Evidence Synthesis

Number 133

Aspirin Use for the Prevention of Colorectal Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force

Investigators:
Jessica Chubak, PhD, MBHL
Aruna Kamineni, PhD, MPH
Diana S.M. Buist, PhD, MPH
Melissa L. Anderson, MS
Evelyn P. Whitlock, MD, MPH

This systematic review was conducted in coordination with two other systematic reviews[1,2] and a decision model[3] to support the U.S. Preventive Services Task Force (USPSTF) in making updated clinical preventive service recommendations for aspirin in primary prevention. The original literature searches were completed in June 2014. In order to prepare a set of manuscripts derived from these reviews, we conducted updated literature searches through January 6, 2015 to identify newly published information since the original searches.

A single open-label randomized, controlled clinical trial in a cardiovascular disease (CVD) primary prevention population—the Japanese Primary Prevention Project (JPPP)[4]—was the only additional clinical research report located through the updated searches that met inclusion/exclusion criteria for any of the reviews. Outcomes from this study (nonfatal myocardial infarction [MI], nonfatal stroke [nonfatal cerebral infarction, intracranial hemorrhage, and undefined cardiovascular events], CVD mortality [fatal MI, cerebral infarction, intracranial hemorrhage, subarachnoid hemorrhage, and other fatal cardiovascular events], hemorrhagic stroke [fatal and nonfatal intracranial hemorrhage], and all-cause mortality) were incorporated into the final evidence reviewed by the USPSTF and resulted in updated inputs into the decision analysis.

This systematic review has NOT been updated to reflect the incorporation of results from JPPP. Updated results are reflected in the manuscript derived from this review, which is available for public comment at http://www.uspreventiveservicestaskforce.org. Results for this systematic review for outcomes unrelated to those reported in JPPP are current through January 6, 2015. No further updated literature searches have been undertaken.

References

1. Whitlock EP, Williams SB, Burda BU, et al. Aspirin Use in Adults: Cancer, All-Cause Mortality, and Harms. A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 132. AHRQ Publication No. 13-05193-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2015.
2. Guirguis-Blake JM, Evans CV, Senger CA, et al. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 131. Rockville, MD: Agency for Healthcare Research and Quality; 2015.
3. Dehmer SP, Maciosek MV, Flottemesch TJ. Aspirin Use to Prevent Cardiovascular Disease and Colorectal Cancer: A Decision Analysis. AHRQ Publication No. 15-05229-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2015.
4. Ikeda Y, Shimada K, Teramoto T, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. *JAMA*. 2014;312(23):2510-20. PMID: 25401325.

Acknowledgments

Suggested Citation

Chubak J, Kamineni A, Buist DS, Anderson ML, Whitlock EP. Aspirin Use for the Prevention of Colorectal Cancer: An Updated Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 133. AHRQ Publication No. 15-05228-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2015.

Structured Abstract

Background: Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both men and women in the United States (U.S.). Aspirin may inhibit CRC development and related mortality.

Purpose: We conducted this systematic evidence review on aspirin use for the prevention of CRC to support the U.S. Preventive Services Task Force (USPSTF) in updating its previous recommendation. Our review addressed four key questions in adults without a history of CRC, familial adenomatous polyposis, or Lynch Syndrome: 1) Does regular aspirin use reduce CRC mortality or all-cause mortality? 2) Does regular aspirin use reduce the incidence of CRC? 3) Does regular aspirin use reduce the incidence of colorectal adenoma? 4) What are the harms of regular aspirin use for the prevention of colorectal cancer?

Data Sources: We performed a search of MEDLINE, PubMed, and the Cochrane Collaboration Registry of Controlled Trials for studies published from January 2004 through May 2014. We supplemented searches by examining bibliographies from previous systematic reviews, retrieved articles, and the previous USPSTF review. We searched federal agency trial registries for ongoing and/or unpublished trials.

Study Selection: We conducted a dual review of 865 abstracts against prespecified inclusion criteria. We retrieved 149 potentially relevant articles, which two reviewers independently evaluated using well-defined inclusion/exclusion criteria and critically appraised for risk of bias. Discrepancies were resolved by discussion with a third reviewer.

Data Extraction and Analysis: For all fair-quality and good-quality studies, a single investigator extracted study characteristics and outcomes into structured tables and a second investigator verified accuracy. Elements abstracted for each study included study design, population characteristics, sample sizes, exposures, outcomes, and measures of association. We created summary evidence tables to capture key study characteristics and sources of heterogeneity. In addition to the overall results for each included study, we also presented results by dose, duration, latency, and adenoma history where possible. We used forest plots stratified by potentially important exposure and study characteristics to visually identify patterns in the study results and help determine if pooling across studies was appropriate. We used the Mantel-Haenszel fixed effects model to estimate the combined effect and confidence interval; for very rare events (incidence less than one percent), we calculated the Peto odds ratio.

Results: Daily or alternate-day aspirin at ≥75 mg was associated with a small reduction in all-cause mortality risk in the first 10 years after randomization (summary relative risk, RR, 0.94, [95% confidence interval, CI, 0.89 to 0.99]) in 11 randomized controlled trials (RCTs) among persons in the general population (i.e., selected without considering their adenoma history). Over a 20+ year period, aspirin appeared to reduce the risk of CRC mortality by approximately 33%. However, long-term data on CRC mortality may have limited applicability, particularly from the perspective of a low-dose aspirin benefits in a primary CVD population addressing women as well as men. Two of four trials were in those with pre-existing cardiovascular disease and two involved dosages of 500 mg or greater daily, with no longer-term mortality results available for alternate-day regimens. Data on mortality among persons with a prior colorectal adenoma were

also sparse. Six RCTs of aspirin for primary and secondary CVD prevention provided data on the effect of regular aspirin use on invasive CRC incidence in the general population. In this population, aspirin had no effect on CRC incidence in the first 10 years following randomization, but reduced CRC incidence by approximately 40 percent after a latency of 10 years (summary RR, 0.60 [95% CI, 0.47 to 0.76]). Over a 20+ year period, aspirin appeared to reduce the risk of CRC incidence by approximately 20 to 24%. Data on aspirin use and CRC incidence in persons with a prior adenoma were limited and represented only short-term followup (fewer than 5 years) and could not, therefore, provide sufficient information on the effect of aspirin use on CRC incidence. In persons with a prior adenoma, data were conflicting, but there was some suggestion of a decreased risk of adenoma incidence over a 3- to 4- year period. Data on aspirin and adenoma risk in the general population were sparse. Data from RCTs suggested that aspirin increased the risk of serious gastrointestinal bleeding (summary OR, 1.94 [95% CI, 1.44 to 2.62]), intracranial bleeding (summary OR, 1.53 [95% CI, 1.21 to 1.93]), and hemorrhagic stroke (summary OR, 1.47 [95% CI, 1.16 to 1.88]), but not fatal gastrointestinal bleeding (summary OR, 1.00 [95% CI, 0.43 to 2.36]).

Limitations: Limited data were available to address differences in possible effects of aspirin in subgroups (e.g., age, sex, race) or to compare daily vs. alternate-day aspirin use. Long-term followup data were not identified for persons with a history of adenoma.

Conclusions: Aspirin appears to reduce the risk of CRC incidence after an induction and latency period of approximately 10 years, with a similar effect on CRC mortality. The applicability of data for long-term effects of low-dose aspirin on CRC mortality, however, is limited, particularly in the context of a population selected for primary CVD prevention. Aspirin does not appear to have a strong effect on all-cause mortality within 10 years of initiating use, and data on long-term cumulative risk of all-cause mortality were sparse.

Abbreviations

AAA	Aspirin for Asymptomatic Atherosclerosis
ABI	ankle brachial index
ACBS	Asymptomatic Cervical Bruit Study
ACM	all-cause mortality
ACP	American College of Physicians
AE	adverse event
AFPP	Aspirin/Folate Polyp Prevention
AHRQ	Agency for Healthcare Research and Quality
AMA	American Medical Association
AMIS	Aspirin Myocardial Infarction Study
APACC	Association pour la Prevention par l'Aspirine de Cancer Colorectal
ARR	absolute risk reduction
ASA	acetylsalicylic acid
ASPIRE	Aspirin to Prevent Recurrent Venous Thromboembolism
ASPREE	ASPirin in Reducing Events in the Elderly
BMD	British Medical Doctors Trial
BMI	body mass index
CCT	controlled clinical trial
CDPA	Coronary Drug Project Aspirin study
CG	control group
CI	confidence interval
cm	centimeter
COX	cyclooxygenase
CPSII	Cancer Prevention Study II
CQ(s)	contextual question(s)
CRC	colorectal cancer
CVD	cardiovascular disease
DAMAD	Males and females with diabetic and diabetic retinopathy
EAFT	European Atrial Fibrillation Study
EPA	eicosapentaenoic acid
EPC	Evidence-based Practice Center
ERK	Extracellular-signal-regulated kinase
ESPS-2	European Stroke Prevention Study 2
ETDRS	Early Treatment Diabetic Retinopathy Study
FAP	familial adenomatous polyposis
g	gram
GI	gastrointestinal
HOT	Hypertension Optimal Treatment study
HPFS	Health Professionals Followup Study
HR	hazard ratio

IG	intervention group
IHD	ischemic heart disease
IKK	IκB kinase
IPD	individual patient data
IQR	interquartile range
ISRCTN Register	World Health Organization International Clinical Trials Registry Platform, Current Controlled Trials
JAST	Japan Atrial Fibrillation Stroke Trial
JPAD	Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes
KQ(s)	key question(s)
MAP	MYH-associated polyposis
mg	milligram
MI	myocardial infarction
mm	millimeter
mo	month
NA	not applicable
NHS	Nurses' Health Study
NR	not reported
NSAIDs	nonsteroidal anti-inflammatory drugs
OR	odds ratio
PACE	Prevention with Low-dose Aspirin of Cardiovascular disease in the Elderly
PARIS	Persantine-Aspirin Reinfarction Study
PHS	Physicians' Health Study
POPADAD	Prevention of Progression of Arterial Disease and Diabetes
PPP	Primary Prevention Project
qd	daily
qod	every other day
RAO	retinal artery occlusion
RCT(s)	randomized controlled trial(s)
RR	relative risk
SALT	Swedish Aspirin Low-dose Trial
SAPAT	Swedish Angina Pectoris Aspirin Trial
SD	standard deviation
SEER	Surveillance, Epidemiology, and End Results Program
SPAF	Stroke Prevention Atrial Fibrillation study
SSRIs	selective serotonin reuptake inhibitors
TIA	transient ischemic attack
TPT	Thrombosis Prevention Trial
ukCAP	United Kingdom Colorectal Adenoma Prevention trial
UK-TIA	United Kingdom Transient Ischaemic Attack
U.S.	United States
USPSTF	U.S. Preventive Services Task Force
VITAL	VITamins and Lifestyle

WHI   Women's Health Initiative
WHS   Women's Health Study
yrs   years

Table of Contents

Figures

Tables

Appendixes

Chapter 1. Introduction

Scope and Purpose

The Agency for Healthcare Research and Quality (AHRQ) commissioned an updated systematic evidence review on the use of aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) for the prevention of colorectal cancer (CRC) incidence and mortality.[1,2] The United States Preventive Services Task Force (USPSTF) will use this report to update its 2007 recommendation on the use of aspirin and NSAIDs for CRC primary prevention, which recommended against the routine prophylactic use of these medicines for individuals at average risk for CRC (Grade D recommendation).[3]

The previous review for the USPSTF on CRC prevention found fair-to-good evidence on the benefits and harms of aspirin and/or NSAID use but lacked details about the doses, duration, and timing of use, particularly for subgroups with varying risk levels. Since the last evidence review in 2007, two selective cyclooxygenase-2 (COX-2) inhibitors, rofecoxib and valdecoxib, are no longer available in the United States (U.S.) because of their increased cardiovascular risk profile. Both the remaining COX-2 inhibitor (celecoxib) and nonselective NSAIDs now include black box warnings on their labels about increased general safety concerns. Because of concerns about NSAIDs, this evidence review update focuses only on use of aspirin for CRC prevention. In 2013, we developed a work plan for this review to address evidence gaps about aspirin chemoprevention and to support the USPSTF in updating its previous recommendation.

A separate systematic review to update the 2009 USPSTF recommendations on the targeted use of aspirin for the primary prevention of cardiovascular events has also been commissioned. A third systematic review assessing the effects of aspirin on total cancer, all-cause mortality (ACM), and harms has also been prepared. These three concurrent systematic reviews will allow the USPSTF to simultaneously consider all three bodies of evidence to evaluate the preventive health benefits of aspirin.

Condition Definition

CRC begins in the large intestine with most cancers originating in the mucosa of this organ. CRC generally develops slowly from benign precursor lesions known as polyps. Adenomatous polyps or adenomas, which are characterized by the loss of normal cell differentiation, can become malignant and give rise to most CRCs.[4] The identification and removal of adenomas via endoscopy prevents their progression into malignant lesions.[5] Symptoms of CRC may include blood in the stool, anemia, a change in bowel habits (including diarrhea and constipation), abdominal pain or tenderness, or unexplained weight loss.[6]

Prevalence and Burden of Disease

CRC is an important public health problem in the United States. It is the third most commonly diagnosed cancer in both men and women with an estimated 136,830 new cases expected to

occur in 2014.[7] It is also the third leading cause of cancer death. Approximately 50,310 CRC deaths are expected in 2014, accounting for 8.6 percent of all expected cancer deaths.[6] According to the most recent Surveillance, Epidemiology, and End Results Program (SEER) data (2004-2010), 5-year survival for CRC is 64.7 percent, ranging from 89.8 percent for local stage disease to 12.9 percent for distant metastatic disease.[8] CRC incidence and mortality have declined over the past 20 years, attributable to both population changes in CRC-related risks and the introduction of screening, with more recent declines largely attributed to increased colonoscopy utilization.[6,9] The estimated costs associated with CRC care in the United States were $14 billion in 2010, and are projected to be $17 billion by 2020 if incidence, survival, and costs remain stable.[10]

Nonmodifiable risk factors that characterize subpopulations at increased CRC risk include:

- **Age.** CRC risk increases with age, with 90 percent of diagnoses in 2010 occurring among individuals aged 50 years or older,[6] although incidence appears to be increasing in those younger than 50 years.[11,12]
- **Gender.** Men are at one-and-a-half to two-fold increased age-specific risk for both advanced adenomas and CRC relative to women,[13-15] although lifetime CRC risk is believed to be comparable between men and women.[13,16] A woman's risk appears to lag behind that of her male counterpart by about five years.[17,18]
- **Race.** CRC incidence and mortality are greatest among African Americans, with the highest incidence rates observed in black men. Per 100,000, rates are 62.3 for black men vs. 49.6 for white men; 47.5 for black women vs. 37.2 for white women.[19] African Americans also develop CRC at younger ages than whites.[20] The median diagnosis age among whites is 70 years, compared to 64 years among African Americans.[21]
- **Type II Diabetes Mellitus.** A meta-analysis of 15 studies including 2.6 million participants found that diabetes was associated with a 30 percent increased CRC risk.[22] A more recent review reported similar results by anatomical subsite: 38 percent elevated risk for colon cancer and 20 percent for rectal cancer, although the association between diabetes and rectal cancer was limited to men.[23]
- **Family History.** CRC risk increases by 200-300 percent above expected population risk for first-degree relatives of affected family members.[24,25] The increased risk associated with having any affected relative is 75 percent.[24] Even more distant familial relations (second or third degree) may also be associated with modest increased risks.[26,27] Diagnosis before age 50 in any affected relative and multiplicity of affected family members confers even greater CRC risk.[24] The importance of family history may not be limited to a CRC history, as family history of adenomas is reported to increase CRC risk by 200 percent.[25]
- **Hereditary CRC Syndromes.** Individuals in families affected by familial polyp and cancer syndromes (hereditary nonpolyposis colorectal cancer or Lynch syndrome, familial adenomatous polyposis [FAP], MYH-associated polyposis [MAP], etc.) are at even higher risk for CRC than individuals with a family history of adenoma or CRC. For example, people with FAP-associated mutations have a 90 percent absolute risk of developing CRC by age 45 and people with mutations associated with Lynch syndrome have a 40 to 80 percent absolute risk of CRC by age 75.[28]

Etiology and Natural History

Colorectal tumors consist of a variety of lesions that can be broadly classified into three groups: 1) non-neoplastic polyps, 2) neoplastic polyps, and 3) cancers.[28] Non-neoplastic lesions such as hyperplastic polyps are generally viewed as not having malignant potential; however increasing evidence suggests that a subset of hyperplastic polyps—sessile serrated polyps—may be neoplastic and confer increased risk.[29][30] The neoplastic group comprises adenomatous polyps (adenomas), which are considered cancer precursors. Larger size, villous features, and a higher degree of dysplasia characterize adenomas with greater malignant potential.[28,31]

CRC is characterized by genomic instability and CRC development is a multistep process involving genetic mutations or epigenetic changes that activate oncogenes or inactivate tumor suppressor genes or mutator genes. The genetic changes that occur and the order in which they occur define various carcinogenesis pathways.[32,33] Below we describe the pathways for sporadic and hereditary cancers.

Sporadic Cancers

Adenoma-Carcinoma Pathway

Most sporadic CRCs are believed to follow the adenoma-carcinoma histological carcinogenesis sequence, which is a common succession of changes in tumor suppressor genes and oncogenes. Progression is estimated to take 10 to 40 years, but most adenomas do not progress to cancer.[34] Most adenomas are polypoid (protruding). Flat and depressed lesions were first characterized in 1985[35] and whether these adenomas represent a separate carcinogenesis pathway or have greater malignant potential remains unclear.[36] Nonetheless, they are being researched since they may be more easily missed by screening. Specific, ordered steps in the adenoma-carcinoma pathway are:

1. Dysplasia develops in a single crypt;
2. Single crypts develop into clusters that form adenomas;
3. Adenoma architecture changes from tubular to tubulovillous to villous with an increase in size;
4. Adenoma cells demonstrate progressively more severe atypia;
5. Adenocarcinoma appears;
6. Local invasion and metastasis.

Serrated Pathway

This is a more recently identified and less well-understood histological sequence associated with different genetic and epigenetic changes.[37,38] This pathway describes the progression of serrated polyps with malignant potential, including both traditional serrated adenomas and sessile serrated adenomas, to CRC. Serrated lesions are characterized by a sawtooth-like infolding of the crypt epithelium and a predisposition to high levels of DNA methylation as the lesions progress.[37]

Hereditary Cancers

Sporadic cancers arise from the stepwise accumulation of multiple somatic mutations. The common inherited CRC syndromes result from specific, single germline mutations. The syndromes include Lynch syndrome, caused by inherited mutations in mismatch repair genes (predominantly MLH1 and MSH2); FAP, caused by inherited mutations in the APC gene; and MAP, caused by biallelic mutations in the MUTYH gene.[39,40] Mutations in STK11 cause Peutz-Jeghers syndrome, whereas mutations in SMAD4 or BMPR1A cause juvenile polyposis syndrome.[40] MAP is currently the only known autosomal recessive hereditary CRC syndrome; all others are characterized by autosomal dominant inheritance.[41]

In contrast to the known mechanisms underlying sporadic cancers (75 percent of all CRCs) and the hereditary syndromes (5 to 6 percent of CRCs), little is known about familial CRCs without an identifiable inherited syndrome. Undiscovered genes acting singly or in concert with nongenetic factors likely contribute to the increased risk of cancer in individuals in these families.[41]

Risk Factors

The epidemiology and risk factors for CRC have been well characterized. Nonmodifiable risk factors have been described for subpopulations of individuals who have increased CRC risk. Modifiable risk factors that may present opportunities for primary prevention of CRC include:[42]

- **Smoking.** Many observational studies report an increased risk associated with long-term cigarette smoking,[43-46] and smoking may be responsible for 20 percent of CRCs in the United States.[47]
- **Obesity.** Increased body mass, regardless of the measure of adiposity (body mass index [BMI], waist circumference, waist-to-hip ratio), is associated with an increased CRC risk.[48-51]
- **Alcohol Consumption.** After adjustment for smoking and other known risk factors, several large prospective studies found that regular alcohol consumption is associated with increased CRC risk.[52-54]
- **Physical Activity.** Many studies suggest an inverse dose-response relationship between physical activity and CRC risk.[55-57]

Interventions to Prevent Colorectal Cancer

Opportunities for primary prevention of CRC include the screening, lifestyle changes, and chemoprevention strategies described below.

- **Screening.** Since most CRCs are thought to arise over a long period from an identifiable precursor adenomatous polyp or adenoma,[34] procedures such as endoscopy or computed tomography colonography can identify these CRC precursors and aid in their removal, preventing these lesions from developing into invasive carcinoma.[58] A number of national organizations have developed clinical guidelines for these screening tests,[59-62]

with the USPSTF recommending colonoscopy every 10 years beginning at age 50 for average-risk individuals, sigmoidoscopy every 5 years.[60] Annual fecal occult blood testing is also a recommended strategy for detecting CRC and may also lead to reduced incidence.

- **Lifestyle Changes.** Reducing or eliminating risk factors such as smoking, regular alcohol intake, obesity, and physical inactivity may prevent a substantial proportion of CRCs.
- **Chemoprevention**.
  a. *Aspirin*. Some evidence suggests an association between regular aspirin use and reduced risk of adenomatous polyps and CRC.[3] In a Health Technology Assessment report,[63] a pooled analysis of four studies of low-dose aspirin (100 to 325 mg every other day) showed no effect on CRC over the first 10 years of followup. In contrast, in the same report, an analysis of two, smaller studies of 300 to 1,200 mg/day of aspirin showed a 26 percent reduction in CRC incidence over a 23-year followup period. Aspirin has not been recommended for CRC prophylaxis in average-risk individuals because of the harms associated with long-term aspirin use (such as gastrointestinal bleeding) combined with limited evidence of benefit.
  b. *Nonaspirin NSAIDs*. Data suggest nonaspirin NSAIDs may reduce the risk of adenomas, but their link to ulcers, gastrointestinal bleeding, and adverse cardiovascular outcomes poses concerns. COX-2 inhibitors appear to reduce the risk of adenomas,[3] but the risk of serious cardiovascular events[64,65] including myocardial infarction does not support their prophylactic use. Ibuprofen and naproxen are the only nonaspirin NSAIDs currently available over the counter in the United States. NSAIDs available by prescription in the U.S. are celecoxib, diclofenac, diflunisal, etodolac, fenoprofen, flurbiprofen, indomethacin, ketorolac, meclofenamate, mefenamic acid, meloxicam, nabumetone, oxaprozin, piroxicam, salsalate, sulindac, and tolmetin. All these NSAIDs, including those available over the counter, have black box warnings about long-term use and cardiovascular disease (CVD) risk.
  c. *Calcium and Vitamin D*. Data suggest an inverse association between calcium intake and risk of CRC.[66,67] The protective effect of calcium dietary supplementation to reduce CRC risk appears to extend well beyond the supplementation period.[68] Two randomized controlled trials (RCTs), the Calcium Polyp Prevention Study[69] and the European Cancer Prevention Organisation Intervention Study,[70] showed that daily supplementation with 1,200 to 2,000 mg calcium was associated with a reduced risk of adenoma recurrence. The American College of Gastroenterology recommends calcium supplementation to decrease the risk of adenoma recurrence.[71] Data from several observational studies indicate that vitamin D status is inversely associated with CRC risk.[72] In contrast, the Women's Health Initiative (WHI) did not find that vitamin D supplementation reduced CRC incidence;[73] however, the relatively low supplementation dose in this trial and the short duration of followup may account for the negative findings.[74] In a recent recommendation statement,[75] the USPSTF found inadequate evidence to determine the effect of vitamin D supplementation on cancer risk.

Molecular Mechanism of Action for Aspirin in Colorectal Cancer Prevention

Evidence from animal models,[76-78] observational studies[79-82] and RCTs[63,81,83-86] suggests that aspirin may inhibit CRC development and related mortality. Some potential mechanisms for these effects have been proposed and broadly classified as COX-dependent and COX-independent, but none is well understood. COX-2 pathways have been the predominant focus for the antineoplastic effects of aspirin, but increasing evidence also supports the role of COX-1 and non-COX pathways.[87,88] COX-dependent mechanisms are currently better understood. The cyclooxygenases COX-1 and COX-2 catalyze the production of a class of tissue-specific signaling lipids[89] including prostaglandins. Prostaglandins promote inflammation, which can create a cellular environment favorable to tumorigenesis.[89-91] Aspirin, in contrast to the reversible action of nonaspirin NSAIDs, is believed to irreversibly inactivate COX enzymes to suppress production of prostaglandins.[89,92] COX-2 increases apoptosis, decreases cellular proliferation, and increases angiogenesis; thus, its suppression should have the opposite effects. Direct COX-2 inhibition is postulated to be the predominant pathway for aspirin's effects on CRC neoplasia.[87,93,94] CRCs have been observed to overexpress COX-2[95,96] and a prospective study of two large cohorts found that the benefit of aspirin use for CRC reduction was limited almost entirely to COX-2-positive CRCs,[97] supporting a COX-2 pathway. At low doses, aspirin is believed to selectively inhibit platelet activation through COX-1 suppression, with little effect on the COX-2 pathways.[87,88] However, it has been hypothesized that suppression of COX-1 may also have a sequential effect on COX-2 suppression.[87]

COX-independent mechanisms have been hypothesized,[87,88] but have been the focus of far fewer studies than the COX pathways. Different mechanisms and pathways may play a role at different points in the disease process, from blocking adenoma development to inhibiting progression[87] at later stages in carcinogenesis. Primary targets of investigation include inhibition of IκB kinase (IKK) β, prevention of NF-κB activation, extracellular-signal-regulated kinase (ERK) inhibition, mitochondrial functions, and inhibition of the Wnt/ β-catenin pathway.[88]

Current Clinical Practice and Recommendations of Other Groups

Currently, no health or professional organizations recommend aspirin for the primary prevention of CRC in average-risk adults. The American Cancer Society,[98] the American Medical Association (AMA),[99] and the American College of Physicians (ACP)[100] explicitly recommend against the use of aspirin for chemoprevention, with the AMA and ACP citing the 2007 USPSTF guidelines[3] as the basis for their recommendation. The American College of Gastroenterology,[101] the National Institute for Health and Care Excellence,[102] and the National Institutes of Health[28] have no chemoprevention recommendations for CRC. However, some organizations acknowledge possible roles for aspirin in both primary and secondary prevention in high-risk adults. The American Gastroenterological Association recommends that aspirin be considered for patients with a personal history of CRC,[103,104] advanced colorectal adenoma, or a strong family history, but not for people with a history of peptic ulcer disease or hemorrhagic stroke. The National Comprehensive Cancer Network[105] limits their recommendation for aspirin use to

primary prevention in adults with a personal history of classical FAP or attenuated FAP to reduce polyp burden as an adjunct to endoscopic surveillance.

Previous USPSTF Recommendation

In 2007, the USPSTF concluded that the harms outweigh the benefits of aspirin use for the prevention of CRC (D recommendation)[3] based on the following evidence.[81]

Benefits of Aspirin Use

- Fair-to-good evidence that aspirin taken in higher doses for longer periods reduces the incidence of adenomatous polyps.
- Good evidence that low-dose aspirin does not lead to a reduction in the incidence of CRC.
- Fair evidence that aspirin used in doses higher than those recommended for prevention of CVD may be associated with a reduction in the incidence of CRC.
- Fair evidence that aspirin used over longer periods may be associated with a reduction in the incidence of CRC.
- Poor-quality evidence that aspirin use leads to a reduction in CRC-associated mortality.

Harms of Aspirin Use

- Good evidence that aspirin increases the incidence of gastrointestinal bleeding in a dose-related manner and fair evidence that aspirin increases the incidence of hemorrhagic stroke.
- Overall, good evidence of at least moderate harms associated with aspirin.

Chapter 2. Methods

The USPSTF will use this systematic review to update its 2007 recommendation on aspirin use for the prevention of CRC.

Analytic Framework and Key Questions

Following the methods of the USPSTF,[106] we developed an analytic framework and key questions (KQs) to guide the literature search, data abstraction, and evidence synthesis for a systematic review of aspirin and CRC. We also included a contextual question (CQ) that was not systematically reviewed, and therefore not included in the analytic framework.

To establish the review scope and develop the analytic framework and KQs, we scanned for evidence published since the previous review to identify new information related to aspirin or NSAID use and CRC. We searched for existing systematic reviews and meta-analyses, using MEDLINE, British Medical Journal Clinical Evidence, Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and publications from the Institute of Medicine and the National Institute for Health and Clinical Excellence (**Appendix A Figure 1A**). We reviewed the titles and abstracts of 103 resultant articles and identified seven relevant reviews.

As part of the scan for new evidence, we examined relevant new and pending trials since the last review. We searched for ongoing trials using selected gray literature sources including ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, Current Controlled Trials (ISRCTN Register), and the Food and Drug Administration website. We searched for results from pending trials using PubMed. Only one of the pending trials was relevant to this updated review because it includes an intervention other than a selective COX-2 inhibitor. Our search identified 38 new trials with seven determined to be potentially relevant because of a focus on aspirin and average-risk or adenoma populations.

The analytic framework addressing aspirin for the prevention of cancer is in **Figure 1**. Our report addresses KQs 1/3 (initially formulated as a combined question focusing on ACM and CRC mortality), KQ 4, KQ 5, and KQ 7. We addressed the following KQs in adults without a history of CRC, FAP, or Lynch syndrome.

Benefits Key Questions

1, 3. Does regular aspirin use reduce CRC mortality or ACM?
4.   Does regular aspirin use reduce the incidence of CRC?
5.   Does regular aspirin use reduce the incidence of colorectal adenoma?

For each of these benefits KQs we also addressed the following subquestions:

- Does the effect of aspirin vary by age, sex, race, comorbidities, or baseline cancer risk?
- Does the effect of aspirin vary by frequency, dosage, duration, or recency of use?

Comorbidities of interest were diabetes, liver disease, ulcer disease, and previous gastrointestinal bleeding as they are prevalent and/or may be affected by aspirin use. Adenoma history, family history and other established risk factors, as specified in the included studies, were considerations for baseline cancer risk.

Harms Key Question

7. What are the harms of regular aspirin use for the prevention of CRC (at the dosage and duration required to achieve a preventive health effect)?

Aspirin harms of interest in this review were gastrointestinal bleeding (any, serious, and fatal); intracranial bleeding (including hemorrhagic stroke); hemorrhagic stroke; and age-related macular degeneration.

In this harms KQ we also addressed the following subquestion:

- Do harms vary by patient characteristics (e.g., age, sex, race, comorbidities, or concomitant medication use)?

In addition to the comorbidities considered for the benefits KQ subquestions, medications considered for this harms subquestion were nonaspirin NSAIDs and selective serotonin reuptake inhibitors (SSRIs).

Contextual Question

What is the level of persistence of aspirin use among adults who initiate a regimen for the prevention of CRC?

Data Sources and Searches

In addition to considering all studies from the previous USPSTF review[1] for inclusion in the updated review, we developed a search strategy designed to capture relevant literature published since the previous review. The previous systematic evidence review searched literature published through 2004 (month and day varied by database). Our experienced medical librarian designed and conducted a comprehensive search for original new research from January 1, 2004 to September 2013 using MEDLINE, PubMed, and Central Register of Controlled Trials (**Appendix A Figure 1B**). We used search terms similar to those used in our scan for new synthesized evidence, but limited our search to studies of aspirin only. We also expanded our search criteria to include observational studies. Additionally, we examined reference lists of published reviews, meta-analyses, and primary studies to identify other potential articles for inclusion. In June 2014, the medical librarian conducted a bridge search through May 2014. In total, we identified 865 potentially relevant abstracts through these efforts.

We obtained data on ACM and harms of aspirin only from studies that reported on CRC outcomes. In other words, we did not conduct a separate search of the entire literature on the effects of aspirin on harms or ACM. The rationale for this decision was that the concurrent

systematic reviews (Aspirin for the Primary Prevention of Cardiovascular Events and Aspirin Use in Adults: Total Cancer, All-Cause Mortality and Harms) were also obtaining data on these outcomes and the USPSTF would consider evidence from all the reviews together.

Study Selection

Two reviewers reviewed the titles and abstracts of 865 unique articles (**Appendix A Figure 2**) against inclusion and exclusion criteria (**Appendix A Table 1**). We retrieved 149 potentially relevant articles (**Appendix A Figure 2**) that two investigators reviewed against the same inclusion and exclusion criteria. Reviewer disagreements at the abstract or full-text review stages were resolved by consensus and consultation with a third investigator if needed. We excluded articles that did not meet inclusion criteria or were rated as poor quality. Excluded articles and reasons for their exclusion by key question are in **Appendix C**.

We developed an *a priori* set of criteria for inclusion and exclusion of studies based on our understanding of the literature and the refined analytic framework and KQs (**Figure 1**). This review focused on average-risk adults, excluding people with inflammatory bowel disease, familial hereditary colorectal syndromes (Lynch, FAP, etc.), or a personal history of cancer. We focused on aspirin for chemoprevention; all nonaspirin NSAIDs were excluded from consideration. For analysis of benefits, we excluded intended or reported durations of use less than 12 months.

For all KQs (benefits and harms), we included RCTs, controlled clinical trials, fair-quality and good-quality systematic reviews and meta-analyses of RCTs, and fair-quality and good-quality prospective cohort studies (**Appendix A Table 1**). We included only studies in which the majority of patients were ≥40 years old (determined by the USPSTF to be the earliest appropriate target age) and at average risk for CRC based on patient characteristics (e.g., excluding for FAP, history of CRC, no colon, and symptoms). The exception to the patient characteristic exclusion was history of adenoma, which is associated with an intermediate CRC risk (depending on adenoma characteristics) due to risk of adenoma recurrence; however, people in this category are still are considered part of the average-risk primary care population. For the benefits KQs (1/3, 4, and 5), we included only articles in which the oral aspirin intervention or exposure was a minimum dose of 75 mg taken daily or on alternate days for a minimum of one year, since lower frequency of use, doses, and durations were less likely to have an effect and to be studied.[81] For studies of alternate day dosing we divided by two to obtain the average daily dose.

No maximum dose or duration was specified. For the harms KQ (7), we required no minimum duration of use since harms could occur soon after initiation. For all KQs (benefits and harms), we were interested in studies in which the comparison group was a placebo, "no treatment," or an unexposed group. To ensure that any effects observed resulted from aspirin and not another factor, we excluded studies with interventions or exposure group categories that combined aspirin with another medication for chemoprevention. However, factorial design studies were eligible for inclusion. For benefits KQs, examining the benefits of aspirin, we included studies that examined mortality (all-cause and CRC-specific), CRC incidence, and adenoma incidence. Studies reporting only on CRC metastasis or progression were excluded. After these inclusion and exclusion criteria were applied, we further limited inclusion to studies rated fair or good

quality according to USPSTF risk-of-bias criteria[106] and Newcastle Ottawa Scales for cohort studies.[107] We excluded studies not published in English.

Quality Assessment

Two investigators independently and critically appraised the methodological quality of each study that met the inclusion criteria. Quality was assessed using design-specific criteria developed by the USPSTF for RCTs[106] and supplemented with Newcastle Ottawa Scales for cohort studies (**Appendix A Table 2**).[107] We rated articles as good, fair, or poor quality with respect to internal validity. In general, a good-quality study clearly met all quality criteria. A fair-quality study did not meet, or did not clearly meet, all criteria for a good-quality study, but also had no important limitations that would suggest invalid results. A poor-quality study had at least one fatal flaw or multiple important limitations that collectively made its findings questionable in our judgment. Discordant quality ratings were resolved by interrater discussion and consultation with a third investigator as needed. We excluded poor-quality studies from this review (**Appendix C**).

Good-quality RCTs demonstrated adequate randomization procedures and allocation concealment; similar groups at baseline (i.e., little-to-no difference between groups in baseline demographics and characteristics); blinded outcome assessment; adherence to the intervention protocol; low attrition (≥90% of participants had followup data with <10 percentage-point difference in loss to followup between groups); and performed an intent-to-treat analysis. Trials were downgraded to fair if they did not meet one or more of the good-quality criteria but had no known threats to validity. Trials were rated as poor quality if attrition was greater than 40 percent or differed between groups by more than 10 percentage points or the analysis did not follow the intent-to-treat principle.

Good-quality cohort studies had unbiased definition and selection of the unexposed group, ascertainment of exposure that preceded the outcome, and an outcome of interest that was not present in the source population at study onset. Good-quality studies also had reliable outcome measures, blinded outcome assessment, low attrition, and adequate adjustment for potential confounders. Cohort studies were downgraded to fair if they did not meet all good-quality criteria. We rated cohort studies as poor quality if the exposed and unexposed groups were derived from different source populations or adjustment for key characteristics associated with CRC risk (e.g., age and gender) was inadequate.

Data Abstraction

A primary reviewer abstracted data from all fair-quality or good-quality studies into structured evidence tables and a secondary reviewer verified all data. For each article, elements abstracted included study design details (e.g., study period, recruitment and enrollment setting and approach, targeted population, inclusion and exclusion criteria, run-in phase for trials, and followup); population characteristics (e.g., age, sex, race/ethnicity, BMI, smoking status, family history, screening history, adenoma history, and medication use); intervention or exposure characteristics (e.g., intervention design and adherence or persistence to study medication for

trials, and dose, intensity, frequency, and duration of aspirin use); and sample sizes (N) recruited, enrolled, eligible, and analyzed.

We abstracted information including method of ascertainment on all study outcomes pertaining to the KQs. Information included ACM and CRC-specific mortality (KQ 1/3); CRC incidence (KQ 4); colorectal adenoma incidence, adenoma number, advanced adenoma incidence, advanced neoplasia, and adenoma size (KQ 5); and gastrointestinal bleeding, colorectal bleeding, esophageal bleeding, fatal bleeds, subarachnoid or subdural hemorrhage, intracranial bleed, stroke, and age-related macular degeneration (KQ 7). For each outcome, we abstracted the number of events, incidence rate, and measures of association or difference (e.g., relative risk [RR], hazard ratio [HR]) when provided. We abstracted outcome data for the overall study population and by intervention and exposure group when reported. We also abstracted outcome information by dose, duration, and time since first or last use separately, if provided.

As necessary, we summed across event subtypes to obtain the total number of events for our primary outcomes (e.g. hemorrhagic intracerebral stroke, subarachnoid stroke, and epidural or subdural hematoma were summed to obtain total number of intracranial bleeding cases). When studies reported gender distributions and means by exposure or treatment groups, we computed weighted averages to obtain study-level information. We used a similar approach for describing study populations in individual patient data (IPD) meta-analyses when pooled study population characteristics were not reported but were available from contributing studies. For factorial studies, we combined data across aspirin groups. The only exception was a factorial study of aspirin and warfarin,[108] for which we examined the effect of aspirin on harms in the groups not receiving warfarin, an anticoagulant because of concerns about effect modification. Calculations not reported by study authors are marked with a symbol in the Tables.

Data Synthesis and Analysis

For each body of literature defined by the KQs, we created summary evidence tables to capture key study characteristics and sources of heterogeneity (e.g., study quality, sample size, geographic location, age, sex, dose, frequency and duration of aspirin use, and duration of followup). These tables were the basis for our qualitative evidence synthesis for each KQ. We identified the range of results for ACM, CRC mortality, CRC incidence, colorectal adenoma incidence, and adverse events in the context of important population characteristics and study design features. In addition to the overall results for each included study, we also presented results by dose, duration, and followup period where possible. Categories of doses used for stratification are shown below.

Category	Aspirin Dose	Included Aspirin Ranges
High	>325 mg	500 mg qd to 1200 mg qd
Low	≤325 mg	100 mg qod to 325 mg qd
Very Low	≤100 mg	100 mg qod to 100 mg qd

Abbreviations: qd = daily; qod = every other day.

In our quantitative synthesis of each body of literature, we used forest plots stratified by potentially important exposure and study characteristics to visually identify patterns in the study results and determine if pooling across studies was appropriate. We present results stratified by

followup period because of apparent differences in effect by time since initiation of aspirin. We did not combine results from bodies of evidence limited to two studies, but instead presented results from each individual study. Decisions to pool were based on clinical and methodological similarity rather than statistical tests of heterogeneity.[109] We did not combine across studies when estimates across studies had unexplained heterogeneity (e.g., not attributable to differences in study populations), with estimates of different magnitude or direction, based on statistical advice.[110] We also did not combine studies if information was insufficient (e.g., rates but no samples sizes and event counts).

We chose a fixed effects model approach for all analyses, due to the relatively small number of studies. Fixed effects models assume a single treatment effect across studies, and assume that any heterogeneity between studies is due to random variation. We used the Peto fixed effects model to estimate the combined effect and confidence interval when the cumulative incidence of the outcome in the control group was less than one percent, or when one of the comparison groups had no events. The Peto method is the recommended meta-analysis method under the circumstance of rare binary outcomes, because it provides the least biased and most powerful estimate of the combined effect, and the best confidence interval coverage.[109] For these analyses, we used a continuity correction factor, adding 0.5 to each cell for studies with no observed events in one or both study arms. When the outcome was less rare, and the cumulative incidence in the control group exceeded one percent, we used the Mantel-Haenszel fixed effects model to estimate the combined effect. We used Stata 12.0 (StataCorp LP, College Station, TX) for all statistical analyses.

Expert Review and Public Comment

We posted the draft Research Plan for this review for public comment from June 13, 2013 to July 10, 2013. We received comments from seven organizations and individuals. All comments were addressed as appropriate. The main changes to the Research Plan based on public comments were: 1) inclusion of prospective observational studies, and 2) inclusion of patients with a history of adenoma. The final Research Plan was posted on the USPSTF website in October 2013. The draft version of this report was reviewed by experts and federal partners from June 2, 2014 to June 20, 2014. In July 2014, all three related aspirin evidence reviews were presented and discussed together at the USPSTF meeting.

USPSTF Involvement

The authors worked with three USPSTF liaisons at key points throughout the review process to refine the analytic framework and KQs, resolve issues around review scope, and finalize the evidence synthesis. This research was funded by AHRQ under a contract to support the work of the USPSTF. AHRQ staff provided oversight for the project and facilitated communication with USPSTF liaisons. The USPSTF and AHRQ had no role in the study selection, quality assessment, or the drafting of this systematic review.

Chapter 3. Results

Literature Search

Our literature searched yielded 865 unique abstracts; 149 met the criteria for full-text review (**Appendix A Figure 2**). We identified 14 RCTs and seven cohort studies of fair or good quality addressing KQ 1/3 (N=16), KQ 4 (N=16), KQ 5 (N=4), and KQ 7 (N=15). Included were 11 RCTs in the general population (i.e., persons selected without consideration of adenoma history) (**Appendix D Table 1**). None of these RCTs excluded patients based on their adenoma history so we presume the studies represent a mix of persons with and without past adenomas; however, these data were not reported. We identified three RCTs in patients with prior adenomas (**Appendix D Table 2**). Results on CRC outcomes and ACM from these 11 trials (all testing daily aspirin) were presented in IPD and study-level meta-analyses by Flossman and colleagues[111] and Rothwell and colleagues.[83,85] In addition, we identified two other RCTs of alternate-day aspirin for CVD and cancer primary prevention (Women's Health Study [WHS][112-116] and Physicians' Health Study [PHS][117-122]). We also report results from an IPD meta-analysis by Cole and colleagues pooling colorectal adenoma and CRC incidence outcomes for the three RCTs conducted among persons with a prior adenoma.[123] We identified seven eligible cohort studies addressing at least one of the KQs (**Appendix D Table 3**). All were in the general population (i.e., persons with a past adenoma were not specifically sampled or excluded) and all had at least one exposure group that met the threshold for frequency of aspirin use (daily or alternate day) for one of the KQs.

Overall Body of Evidence

We included 14 RCTs (eight good quality, six fair quality) and seven prospective cohort studies (one good quality, six fair quality) assessing the effect of aspirin on CRC mortality, ACM, CRC incidence, and colorectal adenoma incidence. Characteristics of the included studies are in **Appendix D Tables 1, 2, and 3**.

Among the 11 trials that provided data on the general population (**Appendix D Table 1**), nine were CVD prevention studies among primary (six trials) and secondary prevention (three trials) populations that Flossman and colleagues[111] and Rothwell and colleagues[83,85] followed for CRC outcomes. They included RCTs of daily aspirin use for which data on CRC incidence or mortality could be obtained. In the 2010 report, Rothwell and colleagues included studies in the United Kingdom and Sweden with ≥1000 participants and a median scheduled duration of at least two and a half years.[85] The report by Rothwell and colleagues in 2011 required a mean or median scheduled trial treatment period of at least four years and a range extending beyond five years.[83] As all were fair or good quality, we included all aspirin versus placebo studies from their reports:

- British Medical Doctors trial (BMD) (fair quality) randomized 5,139 men (mean age: 61.6 years) to 500 mg/day vs. no aspirin. Participants assigned to aspirin were permitted

to take 300 mg/day enteric-coated aspirin if requested. Median duration of treatment was 6.0 (range: 5.0 to 6.0) years.[124]

- UK Transient Ischaemic Attack (UK-TIA) trial (good quality) randomized 2,449 British men and women with recent transient ischemic attack (TIA) or minor ischemic stroke (mean age: 60.3 years) to 300 mg/day aspirin, 1,200 mg/day of aspirin, or placebo. Median duration of treatment was 4.4 (range: 1.0 to 7.1) years.[125,126]

- Thrombosis Prevention Trial (TPT) (good quality) randomized 5,085 men (mean age: 57.5 years) in a 2 x 2 factorial design to 75 mg/day aspirin vs. placebo and warfarin vs. placebo. Median duration of treatment was 6.9 (range: 4.3 to 8.6) years.[108]

- Swedish Aspirin Low-dose Trial (SALT) (good quality) randomized 1,363 Swedish men and women with a recent TIA, minor stroke, or retinal artery occlusion (mean age: 66.9 years) to 75 mg/day aspirin vs. placebo. Median duration of treatment was 2.7 (range: 1.0 to 5.3) years.[127]

- Early Treatment Diabetic Retinopathy Study (ETDRS) (good quality) randomized 3,711 men and women with diabetes with certain categories of diabetic retinopathy (mean age: 51 years) to 650 mg/day of aspirin vs. placebo. Median duration of treatment was 5.0 (range: 4.0 to 9.0) years.[128,129]

- Swedish Angina Pectoris Aspirin Trial (SAPAT) (fair quality) randomized 2,035 Swedish men and women with chronic stable angina pectoris without prior myocardial infarction (mean age: 67 years) to 75 mg/day aspirin vs. placebo. Median duration of treatment was 4.2 (range: 1.9 to 6.3) years.[130]

- Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) (fair quality) randomized 2,539 Japanese men and women with type 2 diabetes but without a history of atherosclerotic disease (mean age: 64.5 years) to aspirin (patient choice of 81 or 100 mg/day) vs. no recommendation to take aspirin. Median duration of treatment was 4.4 (3.0 to 5.4) years.[131]

- Prevention of Progression of Arterial Disease and Diabetes (POPADAD) (fair quality) randomized 1,276 Scottish men and women with diabetes and asymptomatic peripheral arterial disease (mean age: 60.3 years) to 100 mg/day of aspirin vs. placebo. Median duration of treatment was 6.7 (4.5 to 8.6) years.[132]

- Aspirin for Asymptomatic Atherosclerosis (AAA) (fair quality) randomized 3,350 Scottish men and women with no history of vascular disease and with low ankle brachial index (mean age: 62.0 years) to 100 mg/day of aspirin vs. placebo. Median duration of treatment was 8.2 (6.7 to 10.5) years.[133]

The studies were conducted in Europe, the United Kingdom, Japan, and North America. All were studies of daily aspirin use with doses ranging from 75 mg/day to 1,200 mg/day with six studies of 75 mg/day to 100 mg/day aspirin, one each of 300 mg/day, 500 mg/day, or 625 mg/day, and one study with both 300 mg/day and 1,200 mg/day arms. The majority of participants were men in most studies, including several studies restricted to men.

Flossman and colleagues[111] ascertained long-term (~20-year followup) CRC incidence data (good quality) on participants from the BMD and UK-TIA trials (N=7,588) and used individual patient data for their analyses. Subsequently, Rothwell and colleagues[85] analyzed long-term CRC incidence data (fair quality) and CRC mortality data (good quality) from participants in the BMD, UK-TIA, TPT, SALT studies (N=14,033) and presented results from both study-level and

IPD meta-analyses. In 2011, Rothwell and colleagues[83] (good quality) reported on ACM in participants from eight of the trials (all except SALT) (N=25,570) and CRC mortality from BMD, UK-TIA, TPT, JPAD, POPADAD, and AAA (N=19,824). ACM data were reported by trial, while CRC mortality data were reported separately by trial for some analyses and pooled for others.

We identified two additional RCTs providing data on CRC incidence that did not meet Flossman and colleagues' and Rothwell and colleagues' inclusion criteria related to frequency of use (i.e., daily use). WHS[112-116] (good quality) and PHS[117-122,134,135] (good quality) were both conducted among U.S. health professionals to determine whether aspirin reduces the risk of CVD or cancer. WHS randomized 39,876 women in the United States (mean age: 54.6 years) to 100 mg of alternate day aspirin vs. placebo (2 x 2 factorial with vitamin E) for approximately 10 years. Followup extended for a median of 17.5 (range: 10.4 to 18.8) years. PHS randomized 22,071 male doctors (mean age: 53.2 years) to 325 mg of aspirin every other day vs. placebo (2 x 2 factorial with beta carotene). The aspirin part of trial was terminated after an average of five years because of a significant decrease in myocardial infarction incidence in the aspirin arms; however, participants were followed for CRC incidence and ACM for a mean of 12 years. Both WHS and PHS studies provided data on CRC incidence and ACM, but not on CRC mortality.

None of the 11 trials in the general population reported on adenoma incidence. Only WHS and PHS planned to study cancer outcomes as primary aims. However, followup by Flossman and colleagues[111] and Rothwell and colleagues[83,85] for CRC outcomes in CVD trials was based on national cancer registry data and therefore likely to be complete and unbiased by exposure status. The main limitation was with incidence data from the SALT trial, which was limited to fatal cancers. The original CVD trials were good quality (UK-TIA, TPT, SALT, ETDRS, PHS, and WHS) or fair quality (BMD, SAPAT, JPAD, POPADAD, and AAA). Studies were classified as fair based on unblinded exposure (BMD and JPAD), low adherence to treatment (BMD, POPADAD, and AAA), or missing information (AAA, JPAD, and SAPAT).

Three of the 14 identified RCTs focused on patients with a prior adenoma who were adenoma free at baseline (**Appendix D Table 2**). These studies were conducted in France, the United Kingdom, Canada, and the United States. All studies required removal of all polyps at a baseline colonoscopy, and all had protocols with scheduled followup colonoscopies at 3 to 4 years after randomization. Doses ranged from 81 mg/day to 325 mg/day. The primary weakness of these studies was limited followup.

The Aspirin/Folate Polyp Prevention (AFPP) Study[123,136-140] (good quality) was conducted among 1,121 U.S. men and women with a prior adenoma (either ≥1 adenomas in the 3 months before recruitment, ≥1 adenomas removed in the 16 months before recruitment and a lifetime history of ≥2 adenomas, or an adenoma ≥1 cm removed in the 16 months before recruitment) and with confirmation of no remaining polyps in the three months before recruitment. Patients were randomized to 81 mg/day of aspirin, 325 mg/day of aspirin, or placebo in a factorial design with folate vs. placebo. The protocol called for a followup colonoscopy 34 to 40 months after the qualifying colonoscopy; more than 95 percent of participants in each group completed followup examinations.

The Association pour la Prevention par l'Aspirine du Cancer Colorectal (APACC)[123,141-143] study (fair quality) was conducted among 272 French men and women who had undergone a colonoscopy with adequate bowel preparation and visualized cecum, had ≥3 adenomas or ≥1 adenoma 6 millimeters or larger, and removal of all polyps in the three months before study entry. Participants were randomized to 160 mg/day of aspirin, 300 mg/day of aspirin, or placebo. The protocol specified followup colonoscopies at 1 and 4 years. We assigned the study a fair quality rating in part because only 73 percent of participants in the aspirin group and 63 percent in the placebo group received a 4-year colonoscopy (the primary timepoint for the outcome); however, at 1 year, 90 percent were followed in the intervention groups and 85 percent in the placebo group.

The United Kingdom Colorectal Adenoma Prevention trial (ukCAP)[123,144,145] was a good-quality RCT performed among 945 British men and women with a colorectal adenoma ≥0.5 cm that was removed in the 6 months before recruitment (or earlier if they also had ≥1 adenoma removed in the 6 months before randomization). Participants were randomized to either 300 mg/day of aspirin or placebo in a 2 x 2 factorial design with folate. Approximately 91 percent of both intervention and control participants received followup colonoscopies.

Adenomas during followup were diagnosed by pathologists per study protocol. All trials looked at advanced lesions in addition to the main outcome of any adenoma. Advanced lesions were defined by size, percent villous, or presence of severe dysplasia. The definition of advanced lesions differed slightly across studies, mostly about including CRC in the advanced lesions category.

We identified seven cohort studies to supplement data from RCTs on information about duration, dose, and recency of aspirin use. All had at least one exposure group that met the threshold for frequency of aspirin use (daily or alternate day) at ≥75 mg/day. Cohort studies varied in terms of characteristics of populations followed and methods of ascertaining aspirin use.

- Nurses' Health Study (NHS)[146-151] (fair quality) enrolled U.S. women nurses aged 35 to 55 years in 1976. Aspirin use was assessed by baseline survey (including questions about past use) in 1980 and then every two years. Women were followed for CRC through June 2000 (N=82,911 eligible for CRC analyses).
- Health Professionals Followup Study (HPFS)[152] (fair quality) recruited U.S. men health professionals (mean age: 54 years) in 1986 (N=47,363 eligible for CRC analyses). Aspirin use was assessed by baseline survey. Patients were followed for up to 18 years.
- A study by Larsson and colleagues pooled data from the Swedish Mammography Cohort and the Cohort of Swedish Men, collecting outcomes on CRC from 1997 to 2005 (fair quality).[153] Analyzed were 74,250 participants with a mean age at cohort entry of 60.6 years. Data on aspirin use was collected at a baseline survey. Participants were followed for a mean of 7.2 years.
- The Cancer Prevention Study II (CPSII) (N=662,424 included in analysis) and the Nutrition Cohort subset (N=146,113 and N=100,139 included in CRC incidence and mortality analyses, respectively) (fair quality)[154-158] were initiated in 1982 and 1992, respectively. The mean age in CPSII was 57 years at recruitment in 1982. Aspirin use was assessed at CPSII cohort entry and again in 1992-1993 when the Nutrition Cohort

was initiated, and approximately every two years thereafter. Participants in the Nutrition Cohort analyses were followed for up to 16 years.

- The Danish Diet, Cancer, and Health Study (fair quality) was conducted in 1995 to 2006 (N=51,053 included in analyses).[159,160] The mean age of participants was 56.2 years. Aspirin use was assessed in a baseline survey and then from prescription records during followup. Participants were followed for a mean of 9.4 years.
- The VITamins And Lifestyle (VITAL) study (fair quality) was conducted in Washington State beginning in 2000.[161,162] Participants averaged 61 years of age at cohort entry (N=64,847 included in analyses). Aspirin use was ascertained on a baseline survey. Median followup time was 7 years.
- The WHI Observational Cohort[163-167] (good quality) included 91,574 women in CRC analyses. Average age at entry was 63.5 years. Aspirin use was assessed with baseline and 3-year followup questionnaires. Women were followed for an average of 6.4 years.

Cohort studies supplemented RCTs by providing additional data on frequency, dose, duration, and timing of use. In general, the quality of the cohort studies was fair. A main limitation was that several studies assessed exposure only at baseline with a lengthy recall period. In addition, some studies had analytic concerns including handling of potential confounders, exclusion (rather than censoring) of participants who did not complete followup surveys, and lack of clarity around analytic strategies for time-varying confounders. Making valid comparisons across cohort studies and between cohort studies and RCTs was limited based on differences in how exposure to aspirin was assessed and categorized. For many of the cohort studies we did not use the overall reported RR estimates, which included as aspirin users persons who did not meet our minimum use criteria.

Where possible for all outcomes, we emphasize the combined induction and latency period (i.e., the time between initiation of use and the appearance of the outcome effect, hereafter referred to as the "latency period"). In general, the included studies did not provide much data stratified by race, gender, or comorbidities. However, we were able to make some indirect comparisons in RR estimates across studies that differed in included populations, but found little direct evidence for different subgroups.

KQs 1 and 3. Does Regular Aspirin Use Reduce Colorectal Cancer Mortality or All-Cause Mortality in Adults Without a History of Colorectal Cancer, Familial Adenomatous Polyposis, or Lynch Syndrome?

Summary of Results

We stratified study results by whether or not participant adenoma history was considered. In people selected without consideration of adenoma history (i.e., general population) we analyzed available data from 11 RCTs with 88,877 individuals from primary CVD or cancer prevention or secondary CVD prevention populations receiving 75 mg to 1,200 mg aspirin daily or every other day. The results were consistent with a small ACM risk reduction in the first 10 years after randomization (summary RR, 0.94 [95% CI, 0.89 to 0.99]) (**Table 1**, **Figure 2**); data on longer-

term followup were sparse. In contrast, aspirin (75 to 1200 mg per day) was associated with an approximately 33 percent reduced long-term cumulative risk of CRC mortality (k=4 trials, N=14,033, 240 CRC deaths). Risk reduction occurred after a latent period of approximately 10 years since first use (**Table 2**, **Figure 3**). Risk reduction appeared greater with increasing duration of use, but not dose. Two cohort studies supplemented information from RCTs.

Aspirin use and ACM data in persons with a prior adenoma were based on two good-quality and one fair-quality RCTs of 2,332 persons randomized to between 81 mg/day and 325 mg/day of aspirin. Overall, in persons with a prior adenoma, aspirin did not appear to reduce ACM over 3 to 4 years, but data were sparse (**Table 3**, **Figure 4**). No data were available on CRC mortality in persons with a past adenoma.

Detailed Findings: Aspirin and All-Cause Mortality in the General Population

Included Studies and Main Results

Included were 11 RCTs (six good quality, five fair quality) that were primary or secondary CVD prevention studies (two also included cancer as a primary outcome) (**Table 1**, **Figure 2**). The RCTs were WHS, PHS, BMD, UK-TIA, TPT, ETDRS, SAPAT, JPAD, POPADAD, AAA, and SALT. Study-level ACM results for all studies except WHS, PHS, and SALT were reported by Rothwell and colleagues.[83]

Point estimates across trials were similar, and most were in the direction of a small, beneficial effect on ACM (summary RR, 0.94, [95% CI, 0.89 to 0.99]). Very few included studies had followup longer than 10 years, and few studies used dosages other than those considered low dosage (≤325 mg daily). Limited data suggested no variation according to dose or duration studied or followup length.

Rothwell and colleagues[83] presented data for in-trial ACM for 25,570 participants from eight trials of primary and secondary CVD prevention (the same trials as we include minus WHS, PHS, and SALT); median trial duration was 4.2 years in SAPAT to 8.2 years in AAA. Aspirin dosages were 75 mg/day to 1,200 mg/day. At the person-level, the shortest scheduled duration of aspirin use was 1.0 year (UK-TIA) and the longest was 10.5 years (AAA). The average age of participants was 59.8 years and 29.4 percent were women. Rothwell and colleagues reported a pooled odds ratio (OR) of 0.92 (95% CI, 0.85 to 1.00) from a study-level meta-analysis on ACM and aspirin use. In an IPD meta-analysis of 10,502 persons from BMD, UK-TIA, and TPT with a scheduled intervention duration ≥5 years, Rothwell and colleagues found no definite impact on ACM (HR, 0.96 [95% CI, 0.90 to 1.02]) over a 20-year followup.[83]

All-Cause Mortality and Recency of Aspirin Use

Time Since First Use

Data on aspirin and ACM were available according to followup period, defined as the average time since randomization. We divided followup periods into early onset risk (within 10 years of randomization), late onset risk (10 to 20 years after randomization), and long-term cumulative

risk (from randomization to ≥20 years). All 11 RCTs presented data on early onset risk of ACM, although length of followup differed slightly by trial (**Table 1**, **Figure 2**). The summary RR estimate across the trials was 0.94 (95% CI, 0.89 to 0.99). No RCTs provided data on late onset risk of ACM. However, WHS results and pooled results from BMD, UK-TIA, and TPT suggested no reduction in long-term cumulative (0- to 20-year) risk (**Table 1**). The literature search did not identify cohort studies with data on the association between recency of aspirin use and ACM.

Time Since Last Use

None of the studies reported on an association between risk of ACM and time since last aspirin use.

All-Cause Mortality and Aspirin Dose and Frequency

RR estimates were similar across studies that varied by dose or frequency of use (**Table 1**, **Figure 2**). Thus, indirect evidence did not suggest a difference in effect according to dose or use frequency. UK-TIA was the only study that randomized patients to different doses of aspirin and placebo. The original UK-TIA study reported a slightly lower ACM risk in the two aspirin arms compared to placebo (1,200 mg/day aspirin: 13.7%; 300 mg/day aspirin: 13.5%; placebo: 15.0%; p-value not reported).[126]

One cohort study reported on the association between aspirin use and ACM. NHS reported age-standardized mortality rates by number of standard aspirin tablets per week.[146] Number of tablets per week does not have a definitive correspondence with frequency of use; however, we assume that increasing number of tablets per week is related to increased frequency of use. Although no RRs or p-values for trend were presented, no clear association was suggested between tablets per week and mortality rates: 3.86 per 1,000 person-years for 0 tablets/week, 2.70 per 1,000 person-years for 0.5 to 1.5 tablets/week, 3.05 per 1,000 person-years for 2 to 5 tablets/week, 3.36 per 1,000 person-years for 6 to 14 tablets/week, and 4.20 per 1,000 person-years for more than 14 tablets/week.

All-Cause Mortality and Duration of Aspirin Use

None of the RCTs compared the effect of different scheduled durations of aspirin use on ACM. However, RR estimates for ACM risk reductions in PHS, WHS, and Rothwell and colleagues studies were similar even though intervention lengths differed across studies: 5-year median in PHS, 10-year median in WHS, and 1.0- to 10.5-year range in CVD prevention studies reported by Rothwell and colleagues. Thus, indirect evidence did not suggest a difference in effect according to duration of aspirin use. However, it is important to note that the scheduled duration of use may not have been equal to the actual duration. The literature search did not identify cohort studies with additional data on the association between duration of aspirin use and ACM.

All-Cause Mortality: Effect Modification by Age, Sex, Race, and Comorbidities

None of the studies provided within-trial comparisons on differences in the effect of aspirin use on ACM according to age, race, or comorbidities. ETDRS presented 5-year RRs for aspirin use by gender, which were similar in men (RR, 0.94 [95% CI, 0.73 to 1.22]) and women (RR, 0.88

[95% CI, 0.65 to 1.17]).[128] In UK-TIA, the percent of men who died during followup was slightly lower in the intervention groups than the placebo group (1,200 mg/day aspirin: 14.5%; 300 mg/day aspirin: 14.8%; placebo: 17.0%; p-value not reported); however, the same trend was not apparent in women (1,200 mg/day aspirin: 11.7%; 300 mg/day: 9.9%; placebo: 10.0%; p-value not reported).[126] RR estimates were similar across studies limited to men (PHS) vs. women (WHS).

RR estimates were similar across the CVD prevention studies that enrolled patients with different comorbidities, i.e., recent TIA or minor ischemic stroke (UK-TIA, SALT), diabetes (JPAD, ETDRS, POPADAD), angina pectoris (SAPAT), low ankle brachial index (AAA), or high risk of ischemic heart disease (TPT). The literature search did not identify cohort studies with additional data on differences in the association between aspirin use and ACM by age, sex, race, or comorbidities.

Detailed Findings: Aspirin and Colorectal Cancer Mortality in the General Population

Included Studies and Main Results

Rothwell and colleagues[85] presented data on the association between long-term cumulative (0 to 20+ years) risk of CRC mortality and aspirin use from four primary or secondary CVD prevention RCTs (three good quality, one fair quality): BMD, UK-TIA, TPT, and SALT (N=14,033) (**Table 2**, **Figure 3**). They reported a pooled OR, 0.66 (95% CI, 0.51 to 0.85). Using the Mantel-Haenszel method, we obtained similar results: RR, 0.67 (95% CI, 0.52 to 0.86). In addition, Rothwell and colleagues[83] pooled individual patient data from BMD, UK-TIA, TPT, JPAD, POPADAD, and AAA to provide additional information on CRC mortality risk by followup period (N=19,824). They did not observe a statistically significant effect on CRC mortality during the first 5 years after randomization (HR, 0.78 [95% CI, 0.39 to 1.56]), but did observe an effect during ≥5 years of in-trial followup (HR, 0.41 [95% CI, 0.17 to 1.00]).[83] Limited data suggested that duration of use but not dose was related to the magnitude of risk reduction. Based on data from Rothwell and colleagues, Sutcliffe and colleagues[168,169] computed the number of CRC deaths that could be averted by aspirin use as 34 to 36 per 100,000 person-years.

PHS did not report on CRC mortality. WHS reported only that there were a total of 65 deaths due to CRC during the trial period in both arms of the study combined and that there was "no difference" between the groups.[112]

CRC Mortality and Recency of Aspirin Use

Time Since First Use

Data on aspirin and CRC mortality were available according to followup period, defined as average time since randomization. As before, we divided followup periods into early onset risk (within 10 years of randomization), late onset risk (10 to 20 years after randomization), and long-term cumulative risk (from randomization to 20+ years). Data from BMD, UK-TIA, TPT, and SALT (N=14,033) suggested a reduced risk in long-term CRC mortality (pooled OR, 0.66 [95%

CI, 0.51 to 0.85]; p-heterogeneity, 0.84) (**Table 2**, **Figure 3**).[85] Using individual patient data, Rothwell and colleagues restricted analysis to persons in the BMD, UK-TIA, and TPT trials with ≥5 years scheduled intervention duration.[83] The effect of aspirin on CRC mortality was apparent 10 to 20 years after randomization (HR, 0.51 [95% CI, 0.35 to 0.74]), but not before (HR, 0.79 [95% CI, 0.49 to 1.26]). The OR for the long-term cumulative risk (0 to 20 years) of CRC mortality was 0.60 (95% CI, 0.45 to 0.81) for ≥5 years scheduled intervention. Based on individual patient data from BMD, UK-TIA, TPT, JPAD, POPADAD, and AAA (N=19,824), Rothwell and colleagues did not observe an effect of aspirin on CRC mortality during the first 5 years after randomization (HR, 0.78 [95% CI, 0.39 to 1.56]), but did observe an effect during ≥5 years of in-trial followup (HR, 0.41 [95% CI, 0.17 to 1.00]).[83] WHS reported no effect (data not shown) during the first 10 years of followup[112] but did not report on late or long-term risk of CRC mortality.

The SALT study, which had the shortest average intended duration of use (median 2.7 years) among the trials we examined, reported a long-term OR of CRC death of 0.71 (95% CI, 0.27 to 1.86).[85] Though not statistically significant, this finding suggests that latency may not be completely confounded by duration, i.e., there appears to be a long-term effect even with three years of use.

The CPSII Nutrition Cohort provided some evidence that even recent aspirin use may reduce the risk of CRC mortality. Compared to nonusers, current daily aspirin users for less than five years had a lower risk of death due to CRC in the analysis using updated (time-varying) exposure information (RR, 0.62 [95% CI, 0.42 to 0.93]), but not in the analysis using baseline exposure data (RR, 0.85 [95% CI, 0.63 to 1.15]).

Time Since Last Use

None of the studies reported on the association between risk of CRC mortality and time since last aspirin use.

CRC Mortality and Aspirin Dose and Frequency of Use

Rothwell and colleagues[85] performed a study-level meta-analysis of CRC mortality by dose in BMD (500 mg/day), UK-TIA (300 and 1,200 mg/day), TPT (75 mg/day), and SALT (75 mg/day).[85] They found no significant effect of higher doses (500 to 1,200 mg/day) on the long-term cumulative risk of CRC mortality (OR, 0.72 [95% CI, 0.50 to 1.03]; N=6,777). However, they reported a significant reduction in long-term cumulative CRC mortality risk for lower dose aspirin (75 to 300 mg/day), (OR, 0.60 [95% CI, 0.42 to 0.86]; N=8,073). The HR for *colon* cancer mortality was 0.61 (95% CI, 0.38 to 0.98) for 75 mg/day when data from SALT and TPT were pooled (N=6,445). In the one trial that randomized patients to two different aspirin doses (UK-TIA, 300 mg/day and 1200 mg/day), there was a suggestion of effect with both doses (300 mg/day: OR, 0.50 [95% CI, 0.21 to 1.17]; 1200 mg/day: OR, 0.68 [95% CI, 0.31 to 1.47]), but neither was statistically significant.[85]

All included RCTs randomized patients to daily aspirin use and could not, therefore, compare daily to alternate-day use. The CPSII cohort study reported a significant trend for reduced CRC mortality risk with increasing frequency of aspirin use in the past year;[170] however, the most

frequent category of use was ≥16 times per month for at least one year and could not provide information for comparing daily and alternate-day use.

CRC Mortality and Duration of Aspirin Use

Rothwell and colleagues[85] observed a significant association between scheduled duration of aspirin use and mortality reduction (p=0.04; RR not reported) using individual patient data from BMD, UK-TIA, SALT, and TPT (n=14,033); however, the magnitude of the association was not reported for the overall population studied. Among persons randomized to 75 mg/day to 300 mg/day of aspirin, the risk reduction was slightly greater when persons with less than five years scheduled duration (37%) were excluded (RR, 0.48 [95% CI, 0.30 to 0.77]; 20-year absolute risk reduction [ARR], 1.76% [95% CI, 0.61to 2.91]) than when all subjects were analyzed (RR, 0.61 [95% CI, 0.43 to 0.87]; 20-year ARR, 1.36% [95% CI, 0.44 to 2.28]). These findings suggested a possible association between longer duration of aspirin use and greater risk reduction. In contrast, the CPSII Nutrition Cohort study presented similar RR estimates for current daily use less than five years and for currently daily use of five or more years: RR, 0.85 [95% CI, 0.63 to 1.15] and RR, 0.86 [95% CI, 0.61 to 1.22] respectively in the analysis of aspirin use at baseline; and RR, 0.62 [95%, CI 0.42-0.93] and RR, 0.64 [95% CI, 0.42 to 0.98] respectively in the analysis using updated aspirin information.

CRC Mortality: Effect Modification by Age, Sex, Race, and Comorbidities

None of the studies provided information on differences in the effect of aspirin use on CRC mortality according to age, sex, race, or comorbidities. The majority of participants in the CVD prevention studies were men (100% in BMD and TPT, 73% in UK-TIA, 65.8% in SALT, 56.5% in ETDRS, 54.6% in JPAD, and 44.1% in POPADAD) and many had cardiovascular risk factors making them eligible for the CVD prevention studies. The only additional information available from cohort studies identified in this search was from the CPSII cohort. Thun and colleagues reported that RRs for *colon* cancer mortality for aspirin use ≥16 times per month for at least one year compared to nonuse were similar among men (RR, 0.58 [95% CI, 0.36 to 0.93]) and women (RR, 0.61 [95% CI, 0.38 to 0.97]).[157]

Detailed Findings: Aspirin and All-Cause Mortality in Patients With a Prior Adenoma

We identified three RCTs evaluating 81 to 325 mg aspirin per day in persons with a prior adenoma (**Appendix D Table 2**): APACC,[141-143] ukCAP,[144,145] and AFPP (n=2332).[136] All required removal of all polyps at a baseline colonoscopy and all had protocols for scheduled followup colonoscopies at three to four years after randomization. All three RCTs reported the number of deaths from any cause during followup (**Table 3, Figure 4**). Two studies (ukCAP and AFPP) had more deaths in the aspirin group than the placebo group, but the reverse was observed in APACC. Because of the small number of studies and heterogeneity we did not pool results. Our search did not identify any cohort studies with additional evidence on the association between aspirin use and ACM among persons with a prior adenoma.

Detailed Findings: Aspirin and Colorectal Cancer Mortality in Patients With a Prior Adenoma

We did not identify any RCTs or cohort studies reporting on aspirin use and CRC mortality among persons with a prior colorectal adenoma.

KQ 4. Does Regular Aspirin Use Reduce the Incidence of Colorectal Cancer in Adults Without a History of Colorectal Cancer, Familial Adenomatous Polyposis, or Lynch Syndrome?

Summary of Results

We identified six RCTs that reported on the association between risk of CRC incidence and aspirin use in the general population (N=75,980) (**Table 4**). Data from four trials (N=69,535) suggested that aspirin does not affect the risk of CRC within the first 10 years after initiation of use (**Figure 5**). Data from three RCTs (N= 47,464) suggested that daily or alternate daily aspirin at 100 mg to 1,200 mg decreased risk of CRC incidence by approximately 40 percent (summary RR, 0.60 [95% CI, 0.47 to 0.76]) after a latency of approximately 10 years (**Figure 6**). Based on data from five trials, the latent effect of aspirin on CRC incidence resulted in an approximately 20 to 24 percent reduction in long-term cumulative risk (**Table 4**). Data did not suggest a difference in effect by dose and suggestion of an effect for duration of use came from a limited body of evidence. Data on dosage, frequency, formulation, or duration were also limited due to latency of effect analyses requiring at least 10 years of followup. Additional data from seven prospective cohort studies in the general population addressed questions about variations in effect by timing, dose, and duration of aspirin use, and patient characteristics. Data on aspirin use and CRC incidence in people with a prior adenoma were sparse (three trials) and represented only short-term (less than 5 years) followup and did not provide sufficient information on the effect of aspirin use on CRC incidence.

Detailed Findings: Aspirin and Colorectal Cancer Incidence in the General Population

Six RCTs (five good quality, one fair quality) representing 75,980 individuals provided data on the effect of regular aspirin use on invasive CRC incidence in the general population (**Table 4**). Pooled results from individual patient data from four of these trials (BMD, UK-TIA, TPT, and SALT) were reported in publications by Flossman and colleagues[111] (BMD and UK-TIA) and Rothwell and colleagues (all four).[85] Study-level estimates were also available for BMD and UK-TIA. Aspirin dosages in the trials included in the Flossman and colleagues and Rothwell and colleagues analyses ranged from 75 mg/day to 1,200 mg/day taken daily. The median scheduled duration of aspirin use across trials was 6.0 years (range 1.0 to 8.5 years) and some participants were followed for more than 20 years. Most participants were men (92%), and the average age at study entry was 60.4 years.[85] In addition, WHS[112-116] and PHS[117-122] both reported on the association between CRC incidence and alternate-day aspirin use. WHS randomized women

(mean age 54.6 years) to 100 mg of aspirin every other day vs. placebo for approximately 10 years with followup for a median of 17.5 years. PHS randomized men (mean age 53.2 years) to 325 mg of aspirin every other day vs. placebo for approximately 5 years with a mean followup of 12 years. WHS and Rothwell's pooled analysis of BMD, UK-TIA, TPT, and SALT reported on risk of proximal and distal colon cancers separately (**Appendix D Table 4**). Both suggested that aspirin decreased the risk of proximal but not distal colon cancer.

We also identified six fair-quality and one good-quality prospective cohort studies to address questions about variations in effect by timing, dose, and duration of aspirin use and patient characteristics (**Appendix D Table 3**). All included cohort studies had at least one exposure group that met the threshold for frequency of aspirin use (daily or alternate day). Two studies were conducted among health care professionals in the United States (NHS and HPFS). Two were regional or national cohort studies in the U.S. general population (VITAL and CPS II Nutrition Cohort). The WHI observational cohort consisted of women who were ineligible or unwilling to participate in the clinical trial. Two additional studies were population-based international cohorts (Denmark[160] and Sweden[153]). Most of the cohorts were established in the 1980s and 1990s and had a mean or median followup time of approximately 10 years; several cohort studies asked about past aspirin use (before baseline) and could therefore examine longer durations of use. Average age at cohort entry was generally 45 to 65 years old.

CRC Risk and Recency of Aspirin Use

Time Since First Use

Based on four trials (WHS, PHS, BMD, and UK-TIA; combined N=69,535), no effect of aspirin was seen on early risk of CRC (within approximately 10 years of treatment initiation) (summary RR, 0.99 [95% CI, 0.85 to 1.15]) (**Table 4**, **Figure 5**). Three RCTs (BMD, UK-TIA, and WHS, combined N= 47,464) suggested that aspirin reduced the risk of CRC incidence by about 40 percent starting approximately 10 years after initiation of use (**Table 4**, **Figure 6**), with reported HRs ranging from 0.51 to 0.64 across the three studies (summary RR, 0.60 [95% CI, 0.47 to 0.76]). Point estimates were similar in these three studies, even though scheduled duration of use was longer in WHS, suggesting that the apparent latent effect is not completely due to long duration of use. Risk of CRC overall was reduced in trials with long-term followup (17 to 20+ years). The estimate in WHS (HR, 0.80 [95% CI, 0.67 to 0.97]) was similar to Rothwell and colleagues' estimate based on individual patient data from BMD, UK-TIA, TPT, and SALT (HR, 0.76 [95% CI, 0.63 to 0.94]) (**Table 4**, **Figure 7**). We did not pool results from WHS and Rothwell since there were only two point estimates.

Flossman and colleagues analyzed CRC risk by followup interval (based on the BMD and UK-TIA trials; combined N=7,588). Their results suggested that the effect of aspirin on CRC waned after 14 years since first use. Risk of CRC incidence was reduced after 10 to 14 years of followup (HR, 0.51 [95% CI, 0.29 to 0.90]), but not after 15 to 19 years (HR, 0.70 [95% CI, 0.43 to 1.14) or ≥20 years (HR, 0.90 [95% CI, 0.42 to 1.95]). However, whether these results were influenced by duration of aspirin use or time since *last* use is unclear. In the two trials included in the Flossman report, 15 years after first use would have been approximately 10 years on average since last on-trial use.

Data from cohort studies provided little additional information on the timing of the preventive effect of aspirin on CRC incidence. NHS was the only cohort study to examine different followup periods independent of use duration. Similar to the RCT results, Chan and colleagues observed a trend toward reduced CRC risk with increasing number of tablets per week for aspirin use 11 to 20 years in the past but not for more recent use (i.e., in the past 10 years) in their multivariate adjusted analyses.[146]

Time Since Last Use

None of the trials provided data on CRC risk relative to time since last regular aspirin use. Two cohort studies presented analyses on time since last use;[152,160] however, neither study could estimate associations between time since last aspirin use and CRC risk for daily or alternate day users specifically.

Aspirin Dose and Frequency of Use

RCT evidence of aspirin use ≥75 mg daily or every other day did not suggest a difference in effect by aspirin dose. Rothwell and colleagues[85] conducted preplanned analyses of aspirin dose and observed similar effects on CRC incidence whether restricting to patients randomized to 75 or 300 mg/day (N=8,073) (HR, 0.75 [95% CI, 0.56 to 0.97]) or overall (HR, 0.76 [95% CI, 0.63 to 0.94]) including people randomized to 500 mg/day and 1,200 mg/day. In the two studies (TPT and SALT) that randomized patients to 75 mg/day of aspirin (N=6,445) the point estimate for the HR for colon cancer was similar but not statistically significant (HR, 0.76 [95% CI, 0.52 to 1.10]).[85] Additionally, WHS reported a long-term protective effect with very low dose aspirin (100 mg on alternate days) (HR, 0.80 [95% CI, 0.67 to 0.97]). These results suggested low-dose aspirin (≤325 mg daily) can reduce the long-term risk of CRC incidence and that higher doses may not be necessary to achieve an effect.

WHS and PHS studied alternate-day use while Rothwell and colleagues[85] examined daily use. None of the studies directly compared daily vs. alternate-day use. RR estimates for the long-term cumulative effect of aspirin on CRC incidence were similar in WHS (alternate-day use) and Rothwell and colleagues (daily use). PHS did not provide estimates of long-term effects.

Three cohort studies provided RR estimates according to reported number of pills per week, which we used as a surrogate for frequency of use. NHS[146] and HPFS[152] both reported on the risk of CRC among persons using different numbers of 325 mg aspirin tablets per week (0.5 to 1.5, 2 to 5, 6 to 14, more than14 tablets) (**Appendix D Table 5**). These categories do not map clearly into daily vs. alternate-day use. While it is reasonable to assume that individuals taking 6 to 14 tablets/week and more than 14 tablets per week were daily users, not everyone in the 2 to 5 tablet/week group would be an alternate-day user. Both studies suggested a trend toward reduced CRC risk with increasing tablets/week; however, we could not directly compare daily to alternate-day users. Analyses were not adjusted for duration or time since first use. Data from a study of Swedish cohorts also presented results for groups that could approximate daily users (>6 tablets/week) vs. alternate day users (2 to 6 tablets per week).[153] The same limitations that applied to NHS and HPFS apply to these data. VITAL also reported on low use (<4 days/week or <4 years) versus high use (≥4 days/week and ≥4 years), but we did not include these data since frequency and duration of use could not be separated.[161]

Three cohort studies presented CRC risk according to daily aspirin dose. The observational component of the WHI study found no association with <325 mg/day, ≥325 mg/day, or quartiles of daily dose (data not shown).[164] In a Danish study of prescription aspirin use, Friis and colleagues did not observe a significant reduction in CRC risk with either 75 to 100 mg or 150 mg tablets (data not shown).[160] These findings were among prescription aspirin users, whom we assumed were daily or alternate day users. VITAL also did not observe a greater risk reduction in regular-strength vs. low-dose aspirin users.[161] In men, high use (≥4 days per week and ≥4 years) of regular-strength and low-dose aspirin was associated with reduced CRC risk (HR, 0.55 [95% CI, 0.33 to 0.91] and HR, 0.55 [95% CI, 0.33 to 0.92] respectively). In women, a reduced risk of CRC was limited to high use of low-dose aspirin (HR, 0.55 [95% CI, 0.31 to 0.97]) and low use (< 4 days per week or <4 years) of regular-strength aspirin (HR, 0.53 [95% CI, 0.29 to 0.96]). Interpretation of these results is limited by the fact that they are not stratified by time since first use or duration of aspirin use.

In summary, although findings across RCTs and cohort studies are not entirely consistent, evidence suggests a reduced risk of CRC incidence with daily or alternate-daily use of at least 75 mg of aspirin. Overall, data did not suggest differences in effect by dose. Data directly comparing daily to alternate-day use were sparse.

CRC Risk and Duration of Aspirin Use

The reports by Rothwell and colleagues[85] and Flossman and colleagues[111] were the only analyses of RCTs to provide evidence on the effect of duration of aspirin use. Duration of aspirin use was inferred, generally reflecting intended rather than actual duration. We primarily report the results from Rothwell and colleagues[85] rather than Flossman and colleagues[111] because the study populations overlapped but Rothwell and colleagues[85] included more studies. Their primary analysis included four RCTs with a median scheduled aspirin duration use of 6.0 years (range 1.0 to 8.5 years). In secondary analyses, they restricted to persons with scheduled durations ≥5 years (N=10,533). The HR in the secondary analysis (HR, 0.68 [95% CI, 0.54 to 0.87]) was fairly similar to the analysis for all scheduled durations (HR, 0.76 [95% CI, 0.63 to 0.94]). However, in one of the included RCTs, scheduled duration varied from one to seven years and treatment and scheduled duration interacted, with a greater effect for longer duration of use (p-interaction=0.009 with duration as a continuous variable; p-interaction=0.004 for duration dichotomized at five years.)[111]

Several cohort studies presented risk according to aspirin duration. NHS,[146] HPFS,[152] and Larsson and colleagues[153] all observed decreased risk with increased duration of use; however, they did not restrict analyses to daily or alternate-day users. Thus, we do not present results from these three studies, as they may have included persons who used aspirin infrequently (e.g., two times per week). In contrast, WHI focused on daily use. Allison and colleagues reported on duration categories in 1-year increments from 0.1 to ≥5 years (0 years, 0.1 to 0.9 years, 1 to 1.9 years, 2 to 2.9 years, 3 to 3.9 years, 4 to 4.9 years, and ≥5 years), and in 5-year increments from one to >20 years (0 years, 1 to 5 years, 5.1 to 10 years, 10.1 to ≤20 years, and >20 years).[164] They did not observe significant trends, either with small increments between zero to five years or larger increments greater than five years. The CPSII Nutrition Cohort study reported an association with current daily use ≥5 years (RR, 0.68 [95% CI, 0.52 to 0.90]) but not with current daily use <5 years (RR, 0.85 [95% CI, 0.72 to 1.00]).[156] In the Friis and colleagues report, CRC

incidence after ≥5 years of consistent use was reduced (RR, 0.68 [95% CI, 0.34 to 1.34]); however, no reduction in risk was seen for any aspirin users compared to nonusers (RR, 0.93 [95% CI, 0.77 to 1.12]).[160] Finally, in the VITAL study, most subgroups who used aspirin for <4 years or <4 days per week did not have a reduced risk compared to nonusers, although risk was reduced for those who used aspirin for ≥4 years and ≥4 days per week (except for regular-strength aspirin in women). However, as noted above, frequency of use and duration of use could not be disentangled.[161]

In summary, limited data suggest that CRC risk associated with aspirin use is related to duration of daily or alternate-day use. Further, between-study differences complicate comparisons of intended duration of use. Finally, the latency of CRC risk reduction with aspirin use complicates analyses of duration and further limits the applicability of data on duration of use.

CRC Incidence: Effect Modification by Age, Sex, Race, and Comorbidities

Age

None of the studies provided information on differences in the effect of aspirin use on CRC incidence according to age.

Sex

Indirect data from RCTs did not suggest that sex modifies the effect of aspirin on CRC incidence. WHS was conducted in women, while PHS was conducted in men and 92 percent of persons in the four trials reported by Rothwell and colleagues were men.[85] Consequently, none of the RCTs provides a direct comparison of risk estimates in men versus women. The point estimates for aspirin effects were similar in WHS (women), PHS (men), and Rothwell and colleagues (primarily men). While these comparisons may be confounded by other between-study differences, the studies tended to confirm each other.

Three cohort studies provided limited additional information on the association between aspirin use and CRC risk by sex; however, none of the studies reported statistically significant differences in the observed associations. The VITAL study observed some differences in men compared to women. High use (≥4 days/week and ≥4 years use) of regular-strength aspirin was associated with a reduced risk of CRC in men (HR, 0.55 [95% CI, 0.33 to 0.91]) but not in women (HR, 0.84 [95% CI, 0.49 to 1.07]); however, the interaction was not significant (p=0.32).[161] In the CPSII Nutrition Cohort, the association between CRC risk and current daily aspirin use of ≥5 years was significant in women (RR, 0.45 [95% CI, 0.24 to 0.86]) but not in men (RR, 0.76 [95% CI, 0.55 to 1.04]); however the difference was not statistically significant (p-interaction not reported).[156] Findings of difference could also be due to multiple comparisons and chance.

Race

None of the RCTs or cohort studies stratified results by race. Rothwell and colleagues[85] and PHS[135] did not report the racial distribution of participants; however, based on the countries of origin, the majority of participants were likely white. In WHS, 94.8 percent of participants were white.[115] Among the cohort studies, many did not report race;[153,160,171] in those that did, nearly all

participants (>90%) were white (NHS, HPFS, VITAL, and CPSII Nutrition Cohort),[146,152,156,161] except in WHI (83.4% white).[164]

Comorbidities

None of the RCTs or cohort studies stratified results by comorbidities. Many comorbidities of interest were not reported. WHS and PHS excluded persons with CVD and some other chronic diseases, while Rothwell and colleagues[85] included data from both primary and secondary CVD prevention studies.

Baseline Cancer Risk

Studies of patients with a prior adenoma are described below. None of the included RCTs stratified by baseline CRC risk. One cohort study (NHS) examined the association between aspirin use and CRC incidence according to first-degree family history of CRC. Point estimates were very similar: RR, 0.76 (95% CI, 0.57 to 1.02) for women with a family history and RR, 0.78 (95% CI, 0.67 to 0.90) for women without a family history (p-interaction not reported).[146]

Detailed Findings: Aspirin and Colorectal Cancer Incidence in Patients With a Prior Adenoma

In an IPD meta-analysis, Cole and colleagues reported pooled cumulative CRC incidence percentages across ukCAP, AFPP, and APACC (N=2332).[123] They found that CRC incidence in aspirin groups across the three trials was 0.54 percent compared to 0.62 percent in the control groups (p=0.81) during the 3- to 4-year study followup periods. No additional information on incidence was presented.

More detailed results were available from the ukCAP[144,145] and AFPP[136] trials (**Table 5**, **Figure 8**). Both ukCAP and AFPP randomized patients to daily aspirin use with doses ranging from 81 mg to 325 mg for intended durations of 3 to 4 years. Only persons who received the followup colonoscopy were included in the ukCAP analysis (90.8%) but all randomized participants in AFPP were included (N=1,121). In the ukCAP study, CRC incidence appeared lower in the aspirin group than the placebo group (0.7 vs. 1.7%; p-value not reported) (**Table 5**). In contrast, in AFPP, more persons in the aspirin groups developed CRC than in the control group (0.5% in the 81 mg/day aspirin group and 0.8% in the 325 mg/day aspirin group vs. 0.3% in the control group); however, differences across the three groups were not statistically significant (p=0.71). Because of the small number of studies and inconsistent findings we did not pool results.

Our search did not identify eligible cohort studies that examined the risk of CRC in relation to aspirin use among persons with a prior adenoma.

KQ 5. Does Regular Aspirin Use Reduce the Incidence of Colorectal Adenoma in Adults Without a History of Colorectal Cancer, Familial Adenomatous Polyposis, or Lynch Syndrome?

Summary of Results

For this KQ, we focused on colorectal adenomas specifically, not polyps in general. We did not find consistent evidence demonstrating reduced risk of colorectal adenoma incidence with aspirin use. Evidence for persons selected without consideration of adenoma history was limited to a single cohort study that found a statistically significant reduced risk of at least one distal adenoma (32 to 43%) with use of aspirin that was at least every other day, daily, or multiple times per day. Three RCTs (N=2,338 randomized) were conducted in persons with a prior adenoma. Data from an IPD meta-analysis of these studies by Cole and colleagues suggested a reduced risk of adenoma over a 3- to 4-year period with 81 or 160 mg/day of aspirin (RR, 0.83 [95% CI, 0.71 to 0.96]);[123] however, the effect of 300 or 325 mg/day over a 3- to 4-year period was unclear.

Detailed Results: Aspirin and Adenoma in the General Population

For KQ 5, we did not identify any RCTs of aspirin in the general population. WHS and PHS reported on polyp incidence in general (assessed via self-report) and were therefore excluded because they did not report specifically on adenoma incidence. Two cohort studies (NHS and HPFS) reported on the association between aspirin use and adenoma incidence in the general population, but HPFS was excluded for this KQ because the exposed category (regular aspirin users) was not restricted to daily or alternate-day users. In contrast, the NHS reported on the risk of ≥1 distal adenoma (<60 cm from anus) by number of 325 mg tablets per week.[147] As before, we assumed that persons who used 6 to 14 or more than 14 tablets per week were using aspirin at least every other day. Adenomas were ascertained by self-report followed by blinded medical record review by study physicians to determine histology. Chan and colleagues reported a reduced risk of adenoma incidence associated with 6 to 14 tablets/week (RR, 0.68 [95% CI, 0.55 to 0.84]) and more than14 tablets/week (RR, 0.57 [95% CI, 0.42 to 0.77]) of aspirin. Duration of followup was not specified, but RRs were adjusted for duration of aspirin use. In stratified analyses, the risk reduction associated with tablets per week appeared stronger for women reporting short-term (≤5 years) aspirin use compared to women reporting long-term aspirin use (>5 years): the RR for more than 14 tablets/week was 0.36 (95% CI, 0.19 to 0.71) among short-term users and 0.52 (95% CI, 0.38 to 0.72) for long-term users. RRs were attenuated when limited to nurses reporting regular use on three surveys compared to nonregular users on three consecutive surveys (6 to 14 tablets/week: RR, 0.80 [95% CI, 0.59 to 1.10]; more than 14 tablets/week: RR, 0.59 [95% CI, 0.38 to 0.92]).

Detailed Results: Aspirin and Adenoma Incidence in Patients With a Prior Adenoma

Three RCTs (two good quality, one fair quality) assessed the effect of aspirin on colorectal adenoma incidence among persons with a prior adenoma: APACC, ukCAP, and AFPP. In addition to the trial reports, we also examined an IPD meta-analysis by Cole and colleagues in 2009.[123] We did not identify any cohort studies addressing KQ 5 for persons with a prior adenoma.

All three RCTs required that participants recently had an adenoma removed with none remaining. The average age of participants was 57 to 58 years in all three studies; women constituted 30 to 43.1 percent of the study populations. All trials reported on adenoma incidence and advanced lesions at 3 to 4 years (**Table 6**). In addition, APACC reported on adenomas at the 1-year colonoscopy. For APACC (**Table 6**), we present the results from the 4-year colonoscopy, which was the primary endpoint. The 1-year and last colonoscopy (which was the 1-year or the 4-year colonoscopy) results are in **Appendix D Table 6**.

In APACC (fair quality), the incidence of adenoma was lower in the 160 mg/day aspirin arm (27%) compared to placebo (40%) and the incidence in the 300 mg/day arm (57%) was higher than the placebo group (**Table 6**, **Figure 9**), but the differences were not statistically significant. In AFPP, the 81 mg/day aspirin group but not the 325 mg/day aspirin group had a statistically significantly reduced adenoma risk compared to placebo (38.3%, 45.1%, and 47.1%, respectively) although the p-value comparing doses was not significant. In ukCAP, 300 mg/day aspirin appeared protective (RR, 0.79 [95% CI, 0.63 to 0.99]). Results for risk of advanced lesion and mean adenoma number generally paralleled those for any adenoma.

Because of the small number of studies and inconsistent results, we did not pool estimates; however, Cole and colleagues reported a summary estimate based on individual patient data for 81 mg/day or 160 mg/day doses of aspirin (AFPP and APACC, N=1393) of RR, 0.83 (95% CI, 0.71 to 0.96) for any adenoma and RR, 0.83 (95% CI, 0.44 to 1.58) for advanced lesions.[123] Of note, Cole and colleagues used the results from the last APACC colonoscopy (1 or 4 years) rather than the 4-year results. Because the estimates included results from the study of persons with a history of CRC (excluded from our review), we do not report their pooled results for any dose of aspirin or aspirin at 300 or 325 mg/day. For similar reasons, we do not include their results from subgroup analyses.

Timing of Effect

In 2003, the APACC study reported a benefit for aspirin on adenoma prevention after one year (**Appendix D Table 6**). In the aspirin groups combined, 30.2 percent had an adenoma recurrence, compared to 41.1 percent in the placebo group. In 2009, Cole and colleagues further explored the timing of benefit across all three studies, APACC, ukCAP, and AFPP.[123] We could not use the pooled results from Cole and colleagues as they included results from a trial among people treated for CRC. However, they reported RRs by study by interval after randomization (**Appendix D Table 7**). Based on ukCAP and APACC data, risk of colorectal adenoma recurrence appeared to be approximately 34 to 38 percent reduced in the first year of treatment (doses analyzed at one year were 160 mg/day or 300 mg/day). No clear indication of reduced

risk was observed during the other followup intervals. Limitation of these interval analyses were that not all colonoscopies occurred at the time prescribed by the study protocols and numbers were small.

KQ 7. What Are the 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, or Lynch Syndrome?

Summary of Results

A comprehensive review of the harms of aspirin use is included in a concurrent systematic evidence review prepared for the USPSTF. The results in this section are limited to studies of aspirin that reported on colorectal adenoma incidence, CRC incidence, or mortality (CRC-specific or all-cause). All 14 of the RCTs that reported on KQs 1/3, 4, or 5 reported on at least one harm of aspirin use; however, only one included cohort study reported harms (NHS). For KQ 7, we did not stratify results by adenoma history. Most studies reported on harms during scheduled treatment duration, the median of which was between 2.6 and 10.1 years; however, WHS included events during post-trial followup (median 17.5 years from randomization). Twelve RCTs (all except ETDRS and APACC) reported on gastrointestinal bleeding. Compared to controls, patients assigned to aspirin had higher risks of gastrointestinal bleeding (**Table 7**, **Figure 10**) and serious gastrointestinal bleeding (summary OR, 1.94 [95% CI, 1.44 to 2.62]) (**Table 7**, **Figure 11**). Results were not consistent for fatal gastrointestinal bleeding (**Table 7**, **Figure 12**). Intracranial bleeding data were available from 12 RCTs. Patients randomized to aspirin had a higher risk of intracranial bleeding than control patients (summary OR, 1.53 [95% CI, 1.21 to 1.93]) (**Table 8**, **Figure 13**). Aspirin users had a higher risk of hemorrhagic stroke than controls (summary OR, 1.47 [95% CI, 1.16 to 1.88]) (**Table 9**, **Figure 14**). We did not identify publications reporting on age-related macular degeneration as part of our systematic search strategy. However, two studies (WHS[172] and PHS[173]) reported on age-related macular degeneration in other publications; those results are described in the concurrent evidence review for the USPSTF on total cancer, ACM, and harms. For all harms outcomes, very limited data were available on effect modification by age, sex, race, comorbidities, or concomitant medication use and are analyzed in more detail with additional studies in the companion evidence review.

Detailed Results: Gastrointestinal Bleeding

We identified 12 RCTs (seven good quality, five fair quality) comparing gastrointestinal bleeding risk among patients randomized to aspirin vs. placebo (**Table 7**). The median intended treatment duration was 2.6 to 10.1 years. Ten trials were of daily or alternate day aspirin in the general population: WHS, PHS, BMD, UK-TIA, SALT, TPT, SAPAT, JPAD, POPADAD, and AAA. In addition, two RCTs conducted among patients with a prior adenoma (ukCAP and AFPP) also reported on gastrointestinal bleeding. All studies excluded patients with a history of

bleeding, ulcers, contraindication on aspirin, or history of adverse effects from aspirin. All but two studies examined doses ≤325 mg/day, most of which were ≤100 mg/day.

In our analysis of any gastrointestinal bleeding, we examined results from 11 trials (N=79,542). We excluded BMD because it reported on fatal gastrointestinal bleeding only. In most trials, the incidence of gastrointestinal bleeding was higher in the aspirin group than the control group (**Table 7**, **Figure 10**); however, most studies had too few events to report RR estimates. We did not pool results because definitions of gastrointestinal bleeding differed across studies (i.e., some restricted to serious bleeds).

Serious gastrointestinal bleeds were those requiring transfusion or hospitalization, resulting in death, requiring surgical intervention, or defined as severe or major by the authors if not otherwise specified. Studies that reported only fatal events only were excluded from analyses of serious gastrointestinal bleeding because of incomplete capture of serious events. In the eight studies that reported on serious gastrointestinal bleeds (PHS, TPT, UK-TIA, SAPAT, AAA, AFPP, JPAD, and SALT) (N=37,451), the incidence was nearly twice as high in persons randomized to aspirin (0.64%) as in persons randomized to placebo (0.29%); in all but one study, the incidence was higher in the aspirin group than the control group (**Table 7**, **Figure 11**) (summary OR, 1.94 [95% CI, 1.44 to 2.62]).

Six studies reported on fatal gastrointestinal bleeding (N=74,096). Combining PHS, WHS, BMD, UK-TIA, TPT, and SAPAT data (Table 7, Figure 12), we estimated the incidence of fatal bleeding to be 0.03 percent in patients assigned to aspirin compared to 0.02 percent in patients assigned to placebo. RR estimates were not consistent across studies: three had computed ORs greater than one, two had ORs less than one, and one had and OR equal to one. The summary OR was 1.00 (95% CI, 0.43 to 2.36). In the single study that compared two different doses of aspirin to placebo (UK-TIA, N=2,435), there was a suggestion of increased risk of gastrointestinal hemorrhage in the higher-dose aspirin group (1,200 mg/day) than the lower-dose group (300 mg/day) (5% vs. 3%) during a median follow-up of 4.4 years (OR=1.62, [95% CI: 0.94 to 2.79]).

We identified one cohort study that assessed the risk of gastrointestinal bleeding in aspirin nonusers and users at doses and frequencies relevant for this review. NHS reported a higher risk of serious gastrointestinal bleeding in users of 6 to 14 tablets/week of 325 mg aspirin (1.40 per 1,000 person-years) and users of more than 14 tablets/week of 325 mg aspirin (1.57 per 1,000 person-years) compared to nonusers (0.77 per 1000 person-years).[146]

In summary, evidence primarily from RCTs suggested a two-fold increase in risk of serious gastrointestinal bleeding associated with daily or alternate-day aspirin use, but the effects on any gastrointestinal bleeding and fatal gastrointestinal bleeding were less clear.

Detailed Results: Intracranial Bleeding, Including Hemorrhagic Stroke

Definitions of intracranial bleeding differed across studies. Where possible, we summed the number of events of hemorrhagic stroke, subarachnoid hemorrhage or stroke, and epidural and subdural hematoma. Not all event types were reported in all studies. Thus, the estimates in **Table 8** have slightly different interpretations by study; however, within each study the definition was

identical for aspirin users and controls. A total of 12 RCTs were included (N=84,681) (**Table 8**, **Figure 13**). The median intended treatment duration was 2.6 to 10.1 years. Nine studies tested doses of aspirin were ≤100/day. In 11 of 12 studies, the incidence of intracranial bleeding in the aspirin group was equal to or higher than the control group. Overall, the incidence across aspirin groups was 0.40 percent compared to 0.26 percent in the control group. The summary OR was 1.53 (95% CI, 1.21 to 1.93).

Detailed Results: Hemorrhagic Stroke

Eleven RCTs reported on hemorrhagic stroke: WHS, PHS, BMD, UK-TIA, TPT, SALT, SAPAT, JPAD, POPADAD, AAA, and AFPP (N=83,742) (**Table 9**, **Figure 14**). In nearly all studies, the risk of hemorrhagic stroke was higher in the aspirin group than in the control group. Combining results across studies, the incidence of hemorrhagic stroke was 0.38 percent in the aspirin groups and 0.25 percent in the control groups (summary OR, 1.47 [95% CI, 1.16 to 1.88]). In UK-TIA, the risk of major and/or fatal definite hemorrhagic stroke was slightly higher among women than men in both the 1,200 mg/day aspirin group (men: 0.7%, women: 1.4%) and the 300 mg/day aspirin group (men: 0.8%; women: 1.0%), but not the placebo group (men: 0.3%; women: 0%); however the total number events was small (N=16). In the only study that compared doses of aspirin (UK-TIA, N=2,435), the incidence was identical (0.9%) in the two aspirin groups (1,200 mg/day vs. 300 mg/day); however each group had only seven events. None of the included cohort studies reported intracranial bleeding.

None of the included cohort studies reported on hemorrhagic stroke.

Contextual Question. What Is the Level of Persistence of Aspirin Use Among Adults Who Initiate a Regimen for the Prevention of Colorectal Cancer?

Our contextual question focused on *persistence* (continued use after initiation) of aspirin for CRC prevention; however, the body of evidence we examined was broader in two respects. First, some of the studies reported on *adherence* (use as directed), sometimes called compliance, rather than persistence. Second, we included literature that focused on aspirin for CVD prevention, as much of the data on benefits came from such studies. Adherence and persistence had varying definitions and ascertainment across studies. In general, we could not obtain information on persistence from cohort studies.

We summarized persistence and adherence information by indication for use, as evidence supports varying rates of adherence by indication with higher rates in individuals who use aspirin for secondary prevention or have a greater risk profile for the disease of interest.[174] **Appendix D Table 8** provides adherence information from RCTs and one observational study. Our primary interest was aspirin persistence rather than overall persistence in RCTs, which was generally lower than placebo in most trials reporting separate estimates.

Data for primary CRC prevention were the most relevant for this contextual question. These data were available from three trials focused on CRC prevention in persons with a prior adenoma; all

three suggested high compliance within one year (87 to 95% from APACC and AFPP) and two years (91%) (AFPP). APACC reported 88 percent compliance at four years and ukCAP reported 75 percent at year three. Two RCTs targeted CVD prevention and cancer prevention in general (not CRC specifically). Both were conducted among U.S. healthcare professionals. The WHS (women) reported 88 percent 1-year compliance, 76 percent 5-year compliance, 67 percent 10-year compliance. PHS (men) reported 83 percent 4.75-year persistence. Of note, both WHS and PHS reported measures for aspirin and placebo groups combined.

The main primary prevention persistence/adherence literature came from CVD trials. We identified data from 12 RCTs focused on aspirin use for primary CVD prevention. Nearly all studies reporting multiple persistence/adherence measures over time demonstrated declines over the course of the trial. Ten trials reported persistence/adherence within the first year or at year one of 80 to 92 percent. Reported persistence/adherence dropped in all studies except the Primary Prevention Project (PPP),[175] which maintained 81 percent persistence from the first trial year to 3.6 years. By 5 years, 58 to 83 percent of individuals in the CVD primary prevention studies were still persistent/adherent to treatment.

Aspirin persistence/adherence for secondary prevention of CVD was reported in 13 trials[86,108,111,112,121,126-128,130-133,136,142,144,175-189] and one observational study.[190] People with CVD taking aspirin for secondary prevention are theoretically the least relevant group for estimating persistence/adherence among individuals taking aspirin for CRC chemoprevention; however, we found no notable differences in reported adherence relative to the primary prevention trials. The persistence/adherence measures might not have been sensitive enough to detect differences or no differences may exist between primary and secondary CVD prevention users. A recent systematic review suggested adherence generally ranged from 72 to 92 percent over varying followup periods (generally <2 years).[174]

Real-world persistence may be best reflected in observational studies. However, we included only a single cohort study[190] since others we reviewed had limitations in ascertainment of exposure (prior use). The cohort study we included ascertained dispensing data including strength, number of pills dispensed and instructions for use, enabling calculation of daily dose and adherence. In a population from Tayside, Scotland receiving aspirin for secondary CVD prevention,[190] short-term adherence was substantially lower than reported in RCTs (58% at year one vs. 80 to 92 percent in primary CVD prevention RCTs, and 56% at five years vs. 50 to 83 percent in RCTs).

Duffy and colleagues recently reviewed the current literature on aspirin therapy adherence for primary and secondary CVD prevention.[174] The literature on adherence rates, reasons for medication adherence, strategies for improving adherence, predictors of poor patient compliance and interventions for improving adherence are outlined in detail in their review.[174] Of the 12 articles identified in the review, only two focused exclusively on populations taking aspirin for primary prevention and one focused on primary and secondary prevention combined. The review discusses how factors related to patients, providers, and medications can influence adherence. An additional factor affecting adherence to aspirin for prevention is that its use is largely for asymptomatic disease; this factor is associated with lower adherence.[174] Another factor influencing adherence that might be less well known is the mode of use recommendation or

prescription. Receiving a prescription for low-dose aspirin can lead to increased adherence relative to over-the-counter recommendations from providers.[191]

In summary, we found that in RCTs, persistence/adherence to aspirin was generally high (≥85%) in the first year, declining to 50 to 83 percent after three to five years, with substantial variability across studies.

Chapter 4. Discussion

Summary of Evidence

Table 10 presents our summary of benefits and harms across all KQs.

Outcomes in Patients Selected in the General Population

Colorectal Cancer Incidence and Colorectal Cancer Mortality

We identified 11 RCTs and seven cohort studies reporting on aspirin and CRC outcomes or ACM in the general population. In these studies, aspirin appeared to reduce the risk of both CRC incidence and CRC mortality. Timing of aspirin use was important: the effect of aspirin use on these endpoints did not appear until approximately 10 years after treatment initiation. The observed latency in the effect did not necessarily correspond to duration of aspirin use. In fact, we did not find evidence that 10 years of use was absolutely required to achieve an effect on CRC incidence and CRC mortality. Many of the studies that reported an effect of aspirin on CRC incidence and mortality had average scheduled treatment durations of approximately 5 years. Thus, the observed lag in effect is probably not solely a function of longer duration of use. The latency in effect is consistent with the hypothesis that aspirin reduces adenoma development and progression into carcinoma over a period of many years. However, we could not evaluate this hypothesis directly: we were unable to find any RCTs and found only a single cohort study that reported the effect of aspirin on adenoma development in persons without a prior adenoma. Data from the cohort study were consistent with an impact on reduced adenoma incidence, but limited to a single population (women).

Although duration of use is unlikely to explain the latency in effect of aspirin on CRC incidence and CRC mortality entirely, we cannot rule out an association between duration of use and magnitude of effect. While there was some indirect evidence of an effect of duration of aspirin use, the only direct evidence supporting the potential importance of duration of use came from a single RCT[111] and several cohort studies.[160,161] Since most of the included studies had a scheduled duration of 5 years,[83,85,111,135] we can draw only limited conclusions about short durations of use. We did not find evidence on a minimum required duration of use to prevent CRC incidence or CRC mortality.

All RCT data on aspirin and late or long-term risk of CRC mortality came from studies of daily aspirin use at 75 to 1,200 mg/day for primary and secondary CVD prevention.[83,85] Point estimates were similar across the studies during comparable time intervals and did not suggest a difference by dose at or above 75 mg/day. However, only one trial reporting long-term CRC mortality (TPT) evaluated a low-dose ($\leq$ 325 mg/day) aspirin intervention in a population without pre-existing CVD and no long-term studies of CRC mortality included women without pre-existing CVD. Data on late effects or long-term effects were not available from the two large U.S. primary prevention studies (WHS and PHS). Thus, when thinking about these results, carefully considering to whom they would be applied is crucial. In contrast, data on the association between CRC incidence and aspirin use were available from studies of daily and

alternate-day aspirin use, thus more completely representing the primary CVD prevention population.[113,135] Results were consistent across studies.

All-Cause Mortality

There was a small reduction in ACM within a 10-year interval from randomization. Point estimates were similar across 11 RCTs with varied doses and frequency of aspirin use (summary RR, 0.94 [95% CI, 0.89 to 0.99]). Average age at entry for the RCTs was 50 to 60 years. Although statistically significant, the upper confidence interval was near 1.0, possibly reflecting variations in effect by the doses and durations tested, as well as the studies included; for example, the RCTs included studies of primary and secondary prevention of CVD.[83]

We posit that aspirin's effect on ACM was smaller than its effect on CRC mortality for several reasons. First, we note that most of the ACM data were collected within 10 years of treatment initiation, when we did not observe an effect on CRC incidence or CRC mortality. Second, CRC mortality is only one component of ACM. Lack of an effect or an increase in other causes of death could outweigh a reduction in risk of CRC mortality.

Outcomes in Persons With a Prior Adenoma

We found three RCTs (two good quality, one fair quality) of aspirin in persons with a prior adenoma who were adenoma-free at baseline.[136,142,144] Two trials provided evidence of a reduced risk of adenoma recurrence with low-dose aspirin (81 to 160 mg/day) over three to four years.[136] Two showed a reduced risk of 1-year adenoma recurrence with doses of 160 mg/day or 300 mg/day.[123] Evidence for adenoma prevention with 300 to 325 mg/day over three to four years was inconsistent.

Data on CRC incidence and ACM were available from all three trials over the 3- to 4-year followup period. Event numbers were very low, but did not suggest differences between aspirin and placebo groups. Followup time points would not be sufficient to detect an impact on these outcomes if they were delayed 10 years, as was observed in the general population. None of the studies reported on CRC mortality.

Harms

We found evidence that aspirin increases the incidence of gastrointestinal bleeding (any and serious), intracranial bleeding, and hemorrhagic stroke. Evidence for fatal gastrointestinal bleeding was less consistent across studies. However, many of our analyses were limited by low event rates. As described below in the Limitations section, the harms literature considered for this review was a subset of all available evidence, as it was limited to studies that also reported on CRC outcomes. A comprehensive review of harms of aspirin is included in a concurrent systematic evidence review prepared for the USPSTF.

Other Systematic Reviews

Several other systematic reviews have been conducted on aspirin and CRC prevention, including the review conducted for the USPSTF in 2007.[81] In this section, we compare and contrast our findings and propose explanations for noted differences between reviews. We limit our discussions to reviews published since 2007, as earlier reviews had access to a smaller body of literature. As described below, the primary reasons for differences are: 1) our review focused on people without high-risk genetic conditions (e.g., FAP, Lynch syndrome) or CRC; 2) our review focused on RCTs and cohort studies, primarily to fill evidence gaps on duration, frequency, and dose; and 3) our review had access to more recent data.

2007 Review for the USPSTF

In 2007, Dube and colleagues conducted a systematic evidence review for the USPSTF on aspirin for CRC prevention.[81] They found limited and inconsistent evidence on aspirin and CRC mortality. Low-dose aspirin (100 mg or 325 mg every other day) did not decrease CRC incidence. There was fair evidence that high-dose use reduced CRC incidence; however, Dube and colleagues reported good evidence that aspirin reduced adenoma risk. At the time of the prior review, no RCTs had reported on CRC mortality. Since the publication of that review, Flossman and colleagues[111] and Rothwell and colleagues[83,85,86] published data on CRC outcomes during long-term followup using several trials of aspirin for CVD prevention, though these analyses included high-dose interventions and populations with preexisting CVD. Short-term CRC mortality data were available from the followup of seven studies by Rothwell and colleagues.[83,85] However, for CRC incidence, we were also able to include longer-term followup from WHS.[113] These data enabled us to look at CRC risk by followup period, which was not possible in 2007. Our observation of a lack of an early onset effect (0 to 10 years) of aspirin on CRC incidence was consistent with the Dube and colleagues' report on data available in 2007. The additional data permitted us to examine a potentially longer lag in the effect of aspirin on CRC incidence.

The 2007 Dube and colleagues review[81] found evidence that aspirin reduced the risk of colorectal adenomas. We did not find strong evidence for this risk reduction. Dube and colleagues included PHS but we did not since PHS reported on all polyps but not specifically on adenomas. Our review also included 4-year, full-trial data from APACC, which was not available in 2007.[142] Finally, ukCAP was published since the prior review.[144] Based on these new findings, we did not find consistent evidence of a reduced risk of adenoma associated with aspirin use, but we could also not rule out the possibility of reduced risk.

Meta-Analyses by Rothwell and Colleagues

Flossman and colleagues[111] and Rothwell and colleagues[83-85] published four IPD meta-analyses relevant to our systematic review. We identified only two RCTs (WHS and PHS) that were not included in at least one of the Rothwell analyses; thus, our results are fairly similar to the Rothwell and colleagues' reports.

In 2007, Flossman and colleagues published long-term followup data for CRC incidence from two RCTs of daily aspirin for CVD prevention (BMD and UK-TIA) covering 300 mg/day, 500 mg/day, and 1,200 mg/day doses.[111] Subsequently, Rothwell and colleagues expanded this work to examine both CRC incidence and CRC mortality in these studies plus two other studies of low dose (75 mg/day) aspirin (SALT and TPT).[85] In 2011, Rothwell and colleagues pooled individual patient data to study ACM (eight trials) and CRC mortality (six studies);[83] these results were included in our review. Where results from individual trials were available, we included trial-level data. Otherwise, we recorded pooled estimates as reported. The results from Rothwell and colleagues were very influential on our review. They were the only data source for CRC mortality,[83,85] although Cook and colleagues reported there was no early effect on CRC mortality in WHS (no data provided by randomization group).[112] For CRC incidence, we also included data from PHS and WHS, which studied alternate-day aspirin use. Our findings were generally similar to Flossman and colleagues[111] and Rothwell and colleagues[83-85] and complementary, because they provide some evidence of consistency of effect by gender (through inclusion of WHS) and alternate-day aspirin use.

In 2012, Rothwell and colleagues performed a meta-analysis on cancer incidence and mortality using data from 51 trials of daily aspirin.[84] Data were from 34 trials with in-trial (duration unspecified) CRC mortality data, from which Rothwell and colleagues computed OR, 0.58 (95% CI, 0.38 to 0.89) for the association between aspirin use and CRC death. We excluded these results in our review because we could not identify which 34 studies were selected to generate the computed OR and whether they all met our inclusion criteria. Nevertheless, the results of this meta-analysis are important because they provide different information to the previous Rothwell and colleagues reports,[83,85] which were the sole sources of data on CRC mortality we identified in our systematic review. The 2012 Rothwell report focused on the effects of aspirin during the trial period (in contrast to the earlier report, which examined extended follow-up). Most of the trials had mean treatment periods less than five years. Thus, the data from Rothwell and colleagues in 2012[84] suggest that the effect of aspirin on CRC mortality may occur earlier than previously thought, i.e., effects may manifest within 10 years after initiation of aspirin.

Cooper 2010 Health Technology Assessment

As part of the United Kingdom Health Technology Assessment program, Cooper and colleagues prepared a systematic review on chemoprevention of CRC.[63] Aspirin was one of the included agents. Their review of RCTs in the general population, i.e., "individuals at no increased risk of colorectal cancer" yielded four studies: WHS, PHS, BMD, and UK-TIA. These four studies were also included in our review. Qualitatively, our results were similar to the Cooper and colleagues 2010 review, which reported no reduction in risk of incident CRC with followup ≤10 years (pooled RR, 1.01 [95% CI, 0.84 to 1.21]). They reported a reduced risk of CRC during long-term followup in the higher-dose aspirin studies (pooled RR, 0.74 [95% CI, 0.57 to 0.97]), especially during 10 to 19 years of followup (pooled RR, 0.61 [95% CI, 0.43 to 0.88]). Rothwell and colleagues[85] reported a similar finding for long-term followup when data from two very low dose (75 mg/day) trials were included.

Cooper and colleagues also reviewed the literature on RCTs of aspirin use in "intermediate-risk" persons, i.e., those with a prior adenoma (three studies) or CRC (one study). They reported a pooled RR for any adenoma recurrence (across the four studies) of 0.79 (95% CI, 0.68 to 0.92).

Our review differed from Cooper and colleagues in two important ways. First, we excluded studies of patients with a prior CRC, for which the point estimate contributing to the Cooper meta-analysis was RR, 0.61 (95% CI, 0.44 to 0.86) and contributed a weight of 15.1 percent to the pooled estimate. Second, the results from the APACC trial that Cooper and colleagues included were from one year, whereas ours were from four years. APACC observed a benefit at one year but not four years for combined aspirin groups. Thus, the differences between our findings and those in Cooper and colleagues can be explained by differences in data sources.

2013 Health Technology Assessment Review

In their 2013 Health Technology Assessment systematic review, Sutcliffe and colleagues synthesized results from RCTs, systematic reviews, and meta-analyses published since 2008 and report results similar to ours. Using Sutcliffe and colleagues reference list[168,169] we identified one systematic review we had not already retrieved,[192] but no additional sources of primary data. The main contribution of the review by Sutcliffe and colleagues to our report was that it provided an attributable risk (risk difference) of CRC deaths averted with aspirin, as reported in our results section (34 to 36 per 100,000 person-years).

Cole 2009

In 2009, Cole and colleagues published an individual meta-analysis using patient data from AFPP, APACC, and ukCAP, along with an aspirin RCT in people treated for CRC.[123] They concluded that aspirin reduces the risk of colorectal adenomas in people with prior lesions. We included some of their results for KQs 4 and 5. However, not all of their findings were pertinent to our review, because they included a study in people with a personal history of CRC; this is the primary explanation for differences in our conclusions and the conclusions of Cole and colleagues.

Systematic Reviews of Observational Studies

Two recent systematic reviews[80,82] assessed the evidence on aspirin and CRC incidence from observational studies and a third review[79] compared results from observational studies to RCTs. In general, the reviews were consistent, supporting a reduced risk of CRC with aspirin use. Combining case control and cohort studies, Bosetti and colleagues reported a pooled RR of 0.73 (95% CI, 0.67 to 0.79) for regular aspirin use (one or two tablets per week) and 0.66 (95% CI, 0.57 to 0.77) for daily aspirin use. They noted significant heterogeneity and some evidence of publication bias. Estimates of risk according to time since aspirin use were not provided; however, a slightly stronger reduction in risk was suggested for aspirin use ≥5 years compared to use less than 5 years. In addition, risk reduction was stronger for regular/high-dose (300 to 500 mg) compared to low-dose (~100 mg) aspirin use.

In 2013, Ye and colleagues published a systematic review of cohort studies of aspirin and CRC risk, focusing on risk associated with different doses and durations of use.[82] Our review included four of the five studies they included on dose. Of the nine studies they included for duration, we included seven. And, of the nine overlapping but not identical studies that they examined for frequency of use, we also included seven. We excluded studies because they were nested case-

control studies or were missing information on dose. In general, Ye and colleagues found greater CRC risk reduction with higher doses, longer use, and more frequent aspirin use; however, these associations were not linear. People who used aspirin seven times per week had a reduced risk of CRC (RR, 0.82 [95% CI, 0.78 to 0.87]). The RR associated with 75 mg/day increment of aspirin was 0.90 (95% CI, 0.86 to 0.94) compared to 0.80 (95% CI, 0.74 to 0.88) for 325 mg/day and a similar estimate for 650 mg/day. This finding was consistent with our observations for cohort studies but not RCTs.

Algra and Rothwell performed a systematic review published in 2012 to meta-analyze and compare results on the association between aspirin and CRC incidence from RCTs (N=6), "standard" cohort studies (N=11), nested case-control studies (N=6), and case-control studies (N=26).[79] Across all study designs, associations between aspirin and CRC based on pooled results were significant. The pooled OR estimate from case-control studies (0.67, [95% CI, 0.60 to 0.74]) was more similar to RCTs (OR, 0.58 [95% CI, 0.44 to 0.78]) than the estimate from cohort studies (OR, 0.85 [95% CI, 0.82 to 0.89]) or nested case-control studies (OR, 0.87 [95% CI, 0.75 to 1.00]). The authors attributed this finding to more detailed data collection on exposure in case-control studies. Nevertheless, their overall conclusion was that observational data provided results similar to RCT data.

Limitations of the Review and Future Research Needs

Our review has several limitations based on scope, methods, and the available data.

Scope

Because the review was conducted for the USPSTF, we limited our review to primary prevention of CRC in average-risk or intermediate-risk persons. We did not include persons with a history of CRC or known high-risk genetic conditions. There is a body of literature on the effectiveness of aspirin on CRC prevention in high-risk persons, but reviewing it was not within our scope based on our target audience. We also did not focus on short-term aspirin use (<1 year) or attempt to systematically address the benefit of aspirin combined with other interventions (pharmacological or otherwise).

Methods

We followed rigorous systematic review and meta-analysis approaches; however, several elements of our approach warrant discussion. We undertook this review in parallel with two concurrent reviews for the USPSTF (Aspirin for the Primary Prevention of Cardiovascular Events, and Aspirin Use in Adults: Total Cancer, All-Cause Mortality and Harms). Therefore, in our review, we obtained data on ACM and harms of aspirin only from studies that reported on CRC outcomes. Thus, our findings should be considered to come from a specific body of literature focused on CRC. For ACM and aspirin harms, this review should be interpreted alongside other aspirin topic reviews.

For KQ 5 (adenoma incidence), we included only studies with pathologically confirmed outcomes. We excluded studies with self-report of any polyp type (e.g., PHS, WHS). We might

have excluded some relevant data, but these data would not have directly informed our KQ of adenoma incidence and could be biased because of errors in self-report.

Excluding retrospective cohort studies and case-control studies may have influenced our results, primarily by excluding subgroups that may not have been well-represented in trials. However, our inclusion of prospective cohort studies offered some protection against this. Furthermore, as described above, a recent systematic review of observational studies and trials produced findings similar to those in this report.

Available Data

Data for our review came primarily from three sources: 1) long-term followup of trials of aspirin for CVD prevention; 2) two U.S. trials of aspirin for CVD and cancer prevention; 3) trials of aspirin for adenoma recurrence; and 4) prospective cohort studies. All included studies were of fair-to-good quality and had many strengths. Although not necessarily a limitation, all CRC mortality data and much CRC incidence and ACM data were collected as part of followup studies of CVD trials by Flossman and colleagues and Rothwell and colleagues.[83,85,111] No long-term data on CRC mortality were available from WHS or PHS for us to include in a meta-analysis.

The CRC data from the studies included by Rothwell (e.g., BMD, UK-TIA) are therefore not completely independent in the way they were collected and analyzed. This factor is not likely to affect the validity of the results, but is an important note about the size and variability of the literature. Our review yielded important information. However, data were insufficient to adequately address the following questions:

- Does the effect of aspirin on CRC incidence and mortality in average risk persons differ if use is daily or every other day?
- What is the effect of aspirin on CRC incidence and mortality in persons without a prior adenoma?
- Does aspirin reduce the risk of adenoma incidence in persons without a prior adenoma?
- Does aspirin reduce the long-term risk of all-cause or CRC-specific mortality in people with a history of adenoma?
- Does aspirin reduce the long-term risk of CRC incidence in people with a prior adenoma?
- Does the effect of aspirin on CRC incidence and mortality differ by age, sex, race, comorbidities, family history of cancer, or screening history?
- How long do the preventive effects of aspirin on CRC incidence and mortality last after aspirin is discontinued?
- Is there an optimal dose of aspirin for CRC prevention?

Disentangling the effects of recency and duration of aspirin use is inherently difficult. Recency has two dimensions: time since first use and time since last use. These can confound each another and both may be confounded by duration of use. For example, a person cannot have a long duration of use without a long time since first use; however the reverse is possible. We could not always assess the independent effects of these various components of timing of use. However, the consistency across studies in the timing of effect relative to first use (and across

different durations of use) provides some assurance that the observed association with time since first use was not completely confounded by duration. Exposure misclassification presents another challenge in understanding the effects of recency and duration of use. In RCTs, participants may not have followed the study protocol (or may have used aspirin during followup after the active intervention) and in cohort studies they may not have recalled or reported their use accurately. Both scenarios could affect interpretation of recency and duration of use results.

Applicability of Findings to Clinical Practice

In considering whether our findings are applicable to clinical practice in the U.S., we must address at least two important questions: 1) Are the trial populations representative of the U.S. population? And, in particular, how would findings apply to a population taking aspirin for CVD primary prevention? 2) Is aspirin persistence and adherence likely to differ in clinical practice compared to trials? Both questions address whether the benefits seen in trials are likely to be realized in practice.

Representativeness of trial populations is important if effectiveness or harms differ by subgroups (e.g., sex, race, comorbidities). The trials included in our systematic review were primarily among people who were white and did not have contraindications to aspirin, and with the exception of WHS, most trials were primarily in men. We did not find many direct comparisons of effects across subgroups defined by sex, race, or comorbidities, but the limited data we had comparing results across studies with different populations did not suggest differences by sex or CVD comorbidities. However, we did not have any data on potential differences in effect by race. This does not mean findings cannot be extrapolated to different racial and ethnic groups if we assume similar biological mechanisms of aspirin's effects, but we found no data supporting or refuting this assumption.

Adherence and persistence of aspirin use will likely influence effectiveness in clinical practice. The lowest persistence data from our review was from a single observational study using electronic dispensing data and suggested just over 50 percent persistence in the first year of use190 versus 80 to 92 percent reported in RCTs. As part of our analysis for our CQ, we found adherence and persistence levels to be highly consistent across studies regardless of population, country, or prevention target (i.e., adenoma recurrence, cancer prevention, primary CVD prevention, and secondary CVD prevention). Few trials required a run-in phase, suggesting that participants were not selected specifically for ability to comply. Ideally, one could obtain information on persistence from cohort studies in the general population. However, most cohort studies do not have data permitting analysis of persistence. Most present results according to duration of use, which is not the same as persistence. Short-term users may be current users who started recently as opposed to people who started in the past and discontinued. In sum, we have very little evidence on whether persistence and adherence in clinical practice are similar to trials.

Another important consideration for clinical practice is the timing of aspirin's benefits on CRC prevention. The available data suggested a latency of approximately 10 years from initiation of use. Therefore, benefits are not likely to be realized in people not expected to survive at least 10 years.

Conclusion

Our systematic review provides evidence that aspirin reduces the risk of CRC incidence and CRC mortality in average-risk people, with an apparent time to preventive effect of approximately 10 years. Evidence suggests the risk reduction can be attained with 75 mg/day; however, data on duration of use or persistence of effect after discontinuation were limited. However, the applicability of longer-term effects on CRC mortality may be limited, given the paucity of studies including women, low-dose interventions, and populations without preexisting cardiovascular disease.

To date, few studies have examined whether aspirin prevents adenoma incidence in an average-risk population. However, some evidence suggests that using low-dose aspirin over a short time is associated with reduced risk of adenoma recurrence among people with a prior adenoma. Additional data on long-term effects on CRC incidence and CRC mortality in persons with a history of adenoma were lacking, as were results on CRC mortality from PHS and WHS. Despite the apparent protective effect of aspirin on CRC incidence and CRC mortality, data on ACM more than 10 years after initiation were sparse. Data on the effect of aspirin within 10 years of initiation were available and suggested that aspirin does not appear to have a strong effect on ACM within this period and that its use is associated with risks such as intracranial bleeding, gastrointestinal bleeding, and hemorrhagic stroke.

Based on the evidence gaps identified in our review, important directions for future research are to: 1) assess potential differences in subgroups, including demographic characteristics, lifestyle factors, and biomarkers; and 2) determine how long CRC prevention benefits persist after different durations of use and intervals from initiation. Data on potential differences in effects by subgroup and length of benefits may have important implications for clinical practice.

References

1.   Dube C, Rostom A, Lewin G, Tsertsvadze A, Barrowman N, Code C, Sampson M, Moher D, Force USPST. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007;146(5):365-75.

2.   Rostom A, Dube C, Lewin G, Tsertsvadze A, Barrowman N, Code C, Sampson M, Moher D, U. S. Preventive Services Task Force. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007;146(5):376-89.

3.   U. S. Preventive Services Task Force. Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2007;146(5):361-4.

4.   Risio M. The natural history of adenomas. Best Pract Res Clin Gastroenterol. 2010;24(3):271-80.

5.   Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, Ackroyd F, Shike M, Kurtz RC, Hornsby-Lewis L, Gerdes H, Stewart ET, The National Polyp Study Workgroup. Prevention of colorectal cancer by colonoscopic polypectomy. N Engl J Med. 1993;329(27):1977-81.

6.   American Cancer Society. Cancer Facts & Figures 2014. Atlanta, GA: American Cancer Society, 2014 Document No.: 500814.

7.   Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin. 2014;64(1):9-29.

8.   Murtaugh MA, Ma K-N, Caan BJ, Slattery ML. Association of fluids from beverages with risk of rectal cancer. Nutr Cancer. 2004;49(1):25-31.

9.   Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA. Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer. 2010;116(3):544-73. PMCID: PMC3619726.

10.   Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst. 2011;103(2):117-28. PMCID: PMC3107566.

11.   Sturmer T, Buring JE, Lee IM, Kurth T, Gaziano JM, Glynn RJ. Colorectal cancer after start of nonsteroidal anti-inflammatory drug use. Am J Med. 2006;119(6):494-502. PMCID: PMC1475702.

12.   Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):104-17.

13.   Roy HK, Bianchi LK. Differences in colon adenomas and carcinomas among women and men: potential clinical implications. JAMA. 2009;302(15):1696-7. PMCID: PMC2913287.

14.   Nguyen SP, Bent S, Chen YH, Terdiman JP. Gender as a risk factor for advanced neoplasia and colorectal cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2009;7(6):676-81 e1-3.

15. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Colon and Rectum Cancer. Bethesda, MD: National Institutes of Health; [cited December 21 2014]; Available from: http://seer.cancer.gov/statfacts/html/colorect.html.

16. Regula J, Rupinski M, Kraszewska E, Polkowski M, Pachlewski J, Orlowska J, Nowacki MP, Butruk E. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. N Engl J Med. 2006;355(18):1863-72.

17. Brenner H, Hoffmeister M, Arndt V, Haug U. Gender differences in colorectal cancer: implications for age at initiation of screening. Br J Cancer. 2007;96(5):828-31. PMCID: PMC2360074.

18. Lieberman D. Race, gender, and colorectal cancer screening. Am J Gastroenterol. 2005;100(12):2756-8.

19. Yeh RK, Chen J, Williams JL, Baluch M, Hundley TR, Rosenbaum RE, Kalala S, Traganos F, Benardini F, del Soldato P, Kashfi K, Rigas B. NO-donating nonsteroidal antiinflammatory drugs (NSAIDs) inhibit colon cancer cell growth more potently than traditional NSAIDs: a general pharmacological property? Biochemical Pharmacology. 2004;67(12):2197-205.

20. Agrawal S, Bhupinderjit A, Bhutani MS, Boardman L, Nguyen C, Romero Y, Srinivasan R, Figueroa-Moseley C, Committee of Minority Affairs and Cultural Diversity, American College of Gastroenterology. Colorectal cancer in African Americans. Am J Gastroenterol. 2005;100(3):515-23; discussion 4.

21. Ulrich CM, Bigler J, Sparks R, Whitton J, Sibert JG, Goode EL, Yasui Y, Potter JD. Polymorphisms in PTGS1 (=COX-1) and risk of colorectal polyps. Cancer Epidemiology, Biomarkers & Prevention. 2004;13(5):889-93.

22. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: a meta-analysis. J Natl Cancer Inst. 2005;97(22):1679-87.

23. Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? Am J Gastroenterol. 2011;106(11):1911-21; quiz 22.

24. Butterworth AS, Higgins JP, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer. 2006;42(2):216-27.

25. Johns LE, Houlston RS. A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol. 2001;96(10):2992-3003.

26. Taylor DP, Burt RW, Williams MS, Haug PJ, Cannon-Albright LA. Population-based family history-specific risks for colorectal cancer: a constellation approach. Gastroenterology. 2010;138(3):877-85. PMCID: PMC2831153.

27. Burt RW. Colon cancer screening. Gastroenterology. 2000;119(3):837-53.

28. Lynch PM. Does regular use of aspirin reduce the risk of colorectal cancer? Nat Clin Pract Oncol. 2006;3(4):186-7.

29. Huang CS, Farraye FA, Yang S, O'Brien MJ. The clinical significance of serrated polyps. Am J Gastroenterol. 2011;106(2):229-40; quiz 41.

30. Snover DC. Update on the serrated pathway to colorectal carcinoma. Hum Pathol. 2011;42(1):1-10.

31. O'Brien MJ, Winawer SJ, Zauber AG, Gottlieb LS, Sternberg SS, Diaz B, Dickersin GR, Ewing S, Geller S, Kasimian D, et al. The National Polyp Study. Patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. Gastroenterology. 1990;98(2):371-9.

32. Cappell MS. Pathophysiology, clinical presentation, and management of colon cancer. Gastroenterol Clin North Am. 2008;37(1):1-24, v.

33. Pino MS, Chung DC. The chromosomal instability pathway in colon cancer. Gastroenterology. 2010;138(6):2059-72.

34. Rizk P, Barker N. Gut stem cells in tissue renewal and disease: methods, markers, and myths. Wiley Interdiscip Rev Syst Biol Med. 2012;4(5):475-96.

35. Muto T, Kamiya J, Sawada T, Konishi F, Sugihara K, Kubota Y, Adachi M, Agawa S, Saito Y, Morioka Y, et al. Small "flat adenoma" of the large bowel with special reference to its clinicopathologic features. Dis Colon Rectum. 1985;28(11):847-51.

36. Lau PC, Sung JJ. Flat adenoma in colon: two decades of debate. J Dig Dis. 2010;11(4):201-7.

37. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. Gastroenterology. 2010;138(6):2088-100.

38. Noffsinger AE, Hart J. Serrated adenoma: a distinct form of non-polypoid colorectal neoplasia? Gastrointest Endosc Clin N Am. 2010;20(3):543-63.

39. Arends MJ. Pathways of colorectal carcinogenesis. Appl Immunohistochem Mol Morphol. 2013;21(2):97-102.

40. Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology. 2010;138(6):2044-58. PMCID: PMC3057468.

41. National Cancer Institute. PDQ® Genetics of Colorectal Cancer. Bethesda, MD; 2013 [updated 2/28/2013; cited 4/27/2013]; Available from: http://cancer.gov/cancertopics/pdq/genetics/colorectal/HealthProfessional.

42. Anderson JC. Risk factors and screening for colorectal cancer. In: Anderson, Kahi, editors. Colorectal cancer screening. New York: Humana Press; 2011.

43. Newcomb PA, Storer BE, Marcus PM. Cigarette smoking in relation to risk of large bowel cancer in women. Cancer Res. 1995;55(21):4906-9.

44. Chao A, Thun MJ, Jacobs EJ, Henley SJ, Rodriguez C, Calle EE. Cigarette smoking and colorectal cancer mortality in the cancer prevention study II. J Natl Cancer Inst. 2000;92(23):1888-96.

45. Paskett ED, Reeves KW, Rohan TE, Allison MA, Williams CD, Messina CR, Whitlock E, Sato A, Hunt JR. Association between cigarette smoking and colorectal cancer in the Women's Health Initiative. J Natl Cancer Inst. 2007;99(22):1729-35.

46. Leufkens AM, Van Duijnhoven FJ, Siersema PD, Boshuizen HC, Vrieling A, Agudo A, Gram IT, Weiderpass E, Dahm C, Overvad K, Tjonneland A, Olsen A, Boutron-Ruault MC, Clavel-Chapelon F, Morois S, Palli D, Grioni S, Tumino R, Sacerdote C, Mattiello A, Herman S, Kaaks R, Steffen A, Boeing H, Trichopoulou A, Lagiou P, Trichopoulos D, Peeters PH, van Gils CH, van Kranen H, Lund E, Dumeaux V, Engeset D, Rodriguez L, Sanchez MJ, Chirlaque MD, Barricarte A, Manjer J, Almquist M, van Guelpen B, Hallmans G, Khaw KT, Wareham N, Tsilidis KK, Straif K, Leon-Roux M, Vineis P, Norat T, Riboli E, Bueno-de-Mesquita HB. Cigarette smoking and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition study. Clin Gastroenterol Hepatol. 2011;9(2):137-44.

47. Giovannucci E. An updated review of the epidemiological evidence that cigarette smoking increases risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev. 2001;10(7):725-31.

48. Moore LL, Bradlee ML, Singer MR, Splansky GL, Proctor MH, Ellison RC, Kreger BE. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. Int J Obes Relat Metab Disord. 2004;28(4):559-67.

49. Pischon T, Lahmann PH, Boeing H, Friedenreich C, Norat T, Tjonneland A, Halkjaer J, Overvad K, Clavel-Chapelon F, Boutron-Ruault MC, Guernec G, Bergmann MM, Linseisen J, Becker N, Trichopoulou A, Trichopoulos D, Sieri S, Palli D, Tumino R, Vineis P, Panico S, Peeters PH, Bueno-de-Mesquita HB, Boshuizen HC, Van Guelpen B, Palmqvist R, Berglund G, Gonzalez CA, Dorronsoro M, Barricarte A, Navarro C, Martinez C, Quiros JR, Roddam A, Allen N, Bingham S, Khaw KT, Ferrari P, Kaaks R, Slimani N, Riboli E. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst. 2006;98(13):920-31.

50. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. Am J Clin Nutr. 2007;86(3):556-65.

51. Wang Y, Jacobs EJ, Patel AV, Rodriguez C, McCullough ML, Thun MJ, Calle EE. A prospective study of waist circumference and body mass index in relation to colorectal cancer incidence. Cancer Causes Control. 2008;19(7):783-92.

52. Wei EK, Giovannucci E, Wu K, Rosner B, Fuchs CS, Willett WC, Colditz GA. Comparison of risk factors for colon and rectal cancer. Int J Cancer. 2004;108(3):433-42. PMCID: PMC2903217.

53. Ferrari P, Jenab M, Norat T, Moskal A, Slimani N, Olsen A, Tjonneland A, Overvad K, Jensen MK, Boutron-Ruault MC, Clavel-Chapelon F, Morois S, Rohrmann S, Linseisen J, Boeing H, Bergmann M, Kontopoulou D, Trichopoulou A, Kassapa C, Masala G, Krogh V, Vineis P, Panico S, Tumino R, van Gils CH, Peeters P, Bueno-de-Mesquita HB, Ocke MC, Skeie G, Lund E, Agudo A, Ardanaz E, Lopez DC, Sanchez MJ, Quiros JR, Amiano P, Berglund G, Manjer J, Palmqvist R, Van Guelpen B, Allen N, Key T, Bingham S, Mazuir M, Boffetta P, Kaaks R, Riboli E. Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer. 2007;121(9):2065-72.

54. Thygesen LC, Wu K, Gronbaek M, Fuchs CS, Willett WC, Giovannucci E. Alcohol intake and colorectal cancer: a comparison of approaches for including repeated measures of alcohol consumption. Epidemiology. 2008;19(2):258-64.

55. Giovannucci E, Ascherio A, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Physical activity, obesity, and risk for colon cancer and adenoma in men. Ann Intern Med. 1995;122(5):327-34.

56. Martinez ME, Giovannucci E, Spiegelman D, Hunter DJ, Willett WC, Colditz GA. Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J Natl Cancer Inst. 1997;89(13):948-55.

57. Wolin KY, Yan Y, Colditz GA, Lee IM. Physical activity and colon cancer prevention: a meta-analysis. Br J Cancer. 2009;100(4):611-6. PMCID: PMC2653744.

58. Graser A, Stieber P, Nagel D, Schafer C, Horst D, Becker CR, Nikolaou K, Lottes A, Geisbusch S, Kramer H, Wagner AC, Diepolder H, Schirra J, Roth HJ, Seidel D, Goke B, Reiser MF, Kolligs FT. Comparison of CT colonography, colonoscopy, sigmoidoscopy and faecal occult blood tests for the detection of advanced adenoma in an average risk population. Gut. 2009;58(2):241-8.

59.	Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, Dash C, Giardiello FM, Glick S, Johnson D, Johnson CD, Levin TR, Pickhardt PJ, Rex DK, Smith RA, Thorson A, Winawer SJ, American Cancer Society Colorectal Cancer Advisory G, Force USM-ST, American College of Radiology Colon Cancer C. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008;134(5):1570-95.

60.	U. S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008;149(9):627-37.

61.	Rex DK, Johnson, D.A., Anderson, J.C., Schoenfeld, P.S., Burke, C.A., Inadomi, J.M. American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008. Am J Gastroenterol. 2008.

62.	Davila RE, Rajan E, Baron TH, Adler DG, Egan JV, Faigel DO, Gan SI, Hirota WK, Leighton JA, Lichtenstein D, Qureshi WA, Shen B, Zuckerman MJ, VanGuilder T, Fanelli RD, Standards of Practice Committee ASfGE. ASGE guideline: colorectal cancer screening and surveillance. Gastrointest Endosc. 2006;63(4):546-57.

63.	Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, Maguire C, Hind D, Tappenden P. Chemoprevention of colorectal cancer: systematic review and economic evaluation. Health Technol Assess. 2010;14(32):1-206.

64.	Bresalier RS, Sandler RS, Quan H, Bolognese JA, Oxenius B, Horgan K, Lines C, Riddell R, Morton D, Lanas A, Konstam MA, Baron JA. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005;352(11):1092-102.

65.	Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet. 2004;364(9450):2021-9.

66.	Weingarten MA, Zalmanovici A, Yaphe J. Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps. Cochrane Database Syst Rev. 2008(1):CD003548.

67.	Wu K, Willett WC, Fuchs CS, Colditz GA, Giovannucci EL. Calcium intake and risk of colon cancer in women and men. J Natl Cancer Inst. 2002;94(6):437-46.

68.	Grau MV, Baron JA, Sandler RS, Wallace K, Haile RW, Church TR, Beck GJ, Summers RW, Barry EL, Cole BF, Snover DC, Rothstein R, Mandel JS. Prolonged effect of calcium supplementation on risk of colorectal adenomas in a randomized trial. J Natl Cancer Inst. 2007;99(2):129-36.

69.	Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, Rothstein R, Summers RW, Snover DC, Beck GJ, Bond JH, Frankl H, Pearson L, Greenberg ER. Calcium supplements for the prevention of colorectal adenomas. N Engl J Med. 1999;340(2):101-7.

70.	Bonithon-Kopp C, Kronborg O, Giacosa A, Rath U, Faivre J. Calcium and fibre supplementation in prevention of colorectal adenoma recurrence: a randomised intervention trial. The Lancet. 2000;356(9238):1300-6.

71.	Bond JH. Polyp guideline: diagnosis, treatment, and surveillance for patients with colorectal polyps. Practice Parameters Committee of the American College of Gastroenterology. Am J Gastroenterol. 2000;95(11):3053-63.

72. Giovannucci E. Epidemiology of vitamin D and colorectal cancer. Anticancer Agents Med Chem. 2013;13(1):11-9.
73. Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, Margolis KL, Ockene JK, Phillips L, Pottern L, Prentice RL, Robbins J, Rohan TE, Sarto GE, Sharma S, Stefanick ML, Van Horn L, Wallace RB, Whitlock E, Bassford T, Beresford SA, Black HR, Bonds DE, Brzyski RG, Caan B, Chlebowski RT, Cochrane B, Garland C, Gass M, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Jackson RD, Johnson KC, Judd H, Kooperberg CL, Kuller LH, LaCroix AZ, Lane DS, Langer RD, Lasser NL, Lewis CE, Limacher MC, Manson JE, Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of colorectal cancer. N Engl J Med. 2006;354(7):684-96.
74. National Cancer Institute. Vitamin D and cancer rrevention: strengths and limits of the evidence. Rockville, MD: National Institutes of Health; 2010 [updated June 16, 2010; cited May 1 2013]; Available from: http://www.cancer.gov/cancertopics/factsheet/prevention/vitamin-D.
75. U.S. Preventive Services Task Force. Recommendation summary: Vitamin supplementation to prevent cancer and CVD: Counseling. Rockville, MD: U.S. Preventive Services Task Force; 2014 [updated February 2014; cited December 23 2014]; Available from: http://www.uspreventiveservicestaskforce.org/uspstf/uspsvita.htm.
76. Reddy BS, Rao CV, Rivenson A, Kelloff G. Inhibitory effect of aspirin on azoxymethane-induced colon carcinogenesis in F344 rats. Carcinogenesis. 1993;14(8):1493-7.
77. Mereto E, Frencia L, Ghia M. Effect of aspirin on incidence and growth of aberrant crypt foci induced in the rat colon by 1,2-dimethylhydrazine. Cancer Lett. 1994;76(1):5-9.
78. Craven PA, DeRubertis FR. Effects of aspirin on 1,2-dimethylhydrazine-induced colonic carcinogenesis. Carcinogenesis. 1992;13(4):541-6.
79. Algra AM, Rothwell PM. Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials. Lancet Oncol. 2012;13(5):518-27.
80. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. Aspirin and cancer risk: a quantitative review to 2011. Ann Oncol. 2012;23(6):1403-15.
81. Dube C, Rostom A, Lewin G, Tsertsvadze A, Barrowman N, Code C, Sampson M, Moher D, U. S. Preventive Services Task Force. The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force. Ann Intern Med. 2007;146(5):365-75.
82. Ye X, Fu J, Yang Y, Chen S. Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies. PLoS One. 2013;8(2):e57578. PMCID: PMC3581483.
83. Rothwell PM, Fowkes FGR, Belch JFF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet. 2011;377(9759):31-41.
84. Rothwell PM, Price JF, Fowkes FG, Zanchetti A, Roncaglioni MC, Tognoni G, Lee R, Belch JF, Wilson M, Mehta Z, Meade TW. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet. 2012;379(9826):1602-12.

85.   Rothwell PM, Wilson M, Elwin C-E, Norrving B, Algra A, Warlow CP, Meade TW. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet. 2010;376(9754):1741-50.

86.   Rothwell PM, Wilson M, Price JF, Belch JFF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet. 2012;379(9826):1591-601.

87.   Thun MJ, Jacobs EJ, Patrono C. The role of aspirin in cancer prevention. Nat Rev Clin Oncol. 2012;9(5):259-67.

88.   Alfonso L, Ai G, Spitale RC, Bhat GJ. Molecular targets of aspirin and cancer prevention. Br J Cancer. 2014;111(1):61-7. PMCID: PMC4090734.

89.   Trinchieri G. Innate inflammation and cancer: Is it time for cancer prevention? F1000 Med Rep. 2011;3:11. PMCID: PMC3155181.

90.   Dannenberg AJ, Lippman SM, Mann JR, Subbaramaiah K, DuBois RN. Cyclooxygenase-2 and epidermal growth factor receptor: pharmacologic targets for chemoprevention. J Clin Oncol. 2005;23(2):254-66.

91.   Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. Carcinogenesis. 2009;30(7):1073-81.

92.   Berg M, Soreide K. Prevention: will an aspirin a day keep the colorectal cancer away? Nat Rev Clin Oncol. 2011;8(3):130-1.

93.   Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst. 2002;94(4):252-66.

94.   Chan AT, Arber N, Burn J, Chia WK, Elwood P, Hull MA, Logan RF, Rothwell PM, Schror K, Baron JA. Aspirin in the chemoprevention of colorectal neoplasia: an overview. Cancer Prev Res (Phila). 2012;5(2):164-78. PMCID: 3273592.

95.   Eberhart CE, Coffey RJ, Radhika A, Giardiello FM, Ferrenbach S, DuBois RN. Up-regulation of cyclooxygenase 2 gene expression in human colorectal adenomas and adenocarcinomas. Gastroenterology. 1994;107(4):1183-8.

96.   Brown JR, DuBois RN. COX-2: a molecular target for colorectal cancer prevention. J Clin Oncol. 2005;23(12):2840-55.

97.   Chan AT, Ogino S, Fuchs CS. Aspirin and the risk of colorectal cancer in relation to the expression of COX-2. N Engl J Med. 2007;356(21):2131-42.

98.   Colorectal Cancer: Can colorectal cancer be prevented? Atlanta, GA: American Cancer Society; 2013 [updated January 17, 2013; cited April 23 2013]; Available from: http://www.cancer.org/cancer/colonandrectumcancer/detailedguide/colorectal-cancer-prevention.

99.   U.S. Preventive Services Task Force. USPSTF A and B Recommendations. Rockville, MD: U.S. Preventive Services Task Force; 2010 [updated August 2010; cited April 23 2013]; Available from: http://www.ama-assn.org/resources/doc/cpt/aca-uspstf-a-and-b-recs.pdf.

100.   U.S. Preventive Services Task Force. Aspirin and NSAIDS for colorectal cancer prevention. American College of Physicians; 2012 [updated 2007; cited April 23 2013]; Available from: http://www.acponline.org/mobile/cyppocketguide/aspirin_nsaids_colorectal_cancer_prevention.html.

101. Chiu LCM, Tong KF, Ooi VEC. Cytostatic and cytotoxic effects of cyclooxygenase inhibitors and their synergy with docosahexaenoic acid on the growth of human skin melanoma A-375 cells. Biomedicine & Pharmacotherapy. 2005;59 Suppl 2:S293-7.

102. National Institute for Health and Care Excellence. Published clinical guidelines. London: National Institute for Health and Care Excellence; 2013 [updated April 25, 2013; cited April 25 2013]; Available from: http://guidance.nice.org.uk/CG/Published.

103. Burt RW, Winawer SJ, Bond J, et al. Preventing colorectal cancer: a clinician's guide: The American Gastroenterological Association, 2004.

104. Wilcox CM, Allison J, Benzuly K, Borum M, Cryer B, Grosser T, Hunt R, Ladabaum U, Lanas A, Paulus H, Regueiro C, Sandler RS, Simon L. Consensus development conference on the use of nonsteroidal anti-inflammatory agents, including cyclooxygenase-2 enzyme inhibitors and aspirin. Clin Gastroenterol Hepatol. 2006;4(9):1082-9.e4.

105. National Comprehensive Cancer Network. NCCN Guidelines for Detection, Prevention & Risk Reduction: Colorectal Cancer. Fort Washington, PA: National Comprehensive Cancer Network,; 2013 [cited April 25 2013]; Available from: http://www.nccn.org/professionals/physician_gls/pdf/colorectal_screening.pdf.

106. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual, AHRQ Publication No. 08-05118-EF. Rockville, MD: Agency for Healthcare Quality and Research; 2008 [updated August 2011; cited May 1 2014]; Available from: http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.htm.

107. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: Ottawa Hospital Research Institute; 2014 [cited May 20 2014]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

108. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. Lancet. 1998;351(9098):233-41.

109. Fu R, Gartlehner G, Grant M, Shamliyan T, Sedrakyan A, Wilt TJ, Griffith L, Oremus M, Raina P, Ismaila A, Santaguida P, Lau J, Trikalinos TA. Conducting quantitative synthesis when comparing medical interventions: AHRQ and the Effective Health Care Program. Journal of Clinical Epidemiology. 2011;64(11):1187-97.

110. Turner RM, Bird SM, Higgins JP. The impact of study size on meta-analyses: examination of underpowered studies in Cochrane reviews. PLoS One. 2013;8(3):e59202. PMCID: PMC3609745.

111. Flossmann E, Rothwell PM, British Doctors Aspirin Trial, the UK-TIA Aspirin Trial. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. Lancet. 2007;369(9573):1603-13.

112. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, Hennekens CH, Buring JE. Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial. JAMA. 2005;294(1):47-55.

113. Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. Ann Intern Med. 2013;159(2):77-85. PMCID: PMC3713531.

114. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005;352(13):1293-304.

115. Rexrode KM, Lee IM, Cook NR, Hennekens CH, Buring JE. Baseline characteristics of participants in the Women's Health Study. Journal of women's health & gender-based medicine. 2000;9(1):19-27.

116. Buring JE, Hennekens, C.H. for the Women's Health Study Research group. The Women's Health Study: Summary of the study design. Journal of Myocardial Ischemia. 1992;4:27-9.

117. Manson JE, Buring JE, Satterfield S, Hennekens CH. Baseline characteristics of participants in the Physicians' Health Study: a randomized trial of aspirin and beta-carotene in U.S. physicians. Am J Prev Med. 1991;7(3):150-4.

118. Physician's Health Study. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med. 1989;321(3):129-35.

119. Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett W, Peto R. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med. 1996;334(18):1145-9.

120. Findings from the aspirin component of the ongoing Physicians' Health Study. N Engl J Med. 1988;318(4):262-4.

121. Glynn RJ, Buring JE, Manson JE, LaMotte F, Hennekens CH. Adherence to aspirin in the prevention of myocardial infarction. The Physicians' Health Study. Arch Intern Med. 1994;154(23):2649-57.

122. Sturmer T, Buring JE, Glynn RJ. Aspirin and nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer: weighing the evidence. Ann Intern Med. 2007;147(9):674; author reply -5.

123. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, Chaussade S, Baron JA. Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials. J Natl Cancer Inst. 2009;101(4):256-66.

124. Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, Warlow C, Hafner B, Thompson E, Norton S, et al. Randomised trial of prophylactic daily aspirin in British male doctors. British medical journal. 1988;296(6618):313-6. PMCID: 2544821.

125. Group U-TS. United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results. UK-TIA Study Group. British medical journal (Clinical research ed). 1988;296(6618):316-20.

126. Farrell B, Godwin J, Richards S, Warlow C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. Journal of neurology, neurosurgery, and psychiatry. 1991;54(12):1044-54. PMCID: 1014676.

127. SALT. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. The SALT Collaborative Group. Lancet. 1991;338(8779):1345-9.

128. Early Treatment Diabetic Retinopathy Study Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. ETDRS Investigators. JAMA. 1992;268(10):1292-300.

129. Early Treatment Diabetic Retinopathy Study Investigators. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS report number 7. Ophthalmology. 1991;98(5 Suppl):741-56.

130. Juul-Moller S, Edvardsson N, Jahnmatz B, Rosen A, Sorensen S, Omblus R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. Lancet. 1992;340(8833):1421-5.

131. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y, Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes Trial I. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2008;300(18):2134-41.

132. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, Lee R, Bancroft J, MacEwan S, Shepherd J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R, Prevention of Progression of Arterial D, Diabetes Study G, Diabetes Registry G, Royal College of Physicians E. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008;337:a1840. PMCID: 2658865.

133. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD, Aspirin for Asymptomatic Atherosclerosis T. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010;303(9):841-8.

134. Gann PH, Manson JE, Glynn RJ, Buring JE, Hennekens CH. Low-dose aspirin and incidence of colorectal tumors in a randomized trial. J Natl Cancer Inst. 1993;85(15):1220-4.

135. Sturmer T, Glynn RJ, Lee IM, Manson JE, Buring JE, Hennekens CH. Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study. Ann Intern Med. 1998;128(9):713-20.

136. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, McKeown-Eyssen G, Summers RW, Rothstein R, Burke CA, Snover DC, Church TR, Allen JI, Beach M, Beck GJ, Bond JH, Byers T, Greenberg ER, Mandel JS, Marcon N, Mott LA, Pearson L, Saibil F, van Stolk RU. A randomized trial of aspirin to prevent colorectal adenomas. N Engl J Med. 2003;348(10):891-9.

137. Kim S, Baron JA, Mott LA, Burke CA, Church TR, McKeown-Eyssen GE, Cole BF, Haile RW, Sandler RS. Aspirin may be more effective in preventing colorectal adenomas in patients with higher BMI (United States). Cancer Causes & Control. 2006;17(10):1299-304.

138. Grau MV, Sandler RS, McKeown-Eyssen G, Bresalier RS, Haile RW, Barry EL, Ahnen DJ, Gui J, Summers RW, Baron JA. Nonsteroidal anti-inflammatory drug use after 3 years of aspirin use and colorectal adenoma risk: observational follow-up of a randomized study. Journal of the National Cancer Institute. 2009;101(4):267-76. PMCID: PMC2644329.

139. Wallace K, Grau MV, Ahnen D, Snover DC, Robertson DJ, Mahnke D, Gui J, Barry EL, Summers RW, McKeown-Eyssen G, Haile RW, Baron JA. The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. Cancer Epidemiology, Biomarkers & Prevention. 2009;18(8):2310-7.

140. Ho GYF, Xue X, Cushman M, McKeown-Eyssen G, Sandler RS, Ahnen DJ, Barry EL, Saibil F, Bresalier RS, Rohan TE, Baron JA. Antagonistic effects of aspirin and folic acid on inflammation markers and subsequent risk of recurrent colorectal adenomas. Journal of the National Cancer Institute. 2009;101(23):1650-4. PMCID: PMC2786916.

141. Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, Couturier D, Coste T, Little J, Chaussade S. Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial. Gastroenterology. 2003;125(2):328-36.

142. Benamouzig R, Uzzan B, Deyra J, Martin A, Girard B, Little J, Chaussade S, Association pour la Prevention par l'Aspirine du Cancer Colorectal Study G. Prevention by daily soluble aspirin of colorectal adenoma recurrence: 4-year results of the APACC randomised trial.[Erratum appears in Gut. 2012 Mar;61(3):472]. Gut. 2012;61(2):255-61.

143. Benamouzig R, Yoon H, Little J, Martin A, Couturier D, Deyra J, Coste T, Chaussade S, APACC Study Group Association pour la Prevention par Aspirine du Cancer Colorectal. APACC, a French prospective study on aspirin efficacy in reducing colorectal adenoma recurrence: design and baseline findings. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation. 2001;10(4):327-35.

144. Logan RFA, Grainge MJ, Shepherd VC, Armitage NC, Muir KR, UK CAP Trial Group. Aspirin and folic acid for the prevention of recurrent colorectal adenomas. Gastroenterology. 2008;134(1):29-38.

145. Logan RFA, Muir, K.R., et al. Aspirin for the prevention of recurrent colorectal adenomas: results of the UKCAP trial. Gut. 2006;55(A90).

146. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Curhan GC, Fuchs CS. Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer. JAMA. 2005;294(8):914-23. PMCID: PMC1550973.

147. Chan AT, Giovannucci EL, Schernhammer ES, Colditz GA, Hunter DJ, Willett WC, Fuchs CS. A prospective study of aspirin use and the risk for colorectal adenoma. Annals of Internal Medicine. 2004;140(3):157-66.

148. Giovannucci E, Colditz GA, Stampfer MJ, Hunter D, Rosner BA, Willett WC, Speizer FE. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. J Natl Cancer Inst. 1994;86(3):192-9.

149. Giovannucci E, Egan KM, Hunter DJ, Stampfer MJ, Colditz GA, Willett WC, Speizer FE. Aspirin and the risk of colorectal cancer in women. N Engl J Med. 1995;333(10):609-14.

150. Giovannucci E, Stampfer MJ, Colditz GA, Rimm EB, Trichopoulos D, Rosner BA, Speizer FE, Willett WC. Folate, methionine, and alcohol intake and risk of colorectal adenoma. J Natl Cancer Inst. 1993;85(11):875-84.

151. Wei EK, Colditz GA, Giovannucci EL, Fuchs CS, Rosner BA. Cumulative risk of colon cancer up to age 70 years by risk factor status using data from the Nurses' Health Study. American Journal of Epidemiology. 2009;170(7):863-72. PMCID: PMC2800259.

152. Chan AT, Giovannucci EL, Meyerhardt JA, Schernhammer ES, Wu K, Fuchs CS. Aspirin dose and duration of use and risk of colorectal cancer in men. Gastroenterology. 2008;134(1):21-8. PMCID: PMC2719297.

153. Larsson SC, Giovannucci E, Wolk A. Long-term aspirin use and colorectal cancer risk: a cohort study in Sweden. Br J Cancer. 2006;95(9):1277-9. PMCID: PMC2360558.
154. Calle EE, Rodriguez C, Jacobs EJ, Almon ML, Chao A, McCullough ML, Feigelson HS, Thun MJ. The American Cancer Society Cancer Prevention Study II Nutrition Cohort: rationale, study design, and baseline characteristics. Cancer. 2002;94(9):2490-501.
155. Garfinkel L. Selection, follow-up, and analysis in the American Cancer Society prospective studies. National Cancer Institute monograph. 1985;67:49-52.
156. Jacobs EJ, Thun MJ, Bain EB, Rodriguez C, Henley SJ, Calle EE. A large cohort study of long-term daily use of adult-strength aspirin and cancer incidence. J Natl Cancer Inst. 2007;99(8):608-15.
157. Thun MJ, Namboodiri MM, Heath CW, Jr. Aspirin use and reduced risk of fatal colon cancer. N Engl J Med. 1991;325(23):1593-6.
158. Jacobs EJ, Newton CC, Gapstur SM, Thun MJ. Daily aspirin use and cancer mortality in a large US cohort. J Natl Cancer Inst. 2012;104(16):1208-17.
159. Tjonneland A, Olsen A, Boll K, Stripp C, Christensen J, Engholm G, Overvad K. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. Scandinavian journal of public health. 2007;35(4):432-41.
160. Friis S, Poulsen AH, Sorensen HT, Tjonneland A, Overvad K, Vogel U, McLaughlin JK, Blot WJ, Olsen JH. Aspirin and other non-steroidal anti-inflammatory drugs and risk of colorectal cancer: a Danish cohort study. Cancer Causes Control. 2009;20(5):731-40.
161. Brasky TM, Potter JD, Kristal AR, Patterson RE, Peters U, Asgari MM, Thornquist MD, White E. Non-steroidal anti-inflammatory drugs and cancer incidence by sex in the VITamins And Lifestyle (VITAL) cohort. Cancer Causes & Control. 2012;23(3):431-44. PMCID: PMC3319091.
162. White E, Patterson RE, Kristal AR, Thornquist M, King I, Shattuck AL, Evans I, Satia-Abouta J, Littman AJ, Potter JD. Vitamins And Lifestyle cohort study: study design and characteristics of supplement users. Am J Epidemiol. 2004;159(1):83-93.
163. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Controlled clinical trials. 1998;19(1):61-109.
164. Allison M, Garland C, Chlebowski R, Criqui M, Langer R, Wu L, Roy H, McTiernan A, Kuller L, Women's Health Initiative Investigators. The association between aspirin use and the incidence of colorectal cancer in women. Am J Epidemiol. 2006;164(6):567-75.
165. Langer RD, White E, Lewis CE, Kotchen JM, Hendrix SL, Trevisan M. The Women's Health Initiative Observational Study: baseline characteristics of participants and reliability of baseline measures. Annals of epidemiology. 2003;13(9 Suppl):S107-21.
166. Hays J, Hunt JR, Hubbell FA, Anderson GL, Limacher M, Allen C, Rossouw JE. The Women's Health Initiative recruitment methods and results. Annals of epidemiology. 2003;13(9 Suppl):S18-77.
167. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, Hubbell FA, Ascensao J, Rodabough RJ, Rosenberg CA, Taylor VM, Harris R, Chen C, Adams-Campbell LL, White E, Women's Health Initiative I. Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med. 2004;350(10):991-1004.

168.	Sutcliffe P, Connock M, Gurung T, Freeman K, Johnson S, Ngianga-Bakwin K, Grove A, Gurung B, Morrow S, Stranges S, Clarke A. Aspirin in primary prevention of cardiovascular disease and cancer: a systematic review of the balance of evidence from reviews of randomized trials. PLoS ONE [Electronic Resource]. 2013;8(12):e81970. PMCID: PMC3855368.

169.	Sutcliffe P, Connock M, Gurung T, Freeman K, Johnson S, Kandala NB, Grove A, Gurung B, Morrow S, Clarke A. Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews. Health Technology Assessment (Winchester, England). 2013;17(43):1-253.

170.	Thun MJ, Calle EE, Namboodiri MM, Flanders WD, Coates RJ, Byers T, Boffetta P, Garfinkel L, Heath CW, Jr. Risk factors for fatal colon cancer in a large prospective study. J Natl Cancer Inst. 1992;84(19):1491-500.

171.	Huang WK, Chiou MJ, Yu KH, Lin YC, Yang TS, Chen JS, Kuo CF, See LC. The association between low-dose aspirin use and the incidence of colorectal cancer: a nationwide cohort study. Aliment Pharmacol Ther. 2013;38(4):432-9.

172.	Christen WG, Glynn RJ, Chew EY, Buring JE. Low-dose aspirin and medical record-confirmed age-related macular degeneration in a randomized trial of women. Ophthalmology. 2009;116(12):2386-92. PMCID: PMC2787838.

173.	Christen WG, Glynn RJ, Ajani UA, Schaumberg DA, Chew EY, Buring JE, Manson JE, Hennekens CH. Age-related maculopathy in a randomized trial of low-dose aspirin among US physicians. Arch Ophthalmol. 2001;119(8):1143-9.

174.	Duffy D, Kelly E, Trang A, Whellan D, Mills G. Aspirin for cardioprotection and strategies to improve patient adherence. Postgraduate medicine. 2014;126(1):18-28.

175.	de Gaetano G, Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet. 2001;357(9250):89-95.

176.	Cook NR, Cole SR, Buring JE. Aspirin in the primary prevention of cardiovascular disease in the Women's Health Study: effect of noncompliance. European journal of epidemiology. 2012;27(6):431-8. PMCID: 3383873.

177.	Silagy CA, McNeil JJ, Donnan GA, Tonkin AM, Worsam B, Campion K. The PACE pilot study: 12-month results and implications for future primary prevention trials in the elderly. (Prevention with low-dose Aspirin of Cardiovascular disease in the Elderly). Journal of the American Geriatrics Society. 1994;42(6):643-7.

178.	Waeber B, Leonetti G, Kolloch R, McInnes GT. Compliance with aspirin or placebo in the Hypertension Optimal Treatment (HOT) study. Journal of hypertension. 1999;17(7):1041-5.

179.	Effect of aspirin alone and aspirin plus dipyridamole in early diabetic retinopathy. A multicenter randomized controlled clinical trial. The DAMAD Study Group. Diabetes. 1989;38(4):491-8.

180.	Nelson MR, Reid CM, Ames DA, Beilin LJ, Donnan GA, Gibbs P, Johnston CI, Krum H, Storey E, Tonkin A, Wolfe R, Woods R, McNeil JJ. Feasibility of conducting a primary prevention trial of low-dose aspirin for major adverse cardiovascular events in older people in Australia: results from the ASPirin in Reducing Events in the Elderly (ASPREE) pilot study. Med J Aust. 2008;189(2):105-9.

181. Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, Gibbs H, Hague W, Xavier D, Diaz R, Kirby A, Simes J, Investigators A. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med. 2012;367(21):1979-87.

182. Aspirin in coronary heart disease. The Coronary Drug Project Research Group. Circulation. 1980;62(6 Pt 2):V59-62.

183. Cote R, Battista RN, Abrahamowicz M, Langlois Y, Bourque F, Mackey A. Lack of effect of aspirin in asymptomatic patients with carotid bruits and substantial carotid narrowing. The Asymptomatic Cervical Bruit Study Group. Annals of internal medicine. 1995;123(9):649-55.

184. Stroke Prevention in Atrial Fibrillation Study. Final results. Circulation. 1991;84(2):527-39.

185. Sato H, Ishikawa K, Kitabatake A, Ogawa S, Maruyama Y, Yokota Y, Fukuyama T, Doi Y, Mochizuki S, Izumi T, Takekoshi N, Yoshida K, Hiramori K, Origasa H, Uchiyama S, Matsumoto M, Yamaguchi T, Hori M, Japan Atrial Fibrillation Stroke Trial G. Low-dose aspirin for prevention of stroke in low-risk patients with atrial fibrillation: Japan Atrial Fibrillation Stroke Trial. Stroke; a journal of cerebral circulation. 2006;37(2):447-51.

186. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. EAFT (European Atrial Fibrillation Trial) Study Group. Lancet. 1993;342(8882):1255-62.

187. A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. JAMA. 1980;243(7):661-9.

188. Persantine and aspirin in coronary heart disease. The Persantine-Aspirin Reinfarction Study Research Group. Circulation. 1980;62(3):449-61.

189. European Stroke Prevention Study 2. Efficacy and safety data. Journal of the neurological sciences. 1997;151 Suppl:S1-77.

190. Wei L, Fahey T, MacDonald TM. Adherence to statin or aspirin or both in patients with established cardiovascular disease: exploring healthy behaviour vs. drug effects and 10-year follow-up of outcome. British journal of clinical pharmacology. 2008;66(1):110-6. PMCID: 2485263.

191. Bower AB, Grau SL, Taylor VA. Over-the-counter vs. prescription medications: are consumer perceptions of the consequences of drug instruction non-compliance different? Int J Consum Stud. 2013;37(2):228-33.

192. Mills EJ, Wu P, Alberton M, Kanters S, Lanas A, Lester R. Low-dose aspirin and cancer mortality: a meta-analysis of randomized trials. Am J Med. 2012;125(6):560-7.

193. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D, Methods Work Group, USPSTF. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20(3 Suppl):21-35.

194. Hull MA, Sandell AC, Montgomery AA, Logan RF, Clifford GM, Rees CJ, Loadman PM, Whitham D. A randomized controlled trial of eicosapentaenoic acid and/or aspirin for colorectal adenoma prevention during colonoscopic surveillance in the NHS Bowel Cancer Screening Programme (The seAFOod Polyp Prevention Trial): study protocol for a randomized controlled trial. Trials. 2013;14(1):237. PMCID: 3733694.

Figure 1. Analytic Framework
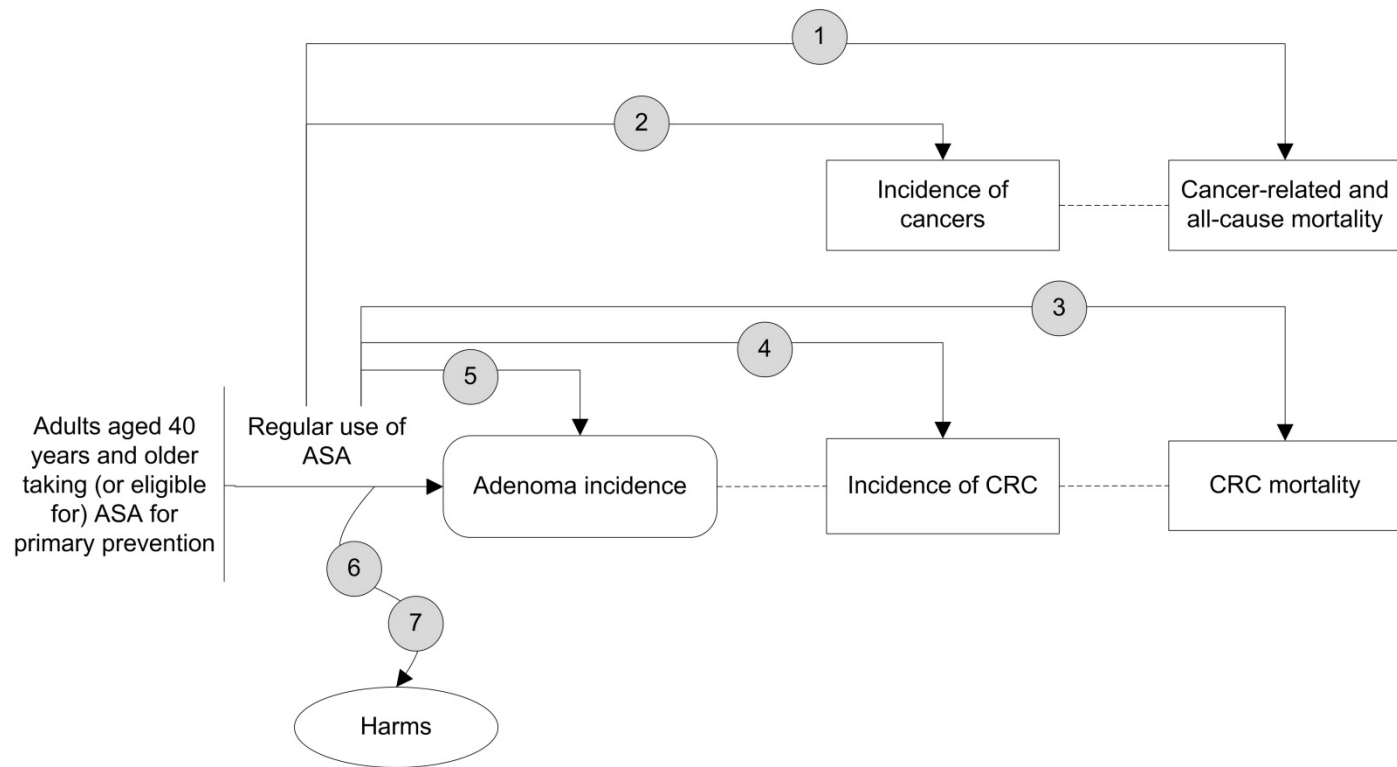
Note: Numbers indicate Key Questions

Abbreviations: ASA = aspirin; CRC = colorectal cancer; FAP = Familial adenomatous polyposis

Figure 2. Effect of Aspirin on Early Risk (0 to 10 years) of All-Cause Mortality

Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description		RR (95% CI)	Events/N, IG	Events/N, CG
SALT	75	2.7	Recent TIA, stroke, or RAO		0.89 (0.64, 1.24)	61/676	69/684
SAPAT	75	4.2	Angina, without prior MI		0.79 (0.60, 1.04)	82/1009	106/1026
UK-TIA	300 or 1200	4.4	Recent TIA or stroke		0.91 (0.74, 1.12)	221/1621	122/814
JPAD	81 or 100	4.4	Diabetes		0.88 (0.55, 1.39)	33/1262	38/1277
ETDRS	650	5.0	Diabetes & diabetic retinopathy		0.93 (0.81, 1.06)	340/1856	366/1855
PHS	162.5	5.0	Male physicians		0.96 (0.79, 1.15)	217/11037	227/11034
BMD	500	6.0	Male physicians		0.89 (0.74, 1.08)	270/3429	151/1710
POPADAD	100	6.7	Diabetes & ABI <= 0.99		0.93 (0.72, 1.21)	94/638	101/638
TPT	75	6.9	Male at high IHD risk		1.05 (0.88, 1.26)	216/2545	205/2540
AAA	100	8.2	ABI <= 0.95		0.95 (0.78, 1.15)	176/1675	186/1675
WHS	50	10.1	Female health professionals		0.95 (0.85, 1.06)	609/19934	642/19942
Overall (I-squared = 0.0%, p = 0.960)					0.94 (0.89, 0.99)		

.5   1   2

Favors Intervention   Favors Control

Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; BMD = British Medical Doctors trial; CI = confidence interval; CG = control group; ETDRS = Early Treatment Diabetic Retinopathy Study; IG = intervention group; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; mg = milligram; MI = myocardial infarction; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RAO = retinal artery occlusion; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack trial; WHS = Women's Health Study; yrs = years

Figure 3. Effect of Aspirin on Long-Term Risk (0 to ≥20 Years) of Colorectal Cancer Mortality

Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description	RR (95% CI)	Events/N, IG	Events/N, CG
SALT	75	2.7	Recent TIA, stroke, or RAO	0.71 (0.27, 1.85)	7/676	10/684
UK-TIA	300 or 1200	4.4	Recent TIA or stroke	0.59 (0.31, 1.15)	19/1632	16/817
BMD	500	6.0	Male physicians	0.74 (0.49, 1.09)	59/3429	40/1710
TPT	75	6.9	Male at high IHD risk	0.62 (0.40, 0.94)	34/2545	55/2540
Overall (I-squared = 0.0%, p = 0.920)				0.67 (0.52, 0.86)		

.25 .5 1 2 4
Favors Intervention   Favors Control

Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance

Abbreviations: BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; IG = intervention group; IHD = ischemic heart disease; mg = milligram; 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; yrs = years

Figure 4. Effect of Aspirin on 3- to 4-Year Risk of All-Cause Mortality in Persons With a Prior Adenoma
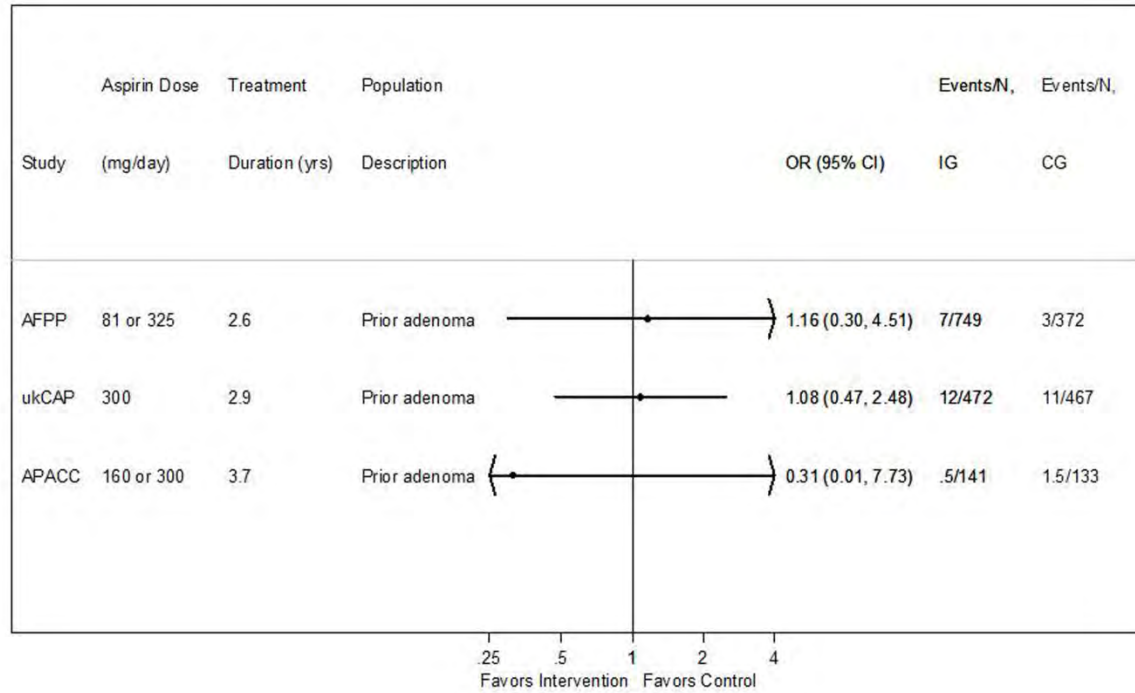
Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description	OR (95% CI)	Events/N, IG	Events/N, CG
AFPP	81 or 325	2.6	Prior adenoma	1.16 (0.30, 4.51)	7/749	3/372
ukCAP	300	2.9	Prior adenoma	1.08 (0.47, 2.48)	12/472	11/467
APACC	160 or 300	3.7	Prior adenoma	0.31 (0.01, 7.73)	.5/141	1.5/133

.25 .5 1 2 4
Favors Intervention   Favors Control

Abbreviations: AFPP = Aspirin/Folate Polyp Prevention study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal study; CG = control group; CI = confidence interval; IG = intervention group; mg = milligram; OR = odds ratio; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; yrs = years

Figure 5. Effect of Aspirin on Early Risk (0 to 12 Years) of Colorectal Cancer Incidence

Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description	RR (95% CI)	Events/N, IG	Events/N, CG
UK-TIA	300 or 1200	4.4	Recent TIA or stroke	1.13 (0.49, 2.58)	18/1632	8/817
PHS	162.5	5.0	Male physicians	1.03 (0.83, 1.27)	173/11037	168/11034
BMD	500	6.0	Male physicians	0.82 (0.45, 1.50)	28/3429	17/1710
WHS	50	10.1	Female health professionals	0.96 (0.76, 1.21)	144/19934	150/19942
Overall (I-squared = 0.0%, p = 0.881)				0.99 (0.85, 1.15)		

.25 .5 1 2 4
Favors Intervention   Favors Control

Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance

Abbreviations: BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; IG = intervention group; mg = milligram; PHS = Physicians' Health Study; RR = relative risk; TIA = transient ischemic attack; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study; yrs = years

Figure 6. Effect of Aspirin on Late Risk (10 to 19 Years) of Colorectal Cancer Incidence
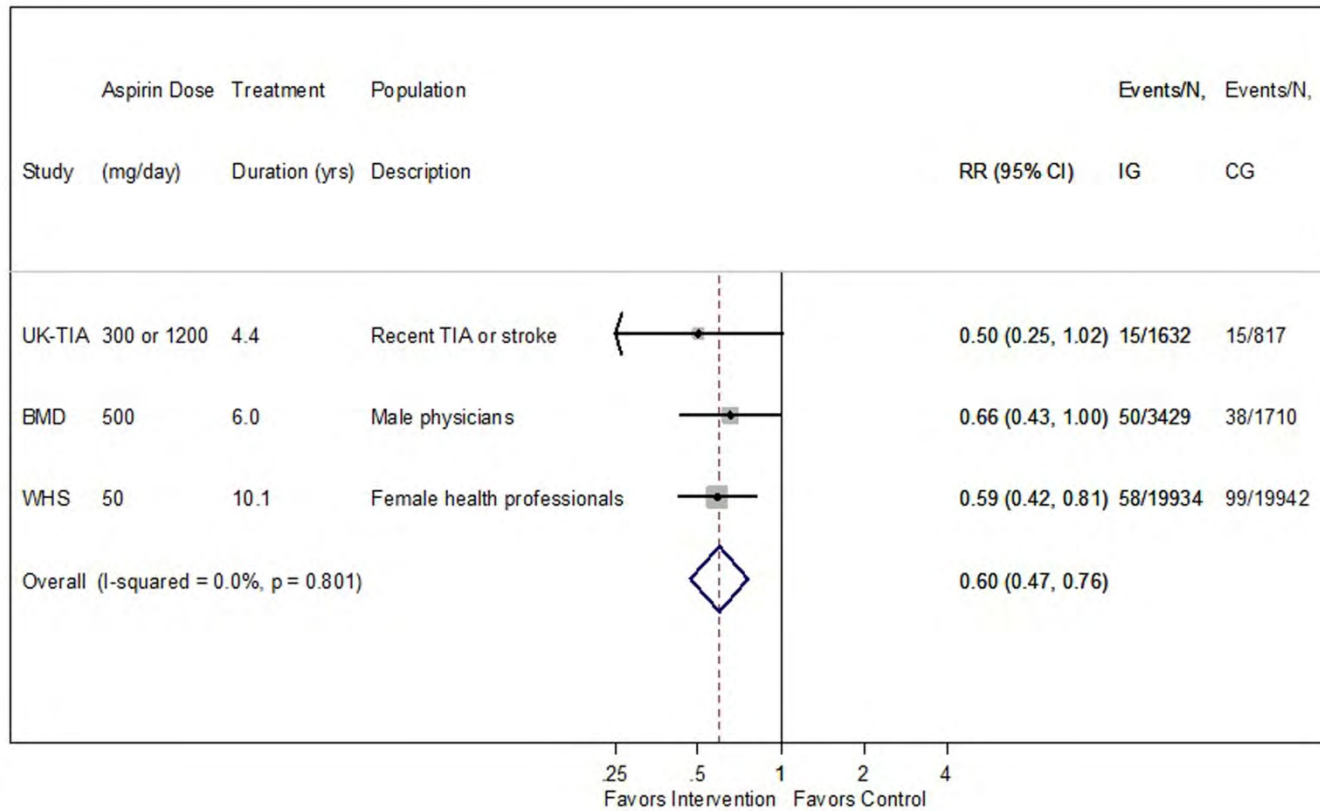
Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance

Abbreviations: BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; IG = intervention group; mg = milligram; RR = relative risk; TIA = transient ischemic attack; UK-TIA = United Kingdom Transient Ischaemic Attack; WHS = Women's Health Study; yrs = years

Figure 7. Effect of Aspirin on Long-Term Risk (0 to ≥20 Years) of Colorectal Cancer Incidence

Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description		RR (95% CI)	Events/N, IG	Events/N, CG
Rothwell	75 to 1200	6.0	Pooled RCTs		0.76 (0.63, 0.94)	NR/8282	NR/5751
WHS	50	10.1	Female health professionals		0.81 (0.67, 0.98)	202/19934	249/19942

.5   1   2
Favors Intervention Favors Control
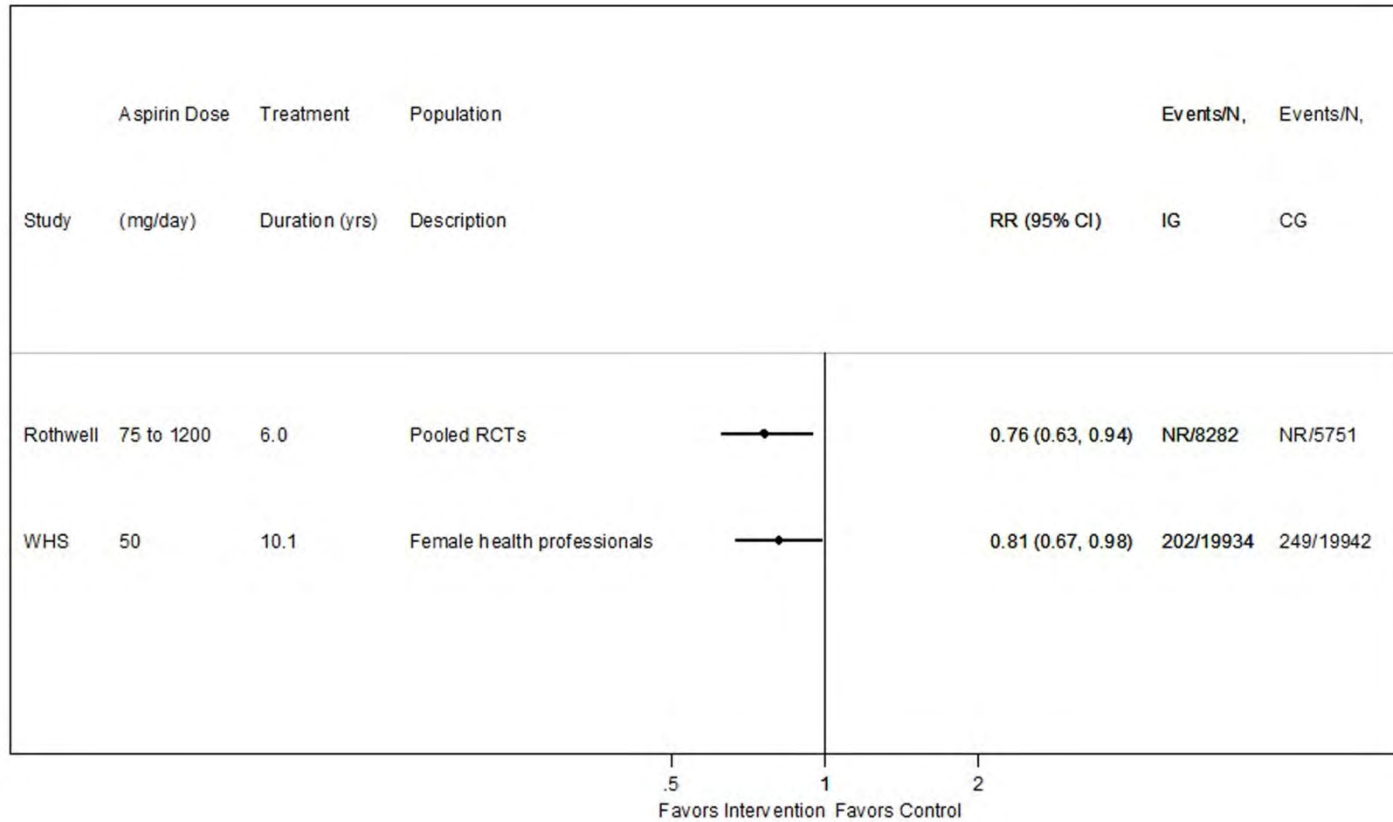
Note: Relative risk estimates and confidence intervals from Rothwell and colleagues[85] are presented in this figure because the raw number of events was not available. Trials included in the pooled result from Rothwell and colleagues were: British Medical Doctors trial, UK Transient Ischaemic Attack study, Swedish Aspirin Low-dose Trial, and Thrombosis Prevention Trial

Abbreviations: CG = control group; CI = confidence interval; IG = intervention group; mg = milligram; RCT = randomized controlled trial; RR = relative risk; WHS = Women's Health Study; yrs = years

Figure 8. Effect of Aspirin on 3- to 4-Year Risk of Colorectal Cancer Incidence in Persons With a Prior Adenoma
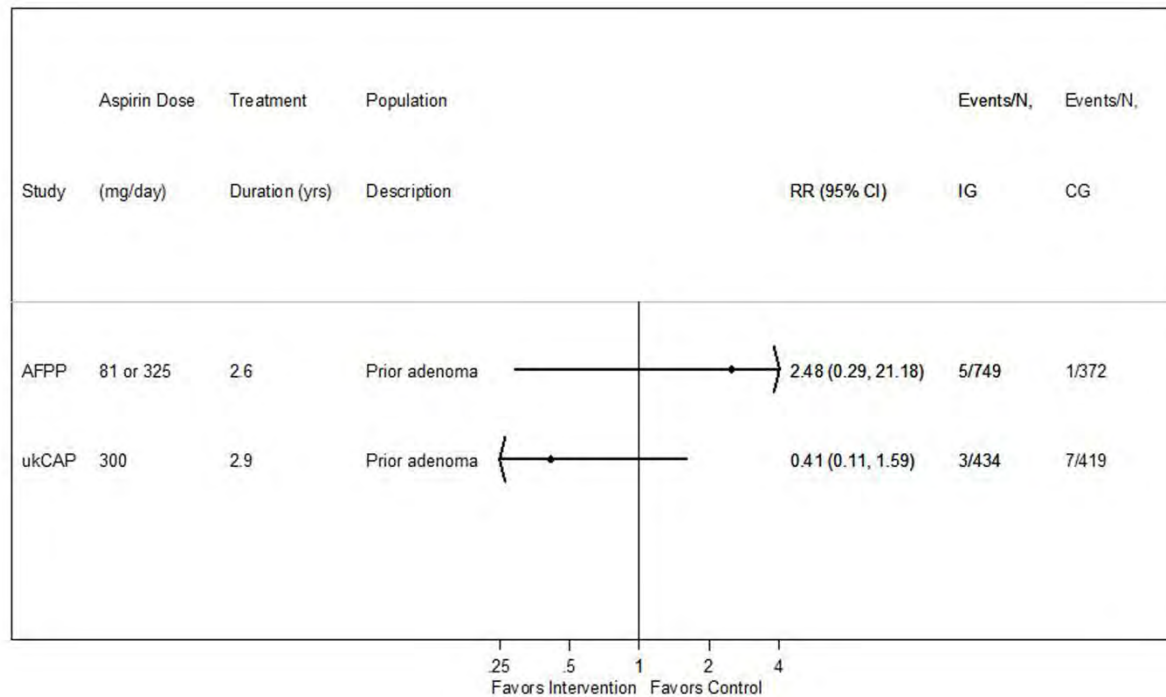
Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description		RR (95% CI)	Events/N, IG	Events/N, CG
AFPP	81 or 325	2.6	Prior adenoma		2.48 (0.29, 21.18)	5/749	1/372
ukCAP	300	2.9	Prior adenoma		0.41 (0.11, 1.59)	3/434	7/419

```
        .25    .5     1     2     4
       Favors Intervention  Favors Control
```

Abbreviations: AFPP = Aspirin/Folate Polyp Prevention study; CG = control group; CI = confidence interval; IG = intervention group; mg = milligram; RR = relative risk; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; yrs = years

Figure 9. Effect of Aspirin on 3- to 4-Year Risk of Colorectal Adenoma Incidence in Persons With a Prior Adenoma

Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description	RR (95% CI)	Events/N, IG	Events/N, CG
Higher dose (300 to 325 mg)						
AFPP	325	2.6	Prior adenoma	0.96 (0.82, 1.12)	160/355	171/363
ukCAP	300	2.9	Prior adenoma	0.79 (0.63, 0.99)	99/434	121/419
APACC	300	3.7	Prior adenoma	1.44 (1.01, 2.07)	27/47	33/83
Low dose (<300 mg)						
AFPP	81	2.6	Prior adenoma	0.81 (0.69, 0.96)	140/366	171/363
APACC	160	3.7	Prior adenoma	0.69 (0.41, 1.14)	15/55	33/83

.25 .5 1 2 4
Favors Intervention   Favors Control
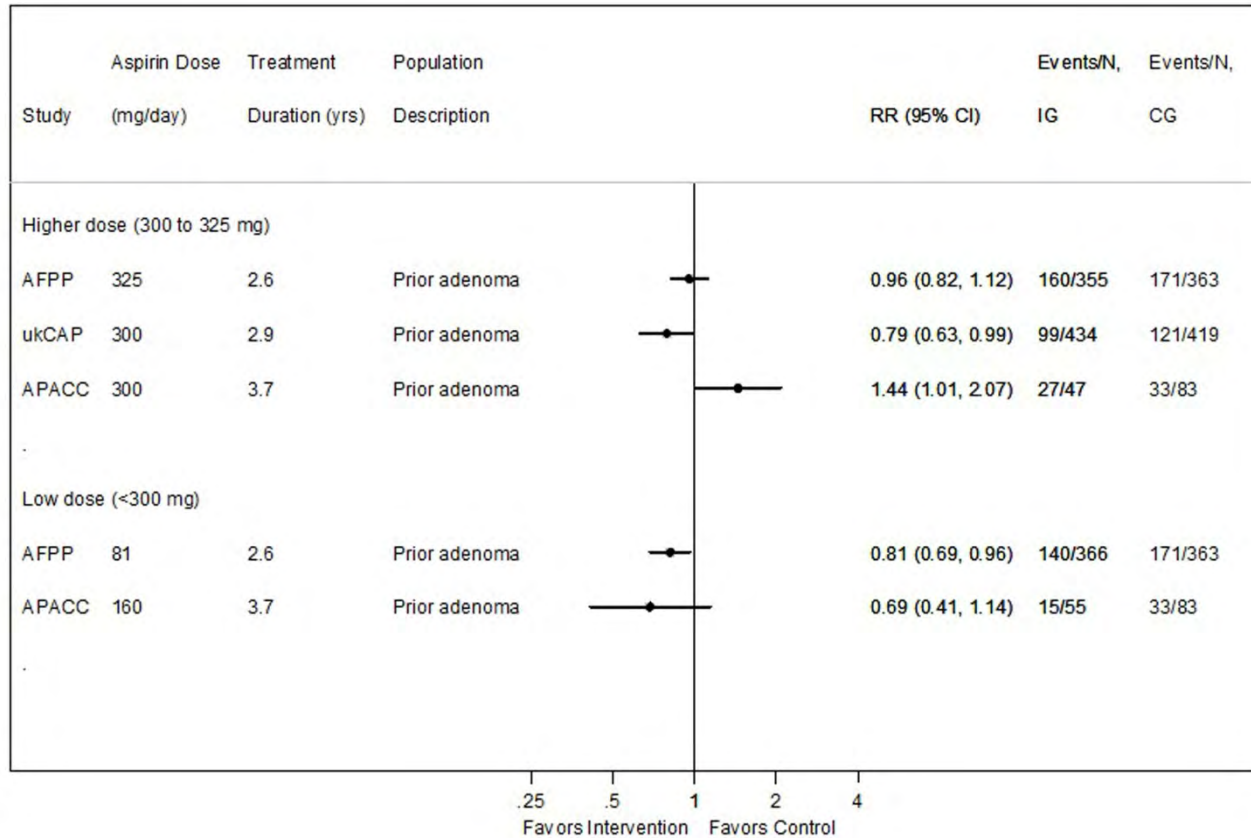
Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance

Abbreviations: AFPP = Aspirin/Folate Polyp Prevention study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal study; CG = control group; CI = confidence interval; IG = intervention group; mg = milligram; RR = relative risk; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; yrs = years

Figure 10. Effect of Aspirin on Gastrointestinal Bleeding Risk

Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description	RR (95% CI)	Events/N, IG	Events/N, CG
AFPP*	81 or 325	2.6	Prior adenoma	0.99 (0.25, 3.95)	6/749	3/372
SALT	75	2.7	Recent TIA, stroke, or RAO	2.78 (0.89, 8.70)	11/676	4/684
ukCAP	300	2.9	Prior adenoma	0.99 (0.29, 3.40)	5/472	5/467
SAPAT*	75	4.2	Angina, without prior MI	1.86 (0.69, 5.02)	11/1009	6/1026
JPAD	81 or 100	4.4	Diabetes	3.04 (0.98, 9.39)	12/1262	4/1277
UK-TIA	300 or 1200	4.4	Recent TIA or stroke	3.57 (1.79, 7.14)	64/1621	9/814
PHS	162.5	5.0	Male physicians	1.04 (0.91, 1.19)	440/11037	422/11034
POPADAD	100	6.7	Diabetes & ABI<= 0.99	0.90 (0.55, 1.49)	28/638	31/638
TPT*	75	6.9	Male at high IHD risk	3.01 (0.61, 14.88)	6/1268	2/1272
AAA*	100	8.2	ABI<= 0.95	1.13 (0.44, 2.91)	9/1675	8/1675
WHS	50	10.1	Female health professionals	1.13 (1.06, 1.21)	1645/19934	1452/19942

.25　.5　1　2　4

Favors Intervention　Favors Control
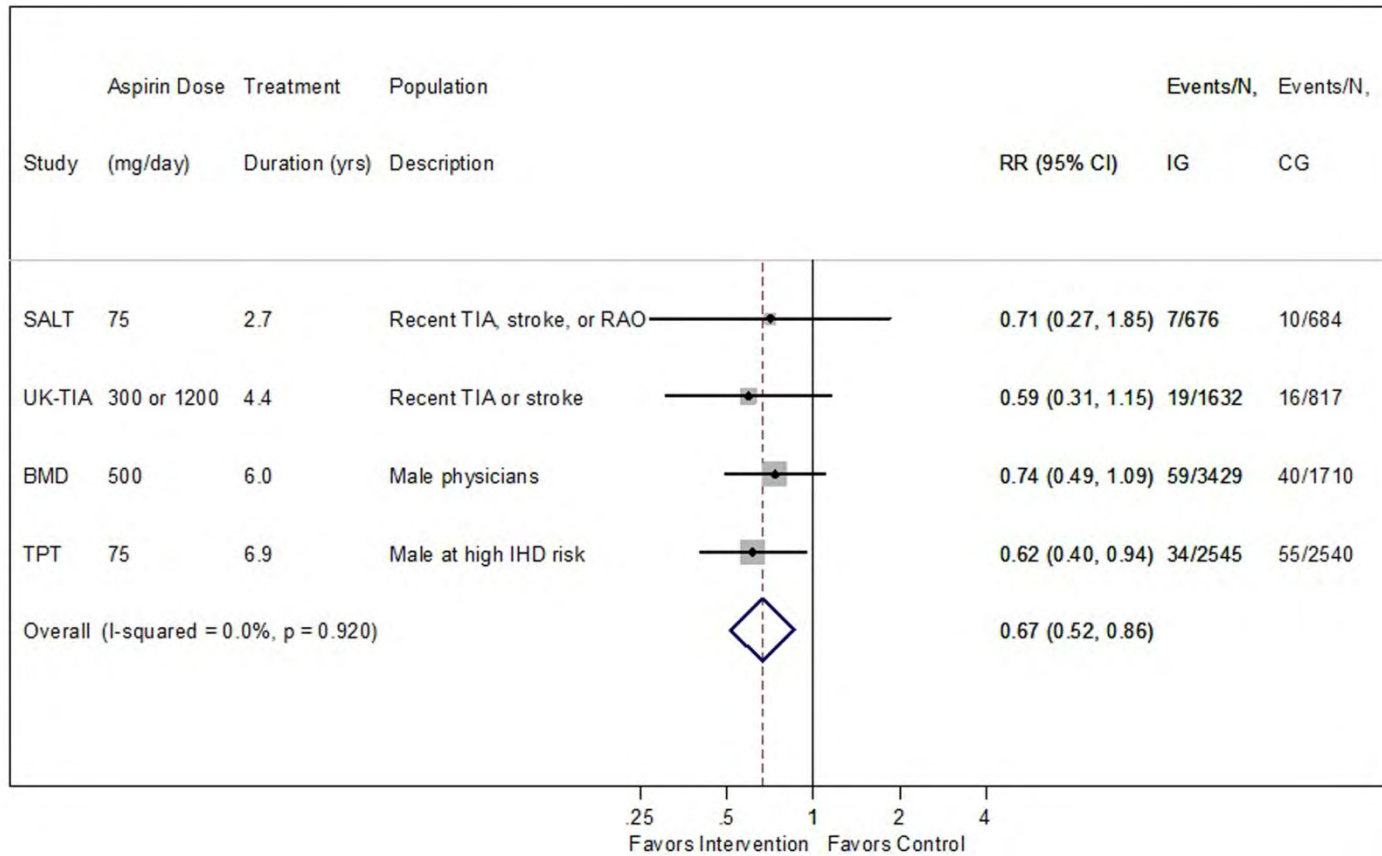
*Serious gastrointestinal bleeding

Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; AFPP = Aspirin/Folate Polyp Prevention study; CG = control group; CI = confidence interval; IG = intervention group; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; MI = myocardial infarction; mg = milligrams; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RAO = retinal artery occlusion; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; UK-TIA = United Kingdom Transient Ischaemic Attack trial; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; WHS = Women's Health Study; yrs = years

Figure 11. Effect of Aspirin on Serious Gastrointestinal Bleeding Risk

Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description	OR (95% CI)	Events/N, IG	Events/N, CG
AFPP	81 or 325	2.6	Prior adenoma	0.99 (0.25, 4.00)	6/749	3/372
SALT	75	2.7	Recent TIA, stroke, or RAO	2.20 (0.74, 6.55)	9/676	4/684
SAPAT	75	4.2	Angina, without prior MI	1.84 (0.71, 4.78)	11/1009	6/1026
JPAD	81 or 100	4.4	Diabetes	5.02 (0.87, 29.05)	4.5/1263	.5/1278
UK-TIA	300 or 1200	4.4	Recent TIA or stroke	3.41 (1.61, 7.23)	29/1621	2/814
PHS	162.5	5.0	Male physicians	1.73 (1.10, 2.70)	49/11037	28/11034
TPT	75	6.9	Male at high IHD risk	2.73 (0.68, 10.95)	6/1268	2/1272
AAA	100	8.2	ABI <= 0.95	1.13 (0.43, 2.92)	9/1675	8/1675
Overall (I-squared = 0.0%, p = 0.540)				1.94 (1.44, 2.62)		

.125 .25 .5 1 2 4 8
Favors Intervention   Favors Control

Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance
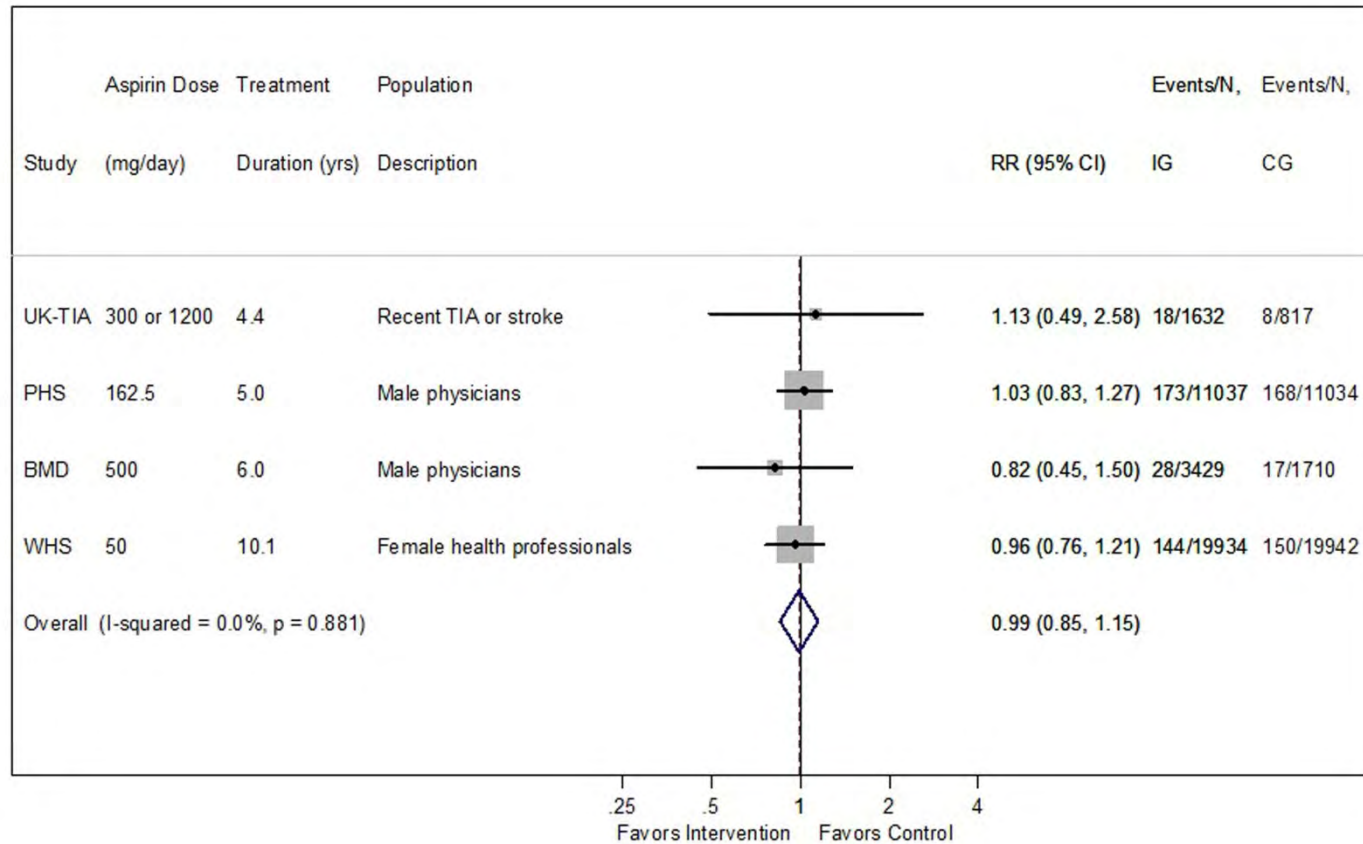
Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; AFPP = Aspirin/Folate Polyp Prevention study; CG = control group; CI = confidence interval; IG = intervention group; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; mg = milligram; MI = myocardial infarction; OR= odds ratio; PHS = Physicians' Health Study; RAO = retinal artery occlusion; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack trial; yrs = years

Figure 12. Effect of Aspirin on Fatal Gastrointestinal Bleeding Risk

Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description	OR (95% CI)	Events/N, IG	Events/N, CG
SAPAT	75	4.2	Angina, without prior MI	1.98 (0.21, 19.08)	2/1009	1/1026
UK-TIA	300 or 1200	4.4	Recent TIA or stroke	2.13 (0.19, 23.42)	2.5/1622	.5/815
PHS	162.5	5.0	Male physicians	2.72 (0.17, 43.45)	1.5/11038	.5/11035
BMD	500	6.0	Male physicians	0.47 (0.09, 2.57)	3/3429	3/1710
TPT	75	6.9	Male at high IHD risk	0.37 (0.02, 5.90)	.5/1269	1.5/1273
WHS	50	10.1	Female health professionals	1.00 (0.20, 4.96)	3/19934	3/19942
Overall (I-squared = 0.0%, p = 0.779)				1.00 (0.43, 2.36)		

.125 .25 .5 1 2 4 8
Favors Intervention   Favors Control

Abbreviations: BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; IG = intervention group; IHD = ischemic heart disease; mg = milligram; MI = myocardial infarction; OR = odds ratio; PHS = Physicians' Health Study; SAPAT = Swedish Angina Pectoris Aspirin Trial; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack trial; WHS = Women's Health Study; yrs = years

Figure 13. Effect of Aspirin on Intracranial Bleeding Risk

Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; AFPP = Aspirin/Folate Polyp Prevention study; BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; IG = intervention group; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; mg = milligram; MI = myocardial infarction: OR = odds ratio; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; RAO = retinal artery occlusion; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; UK-TIA = United Kingdom Transient Ischaemic Attack trial; WHS = Women's Health Study; yrs = years

Figure 14. Effect of Aspirin on Hemorrhagic Stroke Risk

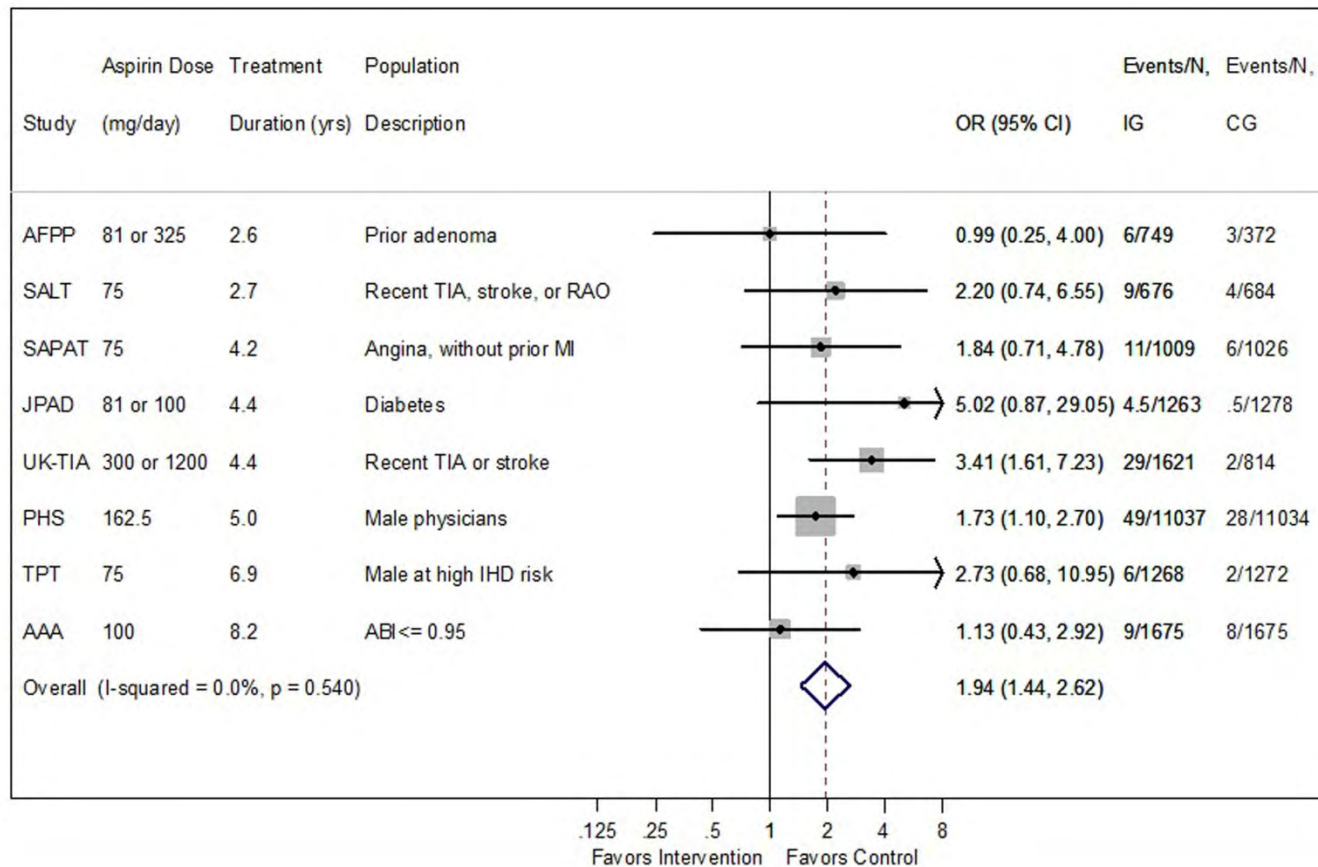| Study	Aspirin Dose (mg/day)	Treatment Duration (yrs)	Population Description	OR (95% CI)	Events/N, IG	Events/N, CG
AFPP	81 or 325	2.6	Prior adenoma	1.45 (0.08, 27.51)	1.5/750	.5/373
SALT	75	2.7	Recent TIA, stroke, or RAO	2.53 (0.77, 8.28)	8/676	3/684
SAPAT	75	4.2	Angina, without prior MI	2.40 (0.54, 10.59)	5/1009	2/1026
JPAD	81 or 100	4.4	Diabetes	0.87 (0.29, 2.58)	6/1262	7/1277
UK-TIA	300 or 1200	4.4	Recent TIA or stroke	2.58 (0.91, 7.30)	14/1621	2/814
PHS	162.5	5.0	Male physicians	1.88 (0.97, 3.64)	23/11037	12/11034
BMD	500	6.0	Male physicians	1.08 (0.42, 2.81)	13/3429	6/1710
POPADAD	100	6.7	Diabetes & ABI <= 0.99	0.67 (0.12, 3.87)	2/638	3/638
TPT	75	6.9	Male at high IHD risk	3.81 (0.40, 36.66)	2.5/1269	.5/1273
AAA	100	8.2	ABI <= 0.95	1.25 (0.34, 4.62)	5/1675	4/1675
WHS	50	10.1	Female health professionals	1.37 (0.99, 1.89)	85/19934	62/19942
Overall (I-squared = 0.0%, p = 0.827)				1.47 (1.16, 1.88)		

Scale: .125 .25 .5 1 2 4 8
Favors Intervention Favors Control

Note: Differences from point estimates or 95% confidence intervals reported in studies are due to use of different statistical programs, and are minor and of no clinical or statistical significance

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ABI = ankle brachial index; AFPP = Aspirin/Folate Polyp Prevention study; BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; IG = intervention group; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; MI = myocardial infarction; mg = milligram; OR = odds ratio; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; RAO = retinal artery occlusion; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; UK-TIA = United Kingdom Transient Ischaemic Attack trial; WHS = Women's Health Study; yrs = years
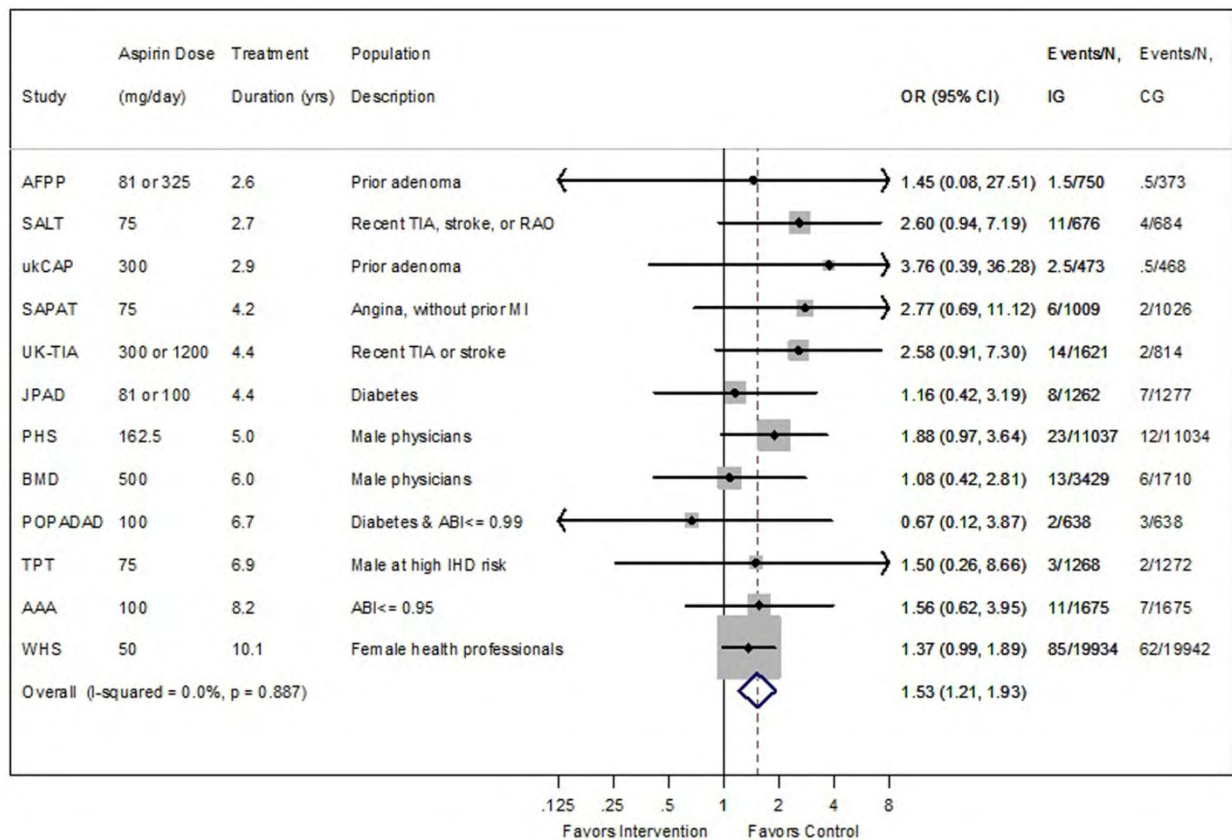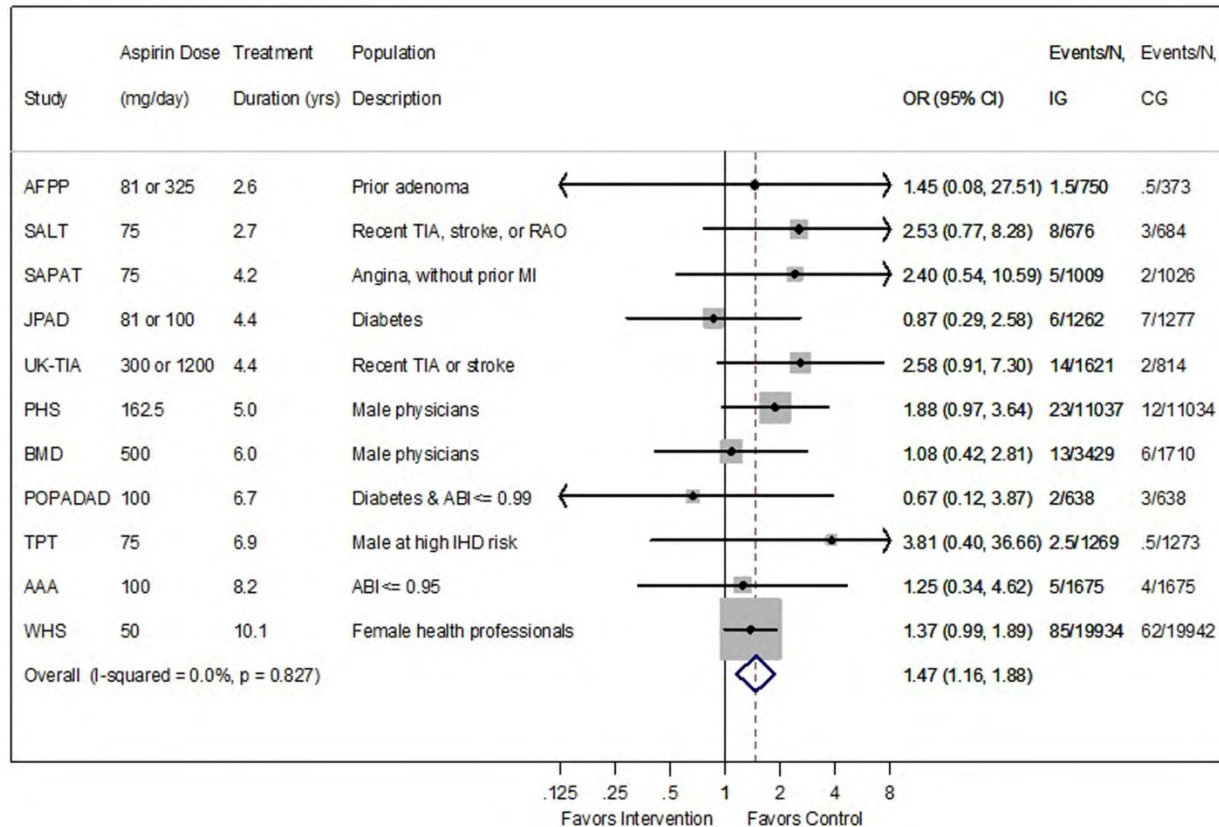
Table 1. Effect of Aspirin on All-Cause Mortality in Randomized, Controlled Trials, Overall and by Followup Period

Study	Treatment Group	Early Onset Risk (0 to 10[†] Years)		Long-Term Cumulative Risk (0 to 20 Years)	
		Events/N (%)	Relative Risk Estimate (95% CI)	Events/N (%)	Relative Risk Estimate (95% CI)
WHS[112-114]	100 mg qod	609/19,934 (3.1%)[*]	RR, 0.95 (0.85 to 1.06)	1,744/19,934 (8.7)[*]	HR, 1.00 (0.94 to 1.07)[‖]
	Placebo	642/19,942 (3.2%)[*]		1,728/19,942 (8.7)[*]	
PHS[118]	325 mg qod	217/11,037 (2.0%)[*]	RR, 0.96 (0.80 to 1.14)	NR	NR
	Placebo	227/11,034 (2.1%)[*]		NR	
BMD[83]	500 mg/day	270/3,429 (7.9%)[*]	OR, 0.88 (0.72 to 1.09)	IG: NR[‡] CG: NR[‡]	HR, 0.96 (0.90 to 1.02)
	Control (no placebo)	151/1,710 (8.8%)[*]			
UK-TIA[83]	300 or 1200 mg/day	221/1,621 (13.6%)[*]	OR, 0.90 (0.70 to 1.14)		
	Placebo	122/814 (15.0%)[*]			
TPT[83]	75 mg/day	216/2,545 (8.5%)[*]	OR, 1.06 (0.87 to 1.29)		
	Placebo	205/2,540 (8.1%)[*]			
SALT[85]	75 mg/day	61/676 (9.0%)[*]	NR	NR	NR
	Placebo	69/684 (10.1%)[*]		NR	
ETDRS[83]	650 mg/day	340/1,856 (18.3%)[*]	OR, 0.91 (0.77 to 1.08)	NR	NR
	Placebo	366/1,855 (19.7%)[*]		NR	
SAPAT[83]	75 mg/day	82/1,009 (8.1%)[*]	OR, 0.77 (0.57 to 1.04)	NR	NR
	Placebo	106/1,026 10.3%)[*]		NR	
JPAD[83]	81 or 100 mg/day[§]	33/1,262 (2.6%)[*][¶]	OR, 0.88 (0.55 to 1.40)	NR	NR
	Placebo	38/1,277 (3.0%)[*]		NR	
POPADAD[83]	100 mg/day	94/638 (14.7%)[*]	OR, 0.92 (0.68 to 1.25)	NR	NR
	Placebo	101/638 (15.8%)[*]		NR	
AAA[83]	100 mg/day	176/1,675 (10.5%)[*]	OR, 0.94 (0.76 to 1.17)	NR	NR
	Placebo	186/1,675 (11.1%)[*]		NR	

[*]Calculated
[†]Variable follow-up by trial duration, in-trial results
[‡]Minimum 5 years scheduled duration of intervention; included BMD, UKTIA, and TPT.[83] Combined N=10,502. Total events, events by group, and denominators by group not reported
[§]Dose not randomized
[‖]Median follow-up in WHS was 17.5 years
[¶]34 events reported in main trial[131]

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; ETDRS = Early Treatment Diabetic Retinopathy Study; HR = hazard ratio; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; mg = milligrams; NR = not reported; OR = odds ratio; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; qod = every other day; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial ; SAPAT = Swedish Angina Pectoris Aspirin Trial; TPT = Thrombosis Prevention Trial; UK-TIA = UK Transient Ischaemic Attack trial; WHS = Women's Health Study

Table 2. Effect of Aspirin on Colorectal Cancer Mortality in Randomized, Controlled Trials, Overall and by Followup Period

Study	Treatment Group[§]	Early Onset Risk (0 to 10 Years)		Late Onset Risk (10 to 20 Years)		Long-Term Cumulative Risk (0 to 20+ Years)[‡]	
		Events/N (%)	Relative Risk Estimate (95 % CI)	Events/N (%)	Relative Risk Estimate (95% CI)	Events/N (%)	Relative Risk Estimate (95% CI)
WHS[112]	100 mg qod	Total: 65	Reported as "no difference"	NR		NR	
	Placebo	IG: NR CG: NR					
PHS	325 mg qod	NR		NR		NR	
	Placebo						
BMD[83,85]	500 mg/day					IG: 59/3,429 (1.7%)[*]	OR, 0.73 (0.49 to 1.10)
	Control (no placebo)					CG: 40/1,710 (2.3%)[*]	
UK-TIA[83,85]	1,200 mg/day	IG: NR[†] CG: NR[†]	HR, 0.79 (0.49 to 1.26)[†]	IG: NR[†] CG: NR[†]	HR, 0.51 (0.35 to 0.74)[†]	IG: 11/821 (1.3%)[*]	OR, 0.68 (0.31 to 1.47)
	300 mg/day					IG: 8/811 (1.0%)[*]	OR, 0.50 (0.21 to 1.17)
	Placebo					CG: 16/817 (2.0%)[*]	
TPT[83,85]	75 mg/day					IG: 34/2,545 (1.3%)[*]	OR, 0.61 (0.40 to 0.94)
	Placebo					CG: 55/2,540 (2.2%)[*]	
SALT[85]	75 mg/day	NR		NR		IG: 7/676 (1.0%)[*]	OR, 0.71 (0.27 to 1.86)
	Placebo					CG: 10/684 (1.5%)[*]	

[*]Calculated
[†]Minimum 5 years scheduled duration of intervention; included BMD, UKTIA, and TPT.[83] Combined N=10,502. Total events by group, and denominators by group not reported
[‡]Reported in Rothwell 2010[85]
[§]Median scheduled treatment duration was: 6.0 years (BMD), 4.4 years (UK-TIA), 6.9 years (TPT), and 2.7 years (SALT)

Abbreviations: BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; HR=hazard ratio; IG = intervention group; mg = milligram; NR = not reported; OR = odds ratio; PHS = Physicians' Health Study; qod = every other day; SALT = Swedish Aspirin Low-dose Trial; TPT = Thrombosis Prevention Trial; UK-TIA = UK Transient Ischaemic Attack trial; WHS = Women's Health Study

Table 3. Effect of Aspirin on 3- to 4-Year All-Cause Mortality From Randomized, Controlled Trials of Persons With a Prior Adenoma

Study	Treatment Group	Death During Followup, Events/N (%)	Relative Risk Estimate (95% CI)
APACC[142]	160 mg/day	0/140 (0%)	NR
	300 mg/day		
	Placebo	1/132 (0.8%)	
ukCAP[144]	300 mg/day	12/472 (2.5%)*	NR
	Placebo	11/467 (2.4%)*	
AFPP[136]	81 mg/day	3/377 (0.8%)	NR
	325 mg/day	4/372 (1.1%)	
	Placebo	3/372 (0.8%)	

*Calculated

Abbreviations: AFPP = Aspirin/Folate Polyp Prevention Study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal (APACC) study; CI = confidence interval; mg = milligrams; NR = not reported; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

Table 4. Effect of Aspirin on Colorectal Cancer Incidence in Randomized, Controlled Trials, by Followup Period

Study[§]	Early Onset Risk (0 to 12 Years)[†]		Late Onset Risk (10 to 19 Years)		Long-Term Cumulative Risk (0 to 20+ Years)[‡]	
	Events/N (%)	Relative Risk Estimate (95% CI)	Events/N (%)	Relative Risk Estimate (95% CI)	Events/N (%)	Relative Risk Estimate (95% CI)
WHS[113]	IG: 144/19,934 (0.7%)	HR, 0.96 (0.76 to 1.20)	IG: 58/19,934 (0.3%)	HR, 0.58 (0.42 to 0.80)	IG: 202/19,934 (1.0%)	HR, 0.80 (0.67 to 0.97)
	CG: 150/19,942 (0.8%)		CG: 99/19,942 (0.5%)*		CG: 249/19,942 (1.2%)	
PHS[135]	IG: 173/11,037 (1.6%)*	RR, 1.03 (0.83 to 1.28)	NR	NR	NR	NR
	CG: 168/11,034 (1.5%)*		NR		NR	
BMD[111]	IG: 28/3,429 (0.8%)*	HR, 0.82 (0.45 to 1.49)	IG: 50/3,429 (1.5%)*	HR, 0.64 (0.42 to 0.97)	IG: 92/3,429 (2.7%)*	HR, 0.70 (0.51 to 0.97)
	CG: 17/1,710 (1.0%)*		CG: 38/1,710 (2.2%)*		CG: 64/1,710 (3.7%)*	
UK-TIA[111]	IG: 18/1,632 (1.1%)*	HR, 1.14 (0.49 to 2.61)	IG: 15/1,632 (0.9%)*	HR, 0.51 (0.25 to 1.00)	IG: 37/1,632 (2.3%)*	HR, 0.82 (0.49 to 1.38)
	CG: 8/817 (1.0%)*		CG: 15/817 (1.8%)*		CG: 23/817 (2.8%)*	
BMD, UK-TIA, TPT, SALT[85]	NR	NR	NR	NR	Total=397/14,033 (2.8%)*	HR, 0.76 (0.63 to 0.94)
	NR		NR			

* Calculated
[†]0 to 9 years in BMD and UK-TIA, 0 to 10 years in WHS, 0 to 12 years in PHS
[‡]Median follow-up in WHS was 17.5 years
[§]Median scheduled treatment duration was: 10.1 years (WHS), 6.0 years (BMD), 4.4 years (UK-TIA), 6.9 years (TPT), and 2.7 years (SALT). The mean scheduled treatment duration was 5.0 years in PHS.

Abbreviations: BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; HR = hazard ratio; IG = intervention group; NR = not reported; PHS = Physicians' Health Study; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; TPT = Thrombosis Prevention Trial; UK-TIA = UK Transient Ischaemic Attack trial; WHS = Women's Health Study

Table 5. Effect of Aspirin on 3- to 4-Year Incidence of Colorectal Cancer in Randomized, Controlled Trials of Persons With a Prior Adenoma

Study	Treatment Group	Colorectal Cancer Incidence Events/N (%)	Relative Risk Estimate (95% CI) p-value
ukCAP[144]	300 mg/day	3/434 (0.7%)[*]	NR
	Placebo	7/419 (1.7%)[*]	
AFPP[136]	81 mg/day	2/377 (0.5%)[*]	NR
	325 mg/day	3/372 (0.8%)[*]	p-value: 0.71 for difference among three groups
	Placebo	1/372 (0.3%)[*]	

[*]Calculated

Abbreviations: AFPP = Aspirin/Folate Polyp Prevention Study; CI = confidence interval; mg = milligram; NR = not reported; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

Table 6. Effect of Aspirin on 3- to 4-Year Incidence of Colorectal Adenoma in Randomized, Controlled Trials of Persons With a Prior Adenoma

Study	Treatment Group	Adenoma Incidence		Advanced Lesion Incidence*		Adenoma Number	
		Events/N (%)	Relative Risk Estimate (95% CI)	Events/N (%)	Relative Risk Estimate (95% CI)	Mean Number (SD)	Relative Risk Estimate (95% CI)
APACC[142†]	160 mg/day	15/55 (27%)	NR, p-value reported as not significant	6/55 (11%)	NR, p-value reported as not significant	0.4 (0.7)	NR Difference in proportions (aspirin 160 mg vs. placebo: p=0.025)
	300 mg/day	27/47 (57%)		4/47 (8.5%)		1 (1.1)	
	Placebo	33/83 (40%)		7/83 (8%)		0.8 (1.3)	
ukCAP[144‡]	300 mg/day	99/434 (22.8%)	0.79 (0.63 to 0.99)	41/434 (9.4%)	0.63 (0.43 to 0.91)	0.31 (0.70)	NR, p=0.015
	Placebo	121/419 (28.9%)		63/419 (15.0%)		0.47 (0.92)	
AFPP[136§]	81 mg/day	140/366 (38.3%)	0.83 (0.70 to 0.98)	28/366 (7.7%)	0.58 (0.37 to 0.90)	NR	NR
	325 mg/day	160/355 (45.1%)	0.95 (0.80 to 1.12)	38/355 (10.7%)	0.83 (0.55 to 1.23)	NR	
	Placebo	171/363 (47.1%)		47/363 (12.9%)		NR	

*Definition of advanced lesion: APACC, diameter ≥10 mm, ≥25% villous, or high grade dysplasia; ukCAP, adenomas ≥1 cm, villous or tubulovillous adenomas, adenomas with severe dysplasia, or colorectal cancer; AFPP, villous or tubulovillous adenoma, adenoma ≥1 cm, severe dysplasia, or invasive cancer
†Among persons who had undergone a colonoscopy with adequate bowel preparation and visualized cecum, had ≥3 adenomas or ≥1 adenoma 6 millimeters or larger, and removal of all polyps in the three months before study entry
‡Among persons with an adenoma ≥0.5 cm that was removed in the 6 months before recruitment (or earlier if they also had ≥1 adenoma removed in the 6 months before randomization)
§Among persons with a prior adenoma (either ≥1 adenomas in the 3 months before recruitment, ≥1 adenomas removed in the 16 months before recruitment and a lifetime history of ≥2 adenomas, or an adenoma ≥1 cm removed in the 16 months before recruitment) and with confirmation of no remaining polyps in the three months before recruitment

Abbreviations: AFPP = Aspirin/Folate Polyp Prevention Study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal; CI = confidence interval; mg = milligram; NR = not reported; SD = standard deviation; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

Table 7. Effect of Aspirin on Risk of Gastrointestinal Bleeding in Randomized, Controlled Trials and Cohort Studies

Study Outcome Definition	Treatment Group	Gastrointestinal Bleeding		Fatal Gastrointestinal Bleed	
		Events/N (%)	Relative Risk Estimate (95% CI)	Events/N (%)	Relative Risk Estimate (95% CI)
RCTs					
WHS[113†] *Nonspecific GI bleeding*	100 mg qod	1,645/19,934 (8.3%)	HR, 1.14 (1.06 to 1.22)	3/19,934 (0.02%)[*]	NR
	Placebo	1,452/19,942 (7.3%)		3/19,942 (0.02%)[*]	
PHS[118] *Nonspecific GI bleeding (major= death or required transfusion)*	325 mg qod	440/11,037 (4.0%) *Major=49/11,037 (0.4%)[*]*	NR, p=0.55 for nonspecific GI bleeding	1/11,037(<0.01%)[*]	NR
	Placebo	422/11,034 (3.8%) *Major=28/11,034 (0.3%)[*]*	RR, 1.71 (1.09 to 2.69) for major GI bleeding, excluding one death	0/11,034 (0.0%)[*]	
BMD[124] *GI hemorrhage, peptic ulcer hemorrhage or perforation*	500 mg/day	NR	NR	3[¶]/3,429 (0.09%)[*]	NR
	Control (no placebo)	NR		3[¶]/1,710 (0.18%)[*]	
UK-TIA[126] *GI hemorrhage (serious=required hospitalization or fatal)*	1,200 mg/day	39/815 (5%) *Serious=19/815 (2.3%)[*]*	*1,200 mg vs. 300 mg:* OR, 1.62 (0.94 to 2.79) *300 mg vs. placebo:* OR, 2.57 (1.20 to 5.53)	2/815 (1%)	NR
	300 mg/day	25/806 (3%) *Serious=10/806 (1.2%)[*]*		0/806 (0%)	
	Placebo	9/814 (1%) *Serious=2/814 (0.2%)[*]*		0/814 (0%)	
SALT[127] *GI bleeding (severe=required hospitalization or discontinued medication)*	75 mg/day	11/676 (1.6%) *Severe=9/676 (1.3%)*	NR	NR	NR
	Placebo	4/684 (0.6%) *Severe=4/684 (0.6%)*		NR	
TPT[108§‡] *Major GI bleeding*	75 mg/day	*Upper GI:* IG: 5/1,268 (0.4%)[*] CG: 1/1,272 (<0.1%)[*]	NR	0/1,268 (0%)	NR
	Placebo	*Lower GI:* IG: 0/1,268 (0%)[*] CG: 1/1,272 (<0.1%)[*] *Unknown GI:* IG: 1/1,268 (<0.1%)[*] CG: 0/1,272 (0%)[*]		1/1,272 (<0.1%)	
SAPAT[130‡] *Major GI bleeding*	75 mg/day	11/1,009 (1.1%)	NR	2/1,009 (0.2%)[*]	NR
	Placebo	6/1,026 (0.6%)[*]		1/1,026 (0.1%)[*]	

Table 7. Effect of Aspirin on Risk of Gastrointestinal Bleeding in Randomized, Controlled Trials and Cohort Studies

Study Outcome Definition	Treatment Group	Gastrointestinal Bleeding		Fatal Gastrointestinal Bleed	
		Events/N (%)	Relative Risk Estimate (95% CI)	Events/N (%)	Relative Risk Estimate (95% CI)
JPAD[131] *GI bleeding (severe=required transfusion)*	81 or 100 mg/day[‖]	12/1,262 (1.0%)* *Severe=4/1,262 (0.32%)**	NR	NR	NR
	Placebo	4/1,277 (0.3%)* *Severe=0/1,277 (0%)**		NR	
POPADAD[132] *GI bleeding*	100 mg/day	28/638 (4.4%)	OR, 0.90 (0.53 to 1.52)	NR	NR
	Placebo	31/638 (4.9%)		NR	
AAA[133‡] *Major GI hemorrhage*	100 mg/day	9/1,675 (0.5%)*	NR	NR	NR
	Placebo	8/1,675 (0.5%)*		NR	
ukCAP[144] *GI bleeding*	300 mg/day	*Upper GI:*	NR	NR	NR
	Placebo	IG: 2/472 (0.4%) CG: 0/467 (0%) *Lower GI:* IG: 3/472 (0.6%) CG: 5/467 (1.1%)		NR	
AFPP[136‡] *Serious GI bleeding (requiring hospitalization or surgical intervention)*	81 mg/day	2/377 (0.5%)*	NR, p=0.65 (three groups)	NR	NR
	325 mg/day	4/372 (1.1%)*		NR	
	Placebo	3/372 (0.8%)*		NR	
Cohort studies					
NHS[146] *GI bleeding requiring hospitalization or transfusion*	0.5 to 1.5 tablets/week (325 mg)	1.07 per 1,000 person-years	NR	NR	NR
	2 to 5 tablets/week (325 mg)	1.07 per 1,000 person-years	NR	NR	NR
	6 to 14 tablets/week (325 mg)	1.40 per 1,000 person-years	NR	NR	NR
	more than 14 tablets/week (325 mg)	1.57 per 1,000 person-years	NR	NR	NR
	No use	0.77 per 1,000 person-years		NR	

*Calculated
[†]In-trial and post-trial
[‡]Restricted to serious or major events
[§]Limited to arms in factorial design that did not receive warfarin, i.e., aspirin only and double placebo
[‖]Dose not randomized

Table 7. Effect of Aspirin on Risk of Gastrointestinal Bleeding in Randomized, Controlled Trials and Cohort Studies

[¶]Number of estimated events = (rate of fatal gastric hemorrhage per 10,000 person-years ∗ number of person-years /10,000) + (rate of fatal peptic ulcer hemorrhage per 10,000 person-years ∗ number of person-years /10,000) + (rate of fatal peptic ulcer perforation per 10,000 person-years * number of person-years /10,000)

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; AFPP = Aspirin/Folate Polyp Prevention study; BMD = British Medical Doctors trial; CG = control group; CI = confidence interval; GI = gastrointestinal; HR = hazard ratio; IG = intervention group; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; mg = milligram; NHS = Nurses' Health Study; NR = not reported; OR = odds ratio; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; qod = every other day; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TPT = Thrombosis Prevention Trial; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; UK-TIA = UK Transient Ischaemic Attack trial; WHS = Women's Health Study

Table 8. Effect of Aspirin on Risk of Intracranial Bleeding in Randomized, Controlled Trials

Study	Treatment Group	Outcome Definition	Intracranial Hemorrhage/Bleeding	
			Events/N (%)	Relative Risk Estimate (95% CI)
WHS[113†]	100 mg qod	Hemorrhagic stroke	85/19,934 (0.4%)	HR, 1.36 (0.98 to 1.88)
	Placebo		62/19,942 (0.3%)	
PHS[118]	325 mg qod	Hemorrhagic stroke	23/11,037 (0.2%)*	RR, 2.14 (0.96 to 4.77)
	Placebo		12/11,034 (0.1%)*	
BMD[124]	500 mg/day	Fatal hemorrhagic stroke and nonfatal stroke, probably hemorrhagic	13[‡]/3,429 (0.4%)*	NR
	Control (no placebo)		6[‡]/1,710 (0.4%)*	
UK-TIA[126]	1,200 mg/day	Intracranial hemorrhage	7/815 (0.9%)	NR
	300 mg/day		7/806 (0.9%)	
	Placebo		2/814 (0.2%)	
SALT[127]	75 mg/day	Intracerebral and subarachnoid hemorrhage	11/676 (1.6%)*	NR
	Placebo		4/684 (0.6%)*	
TPT[108§]	75 mg/day	Hemorrhagic and sub-arachnoid stroke	3/1,268 (0.2%)*	NR
	Placebo		2/1,272 (0.2%)*	
SAPAT[130]	75 mg/day	Subdural hematoma and hemorrhagic stroke	6/1,009 (0.6%)*	NR
	Placebo		2/1,026 (0.2%)*	
JPAD[131]	81 or 100 mg/day[‖]	Subdural hematoma and hemorrhagic stroke	8/1,262 (0.6%)*	NR
	Placebo		7/1,277 (0.5%)*	
POPADAD[132]	100 mg/day	Fatal hemorrhagic stroke	2/638 (0.3%)*	NR
	Placebo		3/638 (0.5%)*	
AAA[133]	100 mg/day	Intracranial hemorrhage	11/1,675 (0.7%)*	NR
	Placebo		7/1,675 (0.4%)*	
AFPP[136]	81 mg/day	Hemorrhagic stroke	1/377 (0.3%)*	NR
	325 mg/day		0/372 (0%)*	
	Placebo		0/372 (0%)*	
ukCAP[144]	300 mg/day	Subarachnoid hemorrhage	2/472 (0.4%)*	NR
	Placebo		0/467 (0%)*	

*Calculated
[†]In-trial and post-trial
[‡]Number of estimated events = (rate of fatal hemorrhagic stroke per 10,000 person-years ∗ number of person-years /10,000) + (rate of nonfatal, probable hemorrhagic stroke per 10,000 person-years ∗ number of person-years /10,000)
[§]Limited to arms in factorial design that did not receive warfarin, i.e., aspirin only and double placebo
[‖]Dose not randomized

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; AFPP = Aspirin/Folate Polyp Prevention study; BMD = British Medical Doctors trial; CI = confidence interval; HR = hazard ratio; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; mg = milligram; NR = not reported; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; qod = every other day; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; UK-TIA = UK Transient Ischaemic Attack trial; TPT = Thrombosis Prevention Trial; WHS = Women's Health Study

Table 9. Effect of Aspirin on Risk of Hemorrhagic Stroke in Randomized, Controlled Trials

Study	Treatment Group	Events/N (%)	Relative Risk Estimate (95% CI)
WHS[113†]	100 mg qod	85/19,934 (0.4%)	HR, 1.36 (0.98 to 1.88)
	Placebo	62/19,942 (0.3%)	
PHS[118]	325 mg qod	23/11,037 (0.2%)*	RR, 2.14 (0.96 to 4.77)
	Placebo	12/11,034 (0.1%)*	
BMD[124]	500 mg/day	13**/3,429 (0.4%)*	NR
	Control (no placebo)	6**/1,710 (0.4%)*	
UK-TIA[126‡]	1,200 mg/day	7/815 (0.9%)	NR
	300 mg/day	7/806 (0.9%)	
	Placebo	2/814 (0.2%)	
TPT[108§]	75 mg/day	2/1,268 (0.2%)	NR
	Placebo	0/1,272 (0%)	
SALT[127]	75 mg/day	8††/676 (1.2%)*	NR
	Placebo	3††/684 (0.4%)*	
SAPAT[130]	75 mg/day	5/1,009 (0.5%)*	NR
	Placebo	2/1,026 (0.2%)*	
JPAD[131]	81 or 100 mg/day‖	6/1,262 (0.5%)*	NR
	Placebo	7/1,277 (0.5%)*	
POPADAD[132¶]	100 mg/day	2/638 (0.3%)*	NR
	Placebo	3/638 (0.5%)*	
AAA[133]	100 mg/day	5/1,675 (0.3%)*	NR
	Placebo	4/1,675 (0.2%)*	
AFPP[136]	81 mg/day	1/377 (0.3%)*	NR
	325 mg/day	0/372 (0%)*	
	Placebo	0/372 (0%)*	

*Calculated
†Includes post-trial followup; fatal stroke, is limited to in-trial followup
‡Limited to major or disabling hemorrhagic stroke
§Limited to arms in factorial design that did not receive warfarin, i.e., aspirin only and double placebo
‖Dose not randomized
¶Limited to fatal hemorrhagic stroke
**Number of events estimated = (rate of fatal hemorrhagic stroke per 10,000 person-years * number of person-years /10,000) + (rate of nonfatal probable hemorrhagic stroke per 10,000 person-years * number of person-years /10,000
††Intracerebral hemorrhage

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; AFPP = Aspirin/Folate Polyp Prevention study; BMD = British Medical Doctors trial; HR = hazard ratio; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; mg = milligram; NR = not reported; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; qod = every other day; RR = relative risk; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; TPT = Thrombosis Prevention Trial; UK-TIA = UK Transient Ischaemic Attack trial; WHS = Women's Health Study

Table 10. Summary of Evidence

Key Question	Number of Studies (k) Design	Major Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
KQ1/3. All-cause mortality and colorectal cancer mortality	*General population* All-cause mortality k=11 RCT k=1 Cohort	Limited data on late-onset risk (≥10 years after aspirin initiation). Limited direct comparisons of dose, frequency, and duration.	Consistent evidence for early risk (0 to 10 years after initiation of aspirin); 9 of 10 showed reduced risk with aspirin use.	RCT populations included primary and secondary CVD prevention patients and varied considerably in risk of all-cause mortality.	Good	Small benefit of aspirin on all-cause mortality within 10 years of starting treatment. Data on longer-term effects or comparing effects in subgroups were sparse.
	General population CRC mortality k=8 RCT[*] k=1 Cohort	Trial-level data not available for early and late risk of CRC mortality, (pooled results only). Long-term data not available from WHS or PHS. Limited direct comparisons of dose, frequency, and duration.	Consistent evidence on longterm cumulative risk from four studies; all showed aspirin reduced CRC mortality risk.	RCT participants were mostly male. Populations included primary and secondary CVD prevention. Studies conducted in United Kingdom, but likely applicable to United States.	Good	Evidence suggests aspirin reduces long-term CRC mortality ~33 percent with an induction period of ~10 years. Limited data suggest no effect on CRC mortality within 5 to 10 years of starting aspirin. Suggestion of greater risk reduction with longer duration of aspirin use but not higher dose. Data comparing effects in subgroups were sparse.
	Persons with a prior adenoma All-cause mortality k=3 RCT	Few studies, short followup, small number of events. Limited direct comparisons of dose, frequency, and duration.	Limited available data appeared somewhat consistent. Too few studies and events for formal analysis.	Good applicability to persons with recent adenoma removal and polyp-free.	Good	Aspirin does not appear to reduce all-cause mortality in persons with a prior adenoma over a 3- to 4-year period. Data comparing effects over a longer followup period or in subgroups were lacking.
	Persons with a prior adenoma CRC mortality k=0	No data.	NA	NA	NA	NA
KQ4. Colorectal cancer incidence	*General population* k=6 RCT k=7 cohort	Trial-level data not available for one of the pooled estimates for long-term cumulative CRC risk. Limited direct comparisons of dose, frequency, and duration.	Evidence that aspirin reduces CRC incidence after 10-year latency and long-term cumulative risk was consistent across included trials.	Study populations included primary and secondary CVD prevention patients.	Good	Evidence suggests aspirin reduces long-term CRC incidence ~20 to 24 percent with an induction period of ~10 years. Limited evidence of differences in effect by dose, frequency, or duration. Data comparing effects in subgroups were lacking.

Table 10. Summary of Evidence

Key Question	Number of Studies (k) Design	Major Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
	Persons with a prior adenoma k=3 RCT	Few studies, short follow-up, small number of events.	In one study, aspirin users had lower risk than controls; in the other study, placebo group had lower risk. Data for third study not available separately from pooled data across three trials.	Applicable to persons with recent adenoma removal and polyp-free.	Good	Limited data did not suggest an association between aspirin use and CRC incidence over the short term (3 to 4 years) in persons with adenoma history.
KQ5. Colorectal adenoma incidence	*General population* k=1 cohort	Limited to one retrospective cohort study.	NA	Limited. Cohort members were all women and majority white.	Fair	A single cohort study reported a reduced risk of at least one distal adenoma with aspirin use.
	Persons with a prior adenoma k=3 RCT	Few studies, short followup.	Not consistent across doses or followup times.	Applicable to persons with recent adenoma removal and polyp free.	Good	Some suggestion of reduced risk with over a 3- to 4-year period with low-dose aspirin (81 or 160 mg/day). Two RCTs suggested reduced risk of adenoma recurrence with 160 or 300 mg/day aspirin after 1 year (at followup colonoscopy), but effect of 300 or 325 mg/day over a 3- to 4-year period was unclear.
KQ7. Harms	Gastrointestinal bleeding k=12 RCT k=1 cohort	Small number of severe and fatal events.	Consistent increase in gastrointestinal bleeding risk in patients assigned to differing aspirin doses. Relative risk estimates for fatal gastrointestinal bleeding not consistent across four studies that reported them.	RCTs restricted to patients without contraindications to aspirin.	Fair	Evidence of increased risk of any gastrointestinal bleeding and serious gastrointestinal bleeding with aspirin use but not fatal gastrointestinal bleeding.
	Intracranial bleeding k=12 RCT	Definition not consistent across studies; small number of events.	Consistent increase in intracranial bleeding risk in patients assigned different aspirin doses.	RCTs restricted to patients without contraindications to aspirin.	Fair	Data suggest increased intracranial bleeding risk with aspirin.

Table 10. Summary of Evidence

Key Question	Number of Studies (k) Design	Major Limitations	Consistency	Applicability	Overall Quality	Summary of Findings
	Hemorrhagic stroke k=11 RCT	RCTs restricted to patients without contraindications to aspirin.	Consistent increased risk of hemorrhagic stroke in patients assigned to aspirin.	RCTs restricted to patients without contraindications to aspirin.	Good	Consistent evidence suggested aspirin increased risk of hemorrhagic stroke.
	Age-related macular degeneration	See Evidence Synthesis for Aspirin for Prevention of All Cancers				

Includes WHS, which reported findings but did not provide data

Abbreviations: CRC = colorectal cancer; CVD = cardiovascular disease; KQ = key question; mg = milligram; NA = not applicable; PHS = Physicians' Health Study; RCT=randomized controlled trial; WHS = Women's Health Study

Appendix A. Literature Search Strategies

A. Systematic Evidence Review Search Strategies

Cochrane Database of Systematic Reviews search strategy

#1 (colorectal or colon or colonic or rectal or rectum or rectosigmoid or adenomat*):ti,ab,kw
#2 (cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour* or neoplasm* or polyp*):ti,ab,kw
#3 #1 and #2
#4 (NSAID* or "Nonsteroidal Antiinflammatory" or "Non steroidal Antiinflammatory" or "Nonsteroidal Anti inflammatory" or "Non steroidal Anti inflammatory"):ti,ab,kw
#5 (Cyclooxygenase next Inhibitor* or Cyclo next Oxygenase next Inhibitor* or Cyclooxygenase next 2 next Inhibitor* or Cyclo next oxygenase next 2 next Inhibitor* or COX2 next Inhibitor* or COX next 2 next Inhibitor*):ti,ab,kw
#6 (Aspirin or "acetylsalicylic acid" or Salicylate*):ti,ab,kw
#7 (Celecoxib or Diclofenac or Diflunisal or Etodolac or Fenoprofen or Flurbiprofen or Indomethacin or Ketroprofen or Ketorolac):ti,ab,kw
#8 (Meclofenamate or "Meclofenamic Acid" or "Mefenamic Acid" or Nabumetone or Naproxen or Oxaprozin or Piroxicam or Sulindac or Tolmetin):ti,ab,kw
#9 (Ibuprofen or Meloxicam):ti,ab,kw
#10 (chemoprevent* or chemoprophyl*):ti,ab,kw
#11 #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 #3 and #11 from 2004 to 2013, in Cochrane Reviews (Reviews and Protocols)

Database of Abstracts of Reviews of Effects search strategy

1 (colorectal) OR (colon) OR (colonic) OR (rectal) OR (rectum) IN DARE FROM 2004 TO 2013
2 (rectosigmoid) OR (adenomat*) IN DARE FROM 2004 TO 2013
3 #1 OR #2
4 (cancer*) OR (carcinoma*) OR (adenocarcinoma*) OR (malignan*) OR (tumor*) IN DARE FROM 2004 TO 2013
5 (tumour*) OR (neoplasm*) OR (polyp*) IN DARE FROM 2004 TO 2013
6 #4 OR #5
7 #3 AND #6
8 (NSAID*) OR (Nonsteroidal ADJ Antiinflammatory) OR (Non ADJ steroidal ADJ Antiinflammatory) OR (Nonsteroidal ADJ Anti ADJ inflammatory) OR (Non ADJ steroidal ADJ Anti ADJ inflammatory) IN DARE FROM 2004 TO 2013
9 (Cyclooxygenase ADJ Inhibitor*) OR (Cyclo ADJ Oxygenase ADJ Inhibitor*) OR (Cyclooxygenase ADJ 2 ADJ Inhibitor*) OR (Cyclo ADJ oxygenase ADJ 2 ADJ Inhibitor*) OR (COX2 ADJ Inhibitor*) IN DARE FROM 2004 TO 2013
10 (COX ADJ 2 ADJ Inhibitor*) OR (Aspirin) OR (acetylsalicylic ADJ acid) OR (Salicylate*) OR (Celecoxib) IN DARE FROM 2004 TO 2013
11 (Diclofenac) OR (Diflunisal) OR (Etodolac) OR (Fenoprofen) OR (Flurbiprofen) IN DARE FROM 2004 TO 2013
12 (Indomethacin) OR (Ketroprofen) OR (Ketorolac) OR (Meclofenamate) OR (Meclofenamic ADJ Acid) IN DARE FROM 2004 TO 2013
13 (Mefenamic ADJ Acid) OR (Nabumetone) OR (Naproxen) OR (Oxaprozin) OR (Piroxicam) IN DARE FROM 2004 TO 2013
14 (Sulindac) OR (Tolmetin) IN DARE FROM 2004 TO 2013
15 (Ibuprofen) OR (Meloxicam) IN DARE FROM 2004 TO 2013
16 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17 #7 AND #16

Appendix A. Literature Search Strategies

PubMed search strategy

#21 #3 AND #18 AND systematic[sb] Filters: Publication date from 2004/01/01; English
#20 #3 AND #18 AND systematic[sb] Filters: English
#19 #3 AND #18 AND systematic[sb]
#18 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #14 OR #15 OR #16 OR #17
#17 chemoprevent*[ti] OR chemoprophyl*[ti]
#16 Ibuprofen[tiab] OR Meloxicam[tiab]
#15 Meclofenamate[tiab] OR Meclofenamic Acid[tiab] OR Mefenamic Acid[tiab] OR Nabumetone[tiab] OR Naproxen[tiab] OR Oxaprozin[tiab] OR Piroxicam[tiab] OR Sulindac[tiab] OR Tolmetin[tiab]
#14 Celecoxib[tiab] OR Diclofenac[tiab] OR Diflunisal[tiab] OR Etodolac[tiab] OR Fenoprofen[tiab] OR Flurbiprofen[tiab] OR Indomethacin[tiab] OR Ketroprofen[tiab] OR Ketorolac[tiab]
#9 Aspirin[tiab] OR acetylsalicylic acid[tiab] OR Salicylate*[tiab]
#8 Cyclooxygenase Inhibitor*[tiab] OR Cyclo Oxygenase Inhibitor*[tiab] OR Cyclooxygenase 2 Inhibitor*[tiab] OR Cyclo oxygenase 2 Inhibitor*[tiab] OR COX2 Inhibitor*[tiab] OR COX 2 Inhibitor*[tiab]
#7 NSAID*[tiab] OR Nonsteroidal Antiinflammatory[tiab] OR Non steroidal Antiinflammatory[tiab] OR Nonsteroidal Anti inflammatory[tiab] OR Non steroidal Anti inflammatory[tiab]
#6 "nabumetone" [Supplementary Concept] OR Naproxen[mesh] OR "oxaprozin" [Supplementary Concept] OR Piroxicam[mesh] OR Sulindac[mesh] OR Tolmetin[mesh] OR "Chemoprevention"[Mesh:NoExp]
#5 Diclofenac[mesh] OR Diflunisal[mesh] OR Ibuprofen[mesh] OR Etodolac[mesh] OR Fenoprofen[mesh] OR Flurbiprofen[mesh] OR "Indomethacin"[Mesh:NoExp] OR Ketoprofen[mesh] OR Ketorolac[mesh] OR "Meclofenamic Acid"[Mesh] OR "Mefenamic Acid"[Mesh] OR "meloxicam" [Supplementary Concept]
#4 "Anti-Inflammatory Agents, Non-Steroidal"[Mesh:noexp] OR "Cyclooxygenase Inhibitors"[Mesh:noexp] OR "Cyclooxygenase 2 Inhibitors"[Mesh] OR "Anti-Inflammatory Agents, Non-Steroidal"[Pharmacological Action] OR "Aspirin"[Mesh] OR "Salicylates"[Mesh:NoExp] OR "celecoxib"[Supplementary Concept]
#3 #1 OR #2
#2 ((colorectal[tiab] OR colon[tiab] OR colonic[tiab] OR rectal[tiab] OR rectum[tiab] OR rectosigmoid*[tiab] OR adenomat*[tiab]) AND (cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab] OR tumor[tiab] OR tumoro* OR tumors OR tumour*[tiab] OR neoplasm*[tiab] OR polyp OR polypo* OR polyps*[tiab]))
#1 "Colorectal Neoplasms"[Mesh:noexp] OR "Adenomatous Polyposis Coli"[Mesh:noexp] OR "Colonic Neoplasms"[Mesh:noexp] OR "Sigmoid Neoplasms"[Mesh:noexp] OR "Colorectal Neoplasms, Hereditary Nonpolyposis"[Mesh] OR "Rectal Neoplasms"[Mesh] OR "Anus Neoplasms"[Mesh:noexp] OR "Anal Gland Neoplasms"[Mesh] OR "Colonic Polyps"[Mesh] OR "Adenomatous Polyps"[Mesh:noexp]

B. Key Question Literature Search Strategies

Database: Ovid MEDLINE(R) without Revisions <1996 to September Week 2 2013>, Ovid MEDLINE(R) Daily Update <September 20, 2013>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <September 20, 2013>

Search Strategy:
--
1   Colorectal Neoplasms/ (44682)
2   Adenomatous Polyposis Coli/ (3261)

Appendix A. Literature Search Strategies

3   Colonic Neoplasms/ (28061)
4   Sigmoid Neoplasms/ (1333)
5   Colorectal Neoplasms, Hereditary Nonpolyposis/ (2858)
6   Rectal Neoplasms/ (13410)
7   Anus Neoplasms/ (2312)
8   Anal Gland Neoplasms/ (56)
9   Colonic Polyps/ (4018)
10   Adenomatous Polyps/ (894)
*11   (colorectal or colon or colonic or rectal or rectum or rectosigmoid$ or adenomat$).ti,ab.
(179977)*
*12   (cancer$ or carcinoma$ or adenocarcinoma$ or malignan$ or tumor$ or tumour$ or
neoplas$ or polyp$).ti,ab. (1471032)*
13   11 and 12 (123625)
14   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 13 (139804)
15   Aspirin/ (17756)
16   Salicylates/ (2799)
17   aspirin.ti,ab. (22644)
18   acetylsalicylic acid.ti,ab. (3377)
19   salicylate$.ti,ab. (3860)
20   15 or 16 or 17 or 18 or 19 (35077)
21   14 and 20 (1162)
22   limit 21 to (english language and yr="2004 -Current") (699)
23   remove duplicates from 22 (699)

Database: *PUBMED-   [publisher supplied references only]*

#6	Search #3 AND publisher[sb] Filters: Publication date from 2004/01/01 to 2013/12/31; English
#5	Search #3 AND publisher[sb] Filters: English
#4	Search #3 AND publisher[sb]
#3	Search #1 AND #2
#2	Search Aspirin[tiab] OR acetylsalicylic acid[tiab] OR Salicylate*[tiab]
#1	Search ((colorectal[tiab] OR colon[tiab] OR colonic[tiab] OR rectal[tiab] OR rectum[tiab] OR rectosigmoid*[tiab] OR adenomat*[tiab]) AND (cancer[tiab] OR cancers[tiab] OR cancerous[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab] OR tumor[tiab] OR tumoro* OR tumors OR tumour*[tiab] OR neoplasm*[tiab] OR polyp OR polypo* OR polyps[tiab]))

Database: *Cochrane Central Register of Controlled Clinical Trials (CENTRAL)*
Issue 8 of 12, August 2013

#1   (colorectal or colon or colonic or rectal or rectum or rectosigmoid or adenomat):ti,ab,kw from
2004 to 2013, in Trials*

Appendix A. Literature Search Strategies

#2   (cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour* or neoplas* or polyp*):ti,ab,kw from 2004 to 2013, in Trials
#3   #1 and #2 from 2004 to 2013, in Trials
#4   (Aspirin or "acetylsalicylic acid" or Salicylate*):ti,ab,kw from 2004 to 2013, in Trials
#5   #3 and #4 from 2004 to 2013, in Trials

Appendix A Figure 1. Literature Flow Diagram

```
┌─────────────────────────────┐        ┌─────────────────────────────┐
│   Number of citations       │        │ Number of citations identified│
│ identified through literature│       │ through other sources (e.g.,  │
│  database searches: 977     │        │   reference lists): 91        │
└─────────────────────────────┘        └─────────────────────────────┘
                  │                              │
                  └──────────────┬───────────────┘
                                 ▼
              ┌────────────────────────────────┐
              │ Number of citations screened after│
              │   duplicates removed: 865      │
              └────────────────────────────────┘
                                 │            ┌──────────────────────┐
                                 ├──────────▶ │ Number of            │
                                 │            │ citations            │
                                 │            │ excluded at          │
                                 │            │ title/abstract       │
                                 ▼            │ stage: 716           │
              ┌────────────────────────────────┐ └──────────────────────┘
              │ Number of full-text articles   │
              │  assessed for eligibility: 149 │
              └────────────────────────────────┘
```

Articles reviewed for Key Question 1/3: 72	Articles reviewed for Key Question 4: 111	Articles reviewed for Key Question 5: 72	Articles reviewed for Key Question 7: 63
Articles excluded for Key Question 1/3: 33 Relevance: 0 Setting: 0 Population: 0 Outcomes: 17 Intervention: 10 Design: 4 Quality: 0 Language: 0 Not found: 0 Systematic Review: 2 Results Not Yet Reported: 0	**Articles excluded for Key Question 4: 66** Relevance: 0 Setting: 0 Population: 2 Outcomes: 10 Intervention: 30 Design: 12 Quality: 0 Language: 0 Not found: 0 Systematic Review: 12 Results Not Yet Reported: 0	**Articles excluded for Key Question 5: 57** Relevance: 0 Setting: 0 Population: 0 Outcomes: 14 Intervention: 28 Design: 9 Quality: 0 Language: 0 Not found: 0 Systematic Review: 4 Results Not Yet Reported: 2	**Articles excluded for Key Question 7: 31** Relevance: 0 Setting: 0 Population: 0 Outcomes: 12 Intervention: 12 Design: 1 Quality: 2 Language: 0 Not found: 0 Systematic Review: 4 Results Not Yet Reported: 0
Articles included for Key Question 1/3: 39 (16 studies)	**Articles included for Key Question 4: 45 (16 studies)**	**Articles included for Key Question 5: 15 (4 studies)**	**Articles included for Key Question 7: 32 (15 studies)**

Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded

Populations	Men and women aged 40 years or older	• Nonhuman populations
		• Studies where the majority of patients were younger than 40 years old
		• Studies limited to or with a high proportion of patients with the following conditions who could not be examined separately:
		  o Familial adenomatous polyposis
		  o Lynch syndrome
		  o Personal history of CRC
		  o Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
		  o No colon
		  o History of another cancer or familial multiple cancer syndrome that includes CRC
		  o Symptomatic (i.e., undergoing diagnostic colonoscopy)

Interventions	**KQs 1/3, 4, and 5:** • Oral aspirin • Aspirin use for any indication (e.g., primary or secondary prevention of cardiovascular disease, arthritis treatment), as long as intended duration is at least 1 year **KQ7:** No minimum intended duration of use	• Interventions/exposures limited to combined products containing levels of aspirin below 75 mg per day or every other day • Interventions/exposures limited to nonaspirin NSAIDs • Interventions/exposures using nonoral routes of delivery • Studies with no information on dose • Interventions/exposures limited to irregular or occasional use only
Comparators	• Placebo • No treatment (Note: includes studies in which both intervention and control (or exposed and unexposed) groups may be taking other medications or supplements.)	• Studies limited to comparison of aspirin with other medications • Studies examining aspirin in combination with other medications (i.e., intentional cotreatment) for chemoprevention
Outcomes	**KQs 1/3, 4, and 5 (benefits):** • Colorectal adenoma incidence • Colorectal adenoma number • Advanced adenoma incidence • Advanced neoplasia • CRC incidence • CRC mortality • All-cause mortality **KQ7 (harms):** • Major nonintracranial bleeding, particularly serious gastrointestinal bleeding • Intracranial bleeding • Stroke (any, hemorrhagic) • Age-related macular degeneration	• CRC metastasis or progression
Study Design	**KQs 1/3, 4, 5, and 7** RCTs, CCTs, fair-quality and good-quality systematic reviews of RCTs, meta-analyses of RCTs, and high-quality prospective cohort studies	**KQ 1/3, 4, 5, and 7** Retrospective cohort studies, case control studies, case series, case reports, narrative reviews, commentaries, or editorials

Appendix A Table 1. Inclusion and Exclusion Criteria

		KQ7 Studies that do not report on CRC outcomes
Timing	No minimum followup	
Setting	Outpatient	Exclusively inpatient
Country	All countries	
Language	English	Non-English

Abbreviations: CCT = controlled clinical trial; CRC = colorectal cancer; KQ = key question; mg = milligram; NSAIDs = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trials

Appendix A Table 2. Quality Assessment Criteria

Study Design	Adapted Quality Criteria
Randomized controlled trials, adapted from the USPSTF methods[193]	• Was random assignment valid? • Was allocation concealed at randomization? • Were eligibility criteria specified? • Were groups similar at baseline? • Were outcome assessors blinded? • Were measurements equal, valid and reliable? • Was adherence to the intervention adequate? • Was followup acceptable? • Were the statistical methods acceptable? • Was an intent-to-treat analysis performed? • Was handling of missing data appropriate? • Was there evidence of selective reporting of outcomes? • What was the funding source?
Cohort studies, adapted from the Newcastle-Ottawa Scales[107]	• Was the exposed cohort representative? • Was the selection of the nonexposed cohort systematic? • Were eligibility criteria specified? • Was the outcome of interest not present at baseline? • Were potential confounders considered in study design? • Were groups similar at baseline? • Was ascertainment of exposure reported? • Were measurements equal, valid and reliable? • Were outcome assessors blinded? • Was followup acceptable? • Were the statistical methods acceptable? • Was there evidence of differential censoring? • Was handling of missing data appropriate? • Was there adjustment for confounders? • What was the funding source?

Abbreviations: USPSTF = U.S. Preventive Services Task Force

Appendix B. Ongoing or Recently Completed Studies

RCT	Aim	Population	Intervention	Control	Relevant Outcomes	Status
Systematic Evaluation of Aspirin and Fish Oil (SeAFOod) polyp prevention trial[194] (ISRCTN05926847)	Determine whether EPA or ASA prevent colorectal adenomas	English Bowel Cancer Screening Program: patients aged 55 to 73 years identified as "high risk" (detection of ≥5 small adenomas or ≥3 adenomas with at least one ≥10 mm in diameter) at first screening colonoscopy	1 g EPA-free fatty acid twice daily or 300 mg ASA daily for 12 months	Placebo	Number of patients with colorectal adenomas, AEs, number of patients with "advanced" adenomas, number of adenomas, number of "advanced" adenomas, location of adenomas	Completed as of May 2014
Aspirin in Preventing Colorectal Cancer in Patients at Increased Risk of Colorectal Cancer (NCT00468910)	Determine how well aspirin prevents CRC in patients with increased CRC risk	Patients up to 75 years old with history of significant colonic neoplasia	Daily aspirin (dose not specified)	Placebo	Spectral markers in distant colonic mucosa	Ongoing as of December 2013

Abbreviations: AE = adverse events; ASA = acetylsalicylic acid; CRC = colorectal cancer; EPA = eicosapentaenoic acid; g = gram; mg = milligram; mm = millimeter; NSAIDs = nonsteroidal antiinflammatory drugs; RCT = randomized controlled trial

Appendix C. Excluded Studies

Code	Reason for Exclusion
E1	Trial results not yet reported
E2	Wrong population
E3	Wrong intervention or exposure
E3a	Exposure to ASA less than 12 months
E3b	No information on ASA dosage
E3c	No minimum ASA dose specified
E3d	Comparison group limited to ASA users or includes regular ASA users
E3f	ASA cannot be separated from other medications
E4	No relevant outcomes
E5	Wrong study design
E6	Systematic review or meta-analysis with no primary data
E7	Wrong setting
E8	Non-English
E9	Poor quality
E10	Unable to locate

Abbreviations: AE = adverse events; ASA = acetylsalicylic acid; CRC = colorectal cancer; EPA = eicosapentaenoic acid; g = gram; mg = milligram; mm = millimeter; N

1. (1991). "A comparison of two doses of aspirin (30 mg vs. 283 mg a day) in patients after a transient ischemic attack or minor ischemic stroke. The Dutch TIA Trial Study Group." N Engl J Med **325**(18): 1261-1266. **KQ4E3d**
2. (2004). "Use of aspirin and its effect on adenoma risk." Managed Care Interface **17**(6): 70-71. **KQ5E5**
3. Algra, A. M. and P. M. Rothwell (2012). "Effects of regular aspirin on long-term cancer incidence and metastasis: a systematic comparison of evidence from observational studies versus randomised trials." Lancet Oncology **13**(5): 518-527. **KQ4E6**
4. Arber N. (2000). Do NSAIDs prevent colorectal cancer? Canadian journal of gastroenterology **14**(4):299-307. **KQ4E5**
5. Arber, N., C. J. Eagle, et al. (2006). "Celecoxib for the prevention of colorectal adenomatous polyps." New England Journal of Medicine **355**(9): 885-895. **KQ5E3c, KQ4E3c**
6. Arber, N., J. Spicak, et al. (2011). "Five-year analysis of the prevention of colorectal sporadic adenomatous polyps trial." American Journal of Gastroenterology **106**(6): 1135-1146. **KQ5E3c, KQ7E3c**
7. Asano, T. K. and R. S. McLeod (2004). "Nonsteroidal anti-inflammatory drugs and aspirin for the prevention of colorectal adenomas and cancer: a systematic review." Diseases of the Colon & Rectum **47**(5): 665-673. **KQ4E6, KQ5E6, KQ7E6**
8. Baron, J. A., R. S. Sandler, et al. (2006). "A randomized trial of rofecoxib for the chemoprevention of colorectal adenomas." Gastroenterology **131**(6): 1674-1682. **KQ5E3c, KQ7E3f**
9. Barry, E. L. R., J. A. Baron, et al. (2006). "Ornithine decarboxylase polymorphism modification of response to aspirin treatment for colorectal adenoma prevention." Journal of the National Cancer Institute(20): 1494-1500TN: NCT00272324/ClinicalTrials.gov. **KQ5E3**
10. Barry, E. L., L. A. Mott, et al. (2011). "Variants downstream of the ornithine decarboxylase gene influence risk of colorectal adenoma and aspirin chemoprevention." Cancer Prevention Research 4(12): 2072-2082. **KQ5E3**
11. Barry, E. L., E. M. Poole, et al. (2013). "CYP2C9 variants increase risk of colorectal adenoma recurrence and modify associations with smoking but not aspirin treatment." Cancer Causes & Control 24(1): 47-54. **KQ5E3**
12. Barry, E. L., L. B. Sansbury, et al. (2009). "Cyclooxygenase-2 polymorphisms, aspirin treatment, and risk for colorectal adenoma recurrence--data from a randomized clinical trial." Cancer Epidemiology, Biomarkers & Prevention 18(10): 2726-2733. **KQ5E3**
13. Bartolucci, A. A. and G. Howard (2006).

Appendix C. Excluded Studies

"Meta-analysis of data from the six primary prevention trials of cardiovascular events using aspirin." Am J Cardiol **98**(6): 746-750. **KQ1/3E4, KQ4E4, KQ5E4, KQ7E4**

14. Benamouzig, R., H. Yoon, et al. (2001). "APACC, a French prospective study on aspirin efficacy in reducing colorectal adenoma recurrence: design and baseline findings." Eur J Cancer Prev **10**(4): 327-335. **KQ4E4**

15. Benamouzig, R., J. Deyra, et al. (2003). "Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial." Gastroenterology **125**(2): 328-336. **KQ1/3E4, KQ4E4, KQ7E4**

16. Benamouzig, R., B. Uzzan, et al. (2010). "Cyclooxygenase-2 expression and recurrence of colorectal adenomas: effect of aspirin chemoprevention." Gut **59**(5): 622-629. **KQ5E3**

17. Beresford, S. A. A., K. C. Johnson, et al. (2006). "Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial." JAMA **295**(6): 643-654. **KQ4E3a**

18. Bertagnolli, M. M., C. J. Eagle, et al. (2006). "Celecoxib for the prevention of sporadic colorectal adenomas." New England Journal of Medicine **355**(9): 873-884. **KQ5E3c, KQ7E3c**

19. Bosetti, C., S. Gallus, et al. (2006). "Aspirin and cancer risk: an updated quantitative review to 2005." Cancer Causes & Control **17**(7): 871-888. **KQ4E6**

20. Bosetti, C., V. Rosato, et al. (2012). "Aspirin and cancer risk: a quantitative review to 2011." Annals of Oncology **23**(6): 1403-1415. **KQ4E6**

21. Brasky T.M., J. Liu, et al. (2014). Non-steroidal Anti-inflammatory Drugs and Cancer Risk in Women: Results from the Women's Health Initiative. Int J Cancer **135**(8):1869-83. **KQ4E3**

22. Brown, C. J., S. Gallinger, et al. (2012). "Long-term effects of aspirin on colorectal cancer." Journal of the American College of Surgeons **214**(6): 1023-1026. **KQ1/3E5, KQ4E5, KQ5E5**

23. Bujanda, L., A. Lanas, et al. (2013). "Effect of aspirin and antiplatelet drugs on the outcome of the fecal immunochemical test." Mayo Clinic Proceedings **88**(7): 683-689. **KQ4E5, KQ5E5**

24. Calton, B. A., J. V. Lacey, Jr., et al. (2006). "Physical activity and the risk of colon cancer among women: a prospective cohort study (United States)." International Journal of Cancer **119**(2): 385-391. **KQ4E3b**

25. Chan, A. T., E. L. Giovannucci, et al. (2005). "Long-term use of aspirin and nonsteroidal anti-inflammatory drugs and risk of colorectal cancer." JAMA **294**(8): 914-923. **KQ5E4**

26. Chan, A. T., G. J. Tranah, et al. (2004). "A prospective study of genetic polymorphisms in the cytochrome P-450 2C9 enzyme and the risk for distal colorectal adenoma." Clinical Gastroenterology & Hepatology **2**(8): 704-712. **KQ5E5**

27. Chan, A. T., M. Hsu, et al. (2012). "The influence of UGT1A6 variants and aspirin use in a randomized trial of celecoxib for prevention of colorectal adenoma." Cancer Prevention Research **5**(1): 61-72. **KQ5E3c**

28. Chan, A. T., S. Ogino, et al. (2007). "Aspirin and the risk of colorectal cancer in relation to the expression of COX-2." New England Journal of Medicine **356**(21): 2131-2142. **KQ4E2**

29. Cibere J., J. Sibley, and M. Haga (1997). Rheumatoid arthritis and the risk of malignancy. Arthritis and rheumatism **40**(9):1580-6. **KQ4E3**

30. Cole, B. F., J. A. Baron, et al. (2007). "Folic acid for the prevention of colorectal adenomas: a randomized clinical trial." JAMA **297**(21): 2351-2359. **KQ5E3**

31. Cooper, K., H. Squires, et al. (2010). "Chemoprevention of colorectal cancer: systematic review and economic evaluation." Health Technology Assessment (Winchester, England) **14**(32): 1-206. **KQ1/3E4, KQ4E6, KQ5E6, KQ7E6**

32. Dube, C., A. Rostom, et al. (2007). "The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force." Annals of Internal Medicine **146**(5): 365-375. **KQ1/3E6, KQ4E6, KQ5E6, KQ7E6**

Appendix C. Excluded Studies

33. (1988). "Findings from the aspirin component of the ongoing Physicians' Health Study." N Engl J Med 318(4): 262-264. **KQ5E4**

34. Friis, S., H. T. Sorensen, et al. (2003). "A population-based cohort study of the risk of colorectal and other cancers among users of low-dose aspirin." Br J Cancer **88**(5): 684-688. **KQ1/3E4, KQ4E3d, KQ5E4, KQ7E4**

35. Gandhi, S., N. Narula, et al. (2013). "Does acetylsalicylic acid or warfarin affect the accuracy of fecal occult blood tests?" Journal of Gastroenterology & Hepatology **28**(6): 931-936. **KQ4E6, KQ5E6**

36. Gann, P. H., J. E. Manson, et al. (1993). "Low-dose aspirin and incidence of colorectal tumors in a randomized trial." J Natl Cancer Inst **85**(15): 1220-1224. **KQ1/3E4, KQ5E4, KQ7E4**

37. Giovannucci, E., E. B. Rimm, et al. (1994). "Aspirin use and the risk for colorectal cancer and adenoma in male health professionals." Ann Intern Med **121**(4): 241-246. **KQ1/3E3b, KQ4E3b, KQ5E3b, KQ7E4**

38. Glynn, R. J., J. E. Buring, et al. (1994). "Adherence to aspirin in the prevention of myocardial infarction. The Physicians' Health Study." Arch Intern Med **154**(23): 2649-2657. **KQ5E4**

39. Grau, M. V., J. A. Baron, et al. (2005). "Interaction of calcium supplementation and nonsteroidal anti-inflammatory drugs and the risk of colorectal adenomas." Cancer Epidemiology, Biomarkers & Prevention **14**(10): 2353-2358. **KQ5E3**

40. Greenberg, E. R., J. A. Baron, et al. (1993). "Reduced risk of large-bowel adenomas among aspirin users. The Polyp Prevention Study Group." J Natl Cancer Inst **85**(11): 912-916. **KQ1/3E3b, KQ4E3b, KQ5E3b, KQ7E3b**

41. Greenspan, E. J., J. P. Madigan, et al. (2011). "Ibuprofen inhibits activation of nuclear [120]-catenin in human colon adenomas and induces the phosphorylation of GSK-3{beta}." Cancer Prevention Research **4**(1): 161-171. **KQ5E3f**

42. Half, E. and N. Arber (2009). "Colon cancer: preventive agents and the present status of chemoprevention." Expert Opinion on Pharmacotherapy **10**(2): 211-219. **KQ4E5, KQ5E5**

43. Harris, R. E., J. Beebe-Donk, et al. (2005). "Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade (review)." Oncology Reports 13(4): 559-583. **KQ4E6**

44. Hart, R. G., J. L. Halperin, et al. (2000). "Aspirin for the primary prevention of stroke and other major vascular events: meta-analysis and hypotheses." Arch Neurol **57**(3): 326-332. **KQ1/3E4, KQ4E4, KQ5E4, KQ7E4**

45. He, J., P. K. Whelton, et al. (1998). "Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials." JAMA **280**(22): 1930-1935. **KQ1/3E4, KQ4E4, KQ5E4, KQ7E4**

46. Hennekens, C. H., J. E. Buring, et al. (1996). "Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease." N Engl J Med **334**(18): 1145-1149. **KQ1/3E3, KQ4E3, KQ5E3, KQ7E3**

47. Hoffmeister, M., J. Chang-Claude, et al. (2006). "Do older adults using NSAIDs have a reduced risk of colorectal cancer?" Drugs & Aging **23**(6): 513-523. **KQ4E6**

48. Hollestein L.M., M.P.P. van Herk-Sukel, et al. (2014). Incident cancer risk after the start of aspirin use: results from a Dutch population-based cohort study of low dose aspirin users. International Journal of Cancer **135**(1):157-65. **KQ4E3d**

49. Hu, F. B., M. J. Stampfer, et al. (1999). "Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements." Am J Epidemiol **149**(6): 531-540. **KQ1/3E3, KQ4E3, KQ5E3, KQ7E3**

50. Huang, L., X. Wang, et al. (2010). "The comparison of the clinical manifestations and risk factors of colorectal cancer and adenomas: results from a colonoscopy-based study in southern Chinese." International Journal of Colorectal Disease **25**(11): 1343-1351. **KQ4E5, KQ5E5**

51. Huang W.K., M.J. Chiou, et al. (2013). The association between low-dose aspirin use and the incidence of colorectal cancer: a nationwide cohort study. Aliment Pharmacol Ther **38**(4):432-9. **KQ1/3E5, KQ4E5**

52. Hubner, R. A., K. R. Muir, et al. (2006). "Genetic variants of UGT1A6 influence risk of colorectal adenoma recurrence." Clinical Cancer Research **12**(21): 6585-6589. **KQ5E3**

53. Hubner, R. A., K. R. Muir, et al. (2007). "Polymorphisms in PTGS1, PTGS2 and IL-10 do not influence colorectal adenoma recurrence in the context of a randomized aspirin intervention trial." International Journal of Cancer **121**(9): 2001-2004. **KQ5E3**

54. Hull, M. A., A. C. Sandell, et al. (2013). "A randomized controlled trial of eicosapentaenoic acid and/or aspirin for colorectal adenoma prevention during colonoscopic surveillance in the NHS Bowel Cancer Screening Programme (The seAFOod Polyp Prevention Trial): study protocol for a randomized controlled trial." Trials **14**(1): 237. **KQ5E1**

55. Johnson, C. C., R. B. Hayes, et al. (2010). "Non-steroidal anti-inflammatory drug use and colorectal polyps in the Prostate, Lung, Colorectal, And Ovarian Cancer Screening Trial." American Journal of Gastroenterology **105**(12): 2646-2655. **KQ5E5**

56. Koretz, R. (2011). "ACP Journal Club. Meta-analysis: aspirin reduces risk for colon cancer and related mortality at 20 years, particularly when taken for >= 5 years." Annals of Internal Medicine **154**(6): JC3-3. **KQ1/3E5, KQ4E5**

57. Levine, A. J., M. V. Grau, et al. (2010). "Baseline plasma total homocysteine and adenoma recurrence: results from a double blind randomized clinical trial of aspirin and folate supplementation." Cancer Epidemiology, Biomarkers & Prevention **19**(10): 2541-2548. **KQ5E3**

58. Liao, X., P. Lochhead, et al. (2012). "Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival." New England Journal of Medicine **367**(17): 1596-1606. **KQ1/3E4, KQ4E4, KQ7E4**

59. Lip, G. Y. and D. C. Felmeden (2004). "Antiplatelet agents and anticoagulants for hypertension." Cochrane Database Syst Rev(3): CD003186. **KQ1/3E4, KQ4E4, KQ5E4, KQ7E4**

60. Lynch, P. M. (2006). "Does regular use of aspirin reduce the risk of colorectal cancer?" Nature Clinical Practice Oncology **3**(4): 186-187. **KQ4E5**

61. Mahipal, A., K. E. Anderson, et al. (2006). "Nonsteroidal anti-inflammatory drugs and subsite-specific colorectal cancer incidence in the Iowa women's health study." Cancer Epidemiology, Biomarkers & Prevention **15**(10): 1785-1790. **KQ4E3b**

62. Manson, J. E., J. E. Buring, et al. (1991). "Baseline characteristics of participants in the Physicians' Health Study: a randomized trial of aspirin and beta-carotene in U.S. physicians." Am J Prev Med **7**(3): 150-154. **KQ5E4**

63. Mansouri, D., D. C. McMillan, et al. (2013). "The impact of aspirin, statins and ACE-inhibitors on the presentation of colorectal neoplasia in a colorectal cancer screening programme." British Journal of Cancer **109**(1): 249-256. **KQ4E3b, KQ5E3b**

64. Massat N.J., S.M. Moss, et al. (2013). Screening and primary prevention of colorectal cancer: a review of sex-specific and site-specific differences. Journal of Medical Screening **20**(3):125-48. **KQ4E6**

65. Meyskens, F. L., Jr., C. E. McLaren, et al. (2008). "Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial." Cancer Prevention Research **1**(1): 32-38. **KQ5E3c, KQ7E3d**

66. Mills E.J., P. Wu, et al. (2012). Low-dose aspirin and cancer mortality: a meta-analysis of randomized trials. Am J Med **125**(6):560-7. **KQ1/3E4**

67. Nishihara, R., P. Lochhead, et al. (2013). "Aspirin use and risk of colorectal cancer according to BRAF mutation status." JAMA **309**(24): 2563-2571. **KQ1/3E4, KQ4E2**

68. Paganini-Hill, A. (1995). "Aspirin and colorectal cancer: the Leisure World cohort revisited." Prev Med **24**(2): 113-115. **KQ1/3E4, KQ4E3b, KQ5E4, KQ7E9**

69. Paganini-Hill, A., A. Chao, et al. (1989). "Aspirin use and chronic diseases: a cohort study of the elderly." BMJ **299**(6710): 1247-1250. **KQ4E3b, KQ7E9**

70. Paganini-Hill, A., G. Hsu, et al. (1991). "Aspirin use and incidence of large-bowel cancer in a California retirement community." J Natl Cancer Inst **83**(16): 1182-1183. **KQ4E3b**

71. Pasche, B. (2013). "Differential effects of aspirin before and after diagnosis of colorectal cancer." JAMA **309**(24): 2598-2599. **KQ1/3E5, KQ4E5, KQ7E5**

72. Perez, R., A. Lasa, et al. (2010). "Relationship between sporadic hyperplastic polyps and colorectal neoplasia in Hispanic veterans." Puerto Rico Health Sciences Journal **29**(4): 372-376. **KQ4E5, KQ5E5**

73. Physician's Health Study (1989). "Final Report on the Aspirin Component of the Ongoing Physicians' Health Study." New England Journal of Medicine **321**(3): 129-135. **KQ5E4**

74. Poynter, J. N., M. Inoue-Choi, et al. (2013). "Reproductive, lifestyle, and anthropometric risk factors for cancer in elderly women." Cancer Epidemiology, Biomarkers & Prevention **22**(4): 681-687. **KQ4E3b**

75. Purdue, M. P., P. J. Mink, et al. (2005). "Hormone replacement therapy, reproductive history, and colorectal adenomas: data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (United States)." Cancer Causes & Control **16**(8): 965-973. **KQ5E3f**

76. Quintero, E., A. Castells, et al. (2012). "Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening." N Engl J Med **366**(8): 697-706. **KQ4E5, KQ5E5**

77. Ratnasinghe, L. D., B. I. Graubard, et al. (2004). "Aspirin use and mortality from cancer in a prospective cohort study." Anticancer Res **24**(5B): 3177-3184. **KQ1/3E3b**

78. Rimm, E. B., E. L. Giovannucci, et al. (1991). "Prospective study of alcohol consumption and risk of coronary disease in men." Lancet **338**(8765): 464-468. **KQ4E3**

79. Rimm, E. B., E. L. Giovannucci, et al. (1992). "Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals." Am J Epidemiol **135**(10): 1114-1126; discussion 1127-1136. **KQ1/3E3, KQ4E3, KQ5E3, KQ7E3**

80. Ritenbaugh, C., R. E. Patterson, et al. (2003). "The Women's Health Initiative Dietary Modification trial: overview and baseline characteristics of participants." Ann Epidemiol **13**(9 Suppl): S87-97. **KQ4E3**

81. Rosenberg L., C. Louik, and S. Shapiro (1998). Nonsteroidal antiinflammatory drug use and reduced risk of large bowel carcinoma. Cancer **82**(12):2326-33. **KQ4E5**

82. Rostom, A., C. Dube, et al. (2007). "Use of Aspirin and NSAIDs to Prevent Colorectal Cancer." **KQ1/3E3, KQ4E3, KQ5E3, KQ7E3**

83. Rothwell, P. M., M. Wilson, et al. (2012). "Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials." Lancet **379**(9826): 1591-1601. **KQ1/3E4**

84. Rothwell P.M., J.F. Price, et al. (2012). Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet **379**(9826):1602-12. **KQ1/3E3a, KQ4E4**

85. Ruder, E. H., A. O. Laiyemo, et al. (2011). "Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort." American Journal of Gastroenterology **106**(7): 1340-1350. **KQ4E3b**

86. Siemes, C., L. E. Visser, et al. (2008). "Protective effect of NSAIDs on cancer and influence of COX-2 C(-765G) genotype." Curr Cancer Drug Targets **8**(8): 753-764. **KQ1/3E4, KQ4E3b**

87. Smalley, W., W. A. Ray, et al. (1999). "Use of nonsteroidal anti-inflammatory drugs and incidence of colorectal cancer: a population-based study." Arch Intern Med **159**(2): 161-166. **KQ4E3**

88. Stampfer, M. J., W. C. Willett, et al. (1984). "Test of the National Death Index." Am J Epidemiol **119**(5): 837-839. **KQ1/3E3, KQ4E3, KQ5E3, KQ7E3**

89. Sturmer, T., J. E. Buring, et al. (2006).

Appendix C. Excluded Studies

"Colorectal cancer after start of nonsteroidal anti-inflammatory drug use." <u>American Journal of Medicine</u> **119**(6): 494-502. **KQ4E3f**

90. Sturmer, T., R. J. Glynn, et al. (1998). "Aspirin use and colorectal cancer: post-trial follow-up data from the Physicians' Health Study." <u>Ann Intern Med</u> **128**(9): 713-720. **KQ1/3E4, KQ5E4, KQ7E4**

91. Sutcliffe P., M. Connock, et al. (2013). Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews. <u>Health Technology Assessment (Winchester, England)</u> **17**(43):1-253. **KQ1/3E6, KQ4E6, KQ7E6**

92. Tangrea, J. A., P. S. Albert, et al. (2003). "Non-steroidal anti-inflammatory drug use is associated with reduction in recurrence of advanced and non-advanced colorectal adenomas (United States)." <u>Cancer Causes Control</u> **14**(5): 403-411. **KQ1/3E4, KQ4E4, KQ5E3a, KQ7E4**

93. Tenenbaum, A., E. Grossman, et al. (2001). "Long-term diuretic therapy in patients with coronary disease: increased colon cancer-related mortality over a 5-year follow-up." <u>J Hum Hypertens</u> **15**(6): 373-379. **KQ4E3b**

94. Thompson, P., D. J. Roe, et al. (2012). "Design and baseline characteristics of participants in a phase III randomized trial of celecoxib and selenium for colorectal adenoma prevention." <u>Cancer Prevention Research</u> **5**(12): 1381-1393. **KQ5E1**

95. Wang, H., D. Taverna, et al. (2013). "Genetic Variation in the Inflammation and Innate Immunity Pathways and Colorectal Cancer Risk." <u>Cancer Epidemiol Biomarkers Prev</u>. **KQ4E3b**

96. Weisman, S. M. and D. Y. Graham (2002). "Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events." <u>Arch Intern Med</u> **162**(19): 2197-2202. **KQ1/3E4, KQ4E4, KQ5E4, KQ7E4**

97. Wells B.J., M.W. Kattan, et al. (2014). ColoRectal Cancer Predicted Risk Online (CRC-PRO) calculator using data from the Multi-Ethnic Cohort Study. <u>Journal of the American Board of Family Medicine: JABFM</u> **27**(1):42-55. **KQ4E3a**

98. Willett, W. C., L. Sampson, et al. (1985). "Reproducibility and validity of a semiquantitative food frequency questionnaire." <u>Am J Epidemiol</u> **122**(1): 51-65. **KQ1/3E3, KQ4E3, KQ5E3, KQ7E3**

99. Ye, X., J. Fu, et al. (2013). "Dose-risk and duration-risk relationships between aspirin and colorectal cancer: a meta-analysis of published cohort studies." <u>PLoS ONE [Electronic Resource]</u> **8**(2): e57578. **KQ4E6**

Appendix D Table 1. Included Randomized, Controlled Trials and Meta-Analyses of Aspirin in the General Population

Study Author Quality	Number of Participants	Year Begun	Population, Mean Age at Study Entry (SD), % Women	Aspirin Dose and Frequency vs. Comparison Group	Treatment Length Median (Range)	Benefits Reported (Followup Length)
WHS Cook, 2005[112] Cook, 2013[113] *Good quality*	N=39,876 IG:19,934 CG:19,942	1992	U.S. women health care professionals, Age: 54.6 (7) years % women: 100%	100 mg qod vs. Placebo (2 x 2 factorial with vitamin E)	10.1 (NR) years	All-cause mortality (Median 17.5 years) CRC mortality (Median: 10.1 years) CRC incidence (Median: 17.5 years)
PHS Stürmer, 1998[135] *Good quality*	N=22,071 IG: 11,037 CG: 11,034	1982	US male physicians Age: 53.2 (9.5) years % women: 0%	325 mg qod vs. Placebo (2 x 2 factorial with beta carotene)	5.0[††] (3.8 to 6.4) years	All-cause mortality CRC incidence (Mean: 12 years)
BMD Peto, 1988[124] *Fair quality*	N=5,139 IG: 3,429 CG: 1,710	1978	British male doctors Age: 61.6 (7.0) years[¶] % women: 0%	500 mg/day vs. no aspirin (Could receive 300 mg enteric coated if requested)	6.0 (5.0 to 6.0) years[¶]	All-cause mortality[‡] CRC mortality[*‡] CRC incidence[*†] *(See Rothwell/Flossman for follow-up)*
UK-TIA UK-TIA Study Group, 1991[126] *Good quality*	N=2,449[§§] IG: 300 mg: 811 IG: 1200mg: 821 CG: 817	1979	British men and women with recent TIA or minor ischemic stroke Age: 60.3 (9.0) years[¶] % women: 27.0%[‡‡]	300 mg/day vs. 1,200 mg/day vs. Placebo	4.4 (1.0 to 7.1) years[¶]	All-cause mortality[‡] CRC mortality[*‡] CRC incidence[*†] *(See Rothwell/Flossman for follow-up)*
TPT Medical Research Council's General Practice Research Framework, 1998[108] *Good quality*	N=5,085 IG: 2,545 CG: 2,540	1989	British men at high risk of IHD Age: 57.5 (6.7) years[¶] % women: 0%	75 mg/day vs. Placebo (2 x 2 factorial with warfarin)	6.9 (4.3 to 8.6) years[¶]	All-cause mortality[‡] CRC mortality[*‡] CRC incidence[*] *(See Rothwell for follow-up)*
SALT The SALT Collaborative Group, 1991[127] *Good quality*	N=1,363[‖] IG: 678 CG: 685	1984	Sweden men and women with recent history of TIA, minor stroke, or retinal artery occlusion Age: 66.9 (7.1) years[**] % women: 34.2%[‡‡]	75 mg/day vs. Placebo	2.7 (1.0 to 5.3) years[**]	All-cause mortality CRC mortality[*] CRC incidence[*] *(See Rothwell for follow-up)*

Appendix D Table 1. Included Randomized, Controlled Trials and Meta-Analyses of Aspirin in the General Population

Study Author Quality	Number of Participants	Year Begun	Population, Mean Age at Study Entry (SD), % Women	Aspirin Dose and Frequency vs. Comparison Group	Treatment Length Median (Range)	Benefits Reported (Followup Length)
ETDRS ETDRS Investigators, 1992[128] *Good quality*	N=3,711 IG: 1,856 CG: 1,855	1980	U.S. men and women with diabetes with certain categories of diabetic retinopathy Age: 51 (NR) years[¶] % women: 43.5%[‡‡]	650 mg/day vs. Placebo	5.0 (4.0 to 9.0) years[¶]	All-cause mortality[‡] *(See Rothwell for follow-up)*
SAPAT Juul-Moller, 1992[130] *Fair quality*	N=2,035 IG:1,009 CG: 1,026	1985	Swedish men and women with chronic stable angina pectoris without prior MI Age: 67 (8) years[¶] % women: 48%[‡‡]	75 mg/day vs. Placebo	4.2 (1.9 to 6.3) years[¶]	All-cause mortality[‡] *(See Rothwell for follow-up)*
JPAD Ogawa, 2008[131] *Fair quality*	N=2,539 IG: 1,262 CG: 1,277	2002	Japanese men and women with type 2 diabetes without history of atherosclerotic disease Age: 64.5 (10.0) years[¶] % women: 45.4%[‡‡]	81 mg/day or 100 mg/day[§] vs. no recommendation to take aspirin	4.4 (3.0 to 5.4) years[¶]	All-cause mortality[‡] CRC mortality[*] *(See Rothwell for follow-up)*
POPADAD Belch, 2008[132] *Fair quality*	N=1,276 IG: 638 CG: 638	1997	Scottish men and women with diabetes and asymptomatic peripheral arterial disease Age: 60.3 (10.0) years[¶] % women: 55.9%[‡‡]	100 mg/day vs. Placebo (2 x 2 factorial with antioxidant)	6.7 (4.5 to 8.6) years[¶]	All-cause mortality[‡] CRC mortality[‡] *(See Rothwell for follow-up)*
AAA Fowkes, 2010[133] *Fair quality*	N=3,350 IG: 1,675 CG: 1,675	1998	Scottish men and women with no history of vascular disease with low ankle brachial index Age: 62.0 (6.6) years[¶] % women: 71.5%[‡‡]	100 mg/day vs. Placebo	8.2 (6.7 to 10.5) years[¶]	All-cause mortality[‡] CRC mortality[*‡] *(See Rothwell for follow-up)*
Flossman, 2007[111] *Good quality*	N=7,588[‡‡] IG: 5,061 CG: 2,527	1978	Participants in BMD and UK-TIA Age: 61.2 (NR) years[‡‡] % women: 8.7%[‡‡]	300 mg/day-1,200 mg/day vs. Placebo/control	5.1 (1.0 to 7.1[‡‡]) years	CRC incidence (Median: 23 years)

Appendix D Table 1. Included Randomized, Controlled Trials and Meta-Analyses of Aspirin in the General Population

Study Author Quality	Number of Participants	Year Begun	Population, Mean Age at Study Entry (SD), % Women	Aspirin Dose and Frequency vs. Comparison Group	Treatment Length Median (Range)	Benefits Reported (Followup Length)
Rothwell, 2010[85] *Fair quality (incidence) Good quality (mortality)*	N=14,033 IG: 8,282 CG: 5,751	1978	Participants in BMD, UK-TIA, TPT, SALT Age: 60.4 (NR) years[‡‡] % women: 8.0%[‡‡]	75 mg/day-1,200 mg/day vs. Placebo/control	5.8 (1.0 to 8.5) years	CRC mortality CRC incidence (median: 18.3 years)
Rothwell, 2011[83] *Good quality*	N=25,570 IG: 14,035 CG: 11,535	1978	Participants in BMD, UK-TIA, TPT, ETDRS, SAPAT, JPAD, POPADAD, AAA (mean scheduled duration ≥ 4 years) Age: 59.8 (NR) years[‡‡] % women: 29.4%[‡‡]	75 mg/day-1,200 mg/day vs. Placebo/control	NR, see individual trials	All-cause mortality: all studies (in-trial followup) CRC mortality: BMD, UK-TIA, TPT, JPAD, POPADAD, AAA; (N=19,824[‡‡]) (In-trial followup) TPT, BMD, UK-TIA: (N=12,659 total, N=10,502 with scheduled treatment duration ≥5 years) (Up to 20 years followup)

* Included in Rothwell 2010[85]
[†]Included in Flossman 2007[111]
[‡]Included in Rothwell 2011[83]
[§]Dose not randomized
[‖]After randomization, three patients were deemed ineligible. Number analyzed was IG: 676 and CG: 684
[¶]As reported in Rothwell 2011[83]
[**]As reported in Rothwell 2010[85]
[††]Mean
[‡‡]Calculated
[§§]Rothwell 2011[83] analyzed N=2,435, excluding three people randomized in error and 14 with an intracranial tumor diagnosed shortly after randomization. N=806 in 300 mg/day group, N=815 in 1,200 mg/day group; N=814 in placebo group

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; BMD = British Medical Doctors trial; CG = control group; CRC = colorectal cancer; ETDRS = Early Treatment Diabetic Retinopathy Study; GI = gastrointestinal; IG = intervention group; IHD = ischemic heart disease; JPAD = Japanese Primary Prevention of

Appendix D Table 1. Included Randomized, Controlled Trials and Meta-Analyses of Aspirin in the General Population

Atherosclerosis With Aspirin for Diabetes; mg = milligram; MI = myocardial infarction; NR = not reported; PHS = Physicians' Health Study; POPADAD = Prevention of Progression of Arterial Disease and Diabetes; qod = every other day; SALT = Swedish Aspirin Low-dose Trial; SAPAT = Swedish Angina Pectoris Aspirin Trial; SD = standard deviation; TIA = transient ischemic attack; TPT = Thrombosis Prevention Trial; UK-TIA = UK Transient Ischaemic Attack trial; WHS = Women's Health Study

Appendix D Table 2. Included Randomized, Controlled Trials of Aspirin in Persons With a Prior Adenoma

Study Author Quality	Number of Participants	Year Begun	Population Mean Age at Study Entry (SD) % Women	Aspirin Dose and Frequency	Treatment Length Median (Range)	Benefits Reported (Followup Length)
APACC Benamouzig, 2012[123,141-143] *Fair quality*	N=272[†] IG 160 mg: 73 IG 300 mg: 67 CG: 132	1996	French men and women who had a colonoscopy with adequate bowel prep and visualized cecum, ≥3 adenomas irrespective of size or ≥1 adenoma ≥6 mm, and removal of all polyps Age: 58 (10) years % women: 30%	160 mg/day vs. 300 mg/day vs. Placebo	44.4 (11.9 to 47.6) months[§]	All-cause mortality, Adenoma incidence, Advanced adenoma incidence, Adenoma number, Adenoma size (Median: 47.2, IQR 14.8 to 48.4 months, N=272)[§]
ukCAP Logan, 2008[129,137,138] *Good quality*	N=945[‡] IG: 472 CG: 467	1997	British men and women with either a colorectal adenoma ≥0.5 cm removed in the 6 months before recruitment (or earlier if they also had ≥1 adenoma removed in the 6 months before randomization). All must have had a clean colon. Age: 57.8 (NR) years % women: 43.1%[*]	300 mg/day vs. Placebo (2 x 2 factorial with folate)	34.9 (13.5 to 38.9) months[§]	All-cause mortality, CRC incidence, Adenoma incidence, Advanced neoplasia incidence, Adenoma number (Median: 37.5, IQR 33.3 to 42.3 months, N=939)[§]
AFPP Baron, 2003[136] *Good quality*	N=1,121 IG 81 mg: 377 IG 325 mg: 372 CG: 372	1994	U.S. and Canadian men and women with a history of adenoma, with confirmation of no remaining polyps in 3 months before study Age: 57.5 (NR) years[*] % women: 36.5%[*]	81 mg/day vs. 325 mg/day vs. Placebo (3 x 2 factorial with folic acid)	31.7 (30.2 to 33.1) months[§]	All-cause mortality, CRC incidence, Adenoma incidence, Advanced lesion incidence, Tubular adenoma incidence (Median: 32.2, IQR 31.1 to 33.6 months, N=1,121)[§]

[*]Calculated
[†]Number analyzed restricted to persons receiving follow-up colonoscopy: IG 160 mg=55; IG 300 mg= 47, CG=82
[‡]Total commencing medication was N=939 since six people were enrolled in error. Number analyzed for CRC and adenoma incidence restricted to persons receiving follow-up colonoscopy: IG=434; CG=419
[§]Reported by Cole 2009[123]

Abbreviations: AFPP = Aspirin/Folate Polyp Prevention study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal; CG = control group; cm = centimeter; CRC = colorectal cancer; IG = intervention group; IQR = interquartile range; NR = not reported; mg = milligram; mm = millimeter; SD = standard deviation; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

Appendix D Table 3. Characteristics of Included Cohort Studies

Study Author Quality	Number of Participants	Year Begun	Population Mean Age at Study Entry (SD) % Women	Relevant Exposure Categories by Key Question
NHS Chan 2005[146] *Fair quality*	Overall: 121,701 Analysis: 82,911	1980	U.S. women registered nurses Age: By baseline number of 325 mg aspirin tablets per week[†]: 0 tables/week: 46 (40 to 53) 0.5 to 1.5 tablets/week: 47 (41 to 53) 2 to 5 tablets/week: 45 (40 to 52) 6 to 14 tablets/week: 47 (41 to 53) more than 14 tablets/week: 49 (43 to 54) % women: 100%	KQ3, KQ4, KQ5: *Frequency:* Number of 325 mg aspirin tablets per week; KQ4: *Recency:* Number of 325 mg aspirin tablets/week in previous 10 years; Number of 325 mg aspirin tablets/week in past ≥10 years
HPFS Chan 2008[152] *Fair quality*	Overall: 51,529 Analysis: 47,363	1986	U.S. men health professionals Age: 54 (NR) years[*] % women: 0%	KQ4: *Frequency:* Number of 325 mg aspirin tablets per week
Swedish Mammography Cohort and the Cohort of Swedish Men Larsson and colleagues 2006[153] *Fair quality*	Overall: 104,880[*] Analysis: 74,250	1997	Members of two Swedish cohorts Age: 60.6 (NR) years[*] % women: 43.2%[*]	KQ4: *Frequency:* Number of aspirin tablets per week (assumed 500 mg tablet)
Danish Diet, Cancer, and Health Study Friis 2009[160] *Fair quality*	Overall: 57,053 Analysis: 51,053	1995	Danish men and women aged 50 to 64 years Age: 56.2 (51.2 to 63.2) years[‡] % women: 52.3%	KQ4: ≥1 pill per day (self-report); prescription use *Dose:* prescription 75 mg or 150 mg
VITAL Brasky 2012[161,162] and White 2004[162] *Fair quality*	Overall: 77,719 Analysis: 64,847	2000	Washington State men and women aged 50 to 76 years Age: 61 (NR) years[†§] % women: 51%[*]	KQ4: *Frequency/duration* Low use (<4 days/week or <4 years); High use (≥4 days/week and ≥4 years); *Dose:* Low-dose; Regular-strength
WHI Observational Cohort Allison 2006[164] and The	Overall: 93,676 Analysis: 91,574	1993	Postmenopausal women aged 50 to 79 years who were screened and not eligible or unwilling to participate in the WHI RCT	KQ4: *Dose:* Daily: 0 mg, less than 165 mg, 165 to less than 330 mg, 330 to 494 mg, ≥495 mg;

Appendix D Table 3. Characteristics of Included Cohort Studies

Study Author Quality	Number of Participants	Year Begun	Population Mean Age at Study Entry (SD) % Women	Relevant Exposure Categories by Key Question
Women's Health Initiative Study Group 1988[163] *Good quality*			Age: 63.5 (NR) years[*] % women: 100%	Daily: 0 mg, less than 325 mg, ≥325 mg *Duration:* Annual increments: 0 years, 0 to 0.9 years, 1 to 1.9 years, 2 to 2.9 years, 3 to 3.9 years, 4 to 4.9 years, ≥5 years Longer increments: 0 years, 1 to 5 years, 5.1 to 10 years, 10.1 to ≤20 years, more than 20 years
CPSII Nutrition Cohort Jacobs 2007,[156] Calle 2002,[154] and Jacobs 2012[158] *Fair quality*	Overall: 184,194[‖] KQ3 Analysis: 100,139 KQ4 Analysis: 146,113	1992	Subset of the CPSII study who responded to a followup questionnaire in 1992 Age: 63 (NR) years[†]	KQ3: *Recency/duration* Current daily use less than 5 years Current daily use ≥5 years Past or occasional use KQ4: *Duration* 325 mg/day current daily use less than 5 years 325 mg/day current daily use ≥5 years
CPSII Thun 1991[170] *Quality not assessed independently from CPSII Nutrition Cohort*	Overall: 1,185,239 Analysis: 662,424	1982	Adults (≥30 years) from households with at least one member 45+ years in all 50 states, Washington D.C., and Puerto Rico Age: 57 (NR) years % women: 57%[154]	KQ3: Use ≥16 times per month for at least 1 year

[*]Calculated
[†]Median (interquartile range)
[‡]Median (10th-90th percentile)
[§]Reported on cohort in White 2004 (N=76,072)
[‖]Total calculated from Jacobs and colleagues 2007[156] is 184,190. Total reported in Calle and colleagues 2002[154] is 184,194

Abbreviations: CPSII = Cancer Prevention Study II; KQ = key question; HPFS = Health Professionals Follow-up Study; mg = milligram; NHS = Nurses' Health Study; NR = not reported; RCT = randomized controlled trial; SD = standard deviation; VITAL = VITamins And Lifestyle study; WHI = Women's Health Initiative

Appendix D Table 4. Effect of Aspirin on Colorectal Cancer Incidence in Randomized, Controlled Trials, Overall and by Proximal vs. Distal Anatomic Region of Colon

Study	All Colon		Proximal Colon		Distal Colon	
	Events/N (%)	Relative Risk Estimate (95% CI)	Events/N (%)	Relative Risk Estimate (95% CI)	Events/N (%)	Relative Risk Estimate (95% CI)
WHS[113]	IG: 155/19,934 (0.8%)	HR, 0.79 (0.64 to 0.97)	IG: 88/19,934 (0.4%)	HR, 0.73 (0.55 to 0.95)	IG: 59/19,934 (0.3%)	HR, 0.87 (0.62 to 1.24)
	CG: 195/19,942 (1.0%)		CG: 120/19,942 (0.6%)[*]		CG: 67/19,942 (0.3%)	
BMD, UK-TIA, TPT, SALT[85†]	IG: 278/14,033 (2.0%)*	HR, 0.76 (0.60 to 0.96)	IG: 69/14,033 (0.5%)*	HR, 0.45 (0.28 to 0.74)	IG: 100/14,033 (0.7%)*	HR, 1.10 (0.73 to 1.64)
	CG: 229/10,533 (2.2%)*‡	HR, 0.75 (0.58 to 0.97)‡	CG: 61/10,533 (0.6%)*‡	HR, 0.35 (0.20 to 0.63)‡	CG: 75/10,533 (0.7%)*‡	HR, 1.14 (0.69 to 1.86)‡

[*]Calculated
[†]All doses (75-1200 mg) vs. control on long-term risk
[‡]Limited to patients with a scheduled treatment duration ≥5 years

Abbreviations: BMD = British Medical Doctors trial; IG = intervention group; CG = control group; CI = confidence interval; HR = hazard ratio; SALT = Swedish Aspirin Low-dose Trial; TPT = Thrombosis Prevention Trial; UK-TIA = UK Transient Ischaemic Attack trial; WHS = Women's Health Study

Appendix D Table 5. Multivariable Adjusted Relative Risk Estimates for Association Between Aspirin Use and Colorectal Cancer Incidence in Cohort Studies, by Dose and Frequency

Aspirin Use	NHS[146] Relative Risk (95% CI)	HPFS[152] Relative Risk (95% CI)	Swedish Mammography Cohort and the Cohort of Swedish Men[153] Aspirin Use	Relative Risk (95% CI)
Nonuse	Referent	Referent	Nonuse	Referent
0.5 to 1.5 tablets/week (325 mg)	1.10 (0.92 to 1.31)	0.94 (0.75 to 1.18)	1 tablet/week (500 mg)	0.83 (0.61 to 1.14)
2 to 5 tablets/week (325 mg)	0.89 (0.73 to 1.10)	0.80 (0.63 to 1.01)	2 to 6 tablets/week (500 mg)	0.88 (0.68 to 1.16)
6 to 14 tablets/week (325 mg)	0.78 (0.62 to 0.97)	0.72 (0.56 to 0.92)	more than 6 tablets/week (500 mg)	0.77 (0.59 to 0.99)
More than 14 tablets/week (325 mg)	0.68 (0.49 to 0.95)	0.30 (0.11 to 0.81)		
	p-trend<0.001	p-trend=0.004		p-trend=0.04

Abbreviations: CI = confidence interval; HPFS = Health Professionals Follow-up Study; mg = milligrams; NHS = Nurses' Health Study.

Appendix D Table 6. Adenoma Incidence at Different Followup Timepoints in the APACC Study

Treatment Group	1 Year[141] Events/N (%)	4 Year[142] Events/N (%)	Last Colonoscopy (1 or 4 Years)[142] Events/N (%)
160 mg/day	NR/66	15/55 (27%)	32/68 (47%)
300 mg/day	NR/60	27/47 (57%)	33/60 (55%)
Both aspirin doses	38/126 (30.2%)	42/102 (41%)	65/128 (51%)
Placebo	46/112 (41.1%)	33/83 (40%)	62/116 (53%)

Abbreviations: mg = milligrams; NR = not reported.

Appendix D Table 7. Adenoma Incidence by Interval After Randomization in Randomized, Controlled Trials of Persons With a Prior Adenoma[123]

Study	Treatment Group	0 to 12 Months Events/N (%)	12 to 24 Months Events/N (%)	24 to 38 Months Events/N (%)	≥38 Months Events/N (%)
APACC	160 or 300 mg/day	19/67 (28.4%)	20/58 (34.5%)	NR	37/94 (39.4%)
	Placebo	30/66 (45.5%)	18/49 (36.7%)	NR	31/81 (38.3%)
	Relative risk (95% CI)	0.62 (0.39 to 0.99)	0.94 (0.56 to 1.56)	NR	1.03 (0.71 to 1.49)
ukCAP	300 mg/day	17/36 (47.2%)	9/35 (25.7%)	38/191 (19.9%)	38/191 (19.9%)
	Placebo	30/42 (71.4%)	16/33 (48.5%)	39/152 (25.7%)	43/209 (20.6%)
	Relative risk (95% CI)	0.66 (0.45 to 0.98)	0.53 (0.27 to 1.03)	0.78 (0.52 to 1.15)	0.97 (0.65 to 1.43)
AFPP	81 or 325 mg/day	NR	15/36 (41.7%)	271/669 (40.5%)	20/42 (47.6%)
	Placebo	NR	3/15 (20.0%)	158/338 (46.7%)	11/23 (47.8%)
	Relative risk (95% CI)	NR	2.08 (0.71 to 6.16)	0.87 (0.75 to 1.00)	1.00 (0.59 to 1.69)

Abbreviations: AFPP = Aspirin/Folate Polyp Prevention Study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal; CI = confidence interval; mg = milligrams; NR = not reported; ukCAP = United Kingdom Colorectal Adenoma Prevention trial

Appendix D Table 8. Persistence and Adherence to Aspirin for Prevention of Colorectal Cancer and Cardiovascular Disease, by Prevention Focus

Population	Definition	<1 Year	1 Year	2 Years	3 to 4 Years	5 Years	>5 Years
				Followup Timepoint			
Primary prevention of colorectal cancer							
APACC[129,134-136]	Compliance: count of returned sachets	87%[†] (4 mo)			88% (4 yrs)[§]		
ukCAP[129,137,138]	Compliance: percent taking ≥95% of medication among those who had a followup colonoscopy				75%[†] (3 yrs)		
AFPP[123,136-140]	Compliance: percent taking medication 6 to 7 days/week		81 mg: 95%[†] 325 mg: 95%[†]	81 mg: 91%[†] 325mg: 91%[†]			
	Compliance: percent taking "virtually all" medication		94%				
Primary prevention of cardiovascular disease							
PACE[177]	Tablet count		87%				
BMD[124]	Persistence: percent who did not stop using		81%[*†]				61%[*†] (6 yrs)
ETDRS[128,129]	Persistence: still taking study medication		92%[*†]			70%[†]	
AAA[133]	Persistence: did not stop taking	85%[†] (6 mo)					
POPADAD[132]	Persistence: did not stop tablets		86%[*]			50%[*]	
JPAD[131]	Persistence: did not stop taking				90%[†] (4 yrs)		
WHS[‡112,176]	Compliance: taking at least two-thirds of the study aspirin or aspirin placebo		88%			76%	67% (10 yrs)
ASPREE[180]	Persistence: still taking study medication		80%				
DAMAD[179]	Adherence: mean rate of aspirin consumption based on pill count in subgroup at 1 center				82%[†] (3 yrs)		
PPP[175]	Persistence: did not stop taking study medication		81%[†]		81%[†] (yr 3.6)		
PHS[‡120]	Persistence: taking both of the study medications	91%[†] (6 mo)				83% (4.75 yrs)	
TPT[108]	Persistence: did not withdraw from trial treatment		86%[*]		71%[*] (3 yrs)	58%[*]	

Appendix D Table 8. Persistence and Adherence to Aspirin for Prevention of Colorectal Cancer and Cardiovascular Disease, by Prevention Focus

Population	Definition	Followup Timepoint					
		<1 Year	1 Year	2 Years	3 to 4 Years	5 Years	>5 Years
Secondary prevention of cardiovascular disease							
UK-TIA[125,126]	4 mo persistence: percent who did not stop using. By 6 yr: Positive urine test, called "compliance" but likely to be persistence	88%* (4 mo)				75%† (by 6 yrs)	
SAPAT[130]	Persistence: did not stop taking				64%*† (4 yrs)		
SALT[127]	Persistence: did not permanently discontinue				83%* (31 mo)		
HOT[178]	"Compliance" measured by electronic cap timing		78%†				
AMIS[187]	Adherence: took an average of 1.6 capsules per day				89% (yr 3)		
ASPIRE[181]	Persistence: percent that did not discontinue		81%*†	73%*†	63%*† (yr 3) 57%*† (yr 4)		
CDPA[182]	Adherence: ≥80% study medication taken over entire study period			81%† (1.8 yrs)			
ACBS[183]	Adherence: fully complied			85%			
ESPS-2[189]	Persistence: did not stop taking treatment	84%† (6 mo)	84%†	82†%			
EAFT[186]	Persistence: did not withdraw from treatment among those still at risk	86%† (6 mo)	80%†	71%†	66%†		
PARIS[188]	Adherence: total number of tablets possible				72%† (3.4 yrs)		
JAST[185]	Adherence: took aspirin regularly			78%*†			
SPAF[184]	Adherence: more than 80% compliance by pill count during study (including interruptions)		88% (1.3 yrs)				
Tayside Scotland (Registry dispensing study)[190]	Adherence: percent with good adherence defined as ≥80% where adherence is number of days with supply/total days since prescription		58%†	56%†	54%† (yr 3) 55%† (yr 4)	56%†	55%† (6 yrs); 53%† (7 yrs); 58%† (8 yrs)

*Calculated
†Measures are for aspirin specifically; others are reported for the overall study population
‡PHS and WHS targeted primary prevention of both cancer and cardiovascular disease
§Among persons who completed the 4 year colonoscopy

Appendix D Table 8. Persistence and Adherence to Aspirin for Prevention of Colorectal Cancer and Cardiovascular Disease, by Prevention Focus

Abbreviations: AAA = Aspirin for Asymptomatic Atherosclerosis; ACBS = Asymptomatic Cervical Bruit Study; AFPP = Aspirin/Folate Polyp Prevention study; AMIS = Aspirin Myocardial Infarction Study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal study; ASPIRE = Aspirin to Prevent Recurrent Venous Thromboembolism; ASPREE = ASPirin in Reducing Events in the Elderly; BMD = British Medical Doctors trial; CDPA = Coronary Drug Project Aspirin study; DAMAD = Males and females w/ diabetics and diabetic retinopathy; EAFT = European Atrial Fibrillation Trial; ESPS-2 = European Stroke Prevention Study 2; ETDRS = Early Treatment Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment study; JAST = Japan Atrial Fibrillation Stroke Trial; JPAD = Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; mg = milligrams; mo = month; PACE = Prevention with Low-dose Aspirin of Cardiovascular disease in the Elderly; PARIS = Persantine-Aspirin Reinfarction Study; PHS = Physicians' Health Study; 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; SPAF = Stroke Prevention in Atrial Fibrillation study; TPT = Thrombosis Prevention Trial; ukCAP = United Kingdom Colorectal Adenoma Prevention trial; UK-TIA = UK Transient Ischaemic Attack trial; WHS = Women's Health Study; yr(s) = year(s)