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REVIEW

Aspirin for the Prevention of Cancer Incidence and Mortality: Systematic Evidence Reviews for the U.S. Preventive Services Task Force

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Background: Cancer is the second leading cause of death in the United States.

Purpose: To conduct systematic reviews of aspirin and 1) total cancer mortality and incidence in persons eligible for primary prevention of cardiovascular disease (CVD) and 2) colorectal cancer (CRC) mortality and incidence in persons at average CRC risk.

Data Sources: MEDLINE, PubMed, and the Cochrane Central Register of Controlled Trials through January 2015 and relevant references from other reviews.

Study Selection: Trials comparing oral aspirin versus placebo or no treatment in adults aged 40 years or older were included. Two investigators independently reviewed abstracts and articles against inclusion and quality criteria.

Data Extraction: Data from 20 good- or fair-quality trials were abstracted by one reviewer and checked by another.

Data Synthesis: In CVD primary prevention trials, cancer mortality (relative risk [RR], 0.96 [95% CI, 0.87 to 1.06]) (10 trials; *n* = 103 787) and incidence (RR, 0.98 [CI, 0.93 to 1.04]) (6 trials; *n* = 72 926) were similar in aspirin and control groups over 3.6 to 10.1 years. In CVD primary and secondary prevention trials, 20-year CRC mortality was reduced among persons assigned to aspirin therapy (RR, 0.67 [CI, 0.52 to 0.86]) (4 trials; *n* = 14 033). Aspirin appeared to reduce CRC incidence beginning 10 to 19 years after initiation (RR, 0.60 [CI, 0.47 to 0.76]) (3 trials; *n* = 47 464).

Limitations: Most data were from clinically and methodologically heterogeneous CVD prevention trials. Outcome assessment and follow-up length varied across studies. Data on non-CRC cancer types and subgroups were limited.

Conclusion: In CVD primary prevention populations, aspirin's effect on total cancer mortality and incidence was not clearly established. Evidence from CVD primary and secondary prevention studies suggested that aspirin therapy reduces CRC incidence and perhaps mortality approximately 10 years after initiation.

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In the United States, the lifetime risk for cancer is 43.3% in men and 37.8% in women (1), and cancer is the second leading cause of death (2). In 2016, there will be an estimated 1 685 210 new cancer cases and 595 690 cancer deaths (3). As such, primary prevention of cancer is an important public health objective. Chemoprevention (4) of cancer with aspirin is of particular interest as a primary prevention strategy.

We found no established groups that currently recommend aspirin use for prevention of cancer in general or for specific cancer types (5–9), except for consideration in certain individuals at high risk for colorectal cancer (CRC), such as persons with Lynch syndrome (10). Consistent with the U.S. Preventive Services Task Force's (USPSTF's) 2007 findings (11), the American Cancer Society recommends against aspirin use for CRC prevention in the general population (3). In updating its recommendation, the USPSTF considered cancer prevention, including CRC, as contributing to an assessment of the net benefits and harms of aspirin use in a population eligible for the primary prevention of cardiovascular disease (CVD). This article summarizes 2 concurrent systematic reviews that addressed the effects of aspirin use on total cancer incidence and mortality and on CRC incidence and mortality (12, 13). These reviews were used in conjunction with systematic reviews on CVD events (14) and harms associated with aspirin use (13) and a decision model (15) to update USPSTF recommendations on aspirin use.

Methods

We developed an analytic framework and key questions to evaluate the relationship between aspirin use and cancer-related and all-cause mortality, total cancer incidence, CRC mortality, CRC incidence, colorectal adenoma incidence, and harms of aspirin use in a CVD primary prevention population and in adults without a history of CRC, familial adenomatous polyposis, or Lynch syndrome (**Appendix Figure 1**, available at www.annals.org). This article focuses on cancer mortality and incidence, with all-cause mortality (16) and harms (17) addressed in companion articles. Results on adenoma incidence and CRC incidence and mortality in persons with prior adenomas are available in the full

See also:

Related articles 1
Editorial comment 2

CRC report (12). The full reports for the USPSTF also describe our methods in detail (12, 13).

Data Sources and Searches

We conducted separate literature searches for total cancer and CRC but used similar methods. For total cancer, we based our review on 2 individual-patient data (IPD) meta-analyses of randomized, controlled trials (RCTs) published through 2010 (18) and 2011 (19) that examined the effects of daily aspirin on cancer incidence and/or mortality. We supplemented these reviews through a comprehensive bridge search of PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials (1 January 2011 to 6 January 2015). We also reviewed bibliographies of previous and concurrent USPSTF reviews and other recent relevant reviews (12, 14, 20, 21). For CRC, we assessed all studies from the previous USPSTF review (20), performed a comprehensive search using the databases listed earlier from 1 January 2004 to 6 January 2015, and examined reference lists of relevant literature.

Study Selection

Total Cancer

Pairs of investigators independently reviewed titles, abstracts, and full-text articles of studies against prespecified criteria (12, 13). We included RCTs and controlled clinical trials conducted in adults (aged ≥40 years) that compared regular oral aspirin use (≥75 mg at least every other day) versus placebo or no treatment for at least 1 year for any indication. We excluded randomized groups that included other antithrombotic or chemopreventive agents and trials in adults with a personal history of cancer or a high prevalence of familial cancer syndromes (such as Lynch syndrome). We limited the review to fair- and good-quality trials (see Data Extraction and Quality Assessment) published in English and conducted in countries with a "very high" Human Development Index in 2013 (22). We included 1 IPD meta-analysis that included studies of less than 1 year of aspirin use because it reported outcomes (time-to-event and individual cancer types) not available from reports of individual trials (19).

CRC

Inclusion and exclusion criteria were similar to those in the total cancer review with a few exceptions: We included prospective cohort studies in the full report (not reported here because they did not alter conclusions [12]), we did not exclude studies of patients with prior cancer types other than CRC, we did not exclude randomization groups that included other antithrombotic agents, and we did not restrict by country.

Data Extraction and Quality Assessment

Pairs of investigators independently assessed the quality of included studies by using USPSTF criteria (23) and supplemented the quality criteria for systematic reviews with AMSTAR (A Measurement Tool to Assess Systematic Reviews) (24). Good-quality studies met the majority of criteria. Fair-quality studies did not meet or did not clearly meet all criteria for a good-quality study. We excluded outcomes from 20 articles (25–44) from the total cancer review and none from the CRC review due to poor quality (>40% attrition, >10% difference in attrition between groups, other fatal flaws, or multiple minor flaws or missing information important enough to limit confidence in the validity of results). One investigator abstracted data from included studies, and another checked the data for accuracy.

Data Synthesis and Analysis

For total cancer, we focused on results from CVD primary prevention trials included in our companion reports (13, 14) for consistency, but we included a broader set of studies in sensitivity analyses. For CRC, we analyzed CVD primary and secondary prevention studies together; we present results stratified by follow-up period after initiation of aspirin therapy (early-onset: 0 to 10 years; late-onset: 10 to 20 years; long-term: 0 to ≥20 years) because of apparent large differences in effect by time since initiation. We planned analyses of dose, frequency, duration, formulation, and recency of use a priori (45) and selected cut points empirically. For consistency with the CVD prevention review, we classified aspirin use by dose (high-dose: >325 mg/d; low-dose: ≤325 mg/d; very-low-dose: ≤100 mg/d [14]). If duration was not reported, we used mean in-trial length of follow-up to represent the intended duration of aspirin use, and the term "duration" in the text refers to this concept.

We used the Mantel–Haenszel fixed-effects model to estimate effects when combining studies (46). We explored prespecified subgroups of interest, including age, sex, race/ethnicity, baseline cancer risk (family history and other cancer risk factors), and diabetes status. We were unable to pool results because of the limited number of contributing studies. We used Stata 12.0 (StataCorp) for all statistical analyses.

Role of the Funding Source

Agency for Healthcare Research and Quality (AHRQ) staff provided oversight for the project. Liaisons from the USPSTF helped to resolve issues around the scope of the review but were not involved in the conduct of the review.

RESULTS

Description of Included Trials

We identified 20 fair- or good-quality RCTs (47–66) and 4 IPD meta-analyses (18, 19, 67, 68) of aspirin use that provided cancer outcomes (Tables 1 and 2). Nine of the RCTs were of daily aspirin use in CVD primary prevention populations (47–55), 1 of which (47) was not included in our companion reports. Two were of alternate-day aspirin use for primary CVD and cancer prevention (56, 57), and 9 were of daily aspirin use for CVD secondary prevention (58–66). Persistence of aspirin use during trials was generally high (≥85%) in the first year of the studies before decreasing to 50% to 83% after 3 to 5 years, with substantial variability across studies (12). Inclusion and exclusion criteria used in the 4 included meta-analyses are compared in Table 2.

Table 1. Brief Description of Included Studies, Limited to Trials Reporting Cancer Outcomes

Study, Year (Reference)	Population	Patients Randomly Assigned, *n*	Mean Age (Range), *y*	Female, %	Aspirin Dose, Concomitant Treatment, and Frequency	Mean Intended Treatment Duration, *y*	Cancer-Specific Key Question*
CVD primary prevention trials							
CVD and cancer outcomes reported							
Belch et al, 2008 (POPADAD) (55)	Diabetes and ABI ≤0.99	1276	60.3 (≥40)	55.9	100 mg alone or with antioxidants qd†	6.7‡	1–3
Cook et al, 2005 (56) Cook et al, 2013 (69) (WHS)§	Health professionals	39 876	54.6 (≥45)	100	100 mg alone or with vitamin E or β-carotene qod†	10.1	1–4
de Gaetano et al, 2001 (PPP) (48)	≥1 CVD risk factor	4495	64.4 (≥50)	57.5	100 mg alone or with 300 mg of vitamin E qd†	3.6	1, 2
ETDRS Investigators, 1992 (49)	Diabetes and diabetic retinopathy	3711	NR (18–70)	43.5	650 mg qd with laser photocoagulation	5	1
Fowkes et al, 2010 (AAA) (50)	ABI ≤0.95	3350	62.0 (50–75)	71.5	100 mg qd	8.2	1–3
Hansson et al, 1998 (HOT) (51)	Hypertension	19 193	61.5 (50–80)	47	75 mg qd with hypertension treatment goals†	3.8	1, 2
MRC, 1998 (TPT) (52)	High risk for IHD	2540 (5085‖)	57.5 (45–69)	0	75 mg alone or with warfarin started at 2.5 mg qd†	6.9‡	1, 3, 4
Ogawa et al, 2008 (JPAD) (53)	Diabetes	2539	64.5 (30–85)	45.4	81 or 100 mg qd	4.4‡	1, 3
Peto et al, 1988 (BMD) (54)	Physicians	5139	61.6 (NR)	0	500 mg (or 300 mg if requested) qd	6	1–4
PHS§, 1989 (57) Stürmer et al, 1998 (70)	Physicians	22 071	53.2 (40–84)	0	325 mg alone or with 50 mg of β-carotene qod†	5.0	1, 4
Only cancer outcomes reported							
DAMAD¶, 1989 (47)	Diabetes and diabetic retinopathy	314	46.7 (17–67)	35.4	330 mg tid (990 mg total per day)	3	1
CVD secondary prevention trials							
AMIS, 1980 (65)	Prior MI	4745	54.8 (30–69)	11.1	500 mg bid (1000 mg total per day)	3.2	2
Brighton et al, 2012 (ASPIRE) (62)	Prior DVT or PE	822	54.5 (≥18)	45.6	100 mg qd	3.1‡	1, 2
CDPRG, 1980 (CDPA) (58)	Prior MI	1529	NR (NR)	0	324 mg tid (972 mg total per day)	1.8	1
ESPS-2, 1997 (59)	Prior TIA or stroke	3298	66.7 (≥18)	42.2	25 mg bid (50 mg total per day)	2	1, 2
EAFT, 1993 (60)	Prior TIA or stroke	782	73 (>25)	44	300 mg qd	2.3	1
Farrell et al, 1991 (UK-TIA) (64)	Prior TIA or stroke	2449	60.3 (≥40)	27.0	300 mg qd or 600 mg bid (1200 mg total per day)	4.4‡	1, 3, 4
Juul-Möller et al, 1992 (SAPAT) (66)	Stable angina	2035	67 (30–80)	48	75 mg qd	4.2	2
PARIS, 1980 (63)	Prior MI	1216	56.3 (30–74)	13.2	324 mg tid (972 mg total per day)	3.4	1
SALT, 1991 (61)	Prior TIA or stroke or retinal artery occlusion	1363	67 (50–79)	34.2	75 mg qd	2.7	1, 3, 4

AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle–brachial index; AMIS = Aspirin Myocardial Infarction Study; ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism; bid = twice daily; BMD = British Male Doctors; CDPA = Coronary Drug Project Aspirin; CDPRG = Coronary Drug Project Research Group; CVD = cardiovascular disease; DAMAD = Dipyridamole Aspirin Microangiopathy of Diabetes; DVT = deep venous thrombosis; EAFT = European Atrial Fibrillation Trial; ESPS-2 = European Stroke Prevention Study 2; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MI = myocardial infarction; MRC = Medical Research Council; NR = not reported; PARIS = Persantine-Aspirin Reinfarction Study; PE = pulmonary embolism; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; qd = once daily; qod = every other day; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TIA = transient ischemic attack; tid = 3 times daily; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study.

* Key questions are listed in **Appendix Figure 1**. Briefly, they focus on the association between aspirin and 1) cancer-related and all-cause mortality, 2) total cancer incidence, 3) colorectal cancer mortality, and 4) colorectal cancer incidence.

† Factorial design.

‡ Median.

§ Cancer also specified as a primary outcome.

‖ Total number randomly assigned when warfarin groups included.

¶ Targeted diabetic retinopathy but excluded patients with coronary artery disease. The trial randomly assigned 475 patients to 3 groups; the group randomly assigned to aspirin plus dipyridamole (*n* = 161) was excluded from our analysis.

Table 2. Comparison of Inclusion Criteria of Included Meta-analyses

Variable	Rothwell et al, 2011 (18)			Rothwell et al, 2012 (19)		Rothwell et al, 2010 (68)	Flossmann et al, 2007 (67)
	Analysis 1*	Analysis 2	Analysis 3	Analysis 1	Analysis 2		
Inclusion criteria							
Included populations	Primary and secondary CVD prevention	Primary and secondary CVD prevention	Primary and secondary CVD prevention	Primary and secondary CVD prevention	Primary CVD prevention	Primary and secondary CVD prevention	Primary and secondary CVD prevention
Aspirin dose, *mg/d*	Any (75–1200)	Any (75–1200)	Any (75–1200)	Any (75–1200)	<300	Any (75–1200)	300–1200
Frequency	Daily	Daily	Daily	Daily	Daily	Daily	Daily
Median intended intervention duration	≥4 y	≥4 y	≥4 y	>90 d†	>90 d†	≥2.5 y	Not specified
Included studies							
Total studies; total participants; cancer outcomes	*k* = 7; *n* = 23 535; 657 cancer deaths	*k* = 3; *n* = 12 659‡; 1634 cancer deaths, CRC deaths not reported	*k* = 6; *n* = 19 824; 54 CRC deaths	*k* = 34§; *n* = 69 224; 1226 cancer deaths	*k* = 6; *n* = 35 535; 1632 incident cancer cases	*k* = 4; *n* = 14 033; 391 incident CRC cases, 240 CRC deaths	*k* = 2; *n* = 7588; 216 incident CRC cases
Primary CVD prevention studies	AAA, BMD, ETDRS, JPAD, POPADAD, TPT‖	BMD, TPT‖	AAA, BMD, JPAD, TPT‖, POPADAD	AAA, BMD, ETDRS, HOT, JPAD, POPADAD, PPP, TPT‖	AAA, HOT, JPAD¶, POPADAD, PPP, TPT‖	BMD, TPT‖	BMD
Secondary CVD prevention studies	UK-TIA	UK-TIA	UK-TIA	UK-TIA, EAFT, SALT, ESPS-2, SAPAT, 21 "small trials"	None	UK-TIA, SALT	UK-TIA

AAA = Aspirin for Asymptomatic Atherosclerosis; BMD = British Male Doctors; CRC = colorectal cancer; CVD = cardiovascular disease; EAFT = European Atrial Fibrillation Trial; ESPS-2 = European Stroke Prevention Study 2; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack.
* In trial-level meta-analyses, data from 1 additional secondary prevention trial (SAPAT) was also included.
† Minimum intended intervention duration.
‡ Also conducted subanalyses on 10 502 patients who had ≥5 y of treatment.
§ Also analyzed nonvascular death among 77 549 participants in 51 trials.
‖ Includes warfarin groups.
¶ Substituted cancer mortality for nonfatal cancer.

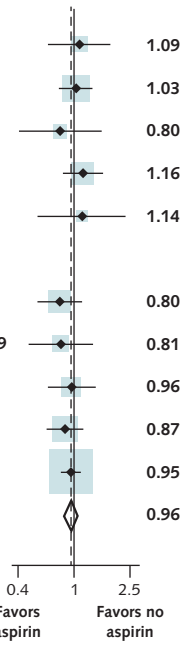
For CRC, most outcomes came from 3 IPD meta-analyses by Rothwell and colleagues (18, 67, 68) of daily aspirin use in trials of either primary or secondary CVD prevention (**Table 2**). Rothwell and colleagues selected trials of daily aspirin use on the basis of availability of follow-up data, scheduled duration of aspirin use, and population size, with specific criteria varying across the analyses. More than three quarters of trial participants were male. Where possible, Rothwell and colleagues linked study populations with national registries to obtain CRC incidence and mortality data. Posttrial persistence information was not available, but approximately 50% to 75% of participants continued to use aspirin 5 years into follow-up. Results from the WHS (Women's Health Study) (56, 69) and the PHS (Physicians' Health Study) (70)—studies of alternate-day aspirin use in U.S. health care workers, which were not included in Rothwell and colleagues' analyses—were reported in separate publications (**Table 1**).

Total Cancer Mortality

Ten CVD primary prevention trials included in our companion report (13), ranging in mean duration from 3.6 to 10.1 years and with 1513 total cancer deaths among 103 787 participants, showed that cancer deaths were similar among participants assigned to aspirin and those who were not (relative risk [RR], 0.96 [95% CI, 0.87 to 1.06]) (**Figure 1**) (48–57). The results were similar in sensitivity analyses restricted to trials of daily use, lower dosage, or longer duration or when additional trials conducted primarily in secondary prevention populations were added (**Appendix Table** and **Appendix Figure 2**, available at www.annals.org). An IPD meta-analysis (18) of 7 primary and secondary prevention trials of daily aspirin use with median duration of at least 4 years reported that aspirin reduced total cancer mortality by 18% (hazard ratio [HR], 0.82 [CI, 0.70 to 0.95]), with effects apparent mainly after 5 years. The analysis excluded 2 of the 10 primary prevention trials that we included (both large, good-quality U.S. trials of alternate-day aspirin use) (56, 57) and included 3 trials of high-dose aspirin (500 to 1200 mg/d) (49, 54, 64). When we applied all trial inclusion and exclusion criteria from that analysis to our included trials (thereby excluding 80% of persons in primary prevention trials), we found a similar 17% reduction in can-

Figure 1. Forest plot of aspirin use and cancer mortality from CVD primary prevention trials.

Study, Year (Reference)	Mean or Median Treatment Duration, *y*	Dose, *mg/d*	Population	RR (95% CI)	Events, *n/N* Aspirin	Events, *n/N* No Aspirin
de Gaetano et al, 2001 (PPP) (48)	3.6	100	Men and women with ≥1 CVD risk factor	1.09 (0.66–1.80)	31/2226	29/2269
Hansson et al, 1998 (HOT) (51)	3.8	75	Men and women with hypertension	1.03 (0.79–1.34)	108/9399	105/9391
Ogawa et al, 2008 (JPAD) (53)	4.4	81 or 100	Men and women with diabetes	0.80 (0.41–1.57)	15/1262	19/1277
PHS, 1989 (57)	5	162.5	Male physicians	1.16 (0.84–1.60)	79/11 037	68/11 034
ETDRS, 1992 (49)	5	650	Men and women with diabetes and diabetic retinopathy	1.14 (0.56–2.33)	16/1856	14/1855
Peto et al, 1988 (BMD) (54)	6	500	Male physicians	0.80 (0.56–1.14)	75/3429	47/1710
Belch et al, 2008 (POPADAD) (55)	6.7	100	Men and women with diabetes and ABI ≤0.99	0.81 (0.48–1.35)	25/638	31/638
MRC, 1998 (TPT) (52)	6.8	75	Men at high risk for IHD	0.96 (0.66–1.42)	49/1268	51/1272
Fowkes et al, 2010 (AAA) (50)	8.2	100	Men and women with ABI ≤0.95	0.87 (0.64–1.16)	78/1675	90/1675
Cook et al, 2005 (WHS) (56)	10.1	50	Female health professionals	0.95 (0.81–1.12)	284/19 934	299/19 942
Overall (I^2 = 0.0%, P = 0.89)				0.96 (0.87–1.06)	760/52 724	753/51 063



WHS and PHS are alternate-day dose studies (100 mg every other day and 325 mg every other day, respectively); TPT data do not include the warfarin groups. We used data from the individual-patient data meta-analysis (if data were not reported in the study or if they differed from those reported in the study) as follows: for BMD and AAA, data from Rothwell and colleagues (18); for PPP and HOT, data from Rothwell and colleagues (19); and for PHS, data from Seshasai and colleagues (71). Differences from point estimates or 95% CIs reported in studies are due to use of different statistical programs and are minor and of no clinical or statistical significance. AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle–brachial index; BMD = British Male Doctors; CVD = cardiovascular disease; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MRC = Medical Research Council; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study.

cer mortality (RR, 0.83 [CI, 0.70 to 0.98]) (Appendix Table).

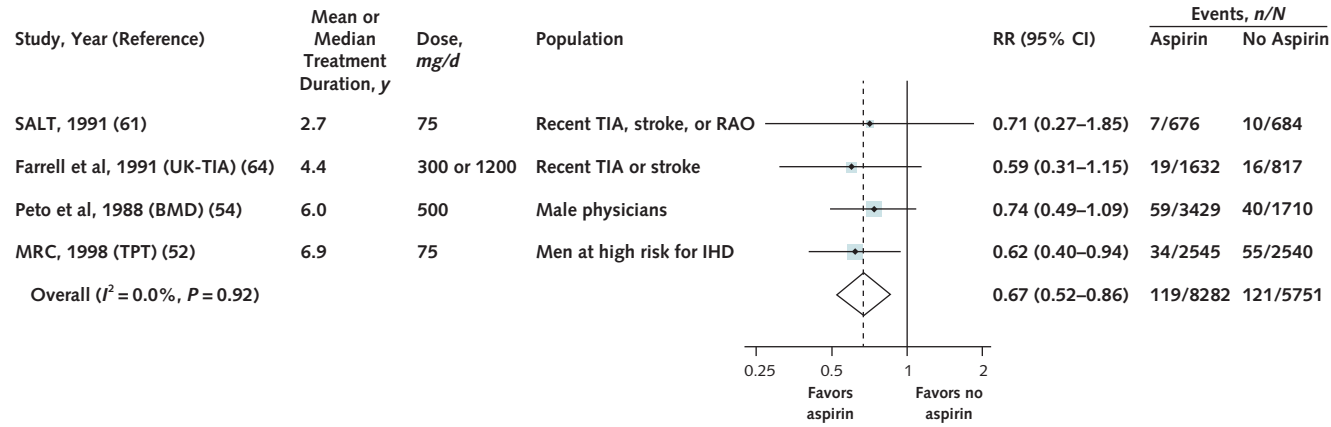
In another meta-analysis of primary and secondary prevention trials testing daily aspirin use for more than 90 days among 69 224 participants (19), a priori–stratified analysis showed no differences in cancer deaths until at least 5 years, except for an effect during the first 3 years among trials of high-dose aspirin. Various analyses of deaths from different cancer types in both meta-analyses (18, 19) suggested reductions in solid gastrointestinal cancer and adenocarcinomas after at least 5 years of aspirin use but were limited by relatively few site-specific cancer deaths and excluded large trials of alternate-day aspirin use (56, 57).

Among 39 876 women in WHS, the cumulative risk for cancer death 17.5 years after randomization (approximately 4%) was similar between groups (HR, 0.97 [CI, 0.88 to 1.07]) (69). In an IPD meta-analysis (18) of 12 659 participants (95% male) in 3 primary or secondary prevention trials (52, 54, 64) with median durations of aspirin use of 4 to 6.8 years, longer treatment duration was statistically significantly related to decreased mortality risk 20 years after randomization for nonhematologic cancer (P for interaction = 0.01), with no benefit for less than 5 years of intended use and the greatest benefit with at least 7.5 years of use. Only 1 of these trials (a secondary prevention trial) included women (64). Among the 83% of participants with at least 5 years of intended treatment, those allocated to aspirin had 22% fewer cancer deaths than control participants from 0 to 20 years (HR, 0.78 [CI, 0.70 to 0.87]). No data were reported to assess whether groups remained comparable at baseline after exclusion of participants (17%) who had less than 5 years of intended treatment. Specific cancer mortality findings were limited by power and methodological and clinical heterogeneity; however, exploratory analyses suggested that minimum treatment duration (5 to 10 years) and time until mortality reduction (5 to 20 years) may vary across cancer types.

Total Cancer Incidence

Among 6 primary prevention trials (Table 1) (48, 50, 51, 54–56) ranging in mean duration from 3.6 to 10.1 years, with 4294 incident cancer cases among 72 926 participants, end-of-trial cancer incidence was similar between aspirin and control groups (RR, 0.98 [CI, 0.93 to 1.04]) (Appendix Figure 3, available at www.annals.org). Sensitivity analyses that were restricted to trials of daily use or longer duration or that included

Figure 2. Forest plot of aspirin use and long-term (0 to ≥20 y) risk for CRC death.



All raw data are from the individual-patient data meta-analysis by Rothwell and colleagues (68). Differences from point estimates or 95% CIs reported in studies are due to use of different statistical programs and are minor and of no clinical or statistical significance. BMD = British Male Doctors; CRC = colorectal cancer; IHD = ischemic heart disease; MRC = Medical Research Council; RAO = retinal artery occlusion; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack.

secondary prevention trials (59, 62, 65, 66) yielded similar results (**Appendix Table** and **Appendix Figure 4**, available at www.annals.org). We observed a marginally statistically significant reduction in cancer incidence only when we restricted our analysis to trials of daily aspirin use with a median intended duration of at least 4 years and also included secondary prevention studies (66) (4 trials; *n* = 11 800; RR, 0.86 [CI, 0.74 to 0.99]).

In a time-to-event IPD meta-analysis (19) of 6 trials of daily low-dose aspirin in primary prevention populations (48, 50–53, 55), cancer incidence (with fatal and nonfatal cancer cases combined) was reduced, with borderline statistical significance (HR, 0.88 [CI, 0.80 to 0.98]), beginning 3 to 4 years after randomization, with statistically significantly greater effects as follow-up duration increased beyond 3 years (*P* for interaction with duration = 0.04) (19). We found no statistically significant effect of aspirin on cancer incidence among this set of trials after a priori exclusion of studies reporting fatal cancer only (53) and warfarin co-treatment (52) (RR, 0.92 [CI, 0.82 to 1.02]) (48, 50, 51, 55).

Overall cancer incidence (5071 cases, excluding nonmelanoma skin cancer) was not reduced among aspirin users in age-adjusted analyses (HR, 0.97 [CI, 0.92 to 1.03]) after a median of 17.5 years in WHS (69), regardless of whether data were analyzed over the entire follow-up or were stratified by within-trial or posttrial period. Cancer incidence was not reduced at any specific non-CRC site (including a priori secondary study outcomes of breast or lung cancer) cumulatively, during the trial, or after the trial. However, most other cancer types were relatively uncommon, and analyses therefore lacked power. Even when grouped by site, only gastrointestinal cancer incidence was reduced in the posttrial follow-up period, whereas incidence of urinary tract, respiratory tract, reproductive tract, and hematologic cancer was unaffected.

CRC Mortality

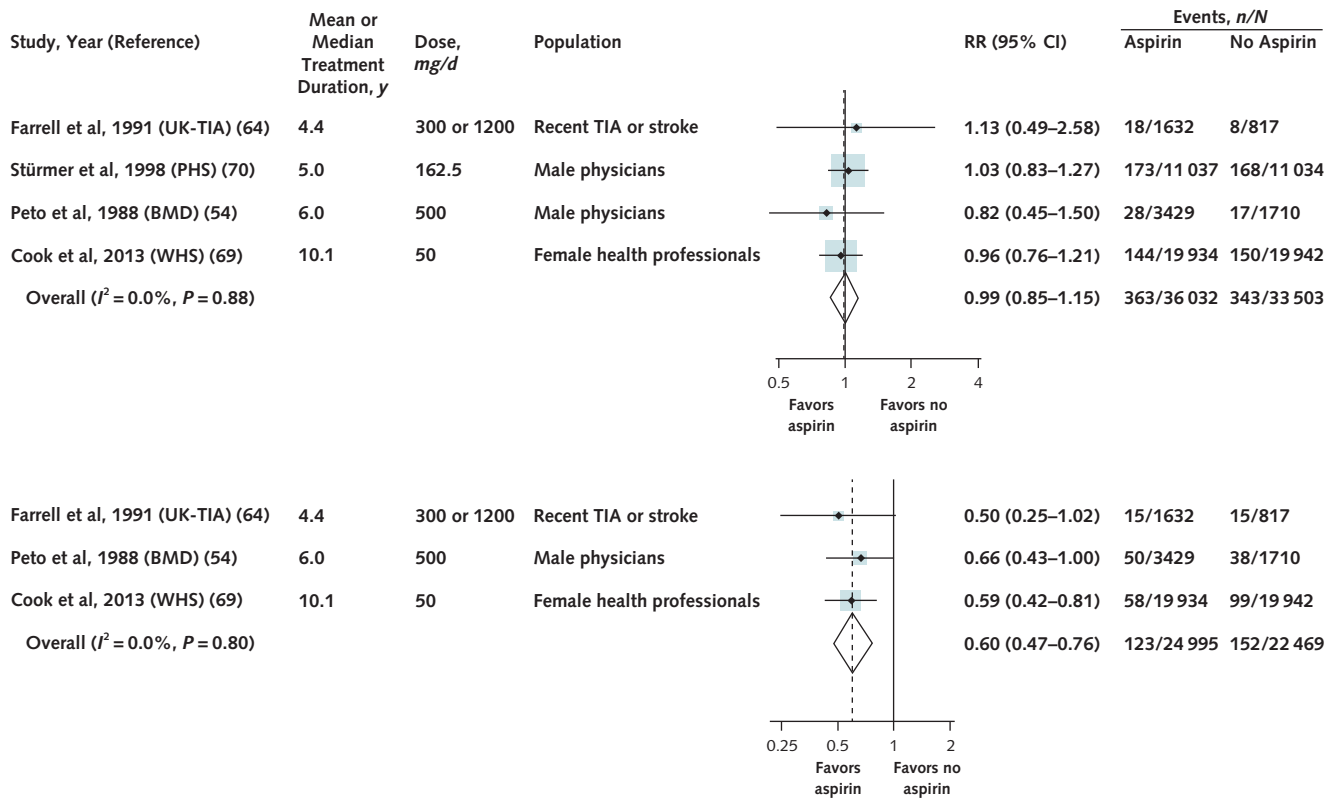
Rothwell and colleagues reported data on long-term CRC mortality (median follow-up, 18.3 years) using pooled data from 2 primary (52, 54) and 2 secondary (61, 64) CVD prevention trials (*n* = 14 033) (68). Long-term cumulative risk for CRC death (0 to ≥20 years) was reduced among patients assigned to take 75 to 1200 mg of aspirin per day for at least 1 year (median intended duration, ≥2.5 years) compared with control participants (RR, 0.67 [CI, 0.52 to 0.86]) (**Figure 2**) (68). Based on data from 3 of these trials with at least 5 years of scheduled daily treatment (52, 54, 64), aspirin reduced CRC mortality beginning 10 to 20 years after randomization (HR, 0.51 [CI, 0.35 to 0.74]) but not before (HR, 0.79 [CI, 0.49 to 1.26]) (18).

In another IPD meta-analysis (18), Rothwell and colleagues used data from 6 trials of primary or secondary CVD prevention with a median intended duration of at least 4 years (50, 52–55, 64) (*n* = 19 824) to examine the in-trial effect of 75 to 1200 mg of aspirin per day (**Table 2**). They did not report a statistically significant effect on CRC mortality during the first 5 years after randomization (HR, 0.78 [CI, 0.39 to 1.56]), but they did find a borderline statistically significant effect after at least 5 years of in-trial follow-up (HR, 0.41 [CI, 0.17 to 1.00]) (18).

Of the 2 CVD primary prevention studies that also had cancer as an a priori outcome, 1 (PHS) did not report on CRC mortality. The WHS (*n* = 39 876) found no effect on CRC mortality with very-low-dose aspirin taken on alternate days during the first 10 years of follow-up (data not shown) but did not report on late or long-term risk for CRC death (56).

Evidence on dose was limited to 4 trials of daily aspirin use for primary (52, 54) or secondary (61, 64) prevention of CVD (*n* = 14 033). Doses ranged from 75

Figure 3. Forest plots of aspirin use and CRC incidence.



Top. Early risk (0 to 12 y). **Bottom.** Late risk (10 to 19 y). WHS and PHS are alternate-day dose studies (100 mg every other day and 325 mg every other day, respectively). Raw data for the BMD and UK-TIA studies are from the individual-patient data meta-analysis by Flossmann and colleagues (67). Differences from point estimates or 95% CIs reported in studies are due to use of different statistical programs and are minor and of no clinical or statistical significance. BMD = British Male Doctors; CRC = colorectal cancer; PHS = Physicians' Health Study; RR = relative risk; TIA = transient ischemic attack; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study.

to 1200 mg/d. All included trials randomly assigned patients to daily aspirin use and could not, therefore, compare daily versus alternate-day use. Analyses did not clearly suggest an effect of the dose (12). An IPD meta-analysis (68) of the same trials reported a statistically significant association between longer scheduled duration of daily aspirin use and greater CRC mortality reduction ($P = 0.04$) (52, 54, 61, 64) but did not report a point estimate. Among persons randomly assigned to 75 to 300 mg of aspirin per day, the risk reduction was slightly greater when those with a scheduled duration less than 5 years (37%) were excluded (RR, 0.48 [CI, 0.30 to 0.77]) than when all participants were analyzed (RR, 0.61 [CI, 0.43 to 0.87]). This finding indirectly suggested a possible association between longer duration of aspirin use and greater risk reduction.

CRC Incidence

Data on CRC incidence came from 2 IPD meta-analyses by Rothwell and colleagues (67, 68) and separate reports from the PHS (70) and the WHS (69). Based on 3 primary (54, 69, 70) and 1 secondary (64) CVD prevention trials, there was no effect on CRC risk within approximately 10 years of initiation of aspirin therapy ($n = 69\,535$) (RR, 0.99 [CI, 0.85 to 1.15]) (**Figure 3**, *top*). Our pooled analyses of 2 primary and 1 secondary CVD prevention trials ($n = 47\,464$) suggested that aspirin therapy reduced the risk for CRC incidence by about 40% between approximately 10 and 19 years after initiation (54, 64, 67, 69) (RR, 0.60 [CI, 0.47 to 0.76]) (**Figure 3**, *bottom*). An IPD meta-analysis of 4 CVD primary and secondary prevention trials (68) suggested that aspirin reduced long-term (0 to ≥20 years) cumulative risk for CRC (HR, 0.76 [CI, 0.63 to 0.94]) (52, 54, 61, 64). The estimate in WHS after a median of 17.5 years was similar (HR, 0.80 [CI, 0.67 to 0.97]) (69).

None of the trials directly compared aspirin doses. However, an IPD meta-analysis that conducted preplanned analyses of aspirin dose observed similar effects on CRC incidence overall and when the analyses were restricted to patients randomly assigned to 75 or 300 mg/d (results not shown) (68). No trial directly compared the effect of daily versus alternate-day aspirin use on CRC incidence. We found few data on the effect of treatment duration (67, 68); our findings are described in detail in the full report (12). Briefly, the point estimates were similar for analyses that included all scheduled durations of use and those that were restricted to persons with scheduled durations of at least 5 years. These findings indirectly suggested no difference in effect by duration of use. However, in 1 of the

included RCTs, scheduled duration varied from 1 to 7 years and the effect of aspirin was greater with longer scheduled durations of use (*P* for interaction = 0.009 with duration as a continuous variable and 0.004 with duration dichotomized at 5 years) (67).

Subgroup Differences

Limited data did not clearly suggest variation in the effect of aspirin use on total cancer or CRC mortality or incidence by age, sex, or other patient characteristics. Details are described in the full reports (12, 13).

DISCUSSION

On the basis of 10 CVD primary prevention trials, we found no statistically significant reduction in total cancer mortality (RR, 0.96 [CI, 0.87 to 1.06]). Others have found no established protective effect for aspirin on total cancer mortality in the CVD primary prevention population in similar analyses (71). In 4 trials in primary and secondary CVD prevention populations, we found that aspirin reduced CRC mortality over approximately 20 years of follow-up (RR, 0.67 [CI, 0.52 to 0.86]). Although the estimate lacked precision, aspirin appeared to reduce CRC incidence after 5 years of follow-up. A large U.S. trial of women taking very-low-dose, alternate-day aspirin for primary prevention of CVD and cancer reported no total cancer mortality effect after 10.1 years of treatment and 17.5 years of follow-up, but the trial did not report results for CRC mortality separately.

Effects of aspirin therapy on total cancer incidence within 10 years of initiation were generally small (2% reduction) and not statistically significant, even when analyses were restricted to studies with daily dosing and median scheduled treatment of at least 4 years. Only the analysis that included both primary and secondary CVD prevention populations assigned to daily aspirin (75 to 500 mg) for at least 4 years showed a statistically significant reduction in cancer incidence after 4.2 to 8.2 years. Longer-term follow-up data were available on CRC incidence in 3 studies, including WHS, and suggested a 40% reduction in risk approximately 10 to 19 years after randomization. A pooled analysis of these studies plus one other showed no effect during the first 10 years after randomization. Over a 20-year period, the cumulative effect was an approximately 20% reduction in CRC incidence in persons assigned to take aspirin; however, the upper CI limits were near 1.0 in both Rothwell and colleagues' analysis and the WHS analysis. Follow-up in PHS was limited to a mean of 12 years and therefore could not contribute to analyses of late and long-term effects. Cohort studies presented some evidence for reduced CRC risk with increases in the number of aspirin tablets per week and duration of use but added little information on timing of effect or dose; results of these studies are presented in more detail in the full report (12).

Data were too limited to generate consistent or definitive results for any specific type of cancer beyond CRC. Nonetheless, exploratory analyses suggested that adenocarcinomas and/or solid cancer of gastrointestinal origin may respond to aspirin chemoprevention. Additional data from applicable populations using low-dose aspirin will likely clarify and extend these findings.

Our findings on aspirin's effect on total cancer differed from those in a widely reported meta-analysis that found a statistically significant 21% reduction (CI, 8% to 32%) in cancer mortality (18). However, this meta-analysis used a different set of studies from the ones in our analysis of CVD primary prevention trials; it included trials of CVD secondary prevention but restricted analyses to daily aspirin use for a median treatment duration of at least 4 years (18). Similarly, other analyses of cancer outcomes from the same group have often relied on subsets of trials that could provide longer-term follow-up (13). However, these analyses also differ in terms of populations and interventions from the body of CVD primary prevention trials, which may explain differences from our results.

Cuzick and colleagues used a modeling approach to conclude that the benefits of initiating therapy with at least 5 years of 75 to 325 mg of aspirin per day at ages 50 to 65 years outweighed the risks (72). Model inputs (RRs) were derived from recent reviews of RCTs and observational studies. The comparability of our 2 reviews is limited given that Cuzick and colleagues did not present an overall estimate for total cancer and we do not present estimates for individual cancer types other than CRC because they were not frequently reported. Relative risk estimates for aspirin use and CRC incidence and mortality differ from ours in part because Cuzick and colleagues focused on daily use (that is, they did not include WHS or PHS) and included observational studies.

In general, our findings on aspirin use and CRC incidence and mortality are similar to those previously reported (73). However, in an article that did not meet the inclusion criteria for our CRC review, Rothwell and colleagues reported that aspirin therapy may reduce CRC mortality within 10 years of initiation (19). Reviews of cohort studies have generally reported stronger protective associations between aspirin and CRC incidence than RCTs (74–76).

Several limitations in the available data affected our review. Most data were collected post hoc as part of follow-up studies of CVD trials (18, 19, 67, 68). Clinical and methodological heterogeneity across studies complicated the interpretation of subsets of trials with the longer-term data needed to study aspirin's effect on cancer. Limited data were available to assess cancer-specific effects (18, 56) and subgroup differences. Data on cancer risk factors, such as family history, were generally unavailable. We also could not address questions about how long the effects of aspirin may continue after the end of treatment.

Because aspirin is one of the most extensively studied medications, establishing appropriate exclusion criteria was essential to managing the scope of this review. Thus, we focused on RCTs and IPD meta-analyses to enhance validity. In addition, for total cancer outcomes, we focused on CVD primary prevention trials to

ensure applicability to the clinical context of primary prevention of both CVD and cancer. Observational studies may provide information on subgroup effects once efficacy is established, particularly for individual cancer types. We considered prospective cohort studies in our review of aspirin use and CRC incidence and mortality and, despite imprecision of exposure data, findings were generally consistent with trial data (12).

Longer-term follow-up from trials could provide important information on the effects of aspirin on cancer-specific sites and cancer overall, particularly with respect to the size and timing of chemopreventive benefits, dose–response relationships, effect of duration of use, and differences across patient subgroups. The primary data for aspirin's effects on a range of health outcomes have not changed substantially over the past several years, but the field is poised to provide additional data in the near future. Several large trials are in progress (77–80), and future syntheses of existing and emerging evidence should be forthcoming from the NoVA (Non-Vascular outcomes on Aspirin) Collaboration, which aims to collate all data from previous and ongoing trials of aspirin to provide data on short- and long-term effects that are as complete as possible (81). Observational studies or trials focused on subgroups defined by genotype, lifestyle factors, or biomarkers may also provide important data to understand which subgroups are more or less likely to benefit from aspirin use (82–86).

In conclusion, in CVD primary prevention populations taking low-dose aspirin for chemoprevention, a beneficial effect on total cancer mortality or incidence is not clearly established. Data are limited for effects on specific cancer types, except perhaps CRC. Evidence from primary and secondary prevention studies suggests that aspirin therapy reduces the risk for CRC incidence and perhaps mortality, with an apparent preventive effect beginning approximately 10 years after initiation.

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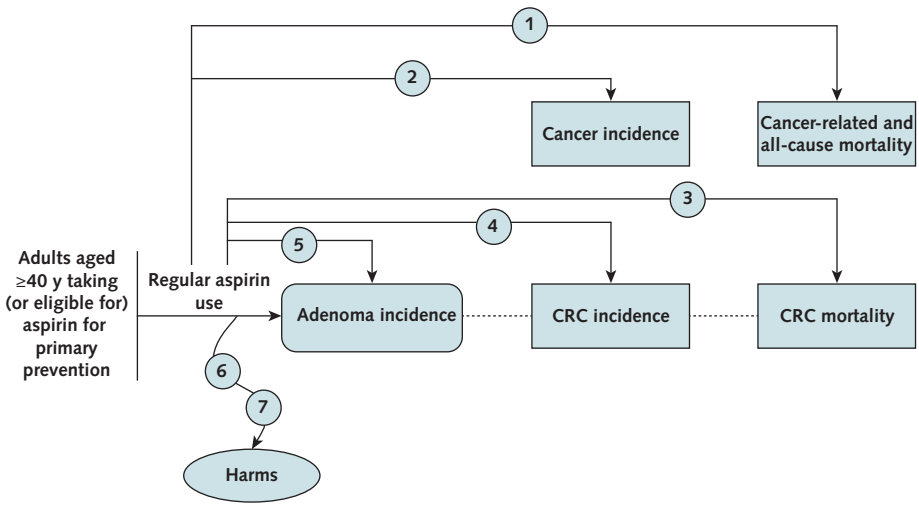
Appendix Figure 1. Analytic framework.



Key questions:

1. Does regular aspirin use reduce total cancer mortality or all-cause mortality in adults taking (or eligible for) aspirin for primary prevention?
   a. Does the effect of aspirin vary by a priori subgroups: age, sex, race/ethnicity, baseline cancer risk*, and comorbidities†?
   b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, and recency of use)?
2. Does regular aspirin use reduce the incidence of cancers in adults taking (or eligible for) aspirin for primary prevention?
   a. Does the effect of aspirin vary by a priori subgroups: age, sex, race/ethnicity, baseline cancer risk*, and comorbidities†?
   b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, and recency of use)?
3. Does regular aspirin use reduce colorectal cancer mortality in adults without a history of colorectal cancer, familial adenomatous polyposis (FAP), or Lynch syndrome?
   a. Does the effect of aspirin vary by a priori subgroups: age, sex, race/ethnicity, baseline cancer risk*, and comorbidities†?
   b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, and recency of use)?
4. Does regular aspirin use reduce the incidence of colorectal cancer in adults without a history of colorectal cancer, familial adenomatous polyposis (FAP), or Lynch syndrome?
   a. Does the effect of aspirin vary by a priori subgroups: age, sex, race/ethnicity, baseline cancer risk*, and comorbidities†?
   b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, and recency of use)?
5. Does regular aspirin use reduce the incidence of colorectal adenoma in adults without a history of colorectal cancer, familial adenomatous polyposis (FAP), or Lynch syndrome?
   a. Does the effect of aspirin vary by a priori subgroups: age, sex, race/ethnicity, baseline cancer risk*, and comorbidities†?
   b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, and recency of use)?
6. What are the serious harms of regular aspirin use for the primary prevention of cancer (i.e., at the dosage and duration required to achieve a preventive health effect) in adults appropriate for aspirin chemoprevention?
   a. Does the effect of aspirin vary by a priori subgroups: age, sex, race/ethnicity, baseline cancer risk*, comorbidities†, and concomitant medication use‡?
   b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, and recency of use)?
7. What are the serious harms of regular aspirin use for the prevention of colorectal cancer (i.e., at the dosage and duration required to achieve a preventive health effect) in adults without a history of colorectal cancer, familial adenomatous polyposis (FAP), or Lynch syndrome?
   a. Does the effect of aspirin vary by a priori subgroups: age, sex, race/ethnicity, baseline cancer risk*, comorbidities†, and concomitant medication use‡?
   b. Does the effect of aspirin vary by delivery of intervention (e.g., dose, frequency, duration, formulation, and recency of use)?

See also www.uspreventiveservicestaskforce.org/Page/Document/final-research-plan-aspirin-to-prevent-cancer/aspirin-to-prevent-cardiovascular-disease-and-cancer. CRC = colorectal cancer.

* Includes family history and other potential risk factors, if specified in the literature.

† We proposed the following comorbidities, which are prevalent and/or may be affected by aspirin use in terms of benefits or harms: diabetes, liver disease, ulcer disease, and previous gastrointestinal bleeding.

‡ Medications include nonaspirin, nonsteroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitors.

Appendix Table. Sensitivity Analyses for Aspirin and Cancer Mortality and Incidence

Analysis	CVD Prevention Level	Mean Follow-up	Dose Schedule	Studies, *k*	Patients, *n*	Pooled RR (95% CI)	Included CVD Primary Prevention Trials (CVD Secondary Prevention Trials)
Cancer mortality							
Main analysis	Primary	≥1 y	Any	10	103 787	0.96 (0.87–1.06)	AAA, BMD*, ETDRS*, HOT, JPAD, PHS, POPADAD, PPP, TPT, WHS
Sensitivity analyses	Primary and secondary	≥1 y	Any	18	116 484	0.93 (0.85–1.03)	AAA, BMD*, ETDRS*,HOT, JPAD, PHS, POPADAD, PPP, TPT, WHS (AMIS, ASPIRE, CDPA*, DAMAD*†, EAFT, ESPS-2, PARIS*, SALT, SAPAT, UK-TIA*)
	Primary	≥1 y	Daily	8	41 840	0.93 (0.81–1.07)	AAA, BMD*, ETDRS*, HOT, JPAD, POPADAD, PPP, TPT
	Primary	≥4 y	Any	8	80 502	0.94 (0.84–1.05)	AAA, BMD*, ETDRS*, JPAD, PHS, POPADAD, TPT, WHS
	Primary	≥4 y	Daily	6	18 555	0.87 (0.73–1.03)	AAA, BMD*, ETDRS*, JPAD, POPADAD, TPT
	Primary and secondary	≥4 y	Daily	7	20 990	0.83 (0.70–0.98)	AAA, BMD*, ETDRS*, JPAD, POPADAD, TPT (UK-TIA*)
	Primary	≥1 y	≤325 mg/d	8	94 937	0.97 (0.87–1.08)	AAA, HOT, JPAD, PHS, POPADAD, PPP, TPT, WHS
	Primary	≥1 y	≤100 mg/d	7	72 866	0.95 (0.85–1.06)	AAA, HOT, JPAD, POPADAD, PPP, TPT, WHS
Rothwell 2011 (18)‡	Primary and secondary	≥4 y	Daily	7	23 535	HR, 0.82 (0.70–0.95) ≤5 y: HR, 0.86 (0.71–1.04) >5 y: HR, 0.66 (0.50–0.87)	AAA, BMD*, ETDRS*, JPAD, POPADAD, TPT§ (UK-TIA*)
Rothwell 2012 (19)‡	Primary and secondary	>90 d	Daily	34	69 224	OR, 0.85 (0.76–0.96) <3 y: OR, 0.90 (0.76–1.06) 3–4.9 y: OR, 0.93 (0.75–1.16) 5 y: OR, 0.63 (0.49–0.82)	AAA, BMD*, ETDRS*, HOT, JPAD, POPADAD, PPP, TPT§ (UK-TIA*, EAFT, SALT, ESPS-2, SAPAT, 21 "small trials")
Cancer incidence							
Main analysis	Primary	≥1 y	Any	6	72 926	0.98 (0.93–1.04)	AAA, BMD*, HOT, POPADAD, PPP, WHS
Sensitivity analyses	Primary and secondary	≥1 y	Any	10	83 605	0.98 (0.93–1.04)	AAA, BMD*, HOT, POPADAD, PPP, WHS (AMIS, ASPIRE, ESPS-2, SAPAT)
	Primary	≥1 y	Daily	5	33 050	0.93 (0.84–1.03)	AAA, BMD*, HOT, POPADAD, PPP
	Primary	≥4 y	Any	4	49 641	0.98 (0.92–1.05)	AAA, BMD*, POPADAD, WHS
	Primary	≥4 y	Daily	3	9765	0.88 (0.75–1.02)	AAA, BMD*, POPADAD
	Primary and secondary	≥4 y	Daily	4	11 800	0.86 (0.74–0.99)	AAA, BMD*, POPADAD (SAPAT)
	Primary	≥1 y	≤325 mg/d	5	67 787	0.98 (0.93–1.04)	AAA, HOT, POPADAD, PPP, WHS
	Primary	≥1 y	≤100 mg/d	5	67 787	0.98 (0.93–1.04)	AAA, HOT, POPADAD, PPP, WHS
Rothwell 2012‖ (19)	Primary	>90 d	Daily¶	6	35 535	HR, 0.88 (0.80–0.98) 0–2.9 y: HR, 1.00 (0.88–1.15) 3–4.9 y: HR, 0.81 (0.67–0.98) ≥5 y: HR, 0.71 (0.57–0.89) ≥5 y (scheduled treatment duration): HR, 0.81 (0.70–0.93) 0–2.9 y: OR, 1.01 (0.88–1.15) ≥3.0 y: OR, 0.76 (0.66–0.88)	AAA, HOT, JPAD, PPP, POPADAD, TPT§
	Primary and secondary	>90 d	Daily	32	65 973	0–3 y: OR, 0.91 (0.81–1.02) >3 y: OR, 0.79 (0.70–0.90)	AAA, BMD*, ETDRS*, HOT, JPAD, POPADAD, PPP, TPT§ (UK-TIA*, EAFT, SALT, ESPS-2, SAPAT, 21 "small trials")

AAA = Aspirin for Asymptomatic Atherosclerosis; AMIS = Aspirin Myocardial Infarction Study; ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism; BMD = British Male Doctors; CDPA = Coronary Drug Project Aspirin; CVD = cardiovascular disease; DAMAD = Dipyridamole Aspirin Microangiopathy of Diabetes; EAFT = European Atrial Fibrillation Trial; ESPS-2 = European Stroke Prevention Study 2; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment; HR = hazard ratio; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; OR = odds ratio; PARIS = Persantine-Aspirin Reinfarction Study; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study.

* Trials testing aspirin dose ≥325 mg/d.

† We considered participants in DAMAD to be a CVD primary prevention population but did not include the study in the main analysis because it did not report CVD outcomes and is not included in the companion CVD report.

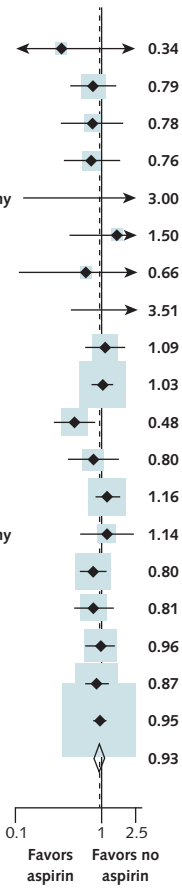
‡ Did not include WHS, PHS, CDPA, and ASPIRE.

§ Includes warfarin groups.

‖ Overall cancer incidence, with fatal and nonfatal cancer combined.

¶ Analyses listed were not restricted by dose except for one, which was limited to trials with aspirin dose <300 mg/d.

Appendix Figure 2. Forest plot of aspirin use and cancer mortality from CVD primary and secondary prevention trials.



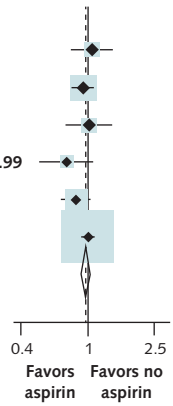
Study, Year (Reference)	Mean or Median Treatment Duration, *y*	Dose, *mg/d*	Population	RR (95% CI)	Events, *n/N*	
					Aspirin	No Aspirin
CDPRG, 1980 (CDPA) (58)	1.8	972	Men with prior MI	0.34 (0.04–3.25)	1/758	3/771
ESPS-2, 1997 (59)	2	50	Men and women with prior TIA or stroke	0.79 (0.44–1.44)	19/1649	24/1649
EAFT, 1993 (60)	2.3	300	Men and women with prior TIA or stroke	0.78 (0.34–1.78)	10/404	12/378
SALT, 1991 (61)	2.7	75	Men and women with prior TIA or stroke	0.76 (0.36–1.59)	12/676	16/684
DAMAD, 1989 (47)	3	990	Men and women with diabetes and diabetic retinopathy	3.00 (0.12–73.08)	1.5/158	0.5/158
Brighton et al, 2012 (ASPIRE) (62)	3.1	100	Men and women with prior DVT or PE	1.50 (0.43–5.28)	6/411	4/411
Logan et al, 2008 (ukCAP) (88)	3.4	300	Men and women with prior colorectal adenoma	0.66 (0.11–3.93)	2/472	3/467
PARIS, 1980 (63)	3.4	972	Men and women with prior MI	3.51 (0.43–28.42)	7/810	1/406
de Gaetano et al, 2001 (PPP) (48)	3.6	100	Men and women with ≥1 CVD risk factor	1.09 (0.66–1.80)	31/2226	29/2269
Hansson et al, 1998 (HOT) (51)	3.8	75	Men and women with hypertension	1.03 (0.79–1.34)	108/9399	105/9391
Farrell et al, 1991 (UK-TIA) (64)	4	300; 1200*	Men and women with prior TIA or stroke	0.48 (0.28–0.84)	24/1621	25/814
Ogawa et al, 2008 (JPAD) (53)	4.4	81 or 100	Men and women with diabetes	0.80 (0.41–1.57)	15/1262	19/1277
PHS, 1989 (57)	5	162.5	Male physicians	1.16 (0.84–1.60)	79/11 037	68/11 034
ETDRS, 1992 (49)	5	650	Men and women with diabetes and diabetic retinopathy	1.14 (0.56–2.33)	16/1856	14/1855
Peto et al, 1988 (BMD) (54)	6	500	Male physicians	0.80 (0.56–1.14)	75/3429	47/1710
Belch et al, 2008 (POPADAD) (55)	6.7	100	Men and women with diabetes and ABI ≤0.99	0.81 (0.48–1.35)	25/638	31/638
MRC, 1998 (TPT) (52)	6.8	75	Men at high risk for IHD	0.96 (0.66–1.42)	49/1268	51/1272
Fowkes et al, 2010 (AAA) (50)	8.2	100	Men and women with ABI ≤0.95	0.87 (0.64–1.16)	78/1675	90/1675
Cook et al, 2005 (WHS) (56)	10.1	50	Female health professionals	0.95 (0.81–1.12)	284/19 934	299/19 942
Overall (I^2 = 0.0%, P = 0.71)				0.93 (0.85–1.03)	842.5/59 683	841.5/56 801

WHS and PHS are alternate-day dose studies (100 mg every other day and 325 mg every other day, respectively). We used a continuity correction factor of 0.5 if a group reported no events. We used data from the individual-patient data meta-analysis (if data were not reported in the study or if they differed from those reported in the study) as follows: for BMD and AAA, data from Rothwell and colleagues (18); for PPP, ESPS-2, EAFT, UK-TIA, HOT, and SALT, data from Rothwell and colleagues (19); and for PHS, data from Seshasai and colleagues (71). Differences from point estimates or 95% CIs reported in studies are due to use of different statistical programs and are minor and of no clinical or statistical significance. AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle–brachial index; ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism; BMD = British Male Doctors; CDPA = Coronary Drug Project Aspirin; CDPRG = Coronary Drug Project Research Group; CVD = cardiovascular disease; DAMAD = Dipyridamole Aspirin Microangiopathy of Diabetes; DVT = deep venous thrombosis; EAFT = European Atrial Fibrillation Trial; ESPS-2 = European Stroke Prevention Study 2; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; MI = myocardial infarction; MRC = Medical Research Council; PARIS = Persantine-Aspirin Reinfarction Study; PE = pulmonary embolism; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; ukCAP = United Kingdom Colorectal Adenoma Prevention; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study.

***** Trials included 2 separate aspirin groups that were combined for analysis.

Appendix Figure 3. Forest plot of aspirin use and cancer incidence from CVD primary prevention trials.

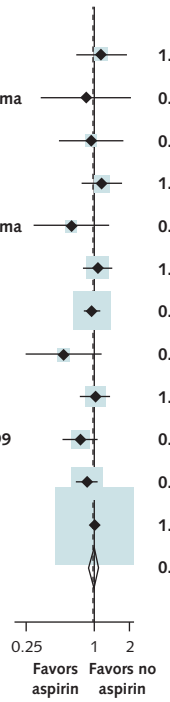
Study, Year (Reference)	Mean or Median Treatment Duration, *y*	Dose, *mg/d*	Population	RR (95% CI)	Events, *n/N*	
					Aspirin	No Aspirin
de Gaetano et al, 2001 (PPP) (48)	3.6	100	Men and women with ≥1 CVD risk factor	1.07 (0.80–1.42)	93/2226	89/2269
Hansson et al, 1998 (HOT) (51)	3.8	75	Men and women with hypertension	0.94 (0.81–1.10)	294/9399	311/9391
Peto et al, 1988 (BMD) (54)	6	500	Male physicians	1.02 (0.75–1.39)	119/3429	58/1710
Belch et al, 2008 (POPADAD) (55)	6.7	100	Men and women with diabetes and ABI ≤0.99	0.75 (0.52–1.09)	45/638	60/638
Fowkes et al, 2010 (AAA) (50)	8.2	100	Men and women with ABI ≤0.95	0.86 (0.70–1.04)	166/1675	194/1675
Cook et al, 2005 (WHS) (56)	10.1	50	Female health professionals	1.01 (0.94–1.08)	1438/19 934	1427/19 942
Overall (I^2 = 1.5%, P = 0.41)				0.98 (0.93–1.04)	2155/37 301	2139/35 625



WHS is a study of alternate-day dose aspirin (100 mg every other day). We used data from the individual-patient data meta-analysis (if data were not reported in the study or if they differed from those reported in the study) as follows: for POPADAD, PPP, AAA, and HOT, data from Rothwell and colleagues (19). Differences from point estimates or 95% CIs reported in studies are due to use of different statistical programs and are minor and of no clinical or statistical significance. AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle–brachial index; BMD = British Male Doctors; CVD = cardiovascular disease; HOT = Hypertension Optimal Treatment; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; WHS = Women's Health Study.

Appendix Figure 4. Forest plot of aspirin use and cancer incidence from CVD primary and secondary prevention trials.

Study, Year (Reference)	Mean or Median Treatment Duration, *y*	Dose, *mg/d*	Population	RR (95% CI)	Events, *n/N*	
					Aspirin	No Aspirin
ESPS-2, 1997 (59)	2	50	Men and women with prior TIA or stroke	1.14 (0.69–1.89)	32/1649	28/1649
Baron et al, 2003 (AFPPS) (87)	2.7	81; 325*	Men and women with prior colorectal adenoma	0.85 (0.34–2.14)	12/749	7/372
Brighton et al, 2012 (ASPIRE) (62)	3.1	100	Men and women with prior DVT or PE	0.94 (0.49–1.81)	17/411	18/411
AMIS, 1980 (65)	3.2	1000	Men and women with prior MI	1.16 (0.77–1.73)	50/2267	43/2257
Logan et al, 2008 (ukCAP) (88)	3.4	300	Men and women with prior colorectal adenoma	0.62 (0.29–1.31)	12/472	15/367
de Gaetano et al, 2001 (PPP) (48)	3.6	100	Men and women with ≥1 CVD risk factor	1.07 (0.80–1.42)	93/2226	89/2269
Hansson et al, 1998 (HOT) (51)	3.8	75	Men and women with hypertension	0.94 (0.81–1.10)	294/9399	311/9391
Juul-Möller et al, 1992 (SAPAT) (66)	4.2	75	Men and women with stable angina	0.54 (0.25–1.15)	10/1009	19/1026
Peto et al, 1988 (BMD) (54)	6	500	Male physicians	1.02 (0.75–1.39)	119/3429	58/1710
Belch et al, 2008 (POPADAD) (55)	6.7	100	Men and women with diabetes and ABI ≤0.99	0.75 (0.52–1.09)	45/638	60/638
Fowkes et al, 2010 (AAA) (50)	8.2	100	Men and women with ABI ≤0.95	0.86 (0.70–1.04)	166/1675	194/1675
Cook et al, 2005 (WHS) (56)	10.1	50	Female health professionals	1.01 (0.94–1.08)	1438/19 934	1427/19 942
Overall (I^2 = 0.0%, P = 0.53)				0.98 (0.93–1.04)	2288/43 858	2269/41 707



WHS is a study of alternate day aspirin (100 mg every other day). We used data from the individual-patient data meta-analysis (if data were not reported in the study or if they differed from those reported in the study) as follows: for POPADAD, PPP, AAA, and HOT, data from Rothwell and colleagues (19). Differences from point estimates or 95% CIs reported in studies are due to use of different statistical programs and are minor and of no clinical or statistical significance. AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle–brachial index; AFPPS = Aspirin/Folate Polyp Prevention Study; AMIS = Aspirin Myocardial Infarction Study; ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism; BMD = British Male Doctors; CVD = cardiovascular disease; DVT = deep venous thrombosis; ESPS-2 = European Stroke Prevention Study 2; HOT = Hypertension Optimal Treatment; MI = myocardial infarction; PE = pulmonary embolism; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; PPP = Primary Prevention Project; RR = relative risk; SAPAT = Swedish Angina Pectoris Aspirin Trial; TIA = transient ischemic attack; ukCAP = United Kingdom Colorectal Adenoma Prevention; WHS = Women's Health Study.
***** Trials included 2 separate aspirin groups that were combined for analysis.