0.90)
Multivariate RR (95% CI)[b]	1.0	0.79 (0.69–0.90)
Men with any colon cancer[c]		
No. of cases/total no. of person-years	355/428,427	281/333,630
Age-adjusted RR (95% CI)	1.0	0.84 (0.72–0.99)
Multivariate RR (95% CI)[b]	1.0	0.83 (0.71–0.98)
Men with proximal colon cancer[c]		
No. of cases/total no. of person-years	176/428,577	139/333,770
Age-adjusted RR (95% CI)	1.0	0.81 (0.65–1.01)
Multivariate RR (95% CI)[b]	1.0	0.80 (0.63–1.00)
Men with distal colon cancer[c]		
No. of cases/total no. of person-years	167/428,582	128/333,773
Age-adjusted RR (95% CI)	1.0	0.85 (0.67–1.08)
Multivariate RR (95% CI)[b]	1.0	0.84 (0.66–1.06)
Men with rectal cancer[c]		
No. of cases/total no. of person-years	126/428,623	78/333,837
Age-adjusted RR (95% CI)	1.0	0.65 (0.48–0.86)
Multivariate RR (95% CI)[b]	1.0	0.64 (0.48–0.85)
Men with stage 1 or 2 colorectal cancer[d]		
No. of cases/total no. of person-years	253/428,494	198/333,697
Age-adjusted RR (95% CI)	1.0	0.84 (0.69–1.00)
Multivariate RR (95% CI)[b]	1.0	0.80 (0.66–0.96)
Men with stage 3 or 4 colorectal cancer[d]		
No. of cases/total no. of person-years	201/428,573	133/333,799
Age-adjusted RR (95% CI)	1.0	0.71 (0.57–0.88)
Multivariate RR (95% CI)[b]	1.0	0.74 (0.59–0.92)

[a]Regular aspirin use was defined as use at least 2 times per week. Non-regular use was defined as use less than 2 times per week. Relative risks (RRs) are for regular users as compared to nonregular users. CI denotes confidence intervals.

[b]Multivariate RRs are adjusted for age (years), calendar time (2-year intervals), smoking before age 30 (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 previous endoscopy (yes or no), history of previous polyp (yes or no), 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, ≥15 g per day), and energy-adjusted quintiles of folate and calcium intake.

[c]Men with colon cancer include men 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). Men with rectal cancer include men with cancers of rectum but not colon. Information on the specific site (proximal vs distal) in the colon was missing in 26 men. Information on the specific site (colon vs rectum) was missing in 135 men.

[d]Information on stage of cancer was incomplete in 190 men.

Table 3. Relative Risk of Colorectal Cancer According to Duration of Aspirin Intake[a]

	Years of regular aspirin use					
	0	1–5	6–10	11–15	>15	*P* for trend[b]
No. of cases/total no. of person-years	387/318,630	218/168,754	221/167,047	88/62,223	61/45,103	
Age-adjusted RR (95% CI)	1.0	0.89 (0.75–1.02)	0.79 (0.67–0.94)	0.74 (0.58–0.94)	0.69 (0.52–0.93)	.01
Multivariate RR[c] (95% CI)	1.0	0.86 (0.72–1.02)	0.78 (0.66–0.93)	0.73 (0.57–0.93)	0.68 (0.51–0.91)	.008

[a]Regular aspirin use was defined as use at least 2 times per week. Nonregular use was defined as use less than 2 times per week. Relative risks (RRs) are for regular users as compared with nonregular users. CI denotes confidence intervals.

[b]*P* value is for the linear trend across the categories of years of regular use, excluding 0 years of use.

[c]Multivariate RRs are adjusted for age (y), calendar time (2-y intervals), smoking before age 30 (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 previous endoscopy (yes or no), history of previous polyp (yes or no), 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, ≥15 g per day), and energy-adjusted quintiles of folate and calcium intake.

was similar for distal colon cancers, proximal colon cancers, and rectal cancers. In addition, regular use of aspirin appeared to offer a significant reduction in risk of both early (stages 1 and 2) cancers (multivariate RR, 0.80; 95% CI, 0.66–0.96) and advanced (stages 3 and 4) cancers (multivariate RR, 0.74; 95% CI, 0.59–0.92).

We assessed the effect of duration of regular aspirin use on colorectal cancer risk (Table 3). Compared with participants who abstained from regular use, aspirin use for 5 or fewer years did not confer a significant reduction in risk. However, beyond 5 years, we observed a significant reduction in risk with longer duration of use (*P* for trend = .008). Notably, for early (stage 1) cancers, the influence of aspirin did not appear stronger with increasing duration of use; compared with men who denied regular use, the multivariate RRs for stage 1 cancer were 0.77 (95% CI, 0.55–1.07) for men reporting regular use for up to 5 years and 0.81 (95% CI, 0.60–1.09) for greater than 5 years (*P* for trend = .31). In contrast, for more advanced cancers (stages 2–4), the benefit of aspirin did appear to increase with longer duration of use. The multivariate RRs for stage 2 cancers were 1.04 (95% CI, 0.72–1.52) for men who used regular aspirin for up to 5 years and 0.68 (95% CI, 0.47–0.98) for greater than 5 years (*P* for trend = .03). Similarly, the multivariate RRs for stage 3 and 4 cancers were 0.90 (95% CI, 0.67–1.19) for 5 or fewer years and 0.67 (95% CI, 0.52–0.88) for greater than 5 years (*P* for trend = .005).

To evaluate whether the effect of aspirin required consistent use, we also examined the risk of colorectal cancer according to time since discontinuation of regular use (Table 4). Compared with participants who had never used aspirin regularly, the multivariate RR among participants who had stopped regular use less than 4 years prior was 0.82 (95% CI, 0.64–1.06). The multivariate RR among those who had discontinued regular use 4–5 years prior was 1.00 (95% CI, 0.72–1.39), comparable to those who had never used aspirin regularly.

The apparent benefit associated with aspirin use was substantially greater with increasing dose (Table 5). Compared with participants who took no aspirin, men who used the equivalent of 0.5–1.5 standard (325 mg) tablets of aspirin per week did not have a significantly lower risk of colorectal cancer (multivariate RR, 0.94; 95% CI, 0.75–1.18). However, men reporting 6–14 standard aspirin

Table 4. Relative Risk of Colorectal Cancer According to Time Since Discontinuation of Aspirin Intake[a]

		Time since discontinuation of regular aspirin use			
	Never used aspirin	≥6 y	4–5 y	<4 y	Current aspirin use
No. of cases/total no. of person-years	387/318,630	52/2996	42/25,551	76/54,099	418/33,3513
Age-adjusted RR (95% CI)	1.0	1.03 (0.77–1.39)	1.03 (0.74–1.42)	0.86 (0.66–1.10)	0.78 (0.67–0.90)
Multivariate RR[b] (95% CI)	1.0	1.02 (0.76–1.38)	1.00 (0.72–1.39)	0.82 (0.64–1.06)	0.76 (0.66–0.88)

[a]Current aspirin use was defined as regular use at least 2 times per week reported on the most recent questionnaire. Never used aspirin was defined as nonregular use (less than 2 times per week) on the most recent questionnaire and on all previous questionnaires. Time since discontinuation of regular use was defined as nonregular use on the most recent questionnaire but regular use <4, 4–5, or ≥6 years in the past. Relative risks (RRs) are for men in each category compared with men in the reference category of never used aspirin. CI denotes confidence intervals.

[b]Multivariate RRs are adjusted for age (y), calendar time (2-year intervals), smoking before age 30 (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 previous endoscopy (yes or no), history of previous polyp (yes or no), 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, ≥15 g per day), and energy-adjusted quintiles of folate and calcium intake.

Table 5. Relative Risk of Colorectal Cancer According to Dose of Aspirin Intake[a]

	Tablets of standard aspirin tablets (325 mg) per week					
	0	0.5–1.5	2–5	6–14	>14	*P* for trend[b]
No. of cases/total no. of person-years	138/88,168	158/111,232	148/108,957	118/873	4/7890	
Age-adjusted RR (95% CI)	1.0	0.94 (0.75–1.19)	0.78 (0.62–0.98)	0.72 (0.56–0.93)	0.30 (0.11–0.81)	.005
Multivariate RR[c] (95% CI)	1.0	0.94 (0.75–1.18)	0.80 (0.63–1.01)	0.72 (0.56–0.92)	0.30 (0.11–0.81)	.004

[a]Relative risks (RRs) are for men in each dose category compared with men in the reference category of 0 aspirin per week. CI denotes confidence intervals. Data on the number of aspirin tablets per week were not collected until 1992. Thus, this analysis includes 566 incident cases of colorectal cancer from 1992 through 2004.

[b]*P* value is for the linear trend across the categories of tablets per week, excluding 0 tablets per week.

[c]Multivariate RRs are adjusted for age (y), calendar time (2-y intervals), smoking before age 30 (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 previous endoscopy (yes or no), history of previous polyp (yes or no), 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, ≥15 g per day), and energy-adjusted quintiles of folate and calcium intake.

tablets per week experienced a multivariate RR of 0.72 (95% CI, 0.56–0.92), and those consuming more than 14 tablets per week experienced a multivariate RR of 0.30 (95% CI, 0.11–0.81; *P* for trend = .004). We considered the possibility that the influence of aspirin dose was due to a longer duration of aspirin use among men taking higher doses. However, when we additionally controlled for the duration of aspirin use, the effect of aspirin dose remained significant (*P* for trend = .03).

We also evaluated the influence of nonaspirin NSAIDs on colorectal cancer risk. We did not observe any reduction in risk with regular use of NSAIDs for 1–5 years (multivariate RR, 0.88; 95% CI, 0.73–1.06) compared with nonregular users. However, there was a significant reduction in risk among men who used NSAIDs greater than 5 years (multivariate RR, 0.72; 95%, 0.55–0.94; *P* for trend = .008). To assess whether these associations reflected a nonspecific analgesic effect, we also examined the influence of regular acetaminophen use on colorectal cancer risk. We did not observe an association with colorectal cancer risk among men who regularly used acetaminophen for 1–5 years (multivariate RR, 0.98; 95% CI, 0.78–1.22) or among men who regularly used acetaminophen for greater than 5 years (multivariate RR, 0.89; 95% CI, 0.65–1.22; *P* for trend = .32).

Finally, we confirmed that risk factors associated with a lower risk of colorectal cancer were similarly associated in this analysis, including screening endoscopy, regular use of multivitamins, and high dietary intake of folate and calcium ($P < .05$ for all comparisons). On the other hand, family history of colorectal cancer, early smoking history, alcohol intake, and high intake of red meat were associated with an increased risk of colorectal cancer ($P < .05$ for all comparisons). In this cohort, each of these risk factors has been shown to be associated independently with risk of colorectal cancer in prior detailed analyses.[15–18]

Discussion

In an average-risk population of men, we found that long-term, regular aspirin use (≥2 times per week) was associated with a significant reduction in the risk of colorectal cancer. Notably, the benefit of aspirin was not apparent until after more than 5 years of use, and the greatest reduction in risk was observed at cumulative doses of more than 14 standard tablets per week. In addition, regular use of nonaspirin NSAIDs for more than 5 years was associated with a comparable risk reduction. We observed a similar risk reduction for cancers in all anatomical sites of the large bowel and for cancers of all stages. Although our study was limited to men, we have previously demonstrated a similar protective association for aspirin in women.[13,14]

Our results are supported by 3 intervention trials of patients with prior colorectal adenoma or cancer that have demonstrated a benefit to aspirin use on the subsequent risk of adenoma.[1–3] However, these prior trials were unable to define the optimal chemopreventive dose of aspirin. One trial demonstrated that both 160 mg and 300 mg of daily soluble aspirin were effective[3]; a second trial, which examined only one dose, showed that standard-dose aspirin (325 mg) reduced risk[2]; and finally, a third trial did not observe any reduction in adenoma recurrence with standard-dose aspirin but did observe a moderate benefit with low-dose (81 mg) aspirin.[1]

In contrast to trials of adenoma recurrence, the Women's Health Study, a randomized trial of aspirin specifically designed to examine incidence of total cancer and cardiovascular events, did not demonstrate a significant benefit for colorectal cancer (a secondary endpoint) after 10 years of treatment.[4] A secondary analysis of the Physicians' Health Study, a trial of aspirin in the prevention of cardiovascular disease, also did not observe any association with colorectal cancer among men after 5 years of treatment.[5] Although our findings might appear to con-

flict with these observations, both the Women's Health Study and Physician's Health Study used relatively low-dose aspirin (100–325 mg every other day). In our cohort, similar doses of aspirin also had no effect on the risk of colorectal cancer (multivariate RR, 0.94; 95% CI, 0.75–1.18), although higher doses (>6 standard tablets per week) did confer progressively greater reductions in cancer risk. Taken together, these data suggest that aspirin at a dose equivalent to 50–162.5 mg per day, over 5–10 years of treatment, appears to be inadequate for prevention of colorectal cancer.[4,5,13]

A recent analysis of pooled data from the British Doctors' Trial and the United Kingdom transient ischemic attack aspirin trial further support our findings on the aspirin dose required to reduce risk of colorectal cancer. Randomization to higher doses of aspirin (300–1200 mg per day) was associated with a significant reduction in risk of colorectal cancer, and the significant benefit associated with aspirin was not apparent until at least 10 years of follow-up.[7] Several lines of evidence support our findings that the anticancer benefit of aspirin is highly dose-dependent. First, experimental data demonstrate that higher doses are needed to inhibit the COX-2 isoenzyme,[19] which is directly relevant to colorectal neoplasia.[20] Previous data from this cohort have also confirmed the importance of inhibition of COX-2 in mediating the anticancer benefit of aspirin.[12] Second, other non-COX-mediated mechanisms associated with aspirin are also maximized at higher doses.[21–26] Third, randomized trials of the COX-2 inhibitor celecoxib demonstrated that higher doses are more effective in reducing adenoma burden in patients with familial polyposis subjects or prior high-risk adenoma.[27,28] Other epidemiological studies generally have found consistent dose relationships for both adenoma[29–33] and cancer.[13,29,34–38]

Although short-term use of aspirin appears to reduce risk of adenoma,[1–3,32] we observed that an overall reduction in risk of cancer required more than 5 years of use. However, because we did not collect data on the number of years of aspirin use at study baseline, duration of use was probably somewhat underestimated. A previous supplementary questionnaire in a subset of regular aspirin users in the current study found that the median duration of use before the baseline questionnaire was at least 5 years.[8] Thus, it is likely that the minimum duration of use necessary to observe a risk reduction may be comparable to the 10 years we observed in a parallel cohort of women.[13] Our results highlighting the necessity of long-term use in reducing risk of colorectal cancer are again supported by findings from the pooled United Kingdom randomized trials as well as other cohorts.[7,38–40]

Given our understanding of the prolonged latency underlying the adenoma-carcinoma pathway, our findings of an overall duration effect are consistent with aspirin having a greater influence on initiation or early promotion of incident neoplasia rather than on progression of established tumors. Our findings across cancer stages support this hypothesis: longer duration was required for an effect of aspirin to become apparent on advanced cancers (stages 2–4) but not early (stage 1) cancers.

Consistent with a prior study of a general practice database,[36] we also observed that a benefit to aspirin use appears to diminish less than 4 years after discontinuing use and is no longer evident after 4–5 years of discontinuing use. This observation suggests that the need for long-term use reflects not only the importance of initiating aspirin in the earliest stages of carcinogenesis but also the necessity for sustained, uninterrupted therapy.

In analyses by anatomical subsite, it appeared that the effect of aspirin was more weakly associated with cancers of the proximal or distal colon as compared with the rectum. However, these findings should be interpreted with caution, given the limited number of cases within each subsite. Further studies should examine the potential for a differential effect of aspirin on the basis of anatomical location, which may be related to differences in the molecular characteristics of tumors.[41]

Although previous studies have demonstrated an inverse relationship between aspirin and colorectal cancer,[7,8,14,29,35–40,42–54] the current study differs in several important ways. First, because we collected detailed, updated information on aspirin at a range of doses over 18 years of follow-up, we were able to evaluate long-term use across a broad range of intake. Second, we obtained aspirin data prospectively, before 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. Third, because participants were all health professionals, the accuracy of self-reported aspirin use is likely to be high and more likely to reflect actual consumption. However, we acknowledge that this aspect may limit the applicability of our findings to other populations. Fourth, we used time-varying, biennially updated aspirin data in our Cox models to account for the effect of changes in aspirin use over time on risk of colorectal cancer. Finally, we also collected detailed data on potential confounders and had a high follow-up response rate.

Our study was observational, and aspirin use was self-selected. However, our results have strong biologic plausibility, and causality has been demonstrated in 3 intervention trials of adenoma recurrence and a pooled analysis of randomized trials of aspirin linked with outcomes derived from a cancer registry. Our data are also remarkably consistent with findings among a distinct, large, prospective cohort of women who used aspirin less frequently for cardiovascular indications. Moreover, acetaminophen, an analgesic used for similar maladies but with a distinct mechanism of action, did not appear to be related to colorectal cancer, and adjustment for a wide

range of risk factors had minimal influence on our findings, suggesting little potential for residual or uncontrolled confounding.

Our results are not as definitive as 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, because of the need for a large number of participants and prolonged follow-up and because of ethical concerns, given the efficacy of currently accepted screening practices. Nonetheless, when viewed in the context of the preponderance of laboratory studies, epidemiological data, adenoma recurrence trials, and the United Kingdom trials, our data do provide convincing evidence that aspirin can reduce the incidence of colorectal cancer.[6] Most importantly, our study provides additional support that aspirin chemoprevention requires use of higher doses over a long period, which raises the risk of adverse events such as gastrointestinal bleeding. Thus, our results suggest that aspirin cannot be recommended for general use by a healthy population for cancer prevention, which is consistent with the conclusions of the US Preventative Services Task Force.[55]

In conclusion, our study demonstrates that aspirin is associated with a reduced risk of colorectal cancer but requires long-term, consistent use with maximal risk reduction at doses considerably higher than those recommended to prevent cardiovascular disease. These data support the need to further characterize those for whom the potential benefits of aspirin outweigh the hazards and to improve our understanding of the mechanisms by which aspirin inhibits carcinogenesis. Such studies may lead to a tailored approach to chemoprevention and highlight additional targets for prevention with future agents that may have more favorable risk-benefit profiles.

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Congenital alimentary tract malformations are rare developmental errors that have been assigned several different names, including enterocystomas, enterogenous cysts, supernumerary accessory organs, ileum duplex, giant diverticula, and unusual Meckel diverticulum.Â This article reviews the incidence, embryology, anatomy, common clinical presentations and principals of diagnosis, and surgical interventions of the spectrum of alimentary tract duplications. History of the Procedure. The European Medicines Agency's scientific guidelines on the clinical evaluation of human medicines used in conditions affecting the gut and metabolism help medicine developers prepare marketing authorisation applications. For a complete list of scientific guidelines currently open for consultation, see Public consultations. Guidelines. Clinical investigation of medicinal products for the management of Crohn's disease. Clinical investigation of medicinal products for the treatment of chronic constipation. Search Engine. Alimentary tract. Published on 10/04/2015 by admin. Filed under Surgery. Last modified 10/04/2015. Print this page. Average : rate 1 star rate 2 star rate 3 star rate 4 star rate 5 star. Your rating: none, Average: 0 (0 votes).Â CHAPTER 14 Alimentary tract. Oesophagus 217. Stomach and duodenum 225. Conditions of the small bowel 233. Tumours of the small intestine 234. Small bowel obstruction 235. Appendicitis 236. 3Department of Nanlou Clinical Laboratory, General Hospital of PLA, No. 28 Fuxing Road, Haidian District, Beijing, 100853, China. Show more. Academic Editor: Takashi Saku.Â Actinomycosis in the alimentary tract is rarely seen and the pathogenesis has not been fully studied. According to the retrieved literature, there are no relevant studies about the biological function of the Actinomyces species in the human digestive tract. Clinicalâ€“alimentary tract. Gastroenterology 2002;123:1763â€“1769. A Randomized Comparison of Quadruple and Triple Therapies for Helicobacter pylori Eradication: The QUADRATE Study.Â The study was performed in accordance with the principles of good clinical research practice, the Declaration of Helsinki, and the Australian National Health and Medical Research Council statement on human experimentation. Study Design.