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

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ASPIRIN DOSE AND DURATION OF USE AND RISK OF COLORECTAL CANCER IN MEN

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Abstract

Background and 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/week) had a multivariate relative risk (RR) for colorectal cancer of 0.79 (95% confidence interval, [CI], 0.69–0.90), compared with non-regular users. However, significant risk reduction required at least 6–10 years of use (Ptrend=0.008) 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 to 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/week, 0.80 (CI, 0.63–1.01) for 2–5 aspirin/week, 0.72 (CI, 0.56–0.92) for 6–14 aspirin/week, and 0.30 (CI, 0.11–0.81) for >14 aspirin/week (Ptrend=0.004).

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/week. The potential hazards associated with long-term use of such doses should be carefully considered.

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Keywords

Colorectal Neoplasms; Colorectal Cancer; Aspirin; Non-steroidal Anti-inflammatory Drugs; Epidemiology; Risk Factors; Prospective Study

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 U.S. Preventive Services Task Force,[6] the failure of aspirin in these 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] Ultimately, well-designed studies examining the optimal dose of aspirin for chemoprevention has been identified as 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 which 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 present study, we offer results that encompass 18 years of follow-up with 975 documented cases of colorectal cancer, and include data on aspirin dose.

METHODS

Study Population

The Health Professionals Follow-up Study (HPFS) is a cohort of 51,529 U.S. male dentists, optometrists, osteopaths, podiatrists, pharmacists, and veterinarians, who returned a mailed health questionnaire in 1986. Participants were 40 to 75 years of age at entry. The questionnaire included a validated assessment of diet,[9] aspirin use, as well as 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 this study.

Assessment of Medication Use

In the 1986 questionnaire and every two years thereafter, we inquired if men used aspirin, two or more times per week ("e.g. Anacin, Bufferin, Alka-Seltzer"), acetaminophen two or more times per week ("e.g. Tylenol"), and other anti-inflammatory medications ("e.g. Motrin, Indocin, Naprosyn, Dolobid"). We did not collect information on individual NSAID types. 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 four baby aspirin to one 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 histological type, anatomic location, and stage of the cancer. We classified stage of cancer according to the 6th version of the American Joint Committee on Cancer.[11]

Statistical Analysis

At baseline, we excluded men with a history of cancer (except non-melanoma skin cancer), inflammatory bowel disease, a familial polyposis syndrome, or recorded implausible dietary data (outside the range of 800 to 4200 kcal/d). After these exclusions, 47,363 men were 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 utilized 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 more times per week were defined as regular users whereas those who reported less aspirin use were defined as non-regular users. [8, 12] As previously described,[12, 13] for our dose analyses, we calculated a cumulative average 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 prior to 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 risks (RR) 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 control for multiple variables simultaneously and 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 prior to 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 to participants who denied aspirin use, men reporting regular use (≥2 times per week) were older, more likely to previously smoke, and more likely to regularly use multivitamins. In addition, men who reported regular aspirin intake consumed slightly more alcohol and folate (TABLE 1).

Compared to men who denied regular 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 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 (stage 1 and 2) cancers (multivariate RR, 0.80; 95% CI, 0.66–0.96) and advanced (stage 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 to participants who abstained from regular use, aspirin use for five 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=0.008). Notably, for early (stage 1) cancers, the influence of aspirin did not appear stonger with increasing duration of use; compared to 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=0.31). In contrast, for more advanced cancers (stages 2 to 4), the benefit of aspirin did appear to increase with longer duration of use. The multivariate RRs for stage 2 cancer were 1.04 (95% CI, 0.72–1.52) for men who used for up to 5 years and 0.68 (95% CI, 0.47–0.98) for greater than 5 years (P for trend=0.03). 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 = 0.005).

To evaluate if 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 to participants who had never used aspirin regularly, the multivariate RR among participants who had stopped regular use less than four years in the past was 0.82 (95% CI, 0.64–1.06). The multivariate RR among those who had discontinued regular use four to five years in the past was 1.00 (95% CI, 0.72–1.39), comparable to those who had never used regularly.

The apparent benefit associated with aspirin use was substantially greater with increasing dose (TABLE 5). Compared to 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 to 14 standard aspirin 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=0.004). 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=0.03).

We also evaluated the influence of non-aspirin NSAIDs on colorectal cancer risk. Compared to non-regular users, we did not observe any reduction in risk with regular use of NSAIDs for 1 to 5 years (multivariate RR 0.88; 95% CI, 0.73–1.06). 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=0.008). To assess whether these associations reflected a non-specific 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 to 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=0.32).

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<0.05 for all comparisions). 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 ($P<0.05$ for all comparisons). In this cohort, each of these risk factors have 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 five 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 non-aspirin NSAIDs for more than 5 years was associated with a comparable risk reduction. We observed a similar risk reduction for cancers in all anatomic 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 three 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 was 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 conflict with these observations, both the Women's Health Study and Physician's Health Study used relatively low-dose aspirin (100 to 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/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 UK-TIA Trial further support our findings on the necessary dose of aspirin to reduce risk of colorectal cancer. Randomization to higher doses of aspirin (300 mg to 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 anti-cancer 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 anti-cancer 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 five 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 present study found that the median duration of use prior 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 present 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 (stage 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 not only reflects the importance of initiating aspirin in the earliest stages of carcinogenesis, but also the necessity for sustained, uninterrupted therapy.

In analyses by anatomic subsite, it appeared that the effect of aspirin was more weakly associated with cancers of the proximal or distal colon as compared with 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 based on anatomic 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 present 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, 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. Third, since 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 this may also limit the generalizability 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 biological plausibility and causality has been demonstrated in three 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 given the need for a large number of participants and prolonged follow-up, as well as 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 U.S. 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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References

1. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers RW, Rothstein R, Burke CA, Snover DC, Church TR, Allen JI, Beach M, Beck GJ, Bond JH, Byers T, Greenberg ER, Mandel JS, Marcon N, Mott LA, Pearson L, Saibil F, van Stolk RU. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med 2003;348:891–9. [PubMed: 12621133]
2. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, Petrelli N, Pipas JM, Karp DD, Loprinzi CL, Steinbach G, Schilsky R. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. N Engl J Med 2003;348:883–90. [PubMed: 12621132]

3. Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, Couturier D, Coste T, Little J, Chaussade S. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. Gastroenterology 2003;125:328–36. [PubMed: 12891533]
4. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. Jama 2005;294:47–55. [PubMed: 15998890]
5. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. J Natl Cancer Inst 1993;85:1220–4. [PubMed: 8331682]
6. Dube C, Rostom A, Lewin G, Tsertsvadze A, Barrowman N, Code C, Sampson M, Moher D. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med 2007;146:365–75. [PubMed: 17339622]
7. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet 2007;369:1603–13. [PubMed: 17499602]
8. Giovannucci E, Rimm EB, Stampfer MJ, Colditz GA, Ascherio A, Willett WC. Aspirin use and the risk for colorectal cancer and adenoma in male health professionals. Ann Intern Med 1994;121:241–6. [PubMed: 8037405]
9. Rimm E, Giovannucci E, Stampfer M, Colditz G, Litin L, Willett W. Reproducibility and validity of an expanded self-administered semiquantitative food questionnaire among health professionals. Am J Epidemiol 1992;135:1114–1126. [PubMed: 1632423]
10. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH. Test of the National Death Index. Am J Epidemiol 1984;119:837–839. [PubMed: 6720679]
11. Greene, F.; Page, D.; Fleming, I.; Fritz, A.; Balch, C.; Haller, D.; Morrow, M. AJCC Cancer Staging Handbook. Springer-Verlag; 2002.
12. Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med 2007;356:2131–42. [PubMed: 17522398]
13. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. Jama 2005;294:914–23. [PubMed: 16118381]
14. Giovannucci E, Egan KM, Hunter DJ, Stampfer MJ, Colditz GA, Willett WC, Speizer FE. Aspirin and the risk of colorectal cancer in women. N Engl J Med 1995;333:609–14. [PubMed: 7637720]
15. Platz EA, Willett WC, Colditz GA, Rimm EB, Spiegelman D, Giovannucci E. Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men. Cancer Causes Control 2000;11:579–88. [PubMed: 10977102]
16. Kavanagh AM, Giovannucci EL, Fuchs CS, Colditz GA. Screening endoscopy and risk of colorectal cancer in United States men. Cancer Causes Control 1998;9:455–62. [PubMed: 9794179]
17. Wu K, Willett WC, Fuchs CS, Colditz GA, Giovannucci EL. Calcium intake and risk of colon cancer in women and men. J Natl Cancer Inst 2002;94:437–46. [PubMed: 11904316]
18. Fuchs C, Giovannucci E, Colditz G, Hunter D, Speizer F, Willett W. A prospective study of family history and the risk of colorectal cancer. N Engl J Med 1994;331:1669–1674. [PubMed: 7969357]
19. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. N Engl J Med 2005;353:2373–83. [PubMed: 16319386]
20. Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology 1994;107:1183–8. [PubMed: 7926468]
21. Kopp E, Ghosh S. Inhibition of NF-kappa B by sodium salicylate and aspirin. Science 1994;265:956–9. [PubMed: 8052854]
22. Tsujii M, Kawano S, Tsuji S, Sawaoka H, Hori M, DuBois RN. Cyclooxygenase regulates angiogenesis induced by colon cancer cells. Cell 1998;93:705–16. [PubMed: 9630216]
23. Chan TA, Morin PJ, Vogelstein B, Kinzler KW. Mechanisms underlying nonsteroidal antiinflammatory drug-mediated apoptosis. Proc Natl Acad Sci U S A 1998;95:681–6. [PubMed: 9435252]
24. He TC, Chan TA, Vogelstein B, Kinzler KW. PPARdelta is an APC-regulated target of nonsteroidal anti-inflammatory drugs. Cell 1999;99:335–45. [PubMed: 10555149]

25. Yamamoto Y, Yin MJ, Lin KM, Gaynor RB. Sulindac inhibits activation of the NF-kappaB pathway. J Biol Chem 1999;274:27307–14. [PubMed: 10480951]
26. Shureiqi I, Chen D, Lotan R, Yang P, Newman RA, Fischer SM, Lippman SM. 15-Lipoxygenase-1 mediates nonsteroidal anti-inflammatory drug-induced apoptosis independently of cyclooxygenase-2 in colon cancer cells. Cancer Res 2000;60:6846–50. [PubMed: 11156377]
27. Steinbach G, Lynch PM, Phillips RK, Wallace MH, Hawk E, Gordon GB, Wakabayashi N, Saunders B, Shen Y, Fujimura T, Su LK, Levin B. The effect of celecoxib, a cyclooxygenase-2 inhibitor, in familial adenomatous polyposis. N Engl J Med 2000;342:1946–52. [PubMed: 10874062]
28. Bertagnolli MM, Eagle CJ, Zauber AG, Redston M, Solomon SD, Kim K, Tang J, Rosenstein RB, Wittes J, Corle D, Hess TM, Woloj GM, Boisserie F, Anderson WF, Viner JL, Bagheri D, Burn J, Chung DC, Dewar T, Foley TR, Hoffman N, Macrae F, Pruitt RE, Saltzman JR, Salzberg B, Sylwestrowicz T, Gordon GB, Hawk ET. Celecoxib for the prevention of sporadic colorectal adenomas. N Engl J Med 2006;355:873–84. [PubMed: 16943400]
29. Peleg II, Lubin MF, Cotsonis GA, Clark WS, Wilcox CM. Long-term use of nonsteroidal antiinflammatory drugs and other chemopreventors and risk of subsequent colorectal neoplasia. Dig Dis Sci 1996;41:1319–26. [PubMed: 8689906]
30. Garcia Rodriguez LA, Huerta-Alvarez C. Reduced incidence of colorectal adenoma among long-term users of nonsteroidal antiinflammatory drugs: a pooled analysis of published studies and a new population-based study. Epidemiology 2000;11:376–81. [PubMed: 10874542]
31. Tangrea JA, Albert PS, Lanza E, Woodson K, Corle D, Hasson M, Burt R, Caan B, Paskett E, Iber F, Kikendall JW, Lance P, Shike M, Weissfeld J, Schatzkin A. Non-steroidal anti-inflammatory drug use is associated with reduction in recurrence of advanced and non-advanced colorectal adenomas (United States). Cancer Causes and Control 2003;14:403–411. [PubMed: 12946034]
32. Chan AT, Giovannucci EL, Schernhammer ES, Colditz GC, Hunter DJ, Willett WC, Fuchs CS. A prospective study of aspirin use and the risk of colorectal adenoma. Ann Intern Med 2004;140:157–166. [PubMed: 14757613]
33. Chan AT, Tranah GJ, Giovannucci EL, Hunter DJ, Fuchs CS. Genetic variants in the UGT1A6 enzyme, aspirin use, and the risk of colorectal adenoma. J Natl Cancer Inst 2005;97:457–60. [PubMed: 15770010]
34. Sorensen HT, Friis S, Norgard B, Mellemkjaer L, Blot WJ, McLaughlin JK, Ekbom A, Baron JA. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. Br J Cancer 2003;88:1687–92. [PubMed: 12771981]
35. Suh O, Mettlin C, Petrelli NJ. Aspirin use, cancer, and polyps of the large bowel. Cancer 1993;72:1171–7. [PubMed: 8339210]
36. Garcia-Rodriguez LA, Huerta-Alvarez C. Reduced risk of colorectal cancer among long-term users of aspirin and nonaspirin nonsteroidal antiinflammatory drugs. Epidemiology 2001;12:88–93. [PubMed: 11138826]
37. Peleg II, Maibach HT, Brown SH, Wilcox CM. Aspirin and nonsteroidal anti-inflammatory drug use and the risk of subsequent colorectal cancer. Arch Intern Med 1994;154:394–9. [PubMed: 8117171]
38. Larsson SC, Giovannucci E, Wolk A. Long-term aspirin use and colorectal cancer risk: a cohort study in Sweden. Br J Cancer 2006;95:1277–9. [PubMed: 17060932]
39. Thun MJ, Namboodiri MM, Calle EE, Flanders WD, Heath CW Jr. Aspirin use and risk of fatal cancer. Cancer Res 1993;53:1322–7. [PubMed: 8443812]
40. Jacobs EJ, Thun MJ, Bain EB, Rodriguez C, Henley SJ, Calle EE. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst 2007;99:608–15. [PubMed: 17440162]
41. Dimberg J, Samuelsson A, Hugander A, Soderkvist P. Differential expression of cyclooxygenase 2 in human colorectal cancer. Gut 1999;45:730–2. [PubMed: 10517910]
42. Kune GA, Kune S, Watson LF. Colorectal cancer risk, chronic illnesses, operations, and medications: case control results from the Melbourne Colorectal Cancer Study. Cancer Res 1988;48:4399–404. [PubMed: 3390835]
43. Thun M, Calle E, Namboodiri M, Heath C. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med 1991;325:1593–1596. [PubMed: 1669840]

44. Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Stolley PD, Shapiro S. A hypothesis: nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. J Natl Cancer Inst 1991;83:355–8. [PubMed: 1759994]
45. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology 1994;5:138–46. [PubMed: 8172988]
46. Muller AD, Sonnenberg A, Wasserman IH. Diseases preceding colon cancer. A case-control study among veterans. Dig Dis Sci 1994;39:2480–4. [PubMed: 7956619]
47. Muscat JE, Stellman SD, Wynder EL. Nonsteroidal antiinflammatory drugs and colorectal cancer. Cancer 1994;74:1847–54. [PubMed: 8082089]
48. Reeves MJ, Newcomb PA, Trentham-Dietz A, Storer BE, Remington PL. Nonsteroidal anti-inflammatory drug use and protection against colorectal cancer in women. Cancer Epidemiol Biomarkers Prev 1996;5:955–60. [PubMed: 8959316]
49. La Vecchia C, Negri E, Franceschi S, Conti E, Montella M, Giacosa A, Falcini A, Decarli A. Aspirin and colorectal cancer. Br J Cancer 1997;76:675–7. [PubMed: 9303370]
50. Rosenberg L, Louik C, Shapiro S. Nonsteroidal antiinflammatory drug use and reduced risk of large bowel carcinoma. Cancer 1998;82:2326–33. [PubMed: 9635524]
51. Collet JP, Sharpe C, Belzile E, Boivin JF, Hanley J, Abenhaim L. Colorectal cancer prevention by non-steroidal anti-inflammatory drugs: effects of dosage and timing. Br J Cancer 1999;81:62–8. [PubMed: 10487613]
52. Langman MJ, Cheng KK, Gilman EA, Lancashire RJ. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. BMJ 2000;320:1642–6. [PubMed: 10856067]
53. Coogan PF, Rosenberg L, Louik C, Zauber AG, Stolley PD, Strom BL, Shapiro S. NSAIDs and risk of colorectal cancer according to presence or absence of family history of the disease. Cancer Causes Control 2000;11:249–55. [PubMed: 10782659]
54. Mahipal A, Anderson KE, Limburg PJ, Folsom AR. Nonsteroidal anti-inflammatory drugs and subsite-specific colorectal cancer incidence in the Iowa women's health study. Cancer Epidemiol Biomarkers Prev 2006;15:1785–90. [PubMed: 17035383]
55. Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: U.S Preventive Services Task Force recommendation statement. Ann Intern Med 2007;146:361–4. [PubMed: 17339621]

Table 1

Baseline Characteristics of the Study Cohort in 1986*

Characteristic	Non-regular user (N=33441)	Regular user (N=13922)
Median age (yr)	53	56
Race		
Non-white (%)	6	4
White (%)	94	96
Former or current smoker (%)	49	58
Pack-yr†	24.2	25.6
Body mass index (kg/m^2)‡	25.5	25.7
Physical activity, METS/wk§	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/day)	10.8	12.6
Dietary intake Ψ		
Beef, pork, or lamb as a main dish (servings per week)	1.8	1.8
Folate (μg/day)	473	498
Calcium (mg/day)	890	917

*Characteristics at baseline in 1986 for men enrolled in the Health Professionals Follow-up Study (HPFS). Regular aspirin use was based on previously described categorization as the consumption of aspirin at least 2 times per week. Non-regular 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.

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

‡The body-mass index is the weight in kilograms divided by the square of the height in meters.

§METS are metabolic equivalents. This was calculated based on the frequency of a range of physical activities (e.g. jogging).

ΨNutrient values (folate and calcium) represent the mean of energy-adjusted intake.

Table 2

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

	Non-regular users	Regular users
All men with colorectal cancer		
No. of cases/Total no. of person-years	557/428244	418/333513
Age-adjusted RR (95% CI)	1.0	0.79 (0.70–0.90)
Multivariate RR (95% CI)†	1.0	0.79 (0.69–0.90)
Men with any colon cancer‡		
No. of cases/Total no. of person-years	355/428427	281/333630
Age-adjusted RR (95% CI)	1.0	0.84 (0.72–0.99)
Multivariate RR (95% CI)†	1.0	0.83 (0.71–0.98)
Men with proximal colon cancer‡		
No. of cases/Total no. of person-years	176/428577	139/333770
Age-adjusted RR (95% CI)	1.0	0.81 (0.65–1.01)
Multivariate RR (95% CI)†	1.0	0.80 (0.63–1.00)
Men with distal colon cancer‡		
No. of cases/Total no. of person-years	167/428582	128/333773
Age-adjusted RR (95% CI)	1.0	0.85 (0.67–1.08)
Multivariate RR (95% CI)†	1.0	0.84 (0.66–1.06)
Men with rectal cancer‡		
No. of cases/Total no. of person-years	126/428623	78/333837
Age-adjusted RR (95% CI)	1.0	0.65 (0.48–0.86)
Multivariate RR (95% CI)†	1.0	0.64 (0.48–0.85)
Men with stage 1 or 2 colorectal cancer§		
No. of cases/Total no. of person-years	253/428494	198/333697
Age-adjusted RR (95% CI)	1.0	0.84 (0.69–1.00)
Multivariate RR (95% CI)†	1.0	0.80 (0.66–0.96)
Men with stage 3 or 4 colorectal cancer§		
No. of cases/Total no. of person-years	201/428573	133/333799
Age-adjusted RR (95% CI)	1.0	0.71 (0.57–0.88)
Multivariate RR (95% CI)†	1.0	0.74 (0.59–0.92)

* 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 non-regular users. CI denotes confidence intervals.

† 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.

‡ 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.

§ Information on stage of cancer was incomplete in 190 men.

Table 3

Relative Risk of Colorectal Cancer According to Duration of Aspirin Intake*

	Years of regular aspirin use					
	0	**1–5**	**6–10**	**11–15**	**> 15**	**P for trend ‡**
No. of cases/Total no. of person-years	387/318630	218/168754	221/167047	88/62223	61/45103	
Age-adjusted RR (95% CI)	1.0	0.89 (0.75–1.05)	0.79 (0.67–0.94)	0.74 (0.58–0.94)	0.69 (0.52–0.93)	0.01
Multivariate RR † (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)	0.008

*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 non-regular users. CI denotes confidence intervals.

†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.

‡P value is for the linear trend across the categories of years of regular use, excluding zero years of use.

Table 4

Relative Risk of Colorectal Cancer According to Time Since Discontinuation of Aspirin Intake*

	Never used aspirin	Time since discontinuation of regular aspirin use			Current aspirin use
		≥ 6 years	4–5 years	< 4 years	
No. of cases/Total no. of person-years	387/318630	52/29964	42/25551	76/54099	418/333513
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 † (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)

*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 non-regular 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 non-regular 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 to men in the reference category of never used aspirin. CI denotes confidence intervals.

†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.

Table 5

Relative Risk of Colorectal Cancer According to Dose of Aspirin Intake*

	Tablets of standard aspirin tablets (325-mg) per week					
	0	**0.5–1.5**	**2–5**	**6–14**	**> 14**	**P for trend ‡**
No. of cases/Total no. of person-years	138/88168	158/111232	148/108957	118/87371	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)	0.005
Multivariate RR † (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)	0.004

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

†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.

‡P value is for the linear trend across the categories of tablets per week, excluding zero tablets per week.