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The Use of Aspirin for Primary Prevention of Colorectal Cancer: A Systematic Review Prepared for the U.S. Preventive Services Task Force

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Background: Aspirin for prevention of colorectal cancer is controversial.

Purpose: To examine the benefits and harms of aspirin chemoprevention.

Data Sources: MEDLINE, 1966 to December 2006; EMBASE, 1980 to April 2005; CENTRAL, Cochrane Collaboration's registry of clinical trials; Cochrane Database of Systematic Reviews.

Study Selection: Two independent reviewers conducted multilevel screening to identify randomized, controlled trials (RCTs), case–control studies, and cohort studies of aspirin chemoprophylaxis. For harms, systematic reviews were sought.

Data Extraction: In duplicate, data were abstracted and checked and quality was assessed.

Data Synthesis: Regular use of aspirin reduced the incidence of colonic adenomas in RCTs (relative risk [RR], 0.82 [95% CI, 0.7 to 0.95]), case–control studies (RR, 0.87 [CI, 0.77 to 0.98]), and cohort studies (RR, 0.72 [CI, 0.61 to 0.85]). In cohort studies, regular use of aspirin was associated with RR reductions of 22% for incidence of colorectal cancer. Two RCTs of low-dose aspirin failed to show a protective effect. Data for colorectal cancer mortality were limited. Benefits from chemoprevention were more evident when aspirin was used at a high dose and for periods longer than 10 years. Aspirin use was associated with a dose-related increase in incidence of gastrointestinal complications.

Limitations: Important clinical and methodological heterogeneity in the definitions of regular use, dose, and duration of use of aspirin necessitated careful grouping for analysis.

Conclusions: Aspirin appears to be effective at reducing the incidence of colonic adenoma and colorectal cancer, especially if used in high doses for more than 10 years. However, the possible harms of such a practice require careful consideration. Further evaluation of the cost-effectiveness of chemoprevention compared with, and in combination with, a screening strategy is required.

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Cancer accounts for 23% of all deaths in the United States. It is the second leading cause of death after heart disease, and the leading cause of death in those younger than age 65 years. Colorectal cancer is the third most common type of cancer in both men and women and is the second and third leading cause of cancer-related deaths in men and women, respectively. In 2006, an estimated 148 610 new cases of colorectal cancer occurred and 51 170 patients died of this disease (1, 2).

It is widely accepted that colorectal adenomatous polyps are the precursors of the vast majority of colorectal cancer cases, so the early detection and removal of these lesions are presumed to reduce the incidence and mortality of colorectal cancer. In addition, cases of cancer detected by screening may be in the early stage and therefore curable. Colorectal cancer has many characteristics of a disorder that would be amenable to screening, as recently reviewed by the U.S. Preventive Services Task Force (USPSTF) (3). Several screening methods are available, but despite the evidence of effectiveness, widespread routine screening of eligible individuals by any method continues to be low in the United States (4–7).

An alternative and possibly complementary strategy to screening is prevention. This can include a variety of lifestyle and dietary changes or, as is the focus of this review, aspirin chemoprevention. Several basic science, population-based, and clinical trials have suggested a protective effect of aspirin as well as nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors, against colorectal adenomas and colorectal cancer. Since age is a major risk factor for colorectal cancer, with approximately 90% of cases occurring after age 50 (1), aspirin may be a particularly attractive intervention; it has documented efficacy in both the primary and the secondary prevention of cardiovascular disease (3).

However, aspirin is not risk free; it can increase the risk for hemorrhagic stroke and gastrointestinal bleeding (3). Potential harms must be considered in light of the possibly long period of aspirin exposure used for colorectal cancer prevention. Furthermore, reductions in colorectal cancer mortality with chemoprevention would have to be

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great enough to compete with the 21% mortality reduction achieved with simple biannual fecal occult blood testing, or with the 60% mortality reduction seen with flexible sigmoidoscopy for lesions within reach of the sigmoidoscope. Furthermore, data suggest that sigmoidoscopy followed by colonoscopy when polyps are found could decrease colorectal cancer incidence by up to 80% (8). The USPSTF strongly recommends screening of men and women older than age 50 years (grade A recommendation) (9). A preventive strategy using aspirin may still have a role as an adjunct treatment, but the benefits would have to balance increased risks; in addition, the cost-effectiveness of this strategy would need to be favorable. Finally, although adherence to colorectal cancer screening is poor, long-term adherence to therapy with a chemopreventive agent in otherwise healthy individuals will probably have a similar limitation.

We conducted this systematic review to examine the evidence on the effectiveness of aspirin for chemoprevention of colorectal adenomas, colorectal cancer, and colorectal cancer mortality, as well as the harms of aspirin use in this setting.

Methods

Data Sources

The search strategy was developed in MEDLINE and modified for the other databases. The search was limited to English-language reports of human studies. Databases searched were MEDLINE, 1966 to December (week 4) 2006; preMEDLINE, through 5 April 2005; EMBASE, 1980 to week 14 of 2005 (publication years 2003 to 2005); and CENTRAL and the Cochrane Library, Issue 4, 2004. Beyond these dates, we surveyed several sources to ascertain additional potentially eligible studies. The PubMed Cancer subset was searched for non-MEDLINE material. Terms were derived from the National Cancer Institute cancer topic searches for *colorectal cancer* and *adenomatous polyps*. A comprehensive retrieval strategy was derived from the indexing in both MEDLINE and EMBASE, investigator-nominated terms, and previous reviews (10–12).

A search strategy to find recent systematic reviews of aspirin that appeared to address harm was developed and run in MEDLINE (2003 to December [week 4] 2006). The Cochrane Database of Systematic Reviews and Database of Abstracts of Reviews of Effects (DARE) (Cochrane Library, third quarter 2004) were searched for all systematic reviews related to aspirin, without date restrictions.

Study Selection

At each screening level, 2 members of the review team independently selected articles for inclusion, after an initial calibration exercise. After identifying potentially relevant articles in the initial screening level, team members assessed whether each article met the inclusion criteria. Conflicts were resolved by consensus. A third level of screening was included to discriminate the different study designs. Data were abstracted by one reviewer and checked by a second reviewer.

Randomized, controlled trials (RCTs); controlled clinical trials; and observational studies (cohort and case–control studies) of the efficacy or effectiveness of aspirin were considered for inclusion if they fulfilled the population and outcome criteria: Participants were at "average" risk for colorectal cancer (that is, they had no known risk factors for colorectal adenoma or colorectal cancer other than age); could have a personal or family history of colorectal adenoma; and could have a family history of sporadic colorectal cancer ("higher risk").

Studies of familial adenomatous polyposis or hereditary nonpolyposis colon cancer syndromes (Lynch I or II) were excluded because these syndromes account for a small percentage of colorectal cancer cases. Secondary prevention studies of patients with a history of colorectal cancer were also excluded. Included studies addressed the incidence of colorectal adenoma or colorectal cancer and reductions in colorectal cancer mortality or overall mortality.

We sought studies on gastrointestinal, cardiovascular, and renal harms associated with the aspirin use by identifying systematic reviews; we chose to identify reviews because of the large number of reviews on harms of aspirin already performed.

Data Extraction and Quality Assessment

Several members of the team extracted data independently by using a computerized Web-based system (SRS 4.0; Trialstat Corp., Ottawa, Ontario, Canada). The PICOS (participant, intervention/exposure, comparator, outcome and study design) approach was applied for data extraction.

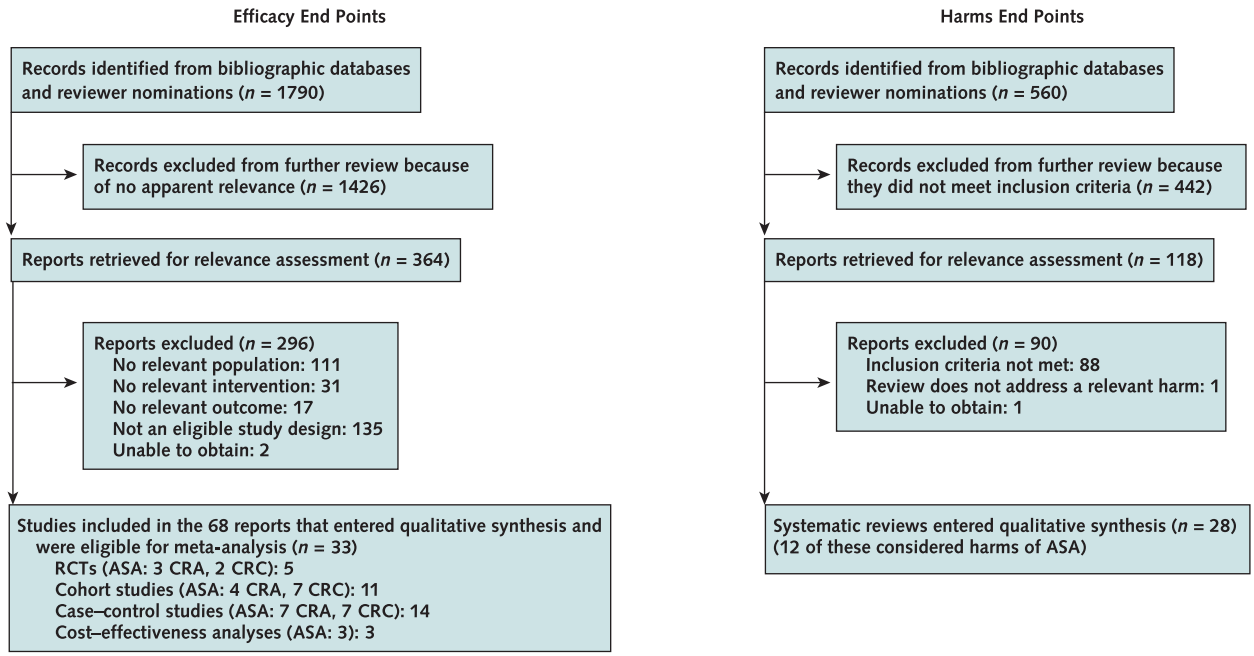
Predefined criteria from the USPSTF were used to assess the quality of included systematic reviews, trials, and observational studies, which were rated as "good," "fair," or "poor" (13). This scale relies on 4 criteria for systematic reviews, 6 criteria for case–control studies, 7 criteria for cohort studies, and 7 criteria for RCTs. Studies with a "good" rating met all criteria, "fair" studies met at least 80% of criteria and had no fatal flaw, and "poor" studies met fewer than 80% of criteria or had a fatal flaw.

Data Synthesis and Analysis

An analytic framework was used to facilitate study grouping and subsequent data analysis in an effort to produce logical groupings and to minimize clinical heterogeneity. Studies were initially grouped by the disorder (that is, colorectal adenoma vs. colorectal cancer), study design, study sample, and medication exposure and were subsequently subcategorized according to measures of dose effect, duration of exposure, and secondary outcomes when reported. Definition of such categories as "regular use" can be found elsewhere (13).

Harms data from the included systematic reviews were summarized and presented as a qualitative systematic review.

Figure. **Study selection, inclusion, and exclusion at each screening phase for the efficacy end points.**



ASA = aspirin; CRA = colorectal adenoma; CRC = colorectal cancer; RCT = randomized, controlled trial.

Results were combined numerically only if clinically and statistically appropriate. The effect measure chosen for synthesis was the relative risk (RR). In case–control studies, a direct estimate of the RR is not possible. The odds ratio (OR) may be estimated, however, and when event rates are low, as is the case here, the OR closely approximates the RR. In what follows, we simply refer to the RR. Heterogeneity was assessed by using the I^2 statistic. Studies were combined when the I^2 value was 50% or less (14). Point estimates of the adjusted RRs and their 95% CIs were directly abstracted from the reports of primary studies. One source of heterogeneity may be study-to-study variation in the method of selecting confounders to adjust for and the final set of confounders chosen. **Appendix Tables 1** and **2** (available at www.annals.org) summarize these characteristics for each study. Furthermore, the USPSTF report discusses the methodologic considerations in detail (13). Standard errors were computed by dividing the CI width by (2×1.96). For 1 study that did not report CIs (15), the standard error was calculated by using a CI imputed from 2 different estimates in the report. Quantitative synthesis was conducted by using inverse-variance weighting and a random-effects model (16).

Role of the Funding Sources

The evidence synthesis upon which this article was based was funded by the Centers for Disease Control and Prevention (CDC) for the Agency for Healthcare Research and Quality (AHRQ) and the USPSTF. Its design, conduct, and reporting were based on specific directives from these agencies.

Data Synthesis

Study Selection

The literature search for the comprehensive USPSTF report (13) yielded 1790 potentially relevant bibliographic records addressing the use of aspirin, COX-2 inhibitors, and other nonaspirin NSAIDs (**Figure**). Aspirin chemoprophylaxis of colorectal cancer was the focus of 8 case–control studies (17–24), 7 cohort studies (15, 25–30), and 2 RCTs (31, 32), and aspirin chemoprophylaxis of colorectal adenoma was the focus of 7 case–control studies (19, 33–38), 4 cohort studies (26, 30, 39–41), and 3 RCTs (31, 42, 43) (**Appendix Table 3**, available at www.annals.org.). A table of duplicate and companion articles is available in the AHRQ report (13). Twelve systematic reviews of the harms of aspirin (3, 44–53, 57) were also identified.

Mortality

The Woman's Health Study (WHS) (32) was a large good-quality RCT in which female health care providers who were older than age 45 years and had no history of cancer, cardiovascular disease, or other diseases were randomly assigned to either 100 mg of aspirin every other day or placebo and followed for 10 years. No statistically significant benefit of aspirin on colorectal cancer mortality was observed. A large, 6-year, fair-quality cohort study (28) of adults treated with various aspirin doses found that reg-

ular aspirin use for longer than 15 years was associated with a significant reduction in colorectal cancer mortality in both men and women, whereas shorter durations of use yielded a protective effect in men only (**Table 2**).

Colorectal Cancer Incidence

Table 2 summarizes the effects of regular aspirin use on colorectal cancer incidence.

RCTs

One fair-quality RCT (31) and 1 good-quality RCT (32) from the United States assessed the effect of low-dose aspirin on colorectal cancer incidence. In the Physicians' Health Study (31), aspirin (325 mg every other day) for 5 years did not significantly reduce colorectal cancer incidence. Similarly, 100 mg of aspirin every other day for 10 years in the similarly designed Women's Health Study did not show a statistically significant reduction in colorectal cancer incidence (32).

Cohort Studies

The effect of regular use of aspirin on the incidence of colorectal cancer in average-risk individuals was assessed in 7 cohort studies (15, 25–27, 29,30, 54). One of these (30) is a follow-up to a previous study (54). One poor-quality study was excluded from the pooled analysis because of its incomplete data presentation (15). Four of the remaining 5 studies were conducted in the United States (25–27, 54), while the other study was conducted in Denmark (29). The studies ranged in quality from fair to good and included a range of follow-up periods and methods of ascertaining aspirin use (**Appendix Table 3**). Quantitative synthesis of the data was possible for regular use of aspirin (that is, $\geq$2 to 3 times weekly for $>$1 year); this analysis showed a statistically significant 22% RR reduction in the incidence of colorectal cancer (**Table 1**). A large, good-quality, long-term follow-up study of aspirin use in average-risk U.S. women revealed a protective effect with more than 10 years of use (RR, 0.67 [CI, 0.54 to 0.85]) as well as for higher doses (30, 54).

Case–Control Studies

Seven case–control studies assessed the effect of aspirin use on colorectal cancer incidence (17–21, 23, 24). Six studies were rated as fair quality, and 1 was rated as good quality (17). Significant heterogeneity, explained predominantly by differences in the methods of exposure and outcome ascertainment among these studies, precluded statistical pooling for the effect of regular use of aspirin on colorectal cancer frequency. These studies reported widely varying statistically significant reductions in the RR for colorectal cancer with regular aspirin use (RR, 0.3 to 0.7) (19,20, 24) or nonsignificant trends in favor of aspirin use (RR, 0.3 to 0.9) (17,18, 21, 23).

The effect of duration of aspirin use on colorectal cancer frequency was assessed in 5 studies (17–19, 55, 56). Quantitative pooling of these results indicated that aspirin use lasting 1 to 3 years showed a nonsignificant trend in favor of aspirin (RR, 0.85 [CI, 0.72 to 1.0]), whereas longer duration of use was associated with a statistically significant protective effect (RR, 0.68 [CI, 0.54 to 0.87]).

Dose response was assessed in 1 small, fair-quality study (17) and 1 larger, good-quality study (55). Statistically significant 40% RR reductions in colorectal cancer frequency were observed with aspirin dosages of 300 and 325 mg/d, but not for lower dosages.

Colorectal Adenoma Incidence

RCTs

The effect of aspirin on the incidence of colorectal adenomas was reported in 2 U.S. RCTs (31, 42) and 1 French RCT (43). Two of these studies were of good quality (42, 43), and 1 was of fair quality (31). Aspirin, 325 mg every other day for 5 years, did not significantly reduce the incidence of adenomas in average-risk men (31). However, in patients with a history of colorectal adenomas, the use of aspirin in dosages of 81 to 325 mg/d for 1 year resulted in a statistically significant reduction in the RR for adenoma (RR, 0.82 [CI, 0.7 to 0.95]) (42, 43) (**Table 2**).

Cohort Studies

Two good-quality cohort studies in average-risk Americans revealed that regular aspirin use was associated with a statistically significant 28% RR reduction in the occurrence of colorectal adenomas (26, 30, 39). The reduction in adenoma risk was seen with the intake of at least six 325-mg aspirin tablets per week; the reduction was similar for small and large polyps and for polyps with advanced histologic features (30, 39) (**Table 1**).

The effect of regular use of aspirin in patients with a history of colorectal adenoma was assessed in 2 small cohort studies (40, 41). In a good-quality study, aspirin used in dosages greater than 325 mg/d was associated with a statistically significant protective effect (41); in the other, a fair-quality study, consistent aspirin use (dose not reported) was also associated with a statistically significant risk reduction in adenomas (40) (**Table 1**).

Case–Control Studies

In a combined analysis of 5 predominantly fair-quality studies lasting 3 to 10 years, the regular use of aspirin in average-risk individuals significantly reduced the incidence of colorectal adenomas (19, 33–35, 37) (**Table 1**). A good-quality database study revealed a nonsignificant trend in favor of higher aspirin doses and longer duration of use (35).

A fair-quality U.S. study in a mixed population of patients with and without a history of colorectal adenoma did not show a statistically significant benefit of an intake of 15 aspirin tablets or more per month for at least 5 years (38). Another fair-quality study in patients with a history

Table 1. **Effects of Regular Use of Aspirin on Colorectal Cancer Incidence and Mortality and on Adenoma Incidence***

Design (Studies)	Study (Reference) (Participants; Quality Rating)	Population	Dose/Duration of Regular Aspirin Use	Relative Risk (95% CI)
CRC mortality in average-risk persons				
RCT (n = 1)	Women's Health Study (32) (n = 39 876; good)	Women	Aspirin, 100 mg every other day for 10 y	NR
Cohort (n = 1)	Cancer Prevention Study II (28) (n = 1 083 531; fair)	Men	≥15 y	0.58 (0.36–0.93)
			<15 y	0.72 (0.52–0.99)
		Women	≥15 y	0.61 (0.38–0.97)
			<15 y	0.72 (0.51–1.02)
CRC incidence in average-risk persons				
RCTs (n = 2)	Physicians' Health Study (31) (n = 22 071; fair)	Men	Aspirin, 325 mg every other day for 5 y	1.15 (0.80–1.65)
	Women's Health Study (32) (n = 39 876; good)	Women	Aspirin, 100 mg every other day for 10 y	0.97 (0.77–1.24)
				Summary: RR, 1.02 (0.84–1.25)
Cohort studies (n = 6)	Physicians' Health Study (25) (n = 22 071; poor)	Men	Aspirin, 325 mg every other day for 12 y	1.03 (0.83–1.28)
	Health Professionals Follow-up Study (26) (n = 47 900; good)	Men	4 y	0.54 (0.34–0.83)
	Leisure World Cohort (15) (n = 13 979; poor)	Men	7–10 y	1.38 (CI not reported)
	Nurses' Health Study (30, 54) (n = 89 446; good)	Women	10 y	0.62 (0.44–0.86)
	Leisure World Cohort (15) (n = 13 979; poor)	Women	7–10 y	1.1 (CI not reported)
	North Jutland Database (29) (n = 29 470; fair)	Men and women	6 y	0.9 (0.7–1.1)
	NHANES/NHEFS (27) (n = 14 407; fair)	Men and women	NR	0.85 (0.63–1.15)
				Summary: RR, 0.78 (0.63-0.97)
Case–control studies (n = 7)	General Practice Research Database (17) (n = 12 005; good)	Men and women	>2 y	0.9 (0.8–1.1)
	Wisconsin Cancer Reporting System (23) (n = 845; fair)	Women	>5 y	0.79 (0.46–1.36)
	Juarranz et al. (21) (n = 502; fair)	Men and women	NR	0.32 (0.09–1.10)
	Multicenter Italian Case Control Study (18) (n = 3248; fair)	Men and women	5 y	0.7 (0.5–1)
	Melbourne Colorectal Cancer Study (20) (n = 1442; fair)	Men and women	NR	0.57 (0.41–0.79)
	Roswell Park Tumor Registry (19) (n = 2704; fair)	Men and women	6 y	0.33 (0.15–0.72)
	Slattery et al. (24) (n = 3051; fair)	Men and women	>5 y	0.7 (0.6–0.8)
Adenoma incidence in average-risk persons				
RCTs (n = 1)	Physicians' Health Study (31) (n = 22 071; fair)	Men	Aspirin, 325 mg every other day for 5 y	0.86 (0.68–1.1)
Cohort studies (n = 2)	Health Professionals Follow-up Study (26) (n = 47 900; good)	Men	4 y	0.65 (0.42–1.02)
	Nurses' Health Study (30, 39) (n = 89 446; good)	Women	10 y	0.61 (0.73–0.87)
				Summary: RR, 0.72 (0.61–0.85)
Case–control studies (n = 5)	General Practice Research Database (35) (n = 943 903; good)	Men and women	5 y	0.9 (0.6–1.3)
	Morimoto et al. (34) (n = 1037; fair)	Men and women	3 y	0.7 (0.5–1.1)
	Logan et al. (33) (n = 476; fair)	Men and women	7 y	0.55 (0.3–1.1)
	Roswell Park Tumor Registry (19) (n = 2704; fair)	Men and women	9 y	0.61 (0.26–1.4)
	CPS-II (37) (n = 177 939; poor)	Men	10 y	0.97 (0.89–1.06)
		Women	10 y	0.85 (0.77–0.95)
				Summary: RR, 0.87 (0.77–0.98)

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Table 1—**Continued**

Design (Studies)	Study (Reference) (Participants; Quality Rating)	Population	Dose/Duration of Regular Aspirin Use	Relative Risk (95% CI)
Adenoma incidence/ frequency in patients with a history of colorectal adenoma				
RCTs (n = 2)	Aspirin/folate Prevention Study (42) (n = 1121; good)	Men and women	Aspirin, 81 mg/d or 325 mg/d for 1 y	0.96 (0.81–1.13)
	Association pour la prevention par l'aspirine du cancer colorectal (43) (n = 272; good)	Men and women	Aspirin, 160 mg/d or 300 mg/d for 1 y	0.61 (0.37–0.99)
				Summary: 0.82 (0.70–0.95)
Cohort studies (n = 2)	Polyp Prevention Study I (40) (n = 864; fair)	Men and women	"Consistent use" for 4 y	0.52 (0.31–0.89)
	Polyp Prevention Study (41) (n = 1905; good)	Men and women	Aspirin, ≤325 mg/d for 4 y	0.82 (0.65–1.02)
			Aspirin, >325 mg/d for 4 y	0.54 (0.3–0.96)
Case–control studies (n = 2)	Sandler et al. (38) (n = 492; fair)	Men and women	Aspirin, >15 tablets/mo for 5 y	0.84 (0.5–1.43)
	Breuer-Katschinski et al. (36) (n = 442; fair)	Men and women (hospital controls)	Aspirin, >4 tablets/wk for <5 y	0.91 (0.32–2.64)
			Aspirin, >4 tablets/wk for ≥5 y	0.09 (0.01–0.82)
		Population controls	Aspirin, >4 tablets/wk for <5 y	0.64 (0.26–1.56)
			Aspirin, >4 tablets/wk for ≥5 y	0.18 (0.02–1.63)

* CPS = Cancer Prevention Study; CRC = colorectal cancer; NHANES = National Health and Nutrition Examination Survey; NHEFS = NHANES I Epidemiologic Follow-up Study; NR = not reported; RCT = randomized, controlled trial; RR = relative risk.

of adenomas showed a statistically significant reduction in the RR for adenomas in the subgroup of patients who used aspirin 4 times per week for more than 5 years compared with hospital controls (36). Comparisons with patients who used aspirin for less than 5 years or comparisons with population controls were nonsignificant (**Table 1**).

Harms Due to Aspirin Use

Twelve good-quality systematic reviews addressed the magnitude of harms due to aspirin use in an adult population (3, 44–53, 57). Eleven of these were systematic reviews of RCTs and provide high-level evidence, while 1 considered observational studies only (51). None addressed the nephrotoxicity of aspirin.

Six systematic reviews addressed general aspirin harms in the adult population (3, 44–47, 57). All-cause mortality was reported in all the reviews. However, mortality and withdrawals due to harms with aspirin use were not consistently reported.

Mortality

In the setting of primary prevention of cardiovascular disease, the all-cause mortality rate with aspirin compared with placebo was not statistically different (3, 45, 57). For secondary prevention of cardiovascular disease, aspirin significantly reduced the RR for death from any cause by 15% to 18% compared with persons not receiving aspirin (46, 47).

Cardiovascular Events

Eight systemic reviews addressed the magnitude of cardiovascular harms associated with aspirin use in an adult population (3, 44–49, 57). Cardiovascular events included acute myocardial infarction (MI), stroke (all, hemorrhagic, or ischemic), and associated death. (**Table 2**).

Four reviews reported on the mortality due to cardiovascular events (3, 45, 46, 57). In a primary prevention setting, mortality due to cardiovascular events was not significantly different between aspirin and placebo (3, 45, 57). In the setting of secondary prevention, aspirin was associated with a statistically significant 16% reduction in the RR for mortality due to cardiovascular events (46).

Seven reviews reported the risk for acute MI with aspirin use (3, 44–47, 49, 57). In the setting of primary prevention, a significantly lower risk for MI with aspirin compared with placebo was reported in 3 reviews (3, 45, 57). In a third review, although the data were not pooled, a significant absolute risk reduction in MI was reported in a trial that compared the use of aspirin with placebo in patients with hypertension (absolute risk reduction, 0.5%; number needed to treat for benefit, 200) (49). In a second-

Table 2. **Cardiovascular Outcomes with Aspirin Use***

Outcome	Primary Cardiovascular Prevention Outcomes (95% CI) (Reference)	Secondary Cardiovascular Prevention Outcomes (95% CI) (Reference)
All-cause mortality	No difference OR, 0.93 (0.84–1.02) (4) RR, 0.94 (0.87–1.01) (45, 57)	Reduced RR, 0.82 (0.70–0.99) (47) RR, 0.85 (0.8–0.9) (46)
Cardiovascular mortality	No difference OR, 0.87 (0.70–1.09) (4) RR, 0.93 (0.83–1.03) (45) OR, 0.89 (0.72–1.10) (57)	Reduced RR, 0.84 (0.79–0.90) (46)
Myocardial infarction	Reduced OR, 0.72 (0.60– 0.87) (4) OR, 0.74 (0.68–0.82) (45) OR, 0.76 (0.67–0.85) (57) ARR, 0.5%; NNT_B, 200 (49)	Reduced RR, 0.68 (0.62–0.74) (46) RR, 0.70 (0.7–0.9) (47)
Stroke	No difference Overall: OR, 1.(0.85–1.23) (4); OR, 0.95 (0.84–1.06) (57) Healthy men: RR, 1.20 (0.96–1.49) (45) Cardiovascular risk factors: RR, 1.02 (0.86–1.21) (45) Hypertension: OR, 0.94 (0.76–1.17) (49)	Reduced (ischemic) Overall: RR, 0.88 (0.76–1.02) (46) and 0.8 (0.7–1.0) (47) Ischemic: RR, 0.82 (0.73–0.92) (46)
Hemorrhagic stroke	No difference OR, 1.4 (0.9–2.0) (4)	Increased RR, 1.84 (1.24–2.74) (46)

* ARR = absolute risk reduction; NNT_B = number needed to treat for benefit; OR = odds ratio; RR = relative risk.

ary prevention setting, 2 reviews reported a significant 30% reduction in the RR for MI with aspirin use compared with placebo (46, 47).

Seven systematic reviews reported the risk for acute stroke (hemorrhagic and ischemic) with aspirin use (3, 45–49, 57). In primary prevention trials, the risk for stroke did not differ between aspirin and placebo (3, 57), in healthy patients (45), in patients with vascular risk factors (45), or in patients with hypertension (49). One review also reported a nonsignificant OR of 1.4 for hemorrhagic stroke (3). In secondary prevention, the overall risk for stroke was not statistically different between aspirin and placebo (46, 47). However, the risk for hemorrhagic stroke was increased by 84% with aspirin (46). In secondary prevention trials, higher rates of hemorrhagic stroke were seen with higher dosages of aspirin (<100 mg/d, 0.3% [CI, 0.2% to 0.4%]; 100 to 325 mg/d, 0.3% [CI, 0.2% to 0.3%]; >325 mg/d, 1.1% [CI, 0.7% to 1.5%]) (48), while the risk for ischemic stroke was decreased by 18% (46). The recent Women's Health Study (32) suggests a possible differential effect of aspirin on women compared with men in the setting of cardiovascular primary prevention. While the Physicians' Health Study demonstrated a reduction in MI risk and no reduction in stroke, the Women's Health Study found no significant reduction in MI but a significant reduction in overall stroke and ischemic stroke.

Gastrointestinal Harms

Gastrointestinal harms of aspirin were considered in 7 systematic reviews (3, 47,48, 50–53). The included reviews summarized data from RCTs (3, 47, 48, 50, 52, 53, 58), cohort studies (3, 51, 53), and case–control studies (51, 52), and some considered low and high doses of aspirin (48, 59).

Aspirin was consistently associated with a statistically significantly elevated risk for gastrointestinal bleeding. The magnitude of this increased RR ranged from 1.6 to 2.5 times that seen among persons who did not use aspirin in the systematic reviews of RCTs, 2.2 times in the systematic review of cohort studies, and 3.1 times in the systematic review of case–control studies. The use of aspirin was also associated with an increased risk for adverse gastrointestinal symptoms, such as nausea and dyspepsia (OR, 1.7 [CI,1.5 to 1.8]) (53).

A dose effect has been suggested for aspirin-induced gastrointestinal toxicity. One systematic review pooled gastrointestinal bleeding incidence among large cardiovascular studies and found that 2.5% (CI, 2.2% to 2.6%) of patients taking more than 100 mg of aspirin per day had gastrointestinal bleeding compared with 1.1% (CI, 0.9% to 1.3%) of those taking fewer than 100 mg/d (48). Ulcer bleeding or perforation occurred in 0.34% and 0.86% of patients taking low-dose (325 mg every 2 days) and high-dose (2.5 to 5.2 g/d) aspirin, respectively ($P < 0.05$) (52). Similarly, a greater risk for gastrointestinal bleeding was seen with high-dose aspirin (1600 mg) (OR, 2.8 [CI, 1.3 to 5.7]) than with lower doses (300 mg/d) (OR, 1.6 [CI, 0.7 to 4.0]) (53). Another systematic review of RCTs demonstrated an increased risk for gastrointestinal bleeding with low-dose aspirin (50 to 162.5 mg) (RR, 1.59 [CI, 1.40 to 1.81]), but the rate of gastrointestinal bleeding with the somewhat higher dose (>162 mg) was not statistically different (RR, 1.68 [CI, 1.51 to 1.88]) (50).

It was estimated that 3 of 1000 middle-aged men

would have gastrointestinal bleeding over a 5-year period of continuous aspirin use, and the rate would be as high as 2 per 1000 patients per year if older, higher-risk patients were considered (3). It has also been suggested that the gastrointestinal bleeding rate with aspirin (300 mg) is 60% higher than with placebo and represents an attributable rate of 2.5 events/1000 patient-years (53). The risk for hospitalization due to gastrointestinal bleeding is also increased (OR, 1.9 [CI, 1.1 to 3.1]), although death from gastrointestinal bleeding itself is rare (53). Of the reviews that reported on this latter outcome (47, 52, 53), only 1 death was recorded with aspirin use (53).

Discussion

Colorectal cancer is a frequent cause of illness and death in the U.S. population. Chemoprevention with aspirin is one possible "simple" strategy to reduce the burden associated with this disease. Our results suggest that such a strategy may be effective, but careful consideration of some remaining inconsistencies in the literature, and the possible harms of chemoprevention, is required before such a strategy can be recommended.

The regular use of aspirin appears to reduce the incidence of colorectal adenoma with RR reductions on the order of 13% to 28% in average-risk individuals. On the basis of a limited number of studies, the RR reductions for individuals with a history of colonic adenoma are probably higher than for those at average risk. Furthermore, it appears that longer duration of aspirin use, as well as higher doses, are associated with greater RR reductions than shorter-term and lower-dose use.

The regular use of aspirin was associated with a pooled 22% RR reduction in colorectal cancer incidence among the included cohort studies. There was significant heterogeneity among the case–control studies, but the individual study results were consistent with a protective effect of aspirin.

Aspirin is a unique agent that may have preventive health benefits. While relatively low doses of aspirin appear to be sufficient for the cardiovascular benefits, it appears that prolonged use of higher doses of aspirin for more than 10 years is required to realize benefits for the chemoprevention of colorectal cancer. The widely cited Physicians' Health Study (31) and the recently published Women's Health Study (32) found no benefit of low-dose aspirin on colorectal cancer incidence. These RCTs shared many similarities, and the strength of their design adds weight to these negative findings. They were conducted in male physicians and female health care workers, respectively. Both used a relatively low dose of aspirin (325 mg every other day and 100 mg every other day, respectively), and both used self-reporting of outcomes in mailed questionnaires, as well as mailed medication packs. Both studies followed patients for a long period (14 and 10 years, respectively), but in the case of the Physicians' Health Study, the RCT portion made up the first 5 years, followed by an observational phase during which patients chose their intervention. The Women's Health Study maintained the RCT design for the entire study period. The Physicians' Health Study could be criticized for its observational phase, which could have introduced several forms of bias, including contamination by intervention. In addition, study participants had a lower rate of colorectal cancer than matched members of the U.S. population, with a standardized mortality ratio of 0.82 (CI, 0.75 to 0.90). Participants in both studies were relatively young (mean age, 53.2 and 54.6 years, respectively), and they were not necessarily free of colorectal adenomas at study onset.

It is difficult to entirely reconcile the discrepancy between the negative RCT data and the generally positive observational data, other than saying that low-dose aspirin every other day does not reduce colorectal cancer incidence but that higher doses used for longer periods may be effective. It is also fair to admit that the overall quality of the observational studies was only "fair" and that these studies exhibited considerable limitations in the ascertainment of aspirin exposure in particular. As a result, it was not always possible for us to pool the data. However, good-quality data from largescale, long-term studies, such as the 82 911 women in the Nurses' Health Study (30), support our overall estimate that aspirin reduces the risk for colorectal cancer. However, this benefit occurs with dosages in the range of 14 or more standard aspirin tablets per week and use lasting for 10 or more years.

The data on colorectal cancer mortality are also inconsistent. One cohort study was positive, while the recently published Women's Health Study also showed no effect of aspirin on mortality. However, it is possible that dosage and duration effects are important in this setting as well, so that higher-dose aspirin for longer periods may still have a beneficial effect on colorectal cancer mortality.

The use of aspirin is associated with an increased incidence of important ulcer complications, with RRs of 1.5 to 3.0. Rates of gastrointestinal toxicity with aspirin appear to be between rates associated with diclofenac and sulindac (60). Aspirin also appears to have a dose effect: The absolute risks for gastrointestinal bleeding are 0.97% per year with a dosage less than 100 mg/d and 2.69% per year for a dosage greater than 200 mg/d (61). A dose effect was also demonstrated with the risk for hemorrhagic stroke. Therefore, the multiyear use of high-dose aspirin that appears to be required for colorectal cancer chemoprevention can be expected to be accompanied by important complications that may adversely affect the overall benefit of a chemoprevention strategy.

The cardiovascular outcomes associated with the use of aspirin depend on the underlying cardiovascular risk among the population under investigation. In low- to average-risk individuals (that is, those receiving primary cardiovascular prevention), aspirin significantly reduces the incidence of total cardiovascular events and myocardial in-

farction but has no effect on coronary heart disease mortality, fatal and nonfatal stroke events, or all-cause mortality. In low- to moderate-risk individuals, the use of aspirin would prevent 3 to 8 fatal or nonfatal coronary heart disease events, would not prevent an ischemic stroke event, and would cause 1 hemorrhagic stroke and 1 major gastrointestinal hemorrhage among 1000 treated patients (3). Data from the Women's Health Study suggest that the risk for stroke (overall as well as ischemic) is significantly reduced by aspirin use in women older than age 65 years (32). In high-risk patients with cardiovascular disease in a secondary prevention setting, the use of aspirin significantly reduces all-cause mortality and cardiovascular mortality, despite the increased incidence of major gastrointestinal hemorrhage. It is suggested that 67 patients would need to be treated to prevent 1 death, at the cost of 1 nonfatal gastrointestinal bleeding episode (47, 50). In the setting of colorectal cancer chemoprevention with aspirin, depending on the age at which the intervention is started, most patients may be at low to moderate cardiovascular risk and may have greater exposure to the harms of aspirin than to its benefits. This may be especially true if one considers that for colorectal cancer prevention, aspirin would need to be used in doses higher than currently recommend for cardiovascular prevention.

In average-risk populations and in the context of regular endoscopic screening for colorectal cancer, aspirin chemoprevention also must be weighted against the relatively large costs associated with its adverse effects, as well as the relative inefficacy of aspirin compared with colonoscopy screening (13).

In conclusion, aspirin appears to reduce the incidence of colorectal adenomas and colorectal cancer. However, the data on colorectal cancer incidence are inconsistent: Observational studies tend to be positive, and 2 large RCTs showed no benefit for low-dose aspirin every other day. The effect of aspirin on colorectal cancer mortality is also mixed, with 1 positive cohort study and negative findings of the Women's Health Study. The available data would suggest that for chemoprevention, aspirin would need to be used in doses greater than used for cardiovascular prevention and for a duration close to 10 years. Therefore, the potential benefit of aspirin chemoprevention would need to be carefully weighed against its harms. More information is still required to clarify the optimal dose, starting age, and duration of use of aspirin. In addition, its effect on colorectal cancer incidence and mortality should be clarified, particularly given the evidence that in patients at average cardiovascular risk, use of aspirin does not reduce all-cause mortality. Further evaluation of the cost-effectiveness of chemoprevention compared with, and in combination with, a screening strategy is required.

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Appendix Table 1. **Confounders Controlled for in the Studies' Adjusted Relative Risk Estimates for the Incidence of Colorectal Cancer (Cohort and Case–Control Studies)***

Study, Year (Reference)	Source of Abstracted Data	Methods for Selection of Confounders	Confounders	Individual Study Estimate RR (95% CI)	Index of Heterogeneity and Pooled Estimate RR (95% CI)
Cohort studies: duration of aspirin use (7–9 y) and risk for CRC					
Friis et al., 2003 (29)	Table 3 (p. 687)	A priori†	Age, sex (women and men)	0.90 (0.70–1.10)	
Giovannucci et al., 1995 (54)	Table 2 (p. 612)	A priori‡	Age, sex (women)	0.84 (0.55–1.28)	
Stürmer et al., 1998 (25)	Table 4	Stepwise model-based selection	Age, sex (men), BMI, smoking, alcohol consumption	1.07 (0.67–1.70)	
					$I^2 = 0$ RR = 0.91 (0.76–1.10)
Cohort studies: regular aspirin use (≥2–3 d per week for ≥1 y) and risk for CRC					
Stürmer et al., 1998 (25)	Table 4	Stepwise model-based selection	Age, sex (men), BMI, smoking, alcohol consumption	1.07 (0.67–1.70)	
Giovannucci et al., 1994 (26)	Table 2 (p. 243)	A priori§	Age; sex (men); family history of CRC; pack-years of smoking; BMI; physical activity levels; alcohol consumption; dietary intake of fat, meat, calcium, and vitamin D	0.54 (0.34–0.83)	
Giovannucci et al., 1995 (54)	Table 1 (p. 611)	A priori§	Age; sex (women); family history of CRC; pack-years of smoking; BMI; physical activity levels; alcohol consumption; dietary intake of fat, meat, calcium, and vitamin D	0.62 (0.44–0.86)	
Friis et al., 2003 (29)	Table 3 (p. 687)	A priori†	Age, sex (women and men)	0.90 (0.70–1.10)	
Schreinemachers and Everson, 1994 (27)		A priori§	Age, sex (women and men)	0.85 (0.63–1.15)	
					$I^2 = 49$ RR = 0.78 (0.63–0.97)
Case-control studies: duration of aspirin use (1–3 y) and risk for CRC					
La Vecchia et al., 1997 (18)	Table 2 (p. 676)	Stepwise model-based selection	Age sex (women and men), center, education, BMI, alcohol consumption, physical activity, total energy, and meat intake	0.90 (0.50–1.70)	
Friedman et al., 1998 (56)	Table 2 (p. 101)	A priori and stepwise model-based selection	Age; sex (women and men); use of NSAIDs; alcohol consumption; family history of CRC; BMI; physical activity; smoking; total energy; fiber, calcium, and meat intake	0.80 (0.60–1.00)	
Rosenberg et al., 1998 (55)	Table 4 (p. 2331)	Stepwise model-based selection	Age, sex (men and women)	1.00 (0.60–1.70)	
García-Rodríguez and Huerta-Alvarez, 2001 (17)	Table 6 (p. 92)	A priori and stepwise model-based selection ‖	Age, sex (men and women)	0.90 (0.70–1.20)	
Slatterly et al., 2004 (24)	Table 2 (p. 216)	A priori and stepwise model-based selection¶	Age, sex (men and women), alcohol consumption, family history of CRC, BMI, smoking, education, dietary fiber intake	0.54 (0.24–1.23)	
					$I^2 = 0$ RR = 0.85 (0.72–1.00)

Appendix Table 1—Continued

Study, Year (Reference)	Source of Abstracted Data	Methods for Selection of Confounders	Confounders	Individual Study Estimate RR (95% CI)	Index of Heterogeneity and Pooled Estimate RR (95% CI)
Case-control studies: duration of aspirin use (4–6 y) and risk for CRC					
La Vecchia et al., 1997 (18)	Table 2 (p. 676)	Stepwise model-based selection	Age, sex (women and men), center, education, BMI, alcohol consumption, physical activity, total energy, and meat intake	0.60 (0.40–1.00)	
Friedman et al., 1998 (56)	Table 2 (p. 101)	A priori and stepwise model-based selection	Age; sex (women and men); use of NSAIDs; alcohol consumption; family history of CRC; BMI; physical activity; smoking; total energy; fiber, calcium, and meat intake	0.80 (0.60–0.90)	
Rosenberg et al., 1998 (55)	Table 4 (p. 2331)	Stepwise model-based selection	Age, sex (men and women)	0.50 (0.30–0.70)	
García-Rodríguez and Huerta-Alvarez, 2001 (17)	Table 6 (p. 92)	A priori and stepwise model-based selection ‖	Age, sex (men and women)	0.90 (0.70–1.20)	
					$I^2 = 39$ RR = 0.74 (0.60–0.90)
Case–control studies: recency (>1 y) of aspirin use and risk for CRC					
Friedman et al., 1998 (56)	Table 2 (p. 101)	A priori and stepwise model-based selection	Age; sex (women and men); use of NSAIDs; alcohol consumption; family history of CRC; BMI; smoking; physical activity; total energy; fiber, calcium, and meat intake	1.00 (0.80–1.20)	
La Vecchia et al., 1997 (18)	Table 2 (p. 676)	Stepwise model-based selection	Age, sex (women and men), center, education, BMI, alcohol consumption, physical activity, total energy, and meat intake	0.90 (0.50–1.60)	
García-Rodríguez and Huerta-Alvarez, 2001 (17)	Table 6 (p. 92)	A priori and stepwise model-based selection‖	Age, sex (men and women)	1.00 (0.70–1.30)	
					$I^2 = 0$ RR = 0.99 (0.84–1.17)

* BMI = body mass index; CRC = colorectal cancer; NSAIDs = nonsteroidal anti-inflammatory drugs; RR = relative risk.
† The authors calculated standardized incidence ratio, which incorporates age- and sex-specific cancer rates in population.
‡ Cox proportional-hazards modeling (adjusted for age).
§ Cox proportional-hazards modeling (adjusted for potential confounders).
‖ Poisson regression modelling.
¶ Unconditional logistic regression model.

Appendix Table 2. **Confounders Controlled for in the Studies' Adjusted Relative Risk Estimates for the Incidence of Colorectal Adenoma (Cohort and Case–Control Studies)***

Study, Year (Reference)	Source of Abstracted Data	Methods for Selection of Confounders	Confounders	Individual Study Estimate RR (95% CI)	Index of Heterogeneity and Pooled Estimate RR (95% CI)
Cohort studies: regular aspirin use (≥2–3 d per week for ≥1 y) and risk for adenomas					
Giovannucci et al., 1994 (26)	Table 4 (p. 244)	A priori†	Age; sex (men); family history of CRC; pack-years of smoking; BMI; physical activity levels; dietary intake of fat, meat, calcium, alcohol, and vitamin D	0.65 (0.42–1.02)	
Chan et al., 2004 (39)	Table 3 (p. 161)	A priori and stepwise model-based selection†	Age; sex (women); pack-years of smoking; BMI; physical activity levels; history of CRC in sibling or parent; alcohol intake; postmenopausal HRT; meat, calcium, and vitamin intake	0.73 (0.61–0.87)	
					$I^2 = 0$ RR = 0.72 (0.61–0.85)
Case–control studies: regular aspirin use and risk for adenomas					
Morimoto et al., 2002 (34)	Table 3 (p.1016)	Backwards stepwise model-based selection†	Age, sex, BMI, HRT, pack-years of smoking, alcohol consumption	0.70 (0.50–1.10)	
Kahn et al., 1998 (37)	Table 3 (p. 307)	Stepwise model-based selection†	Age; education; race; gallbladder status; BMI; exercise; smoking; alcohol and coffee consumption; multivitamin use; family history of CRC; dietary intake of eggs, vegetables, and meat	0.97 (0.89–1.06) Sample of men	
Kahn et al., 1998 (37)	Table 3 (p. 307)	Stepwise model-based selection†	Same as in men, plus parity, HRT, and menopausal status	0.85 (0.77–0.95) Sample of women	
Suh et al., 1993 (19)	Table 2 (p. 1174)	A priori and stepwise model-based selection†	Age, sex, residence, and level of education	0.61 (0.26–1.40)	
García-Rodríguez and Huerta-Alvarez, 2000 (35)	Table 5 (p. 380)	Stepwise model-based selection†	Age, sex, ischemic heart disease, constipation	0.90 (0.60–1.30)	
Logan et al., 1993 (33)	Table 2 (p. 286)	A priori and stepwise model-based selection†	Age- and sex-matched case-patients and controls	0.55 (0.30–1.10)	
					$I^2 = 41$ RR = 0.97 (0.77–0.98)

* BMI = body mass index; CRC = colorectal cancer; HRT = hormone replacement therapy; RR = relative risk.
† Multiple logistic regression model.

Appendix Table 3. Included Studies: Aspirin Chemoprevention of Colonic Adenomas and Colorectal Cancer, by Study Design*

Colorectal Cancer—Case–Control Studies (*n* = 7)

Study, Year, Location (Reference)	Participants Enrolled/ Completed Study, *n/n*	Duration	Case-Patients	Controls	Exposure (Ascertainment)	Quality Rating
García Rodriguez et al., 2001, Spain (17)	12 005/12 002	3 y	Persons age 40–79 y with biopsy-proven CRC from the General Practice Research Database (*n* = 2002)	Randomly selected persons age 40–79 y free of CRC at the index date of case (*n* = 10 000), frequency-matched by sex and age to case-patients	Nonaspirin NSAIDs and aspirin (prescription drug database)	Good
La Vecchia et al., 1997, Italy (18)	3248/3248	4.5 y	Patients with histologically confirmed CRC (*n* = 860 colon; *n* = 497 rectum)	Patients in same residing area/hospital as case-patients, identified for acute conditions unrelated to known or likely risk factors for CRC (*n* = 1891)	Aspirin (questionnaire)	Fair
Suh et al., 1993, U.S. (19)	2704/NR	9 y	Case-patients 1: first primary colon cancer (*n* = 490) Case-patients 2: first primary rectal cancer (*n* = 340)	Controls 1: Healthy persons at preventive health visit (*n* = 1138) Controls 2: healthy persons without cancer (*n* = 524)	Aspirin (questionnaire)	Fair
Kune et al., 1988, Australia (20)	1442/1367	1 y	Persons with newly diagnosed CRC between April 1980 and April 1981 (*n* = 715)	Randomly selected patients matched for age, sex, and geographic area	Aspirin, NSAID (questionnaire)	Fair
Juarranz et al., 2002, Spain (21)	502/424	NR	Patients with biopsy-proven colon cancer between January 1995 and December 1996, residing in Madrid (*n* = 196)	Persons free of neoplasm or severe digestive disease (Crohn disease or ulcerative colitis) at enrollment, randomly chosen from electoral lists from same area as case-patients and matched to case-patients for age and sex	Aspirin and NSAIDs (questionnaire)	Fair
Reeves et al., 1996, U.S. (23)	845/400	1 y	Women age 40–74 y, local residents with new diagnosis of invasive cancer of the colon or rectum, with listed telephone number (*n* = 184)	Persons with listed telephone number and either a current Wisconsin driver's license (age <65 y) or a Medicare card (age >65 y) (*n* = 293)	Aspirin, NSAID, (questionnaire)	Fair
Slattery et al., 2004, U.S. (24)	3051/2157	5 y, 2 mo	English-speaking persons mentally competent to complete the interview, age 30–79 y; first primary tumor in the rectosigmoid junction or rectum diagnosed between May 1997 and May 2001 (*n* = 952)	Patients matched by sex and 5-y age group; those > age 65 y randomly selected from Health Care Financing Administration lists; those < age 65 y selected from driver's license lists (*n* = 1205)	Aspirin, NSAID (questionnaire)	Fair

Colorectal Cancer—Cohort Studies (*n* = 7)

Study, Year, Location (Reference)	Participants Enrolled/ Completed Study, *n/n*	Study Duration	Population	Cohort Name	Exposure	Quality Rating
Chan et al., 2005, U.S. (30)	89 446/82 911	20 y	Inclusion criteria: female registered nurses age 30–55 y (in 1976) Exclusion criteria: baseline cancer, did not fill out questionnaire	Nurses' Health Study	Aspirin Nonaspirin NSAIDs Assessed tablets/ week (1–3, 4–6, 7–14, >14); number of days/month of use; frequency per week; regular use	Good

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Appendix Table 3—**Continued**

Giovannucci et al., 1994, U.S. (26)	47 900/45 505	7 y	Inclusion criteria: Male health professionals; respondents to mailed questionnaire in 1986; age 40–75 y Exclusion criteria: NR	Health Professionals Follow-up Study	Aspirin: in all 3 questionnaires (n = 11 260 person-years) in CRC study Nonexposed: n = 30 020 person-years in CRC study	Good
Schreinemachers et al., 1994, U.S. (27)	14 407/12 668	16 y	Inclusion criteria: Patients with medical examination and age 25–74 y at time of NHANES I Exclusion criteria: Case-patients: diagnosis occurring ≥2 y of NHANES I; controls: incomplete surveys or data on aspirin use	NHANES/NHEFS	Aspirin: within 30 d of baseline interview (n = 7438); Nonexposed: within 30 d of baseline interview (n = 5250)	Fair
Thun et al., 1991, U.S. (28)	1 083 531/662 424	6 y	Inclusion criteria: White adults (friends/family of volunteers for Cancer Prevention Study II in 1982) who provided information in 1982 on the frequency and duration of aspirin use Exclusion criteria: Nonwhite (due to small number of deaths in this group); aspirin use <1 y	Cancer Prevention Study II	Aspirin: <1 time/mo (n = 486 620 person-years for men and n = 671 927 person-years for women); 1–15 times/mo (389 083 person-years for men and 505 854 person-years for women); ≥16 times/mo (n = 201 638 person-years for men and n = 265 424 person-years for women); Nonexposed: n = 646 346 person-years for men and n = 705 064 person-years for women	Fair
Friis et al., 2003, Denmark (29)	29 470/29 470	9 y	Inclusion criteria: Patients with prescribed low-dose aspirin (maximum dose, 150 mg), Danish Cancer registry, controlled for age, sex, and county Exclusion criteria: Residency outside county of North Jutland; invalid civil registry number; death before/at date of prescription; parent (of patient) registered as customer	North Jutland cohort database	Low-dose aspirin (follow-up: 6 y): n = 29 470	Fair

Appendix Table 3—**Continued**

Paganini-Hill, 1995, U.S. (15)	13 979/12 180	11 y	Inclusion criteria: Community residents with returned questionnaire on medical history; use of drugs, laxatives, and supplements; smoking; alcohol consumption; exercise habits; health care utilization; and, for women, menstrual history (i.e., use of estrogen) Exclusion criteria: NR	Leisure World Cohort	Aspirin: Less than daily or daily	Poor
Stürmer et al., 1998, U.S. (25)	22 071/22 071	12 y (RCT, first 5 y; cohort study, next 7 y)	Inclusion criteria: U.S. male physicians, age 40–84 y in 1982 Exclusion criteria: Regular use of aspirin or other NSAIDs; history of myocardial infarction, stroke, cancer, liver or renal disease, gout, peptic ulcer, or contraindications to aspirin	Physicians' Health Study	Randomly assigned to aspirin/regular aspirin use thereafter (n = 41 869 person-years); randomly assigned to placebo/irregular aspirin use thereafter (n = 18 342 person-years)	Poor

Colorectal Cancer—RCTs (n = 2)

Study, Year, Location (Reference)	Participants Enrolled/ Completed Study, *n/n*	Study Duration	Population	Control Group	Exposure(s)	Quality Rating
Gann et al., 1993, U.S. (31)	22 071/NR	6 y	Inclusion criteria: U.S. male physicians, age 40–84 y Exclusion criteria: History of CVD, cancer, liver or renal disease, gout, peptic ulcer, contraindications to aspirin, or current use of NSAIDs or vitamin A	Placebo	Aspirin	Fair
Cook et al., 2005, U.S. (32)	39 876 (39 876/39 876)	10 y	Inclusion criteria: U.S. female health care workers age >45 y, no history of cancer, CVD, or other major disease Exclusion criteria: Sensitivity to aspirin; aspirin use >1 time/wk; use of oral anticoagulants, vitamin A or E supplements	Placebo	Aspirin, 100 mg every other day	Good

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Appendix Table 3—Continued

Colonic Adenomas—Cohort Studies (*n* = 4)

Study, Year, Location (Reference)	Participants Enrolled/ Completed Study, *n/n*	Study Duration	Population	Cohort Name	Exposure	Quality Rating
Giovannucci et al., 1994, U.S. (26)	47 900/45 505	7 y	Inclusion criteria: Male health professionals responding to mailed questionnaire in 1986, age 40–75 y Exclusion criteria: NR	Health Professionals Follow-up Study	Aspirin: in all 3 questionnaires (*n* = 11 260 person-years in CRC study) Aspirin: *n* = 1242 person-years in 1986 survey only Nonexposed: *n* = 30 020 person-years in CRC study Nonexposed: *n* = 2472 person-years in adenoma study	Good
Chan et al., 2004, U.S. (30, 39)	27 077/27 077	21 y	Inclusion criteria: Women (registered U.S. nurses), age 30–55 y, who completed baseline dietary questionnaire and underwent colonoscopy or sigmoidoscopy during study period Exclusion criteria: Incomplete questionnaires; no data/implausible dietary/aspirin data; history of cancer (except nonmelanoma skin cancer), CRA, IBD, or FAP	Nurses' Health Study	Aspirin: 0.5–1.5 tablets/wk: *n* = 6340; 2–5 tablets/wk: *n* = 4172; 6–14 tablets/wk: *n* = 4352; >14 tablets/wk: *n* = 1634 Nonexposed: *n* = 10 579	Good
Polyp Prevention Study, 2003, U.S. (41)	NR/1905	4 y	Inclusion criteria: Enrollees of the Polyp Prevention Trial, 1991, ≥ age 35 y with ≥1 histologically confirmed colorectal adenoma identified by complete colonoscopy within 6 mo before randomization Exclusion criteria: History of colorectal cancer, surgical resection of adenomas, IBD, or FAP	Polyp Prevention Study	Aspirin: any use (*n* = 431); up to 325 mg/d (*n* = 369); >325 mg/d (*n* = 62); unexposed (*n* = 1474); NSAID: any use (*n* = 629); unexposed (*n* = 1276); use reported at all 5 visits (*n* = 253); no use reported at all 5 visits (*n* = 1462)	Good
Greenberg et al., 1993, U.S. (40)	864/793	~4 y	Inclusion criteria: Patients with ≥1 histologically confirmed adenoma removed within 3 mo before study entry, free of further polyps, age <80 y, otherwise healthy Exclusion criteria: Invasive large-bowel cancer; IBD; malabsorption; or any contraindication to β-carotene, vitamin C, vitamin E (history of kidney stones or thrombophlebitis)	Polyp Prevention Study I	Aspirin: consistent use (*n* = 102); Aspirin: intermittent use (*n* = 98); Nonexposed: *n* = 593	Fair

Appendix Table 3—Continued

Colonic Adenomas—RCTs (n = 3)

Study, Year, Location (Reference)	Participants Enrolled/ Completed Study, *n/n*	Study Duration	Population	Study Name	Exposure	Quality Rating
Gann et al., 1993, U.S. (31)	22 071/NR	6 y	Inclusion criteria: U.S. male physicians, age 40–84 y Exclusion criteria: History of CVD, cancer, liver or renal disease, gout, peptic ulcer, contraindications to aspirin, or current use of NSAIDs or vitamin A	Physician's Health Study	Aspirin vs. placebo	Fair
Baron et al., 2003, U.S. (42)	1121/1084	7 y	Inclusion criteria: Healthy patients age 21–80 y; ≥1 histologically confirmed CRA removed within 3 mo, or within 16 mo with history of ≥2 confirmed CRAs, or a histologically confirmed adenoma ≥1 cm in diameter removed within 16 mo; complete colonoscopy within 3 mo with no colorectal polyps remaining Exclusion criteria: History of familial CRC syndrome; invasive large-bowel cancer; malabsorption syndromes; contraindications to aspirin, NSAIDs, or folate	Aspirin/Folate Prevention Study	Aspirin, 81 mg/d, vs. aspirin, 325 mg, vs. placebo	Good
Benamouzig et al., 2003, France (43)	272/238	>8 y	Inclusion criteria: Patients age 18–75 y with ≥3 CRAs of any size or 1 CRA ≥6 mm in diameter; no regular use of aspirin or other NSAIDs (7 consecutive d >3 wk/y or >21 d/y); removed polyps <3 mo after consultation; clean colon/rectum at entry; eligible women: menopausal or using efficient contraception Exclusion criteria: History of CRC, FAP, bowel resection excluding appendectomy, IBD, or debilitating or life-threatening diagnosis	Association pour la prèvention par l'aspirin du colorectal cancer	Lysine acetylsalicylate, 160 mg/d (n = 73), vs. lysine acetylsalicylate, 300 mg/d (n = 67), vs. placebo	Good

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Appendix Table 3—Continued

Colonic Adenomas—Case–Control Studies (*n* = 7)

Study, Year, Location (Reference)	Participants Enrolled/ Completed Study, *n/n*	Duration	Case-Patients	Controls	Exposure (Ascertainment)	Quality Rating
García Rodríguez et al., 2000, Spain (35)	943 903/NR	5 y, 8 mo	Adenoma case-patients: adenoma on medical records database with biopsy (*n* = 1864); CRC case-patients: incident of CRC (*n* = 2002)	Randomly selected age- and sex-matched persons from database; absence of adenoma (*n* = 10 000)	Nonaspirin NSAIDs, aspirin, ibuprofen, diclofenac, naproxen, indomethacin, piroxicam, ketoprofen (prescription database)	Good
Morimoto et al., 2002, U.S. (34)	1037/1037	3 y	Incident adenomatous polyp (*n* = 474)	Persons negative for CRC on colonoscopy (*n* = 563)	Aspirin, nonaspirin NSAIDs (questionnaire)	Fair
Logan et al., 1993, United Kingdom (33)	476/NR	7 y	Patients with positive results on fecal occult blood tests with CRA (*n* = 147)	Patients matched for age and sex; negative controls—patients with negative results on fecal occult blood test; positive controls—patients with positive results on screening found to be free of adenomas and carcinomas on sigmoidoscopy and barium enema (*n* = 153)	Aspirin, NSAIDs, nonaspirin NSAIDs (questionnaire)	Fair
Breuer-Katschinski et al., 2000, Germany (36)	1265/550	3.5 y	Patients with histologically proven and endoscopically removed adenoma of colon or rectum (*n* = 182)	Hospital controls: matched for age and sex, free of adenomatous polyps at colonoscopy (*n* = 178) Nonhospital (community) controls: persons of same age and sex as case-patients, selected from inhabitants list of city of Essen (*n* = 182)	NSAID (questionnaire)	Fair
Suh et al., 1993, U.S. (19)	2704/NR	9 y	Case-patients 1: first primary colon cancer (*n* = 490) Case-patients 2: first primary rectal cancer (*n* = 340)	Controls 1: healthy persons at preventive health visit (*n* = 1138) Controls 2: healthy persons without cancer (*n* = 524)	Aspirin (questionnaire)	Fair
Sandler et al., 1998, U.S. (38)	492/379	3 y	Patients with incident adenoma (*n* = 142)	Persons free of adenomatous polyps or having hyperplastic polyps (*n* = 169)	Aspirin, NSAID, nonaspirin NSAID (questionnaire)	Fair
Kahn et al., 1998, U.S. (37)	177 939/154 224	10 y	Patients with self-reported polyps per mailed questionnaire (*n* = 7504 men; *n* = 5111 women)	Persons who did not report polyps (*n* = 65 364 men; *n* = 76 245 women)	Aspirin (questionnaire)	Poor

* CRA = colorectal adenoma; CRC = colorectal cancer; CVD = cardiovascular disease; FAP = familial adenomatous polyposis; IBD = inflammatory bowel disease; NHANES = National Health and Nutrition Examination Survey; NHEFS = NHANES I Epidemiologic Follow-up Study; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized, controlled trial; U.S. = United States.