Systematic review report for question PPR1

Clinical Question: *What is the risk-benefit ratio for use of aspirin for prevention of colorectal cancer stratified by risk of colorectal cancer itself? (What is the optimal dose and frequency of administration?)*

PICO Question: *In an asymptomatic population at average risk or increased risk of colorectal cancer, what is the cost-benefit ratio of prophylactic Aspirin use in reducing the mortality and incidence of colorectal cancer?*

Population	Intervention	Comparator	Outcomes	Study Design
- Asymptomatic western population at average risk of colorectal cancer, or - Populations at increased risk of colorectal cancer	Prophylactic aspirin use	Placebo or no Aspirin use	- Colorectal cancer incidence - Colorectal cancer mortality - Adverse effects	Systematic reviews of Level II evidence or randomised controlled trials.

1. Methods

1.1. Guidelines

Relevant recent (2005 onwards) guidelines were identified by scanning the citations identified by the literature search and searching the National Guideline Clearinghouse (http://guideline.gov/) and the Guidelines Resource Centre (www.cancerview.ca).

To be considered for adoption guidelines had to meet the pre-specified criteria of scores of greater or equal to 70% for the domains rigour of development, clarity of presentation and editorial independence of the AGREE II instrument (http://www.agreetrust.org/resource-centre/agree-ii/).

1.2. Literature Search

PubMed (01/01/2004 - 31/08/2016), Embase (01/01/2004 - 31/08/2016), CINAHL (01/01/2004 - 31/08/2016), PsycINFO (01/01/2004 - 31/08/2016), Cochrane Database of Systematic Reviews (01/01/2004 - 31/08/2016), Database of Abstracts of Reviews of Effects and Health Technology Assessment databases (up until 31/08/2016) were searched using text terms and, where available, database specific subject headings. Each database was searched for articles dealing with colorectal cancer. In PubMed, Embase, CINAHL and PsycINFO databases the colorectal cancer search was coupled with a search for aspirin, and database specific filters for identifying randomised controlled trials/ systematic review and meta-analyses then applied. To identify studies which considered Aboriginal and Torres Strait Islanders (ATSI) these searches were then coupled with search

terms for ATSI. A complete list of the terms used for all search strategies are included as Appendix A. Reference lists of all relevant articles were checked for potential additional articles.

Inclusion and exclusion Criteria

Selection criteria	Inclusion criteria	Exclusion criteria
Study type	Intervention studies	
Study design	Systematic reviews of Level II evidence or randomised controlled trials.	In vitro studies or preclinical trials
Population	- Asymptomatic western population at average risk of colorectal cancer, or - Populations at increased risk of colorectal cancer due to either: - Family history of colorectal cancer, or - Previous colorectal cancer or adenomas, or - Familial adenomatous polyposis, or - Lynch Syndrome	- diagnosis of FAP or suspected FAP without genetic testing - genetic or clinical diagnosis of HNPCC, or increased risk - A non-syndromic family history of colorectal cancer - inflammatory bowel disease, chronic ulcerative colitis, or Crohn disease - other hereditary polyposis syndromes - Studies in children (<25 yrs)
Intervention	Prophylactic use of Aspirin for the primary prevention of colorectal cancer, with any of the following: - Aspirin at ≤100mg, 100-325mg, or >325mg/day - Aspirin at alternate days (any dosage) - Duration of ≤2 yrs, >2-4 yrs, or >4 yrs - Exposure commencing <50yrs, 50-70yrs, >70yrs	- Aspirin in combination therapy (where separate placebo and aspirin only groups were not reported separately) - Studies of aspirin with only cardiovascular endpoint analysis
Comparator	Placebo or no Aspirin use	Long term use of Aspirin or NSAID
Outcomes	- Colorectal cancer incidence - Colorectal cancer mortality - Adverse effects, including either: - Incidence of peptic ulcers - Incidence of GI bleeding - Incidence of intracranial haemorrhage - Incidence of stroke (haemorrhagic or thrombotic) - Incidence of Aspirin hypersensitivity - Incidence of renal impairment - Death due to side effects	
Language	English	
Publication period	01/01/2004 to 31/08/2016	

2. Results

2.1. Guidelines

Nine potentially relevant guidelines were identified however these were not included as they did not meet the pre-specified criteria.

2.2. Results of Literature Search

Figure 1 outlines the process of identifying relevant articles for the systematic review. The PubMed search identified 971 citations, the Embase search identified 1500 citations, the Cochrane Database of Systematic Reviews search identified 36 citations, the Database of Abstracts of Reviews of Effects (DARE) search identified 23 citations, the Health Technology Assessment search identified 5 citations, PsycINFO search identified 12 citations, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) search identified an additional 166 citations resulting in a total of 2713 citations. Titles and abstracts were examined and 110 articles were retrieved for a more detailed evaluation. An additional 8 potential citations were identified from the reference list of retrieved articles.

A total of 10 clinical trials reported in 17 articles met the inclusion criteria and were included in the review. There were no studies of ATSI that met the inclusion criteria.

The retrieved articles that were not included and the reason for their exclusion are documented in Appendix C. In summary, most articles were excluded because they had used an inappropriate study design, or were review articles.

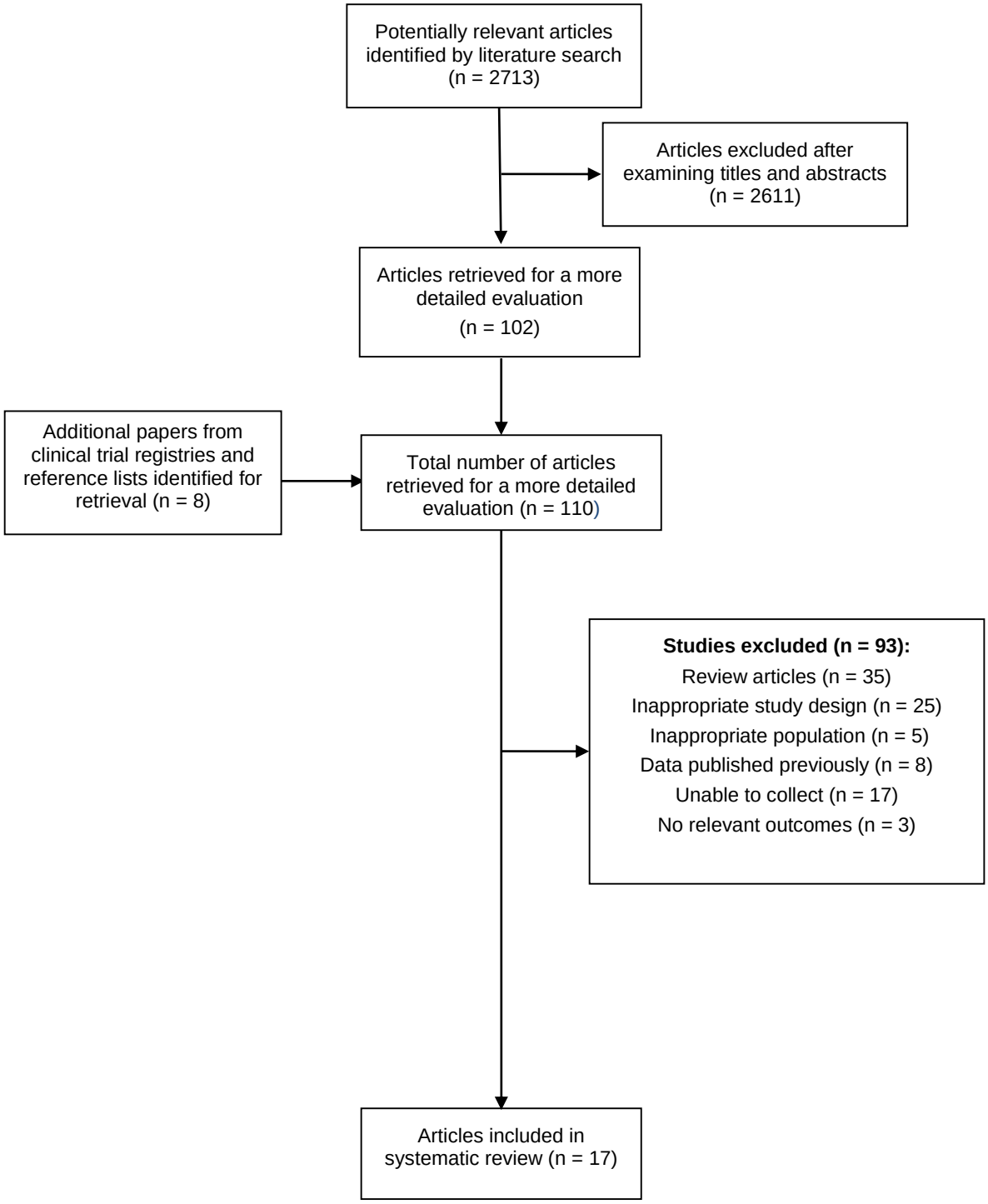

Figure 1. Process of inclusion and exclusion of studies

2.3. Study Characteristics

Characteristics of included studies are described in Tables 1 - 9.

Table 1: Intervention studies examining Aspirin for improving colorectal cancer mortality and incidence: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Burn 2008 (UK) Colorectal Adenoma/ Carcinoma Prevention Programme 2 (CAPP2)	Eligible patients were >25 yrs of age and were proven carriers of a pathologic mismatch-repair mutation or members of a family that met the Amsterdam diagnostic criteria and had a personal history of a cured Lynch syndrome neoplasm but an intact colon. **Mean age** (range): 46 years (25-79) **Gender (%):** F/M = 55.0/45.0 **Mutation (no/total no (%):** *MLH1* 358/614 (58.3%) *MSH2* 235/614 (38.3%) *MSH6* 21/614 (3.4%) **Follow up mean** (range): 29.0 months (7-74) **Mean duration of receipt of study drug** (range): 26.5 months (1-67) **N = 693**	RCT (multi centre – 43 international centres)	600 mg Aspirin daily for ≤4 years N=175 patients received resistant starch and N=166 received placebo starch. N=9 received neither. **N = 350**	Placebo daily for ≤4 years N=157 patients received resistant starch and N=176 received placebo starch. N=10 received neither. **N = 343**	**Primary:** *Detection of at least one adenoma or colorectal carcinoma at follow up* **Secondary:** *Detection of an adenoma only, colorectal cancer only, adenoma and colorectal cancer and advanced adenoma or colorectal cancer*	Double blinded randomisation was done in blocks of 16 in a two-by-two factorial design to aspirin (600 mg), aspirin placebo, resistant starch (30 g) and starch placebo (cornstarch) N=332 received resistant starch, N=342 placebo starch, N=19 received neither resistant or placebo starch
Burn 2011	**Follow up mean** (range): 66.1 months (2.5-128) **N = 671**	RCT	600 mg Aspirin daily for ≤4 years **N = 342**	Placebo daily for ≤4 years **N = 329**	**Primary:** *Detection of at least one adenoma or colorectal carcinoma at follow up* **Secondary:** *Detection of an adenoma only, colorectal cancer only, adenoma and colorectal cancer and advanced adenoma or colorectal cancer*	

N = number of participants; mg = milligrams; F = female; M = male; yrs = years; MLH1 = MutL homolog 1; MSH2 = MutS homolog 2; MSH6 = mutS homolog 6; RCT = randomized controlled trial.

Table 2: Intervention studies examining Aspirin for improving colorectal cancer mortality and incidence: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Cook 2005 **van Kruijsdijk 2015** (USA) Women's Health Study (WHS)	Healthy female (≥45 years old) healthcare professionals were recruited via letters of invitation from 30/4/1993 to 24/1/1996. **Mean Age** (SD): 54.6 years (7.0) **Mean BMI** (SD): 26.0 (5.1) **Smoking status** (n/%)**:** Current: 5235/13.1% Past: 14,265/35.8% Never: 20,340/51.1% **Alcohol use** (drinks/wk)(n/%): <1: 23,226/58.3% ≥1: 16,640/41.7% **Physical activity** (Kcal/wk)**:** <1000: 25,994/66.0% ≥1000: 13,383/34.0% **Mean follow up:** 10.1 years **N = 39,876**	RCT	100 mg Aspirin on alternate days 50% (N=9966) were randomised to receive Vitamin E **N = 19,934**	Placebo on alternate days 50% (N=9971) were randomised to receive Vitamin E **N = 19,942**	**Primary**: *Incidence of invasive cancer excluding non-melanoma skin cancer.* **Secondary**: *Incidence of breast, colorectal and lung cancer.* *Incidence of gastrointestinal side effects.*	Double blinded randomisation was done in blocks of 16 within 5 years age strata in a two-by-two factorial design to compare aspirin (100 mg), aspirin placebo, Vitamin E (600 IU) and Vitamin E placebo. The trial initially contained a beta carotene component which was terminated after an average of 2 yrs of follow up.
Cook 2013	**Mean follow up** (range)**:** 17.5 years (10.4-18.8) **N = 39,876**	RCT	100 mg Aspirin on alternate days **N = 19,934**	Placebo on alternate days **N = 19,942**	**Primary**: *Incidence of invasive cancer excluding non-melanoma skin cancer.* **Secondary**: *Incidence of breast, colorectal and lung cancer.* *Incidence of gastrointestinal side effects.*	A total of 6,194 lost to follow up due to death (N=1875), or opted out of further follow up.

N = number of participants; mg = milligrams; Kcal = kilo calories; wk = week; BMI = body mass index; SD = Standard deviation; RCT = randomized controlled trial.

Table 3: Intervention studies examining Aspirin for improving colorectal cancer mortality and incidence: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Peto 1988 **Flossman 2007** **Rothwell 2010** (UK) British Doctors Aspirin Trial (BDAT)	Healthy male British doctors were recruited between 1978-1979. **Mean Age** (SD): 61.7 years (7.0) **Smoking status** (n/%): Never: 1254/24.4 Past: 2288/44.6 Current (<20/day): 347/ 6.8 Current (≥20/day): 314/ 6.1 Other/mixed: 932/18.1 **Mean trial duration** (range): 5.7 years (5–6) **Median follow up:** 23 years **N = 5139**	RCT	300 mg or 500 mg Aspirin daily **N = 3429**	No Aspirin or no placebo pill **N = 1710**	**Primary**: *Mortality due to cardiovascular, other vascular and non-vascular events including cancer.* *Incidence of non-fatal cardiovascular, other vascular and non-vascular events including cancer.* **During long term follow up:** **Primary:** *Incidence of colorectal cancer* **Secondary:** *Incidence of other cancers*	Randomisation was done by computer. The trial included 500 mg ordinary soluble or effervescent aspirin or 300 mg enteric coated aspirin. Two-thirds were randomised to aspirin and the other third told to avoid aspirin or products containing aspirin.
Meade 1998 **Rothwell 2010** (UK) Thrombosis Prevention Trial (TPT)	Male aged between 45 – 69 years at high risk of ischaemic heart disease were recruited from 108 practices in the UK **Mean Age (SD)** 57.5 years (6.7 years) **Trial duration** (mean/range) 6.9 years/4.3-8.6 years **Follow up range** 17-20 years **N = 5085**	RCT (multi centre)	75 mg Aspirin daily 50% (N=1277) were randomised to receive active warfarin daily and the other 50% received warfarin placebo daily **N = 2545**	Aspirin placebo daily 50% (N=1268) were randomised to receive active warfarin daily and the other 50% received warfarin placebo daily **N = 2540**	**Primary**: *Incidence of all ischaemic heart disease (defined as the sum of all fatal and non-fatal events including coronary death and fatal and non-fatal myocardial infarction* **Secondary**: *Incidence of stroke. Mortality due to cancer and cancer incidence.*	Two-by-two factorial double blinded designed to compare aspirin (75 mg) to aspirin placebo, or active warfarin to placebo. Warfarin was started at 2.5 mg a day and this dose was adjusted once a month depending on the INR. The mean warfarin dose was 4.1 mg a day (0.5-12.5 mg)

INR = International normalised ratio, WF = Warfarin; N = number of participants; mg = milligrams; yrs = years; SD = standard deviation; RCT = randomized controlled trial.

Table 4: Intervention studies examining Aspirin for improving colorectal cancer mortality and incidence: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Norrving 1991 **Rothwell 2010** (Sweden) Swedish Aspirin Low Dose Trial (SALT)	Patients who had transient ischaemic attack (including amaurosis fugax), minor ischaemic stroke, or retinal artery occlusion within the previous 3 months **Age range** 50-79 years **Gender (%)** F: 34.2 M: 65.8 **Smoking Status** Current Smoker AS: 26.0 PI: 27.9 Ex-smoker AS: 21.3 PI: 24.7 Never Smoked AS: 52.7 PI: 47.4 **Duration of drug treatment:** AS: 30.6 mths PI: 27.5 mths **Trial duration** (median/range) 2.7 yrs/1.0 – 5.3 yrs **Follow up range** 18 - 23 yrs **N = 1360**	RCT (16 centres – multicentre)	75 mg Aspirin daily **N = 676**	Placebo daily **N = 684**	**Primary**: *Incidence of stroke (minor or major) or death from any cause* **Secondary**: *Incidence of stroke (minor or major); stroke or two or more TIAs within a week of each other necessitating a change of therapy and fatal or non-fatal myocardial infarction. All-cause mortality.*	Double blinded randomisation was done in blocks of 8. Aspirin tablets were film coated.

AS = Aspirin; PI = Placebo; N = number of participants; mg = milligrams; mths = months; F = female; M = male; yrs = years; RCT = randomized controlled trial.

Table 5: Intervention studies examining Aspirin for improving colorectal cancer mortality and incidence: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
UK-TIA Study Group 1988 **Farrell 1991** **Flossman 2007** **Rothwell 2010** (UK) UK-TIA Trial	Patients with a transient ischemic attack or minor ischaemic stroke were recruited between 25/07/1979 and 8/10/1985. **Mean Age**(SD): 59.8 years(9.0) **Gender F/M (%):** 26.9/73.1 **Obesity index (kg/m^2)**(mean/SD): 1200 mg aspirin: 25.3/3.39 300 mg aspirin: 25.5/3.82 Control: 25.1/3.43 **Regular Smokers (n/%):** 1200 mg aspirin: 444/54 300 mg aspirin: 431/53 Control: 417/51 **Trial duration** (mean/range) 4.4 yrs/1.0 – 7.1 yrs **Follow up range:** 21-27 years **N = 2435**	RCT (33 centres)	300 mg aspirin daily (two 150 mg tablets in the morning and two placebo tablets in the evening) **N = 806** OR 1200 mg aspirin daily (two 300 mg aspirin tables twice a day) **N = 815** **N = 1621**	Placebo daily (two placebo tables twice a day) **N = 814**	**Primary**: *Incidence of non-fatal major stroke, non-fatal myocardial infarction, vascular death or non-vascular death* **Secondary:** *Adverse effects, mortality due to colorectal cancer, incidence of colorectal cancer*	Double blinded randomisation was done by telephone contact with the Clinical Trial Service Unit

N = number of participants; mg = milligrams; F = female; M = male; yrs = years; RCT = randomized controlled trial; SD = standard deviation.

Table 6: Intervention studies examining Aspirin for improving colorectal cancer mortality and incidence: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Baron 2003 **Cole 2009** (US, Canada) AFPPS Trial	Recent history of sporadic colorectal adenomas with complete colonoscopy and removal of polyps within 3 months prior to randomisation were recruited between July 1994-March 1998 **Mean age (SD)**: Placebo: 57.4 (9.9) 81mg/d aspirin: 57.3 (9.9) 325mg/d aspirin: 57.7 (9.1) **Gender: Male no. (%)**: Placebo: 233 (62.6) 81mg/d aspirin: 244 (64.7) 325mg/d aspirin: 235 (63.2) **No. of adenomas before randomisation (mean, SD):** Placebo: 2.4 (2.2) 81mg/d aspirin: 2.2 (2.0) 325mg/d aspirin: 2.4 (2.4) **Mean (SD) follow-up months:** Placebo: 32.9 (4.2) 81mg/d aspirin: 32.5 (3.4) 325mg/d aspirin: 32.8 (3.7) **N = 1121**	RCT (9 clinical centres)	81 mg aspirin daily with or without 1mg folic acid daily **N = 377** OR 325 mg aspirin daily with or without 1mg folic acid daily **N = 372** **N = 749**	Placebo taken once per day (cellulose-sucrose) with or without 1mg folic acid daily **N = 372**	**Primary:** *Proportion of patients in whom one or more colorectal adenomas were detected from one year after randomisation through the anticipated surveillance follow-up examination* *Risk of one or more colorectal adenomas after randomisation* **Secondary:** *Number of colorectal adenomas and advanced lesions* *Number of lesions in the left side of the colorectum (descending colon, sigmoid colon, and rectum) and right side of the colorectum (remainder of the bowel)*	Blocked randomisation with use of computer-generated random numbers was stratified according to study centre, sex and age (≤60y vs >60y) Exclusion criteria: Individuals with history of familial colorectal cancer syndrome, invasive large-bowel cancer, inflammatory bowel disease, malabsorption syndromes, those with a clinical need for aspirin, NSAIDs or folate treatment.

AFPPS = Aspirin/Folate Polyp Prevention Study

Table 7: Intervention studies examining Aspirin for improving colorectal cancer mortality and incidence: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Benamouzig 2003 **Cole 2009** (France) APACC Trial	Recent history of sporadic colorectal adenomas with adequately prepared colonoscopy and polyps removed up to three months before initial consultation were recruited between December 1996-February 2000 **Mean Age (SD)**: Aspirin: 57.8 (1.5) years Placebo: 57.7 (1.7) years **Gender F/M (%)** Aspirin: 30/70 Placebo: 30.3/69.7 **History of adenomas N (%)** Aspirin: 30 (21.9) Placebo: 34 (26.6) **Advanced adenomas**[a] **N (%)** Aspirin: 111 (79.3) Placebo: 90 (68.2) **Follow-up time:** 12 months for all arms **N = 272**	RCT (49 gastroenterology centres)	160 mg aspirin per day **N = 73** OR 300 mg aspirin per day **N = 67** **N = 140**	Placebo taken once per day **N = 132**	**Primary:** *Proportion of subjects in whom at least one new adenoma was detected, new adenoma size and adenomatous polyp burden* **Secondary:** *None*	Randomisation was balanced every 4 patients – one to 160mg aspirin, one to 300 mg aspirin and two to placebo. Exclusion criteria: Individuals with colorectal cancer (unless *in situ*), familial adenomatous polyposis, bowel resection excluding appendectomy, chronic inflammatory bowel disease or debilitating or life-threatening disease

APACC =Association pour la Prevention par l'Aspirine du Cancer Colorectal

[a] *An advanced adenoma was defined as a villous adenoma, adenoma > 10mm, or adenoma with high-grade dysplasia*

Table 8: Intervention studies examining Aspirin for improving colorectal cancer mortality and incidence: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Logan 2008 **Cole 2009** (UK, Denmark) ukCAP Trial	Recent history of sporadic colorectal adenomas with complete colonoscopy or barium enema if incomplete and removal of an initial or recurrent 0.5cm or greater colorectal adenoma 6 months prior were recruited between December 1997-November 2001 **Mean age** Aspirin: 57.39 years Placebo: 58.00 years **Gender F/M (%)** Aspirin: 42.37/57.63 Placebo: 39.06/60.94 **Mean no. of qualifying baseline adenomas** Aspirin: 1.38 Placebo: 1.38 **Mean follow-up duration months** Aspirin: 40.2 Placebo: 41.04 **N = 939**	RCT (10 centres)	300mg per day aspirin with or without folate **N = 472**	Placebo taken once per day or folate **N = 467**	**Primary:** *Percentage of patients who developed one or more recurrent colorectal adenomas or cancers during the follow-up period* **Secondary:** *Number of adenomas detected during follow-up evaluation* *Percentage of patients who developed advanced colorectal neoplasia (defined as adenomas that were either 1 cm or larger in diameter, villous or tubulovillous, or showed severe dysplasia)*	Randomisation performed centrally where patients were randomised to 1 of 4 treatment arms using a computer generated randomisation list with a block size of 8 with randomisation stratified by centre Exclusion criteria: Individuals with serious medical conditions that might preclude successful completion of the trial, the need for regular treatment with nonsteroidal anti-inflammatory drugs (including aspirin), known intolerance or sensitivity to aspirin, or active ulcer disease, bleeding disorders, or anticoagulant treatment, previous resection of the large bowel or incomplete adenoma removal. Any colorectal cancer that developed among trial participants were included in the category of advanced neoplasia

ukCAP = United Kingdom Colorectal Adenoma Prevention Study

Table 9: Intervention studies examining Aspirin for improving colorectal cancer mortality and incidence: study characteristics

Study	Participants	Design	Intervention	Comparison	Outcomes	Comments
Sandler 2003 **Cole 2009** (US) CALGB Trial	Previous colorectal cancer with low risk of recurrent disease and adequately prepared colonoscopy with removal of all polyps within four months prior to study entry were recruited between May 1993-January 2000 **Total age ranges (%)** ≤49: 15% 50-59: 24% 60-69: 33% ≥70: 28% **Gender F/M (%)** Aspirin: 48/52 Placebo: 47/53 **Cancer stage N (%)** *Dukes' A or B1* Aspirin: 196 (62) Placebo: 121 (38) *Dukes' B2 or C* Aspirin: 200 (63) Placebo: 118 (37) **Median (IQR) duration of follow-up months:** Aspirin: 30.9 (20.1-35.3) Placebo:31.6 (19.9-35.3) **N = 635**	RCT (multi-centre)	325 mg aspirin per day **N = 317**	Placebo taken once per day **N = 318**	**Primary:** *Detection of adenomas in the large bowel by either colonoscopy or sigmoidoscopy after randomisation* **Secondary:** *Comparison of aspirin and placebo group with respect to proportion who had at least one adenoma after randomisation, the size of the largest adenoma among patients who had at least one adenoma, the time to the detection of the first adenoma, the proportion of patients with advanced adenomas (those at least 1 cm in diameter or had villous components)*	Randomisation was stratified according to the stage of cancer (Dukes' A or B1 vs. Dukes' B2 or C) and sex Exclusion criteria: Familial polyposis, had had invasive cancer other than non-melanoma skin cancer within 5 years before intake appointment, had cardiovascular disease, had received immunosuppressive therapy or had clinically obvious narcotic or alcohol dependence during previous 6 months, had a history of inflammatory bowel disease, had possible contraindications to aspirin administration, had a likelihood of requiring NSAID use, had used NSAIDs including aspirin at any dose on 3 or more days per month during each of the 3 months before enrolment or for a period of 36 days in the previous year, or had a history of stroke, transient ischemic attacks, angina, myocardial infarction, or atherosclerotic peripheral vascular disease

CALGB = Colorectal Adenoma Prevention Study [Cancer and Leukemia Group B]

2.4. Study risk of bias

Table 10: Methodological risk of bias of included randomised controlled trials (n = 10)

Risk of bias categories	N (%)
I. Was the allocation sequence adequately generated?	
LOW = a random component in the sequence generation process	9 (90%)
HIGH = a non-random component in the sequence generation process	1 (10%)
UNCLEAR = Insufficient information about the sequence generation process	0 (0%)
II. Was allocation adequately concealed?	
LOW = Participants and investigators could not foresee assignment	10 (100%)
HIGH = Participants and investigators could possibly foresee assignments	0 (0%)
UNCLEAR = Insufficient information to permit judgement	0 (0%)
III. Was knowledge of the allocated interventions adequately prevented during the study?	
LOW = Blinding of participants and key study personnel ensured	9 (90%)
HIGH = No blinding or incomplete blinding	1 (10%)
UNCLEAR = Insufficient information to permit judgement	0 (0%)
IV. Were incomplete outcome data adequately addressed?	
LOW = No missing outcome data (LOW)	10 (100%)
HIGH = Reason for missing outcome data likely to be related to true outcome	0 (0%)
UNCLEAR = Insufficient reporting of attrition/exclusions to permit judgement	0 (0%)
V. Are reports of the study free of suggestion of selective outcome reporting?	
LOW = study protocol is available and all of the study's pre-specified outcome	10 (100%)
HIGH = Not all of the study's pre-specified primary outcomes have been reported	0 (0%)
UNCLEAR = Insufficient information to permit judgement	0 (0%)
VI. Was the study apparently free of other problems that could put it at a risk of bias?	
LOW = study appears to be free of other sources of bias	10 (100%)
HIGH = There is at least one important risk of bias	0 (0%)
UNCLEAR = Insufficient information to assess	0 (0%)

Table 11. Methodological risk of bias of systematic reviews of randomised controlled trials (n=3)

Risk of bias categories	N (%)
1. Studies included in the systematic review or meta-analysis	
a) Was an adequate search strategy used?	
Very thorough – included appropriate search terms and databases	3 (100%)
Adequate – search terms and/or choice of databases could have been improved upon	0 (0%)
No or not described	0 (0%)
b) Were the inclusion criteria appropriate and applied in an unbiased way?	
2 = Yes – pre-specified inclusion criteria applied independently by two people	3 (100%)
1 = Adequate – inclusion criteria were pre-specified and applied by one person	0 (0%)
0 = No – inclusion was decided in an arbitrary fashion or not described	0 (0%)
2. Were the studies assessed for quality (relating to the minimisation of biases)?	
2 = Yes – appropriate quality issues were assessed independently by two people	0 (0%)
1 = Adequate – some problems with quality issues or assessed by one person only	1 (33%)
0 = No – inappropriate, no quality assessment undertaken or not described	2 (66%)
3. Were the characteristics and results of individual studies appropriately	
2 = Yes - summary descriptive tables of subjects, intervention, outcomes etc. are provided and estimates of treatment effect displayed	2 (66%)
1 = Adequate – more information would be desirable	1 (33%)
0 = No The following questions are only relevant for systematic reviews that pooled data	0 (0%)
4. Were the methods used for pooling the data appropriate?	
2 = Yes	3 (100%)
0 = No	0 (0%)
5. If there was heterogeneity, were sources of heterogeneity explored?	
2 = Yes	3 (100%)
1 = Some attempt was made	0 (0%)
0 = No	0 (0%)
N/A No heterogeneity	0 (0%)

Table 12: Risk of bias summary assessment of included randomised controlled trials (n = 10)

Trial/article(s)	Outcome	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall risk of bias
CAPP2/Burn 2008	CRC incidence	Low	Low	Low	Low	Low	Low	Low risk of bias
CAPP2/Burn 2011	CRC incidence	Low	Low	Low	Low	Low	Low	Low risk of bias
WHS/Cook 2005	CRC incidence	Low	Low	Low	Low	Low	Low	Low risk of bias
WHS/Cook 2013	CRC incidence	Low	Low	Low	Low	Low	Low	Low risk of bias
WHS/Cook 2013	Adverse effects	Low	Low	Low	Low	Low	Low	Low risk of bias
WHS/van Kruijsdijk 2015	CRC risk	Low	Low	Low	Low	Low	Low	Low risk of bias
BDAT/Flossman 2007	CRC incidence	Low	Low	High	Low	Low	Low	At risk of bias
BDAT/Flossman 2007	CRC mortality	Low	Low	High	Low	Low	Low	At risk of bias
SALT/Rothwell 2010	CRC mortality	Low	Low	Low	Low	Low	Low	Low risk of bias
TPT/Rothwell 2010	CRC mortality	Low	Low	Low	Low	Low	Low	Low risk of bias
UK-TIA/Flossman 2007	CRC incidence	Low	Low	Low	Low	Low	Low	Low risk of bias
UK-TIA/Flossman 2007	CRC mortality	Low	Low	Low	Low	Low	Low	Low risk of bias
UK-TIA/Farrell 1991	Adverse events	Low	Low	Low	Low	Low	Low	Low risk of bias
AFPPS/Cole 2009	Adenoma incidence	Low	Low	Low	Low	Low	Low	Low risk of bias
CALGB/Cole 2009	Adenoma incidence	High	Low	Low	Low	Low	Low	Low risk of bias
ukCAP/Cole 2009	Adenoma incidence	Low	Low	Low	Low	Low	Low	Low risk of bias
APACC/Cole 2009	Adenoma incidence	Low	Low	Low	Low	Low	Low	Low risk of bias

Key to overall risk of bias rating
Low risk of bias: A study rated at low risk of bias for all domains
At risk of bias: A study rated at high or unclear risk of bias for one or more domains

Table 13: Risk of bias summary assessment of systematic reviews (n = 3)

Trial/article(s)	Outcome	Search strategy	Inclusion criteria	Quality assessment	Study characteristics	Pooled data	Heterogeneity	Overall risk of bias
BDAT/SALT/TPT/UK-TIA Rothwell 2010	CRC incidence	Very thorough	Yes	Adequate	Yes	Yes	Yes	Moderate risk of bias
BDAT/SALT/TPT/UK-TIA Rothwell 2010	CRC mortality	Very thorough	Yes	Adequate	Yes	Yes	Yes	Moderate risk of bias
BDAT/UK-TIA Flossman 2007	CRC incidence	Very thorough	Yes	No	Yes	Yes	Yes	High risk of bias
AFPPS/CALGB/ukCAP/APACC Cole 2009	Adenoma incidence	Very thorough	Yes	No	Adequate	Yes	Yes	Low risk of bias

Key to overall risk of bias rating
Low risk of bias: A review that received a score of 2 for Questions Ia, Ib, II, and III
Moderate risk of bias: A review that received a score of 1 or 2 for Questions Ia, Ib, II, and III
High risk of bias: A review that received a score of 0 for any of the Questions Ia, Ib, II, or III

2.5 OUTCOMES

Table 14: Results of studies examining effects of Aspirin on colorectal cancer outcomes

Study	Outcome		N actual	Aspirin % (n)	Placebo % (n)	Size of effect	CI (95%)	p-value[a]	Follow up (mean)
Burn 2008 **Burn 2011** (UK) CAPP2 Trial	**Neoplasm Incidence** *The use of 600 mg enteric-coated aspirin vs placebo daily. Participates (N=674) also randomised to receive either 30 g resistant starch vs placebo starch.*		693	18.9 (66) N = 350	19.0 (65) N = 343	RR=1.0	0.7-1.4	NS	29 months
	Subgroup analyses (neoplasm incidence)								
	Neoplasms	Adenoma only	693	16.0 (56) N = 350	16.0 (55) N = 343	NR	NR	0.96	29 months
		Colorectal cancer only	693	1.4 (5) N = 350	2.0 (7) N = 343	NR	NR	0.54	
		Adenoma and colorectal cancer	693	1.4 (5) N = 350	0.9 (3) N = 343	NR	NR	0.45	
		Advanced neoplasms (adenoma or colorectal cancer)	693	7.4 (26) N = 350	9.9 (34) N = 343	NR	NR	0.33	
	Neoplasm Incidence *The use of 600 mg enteric-coated aspirin vs placebo daily. Participates only received aspirin or placebo and did not receive resistant starch/placebo starch.*		19	44.4 (4) N = 9	20.0 (2) N =10	NR	NR	NR	29 months
	Subgroup analyses (neoplasm incidence)								
	Neoplasms	Adenoma only	19	33.3 (3) N = 9	20 (2) N = 10	NR	NR	NR	29 months
		Colorectal cancer only	19	11.1 (1) N = 9	0 (0) N = 10	NR	NR	NR	
		Adenoma and colorectal cancer	19	0 (0) N = 9	0 (0) N = 10	NR	NR	NR	
		Advanced neoplasms (adenoma or colorectal cancer)	19	11.1 (1) N = 9	10 (1) N = 10	NR	NR	NR	
	Neoplasm incidence (individual events) *Neoplasma incidence from all colonoscopies with four time groups. Neoplasms are treated as individual events.*		1094	13.3 (71) N = 533	12.7 (71) N = 561	NR	NR	NR	29 months

Subgroup analysis								
Time on study	6-18 months	300	8.2 (12) N = 146	13.6 (21) N = 154	RR=0.6	0.3-1.2	NS	29 months
	19-30 months	546	15.8 (44) N = 278	13.8 (37) N = 268	RR=1.1	0.8-1.7	NS	
	31-42 months	130	11.7 (7) N = 60	10.0 (7) N =70	RR=1.2	0.4-3.1	NS	
	≥43 months	118	16.3 (8) N = 49	8.7 (6) N = 69	RR=1.9	0.7-5.1	NS	
Colorectal cancer incidence *Incidence of colorectal cancer measured from the date of randomisation with long term follow up.*		671	3.8 (13) N = 342	8.2 (27) N = 329	HR=0.63	0.35-1.13	0.12	66.1 months
Subgroup analysis								
Colorectal cancer incidence	≥2 yrs aspirin vs ≥2 yrs aspirin placebo	NR	NR	NR	HR=0.41	0.19-0.86	0.02	66.1 months
	<2 yrs aspirin vs ≥2 yrs aspirin placebo	NR	NR	NR	HR=1.07	0.47-2.41	0.87	
	<2 yrs aspirin placebo vs ≥2 yrs aspirin placebo	NR	NR	NR	HR=0.62	0.25-1.52	0.30	

N = number of participants; mg = milligrams; g = grams; yrs = years; CI = confidence interval; NR = not reported; NS = not statistically significantly different; RR = relative risk ratio; HR = hazards ratio; CAPP2 = Colorectal Adenoma/Carcinoma Prevention Programme 2. [a] *P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.*

Table 15: Results of studies examining effects of Aspirin on colorectal cancer outcomes

Study	Outcome		N actual	Aspirin % (n)	Placebo % (n)	Size of effect	CI (95%)	p-value[a]	Follow up (mean)
Cook 2005 **Cook 2013** **van Kruijsdijk 2015** (USA) WHS Trial	**Colorectal cancer incidence** *The use of 100 mg aspirin vs placebo and 600 IU Vitamin E vs placebo on alternate days for 10 years*		39,876	0.67 (133) N = 19,934	0.69 (139) N = 19,942	RR=0.97	0.77 – 1.24	0.83	10.1 years
	Subgroup analysis (colorectal cancer incidence)								
	Sites of colorectal cancer	Colon	39,876	0.52 (103) N = 19,934	0.56 (111) N = 19,942	RR=0.92	0.71–1.21	0.57	10.1 years
		Rectal		0.15 (30) N = 19,934	0.13 (25) N = 19,942	RR=1.20	0.70–2.04	0.50	
	Colorectal cancer incidence *Incidence of colorectal cancer measured from the date of randomisation with long term follow up*		39,876	1.0 (202) N = 19,934	1.2 (249) N = 19,942	HR=0.80	0.67 – 0.97	0.021	16 years
	Subgroup analysis (Colorectal cancer incidence)								
	Sites of colorectal cancer	Colon	39,876	0.8 (155) N = 19,934	1.0 (195) N = 19,942	HR=0.79	0.64 – 0.97	0.026	18 years
		Site of colon cancer: Proximal cancers		0.4 (88) N = 19,934	0.6 (120) N = 19,942	HR=0.73	0.55 – 0.95	0.022	
		Site of colon cancer: Distal cancers		0.3 (59) N = 19,934	0.3 (67) N = 19,942	HR=0.87	0.62 – 1.24	0.45	
		Rectal (includes rectosigmoid junction)		0.2 (47) N = 19,934	0.3 (54) N = 19,942	HR=0.86	0.58 – 1.28	0.46	
	Colorectal cancer stage	Duke's stage C or D	39,876	0.4 (82) N = 19,934	0.5 (102) N = 19,942	HR=0.80	0.60 – 1.07	0.126	18 years
		Duke's stage A or B		0.6 (117) N = 19,934	0.7 (142) N = 19,942	HR=0.82	0.64 – 1.04	0.10	
	Adverse Events - *Reported cases gastrointestinal side effects and polyps*								
	Gastrointestinal bleeding		39,876	8.3 (1645) N = 19,934	7.3 (1452) N = 19,942	HR=1.14	1.06 – 1.22	<0.001	18 years
	Peptic ulcer			7.3 (1456) N = 19,934	6.2 (1242) N = 19,942	HR=1.17	1.09 – 1.27	<0.001	18 years
	Colon polyp			26.0 (5187) N = 19,934	25.8 (5151) N = 19,942	HR=1.00	0.96 – 1.04	0.94	18 years

Colorectal Cancer Predicted Risk Treatment effect prediction of alternate-day aspirin use at 10 years and 15 years							
	Total study population	27,939	AR=0.60% CI=0.48-0.74%	AR=0.61% CI=0.49-0.75%	ARR=0.01% CI=0.00%-32.05%	NNT= >1000 CI=3 to >1000	10 years
			AR=0.86% CI=0.72-1.03%	AR=1.01% CI=0.85-1.18%	ARR=0.14% CI=0.02%-0.59%	NNT= 709 CI=170 to >1000	15 years
	Women <65 years	24,971	AR=0.47% CI=0.36-0.60%	AR=0.51% CI=0.40-0.65%	ARR=0.05% CI=0.00%-0.96%	NNT= >1000 CI=105 to >1000	10 years
			AR=0.71% CI=0.57-0.87%	AR=0.88% CI=0.73-1.06%	ARR=0.17% CI=0.04%-0.55%	NNT= 581 CI=181 to >1000	15 years
	Women ≥65 years	2,968	AR=1.71% CI=1.13-2.47%	AR=1.43% CI=0.92-2.15%	ARR= -0.27% CI=-1.17%-0.63%	NNH= 369 CI=85[NNH] to 158[NNT]	10 years
			AR=2.17% CI=1.51-3.01%	AR=2.06% CI=1.42-2.89%	ARR= -0.11% CI=-1.15%-0.93%	NNH= 924 CI=87[NNH] to 107[NNT]	15 years

AR = absolute risk; ARR = absolute risk reduction; N = number of participants; NNH = Numbers needed to harm; NNT = numbers needed to treat; mg = milligrams; CI = confidence interval; RR = relative risk ratio; HR = hazards ratio; IU = international units; WHS = Women's Health Study. [a] *P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.*

Table 16: Results of studies examining effects of Aspirin on colorectal cancer outcomes

Study	Outcome		N actual	Aspirin % (n)	Control % (n)	Size of effect	CI (95%)	p-value[a]	Follow up (mean)
Peto 1988 **Flossman 2007** (UK) BDAT	**Colorectal cancer incidence** *Incidence of colorectal cancer measured from the date of randomisation with long term follow up*		5,139	2.68 (92) N = 3429	3.74 (64) N = 1710	HR=0.70	0.51 – 0.97	0.04	≥20 years
	Subgroup analysis (Colorectal cancer incidence)								
	Incidence of colorectal cancer measured from the date of randomisation	0-9 years	5,139	0.81 (28) N = 3429	0.99 (17) N = 1710	HR=0.82	0.45 – 1.49	0.52	≤9 years
		10-19 years		1.46 (50) N = 3429	2.22 (38) N = 1710	HR=0.64	0.42 – 0.97	0.05	10-19 years
	Colorectal cancer mortality *Effect of 500 mg aspirin on long term risk of death due to colorectal cancer*		5,139	1.72 (59) N = 3429	2.34 (40) N = 1710	OR=0.73	0.49 – 1.10	NS	22-23 years
Norrving 1991 **Rothwell 2010** (Sweden) SALT	**Colorectal cancer mortality** *Effect of 75 mg aspirin on long term risk of death due to colorectal cancer*		1360	1.04 (7) N = 676	1.46 (10) N = 684	OR=0.71	0.27 – 1.86	NS	18-23 years
	Colorectal cancer mortality *Effect of 75 mg aspirin on long term risk of death due to colorectal cancer excluding patients with scheduled duration of trial treatment < 2.5 years*		912	0.45 (2) N = 444	1.50 (7) N = 468	OR=0.30	0.06 – 1.44	NS	
Meade 1998 **Rothwell 2010** (UK) TPT	**Colorectal cancer mortality** *Effect of 75 mg aspirin on long term risk of death due to colorectal cancer*		5085	1.34 (34) N = 2545	2.16 (55) N = 2540	OR=0.61	0.40 – 0.94	SSD	17-20 years
	Colorectal cancer mortality *Effect of 75 mg aspirin on long term risk of death due to colorectal cancer excluding patients with scheduled duration of trial treatment < 2.5 years*			1.34 (34) N = 2545	2.16 (55) N = 2540	OR=0.61	0.40 – 0.94	SSD	

N = number of participants; mg = milligrams; CI = confidence interval; NR = not reported; NS = not statistically significantly different; HR = hazards ratio; OR = odds ratio; SSD = statistically significantly different; BDA = British Doctors Aspirin Trial; SALT = Swedish Aspirin Low Dose Trial; TPT = Thrombosis Prevention Trial. [a] *P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.*

Table 17: Results of studies examining effects of Aspirin on colorectal cancer outcomes

Study	Outcome		N actual	Aspirin % (n)	Placebo % (n)	Size of effect	CI (95%)	p-value[a]	Follow up (mean)
UK-TIA Study Group 1988 **Farrell 1991** **Flossman 2007** (UK) UK-TIA Trial	**Colorectal cancer incidence** *Incidence of colorectal cancer measured from the date of randomisation with long term follow up*		2,449	1.5 (37) N = 1632	2.8 (23) N = 817	HR=0.82	0.49 – 1.38	0.41	≥20 years
	Subgroup analysis (Colorectal cancer incidence)								
	Incidence of colorectal cancer measured from the date of randomisation	0-9 years	2,449	1.1 (18) N = 1632	1.0 (8) N = 817	HR=1.14	0.49 – 2.61	0.78	≤9 years
		10-19 years		0.9 (15) N = 1632	1.8 (15) N = 817	HR=0.51	0.25 – 1.00	0.05	10-19 years
	Colorectal cancer mortality *Effect of 300 mg aspirin on long term risk of death due to colorectal cancer*		1628	0.99 (8) N = 811	1.96 (16) N = 817	OR=0.50	0.21 – 1.17	NS	21-27 years
	Colorectal cancer mortality *Effect of 1200 mg aspirin on long term risk of death due to colorectal cancer*		1638	1.34 (11) N = 821	1.96 (16) N = 817	OR=0.68	0.31 – 1.47	NS	
	Adverse events incidence *Adverse events reported during follow-up measured from the date of randomisation to 30/9/1986. For each type of adverse effect patients were only counted once.*		**N**	**1200mg aspirin**	**300mg aspirin**	**Placebo**	**Size of effect**	**CI (95%)**	**p-value**	**Follow up**
	Upper gastrointestinal symptoms (nausea, abdominal pain, vomiting, heartburn)		1,620	-	31 (253) N = 806	26 (209) N = 814	OR=1.32	1.06-1.65	SSD	1-8 years
			1,621	41 (338) N = 815	31 (253) N = 806	-	OR=1.54	1.25-1.89	SSD	
	Constipation		2435	**Combined 1200mg + 300mg** 6 (104) N = 1621		2 (20) N = 814	OR=2.72	1.68-4.40	SSD	1-8 years
	Gastrointestinal haemorrhage		1,620	-	3 (25) N = 806	1 (9) N = 814	OR=2.57	1.20-5.53	SSD	1-8 years
			1,621	5 (39) N = 815	3 (25) N = 806	-	OR=1.62	0.94-2.79	NS	

N = number of participants; mg = milligrams; CI = confidence interval; SSD = statistically significantly different, NS = not statistically significantly different; HR = hazards ratio; OR = odds ratio; UK-TIA = The United Kingdom Transient Ischaemic Attack Trial. [a] *P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.*

Table 18: Results of studies examining effects of Aspirin on colorectal cancer outcomes

Study	Outcome		N actual	Aspirin % (n)	Placebo % (n)	Size of effect	CI (95%)	p-value[a]	Follow up (median)
Flossman 2007 (UK)	**Colorectal cancer incidence** *Pooled analysis of data from the BDAT and the UK-TIA on the effect of randomisation to a period of treatment with aspirin on the incidence of colorectal cancer (all patients)*		7,588	2.5 (129) N = 5061	3.4 (87) N = 2527	HR=0.74	0.56 – 0.97	0.02	23 years
BDAT UK-TIA	**Colorectal cancer incidence** *All patients allocated to aspirin for at least 5 years (i.e. all BDAT and first 937 patients in UK-TIA aspirin trial.*		6,076	2.5 (100) N = 4051	3.8 (77) N = 2025	HR=0.63	0.47 – 0.85	0.002	23 years
	Colorectal cancer incidence *Incidence of colorectal cancer in all patients in the UK-TIA and the BDAT trials stratified into 10-year follow up periods*		7,588	2.5 (129) N = 5061	3.4 (87) N = 2527	HR=0.74	0.56 – 0.97	0.02	23 years
	Subgroup analysis (Colorectal cancer incidence)								
	Incidence of colorectal cancer measured from the date of randomisation	0-9 years	7,588	0.9 (46) N = 5061	0.9 (25) N = 2527	HR=0.92	0.56 – 1.49	0.73	≤9 years
		10-19 years		1.3 (65) N = 5061	2.1 (53) N = 2527	HR=0.60	0.42 – 0.87	0.007	10-19 years

N = number of participants; mg = milligrams; CI = confidence interval; NR = not reported; HR = hazards ratio; ARR = absolute risk reduction; BDAT = British Doctors Aspirin Trial; SALT = Swedish Aspirin Low Dose Trial; TPT = Thrombosis Prevention Trial; UK-TIA = The United Kingdom Transient Ischaemic Attack Trial. [a] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 19: Meta-analysis of colorectal cancer incidence in randomised controlled trials comparing Aspirin to placebo.

Study	Outcome			N actual	Aspirin % (n)	Placebo % (n)	Size of effect	CI (95%)	p-value [a]	Follow up (median)
Rothwell 2010 (UK)	**Colorectal cancer incidence** *Pooled analysis of the effect of low dose (75–300 mg) aspirin on subsequent long-term incidence of colorectal cancer in 4 randomised controlled trials of aspirin vs control: BDAT, SALT, TPT, UK-TIA*			8,073	NR	NR	HR=0.75 ARR=1.21%	0.56 – 0.97 0.19 – 2.22	0.02	18.3 years
BDAT SALT TPT UK-TIA	**Subgroup analysis (incidence of colorectal cancer/duration of treatment)**									
	Scheduled treatment	≥ 2.5 years		7,383	NR	NR	HR=0.69 ARR=1.33%	0.51 – 0.93 0.30 – 2.36	0.003	18.3 years
		≥ 5 years		5,077	NR	NR	HR=0.62 ARR=1.55%	0.43 – 0.94 0.34 – 2.76	0.003	
	Colorectal cancer incidence *Effect of aspirin versus control on long-term risk of colorectal cancer incidence stratified by site of tumour in a pooled analysis of TPT, SALT, UK-TIA and BDAT (75-1200 mg)*			14,033	NR	NR	HR=0.76	0.63-0.94	0.01	18.3 years
	Sites of colorectal cancer	All Colon cancer		14,033	NR	NR	HR=0.76	0.60 – 0.96	0.02	18.3 years
		Site of colon cancer	Proximal colon	14,033	NR	NR	HR=0.45	0.28 – 0.74	0.001	18.3 years
			Distal colon		NR	NR	HR=1.10	0.73 – 1.64	0.66	
			Site unspecified		NR	NR	HR=0.74	0.51 – 1.07	0.11	
		Rectal cancer		14,033	NR	NR	HR=0.90	0.63 – 1.30	0.58	18.3 years

ARR = absolute risk reduction; BDAT = British Doctors Aspirin Trial; CI = confidence interval; HR = hazards ratio; mg = milligrams; N = number of participants; NR = not reported; SALT = Swedish Aspirin Low Dose Trial; TPT = Thrombosis Prevention Trial; UK-TIA = The United Kingdom Transient Ischaemic Attack Trial. [a] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 20: Meta-analysis of colorectal cancer mortality in randomised controlled trials comparing Aspirin to placebo.

Study	Outcome			N actual	Aspirin % (n)	Placebo % (n)	Size of effect	CI (95%)	p-value [a]	Follow up (median)
Rothwell 2010 (UK) BDAT SALT TPT UK-TIA	**Colorectal cancer mortality** *Meta-analysis of the effect of aspirin (75-1200 mg) on long-term risk of death due to colorectal cancer in 4 randomised controlled trials of aspirin vs control: BDAT, SALT, TPT, UK-TIA*			14,033	1.44 (119) N = 8282	2.10 (121) N = 5751	OR = 0.66	0.51 – 0.85	0.002	18.3 years
	Subgroup analysis (Effect of aspirin on long-term risk of mortality due to colorectal cancer in RCTs)									
	Doses of aspirin	500 – 1200 mg daily *(BDAT, UK-TIA)*		6,777	1.65 (70) N = 4250	2.22 (56) N = 2527	OR=0.72	0.50 – 1.03	NS	18.3 years
		75 – 300 mg daily *(UK-TIA, TPT, SALT)*		8,073	1.22 (49) N = 4032	2.00 (81) N = 4041	OR=0.60	0.42 – 0.86	SSD	
	Colorectal cancer mortality *Pooled analysis of the effect of low dose (75–300 mg) aspirin on subsequent long-term mortality due to colorectal cancer in 4 randomised controlled trials of aspirin vs control: BDAT, SALT, TPT, UK-TIA*			8,073	1.22 (49) N = 4032	2.00 (81) N = 4041	HR=0.61 ARR=1.36%	0.43 – 0.87 0.44 – 2.28	0.005	18.3 years
	Scheduled treatment	≥ 2.5 years		7,383	NR	NR	HR=0.54 ARR=1.49%	0.36–0.80 0.55–2.43	0.001	18.3 years
		≥ 5 years		5,077	NR	NR	HR=0.48 ARR=1.76%	0.30–0.77 0.61–2.91	0.001	
	Colorectal cancer mortality *Effect of aspirin versus control on long-term risk of mortality due to colorectal cancer stratified by site of tumour in a pooled analysis of TPT, SALT, UK-TIA and BDAT (75-1200 mg)*			14,033	NR	NR	HR=0.66	0.52-0.86	0.002	18.3 years
	Sites of colorectal cancer	All Colon cancer		14,033	NR	NR	HR=0.65	0.48–0.88	0.005	18.3 years
		Site of colon cancer	Proximal colon	14,033	NR	NR	HR=0.34	0.18–0.66	0.001	18.3 years
			Distal colon		NR	NR	HR=1.21	0.66–2.24	0.54	
			Site unspecified		NR	NR	HR=0.61	0.40–0.94	0.02	
		Rectal cancer		14,033	NR	NR	HR=0.80	0.50–1.28	0.35	18.3 years

N = number of participants; mg = milligrams; CI = confidence interval; NR = not reported; HR = hazards ratio; OR = odds ratio; ARR = absolute risk reduction; BDAT = British Doctors Aspirin Trial; SALT = Swedish Aspirin Low Dose Trial; TPT = Thrombosis Prevention Trial; UK-TIA = The United Kingdom Transient Ischaemic Attack Trial. [a] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 21: Benefits and harms of 10 years of aspirin use on the incidence of major events and on mortality by age and sex.

Study	Outcome		50 years		55 years		60 years		65 years	
			Baseline	Reduction	Baseline	Reduction	Baseline	Reduction	Baseline	Reduction
Cuzick 2015	**Incidence** *Benefits of 10 years of aspirin use on incidence of major events*	Men	16.97	**1.50 (1.22)**	25.11	**2.29 (1.83)**	34.13	**3.10 (2.47)**	42.97	**3.84 (3.09)**
		Women	13.74	**0.95 (0.68)**	18.32	**1.32 (0.97)**	23.83	**1.73 (1.32)**	30.53	**2.24(1.79)**
	Subgroup analysis (incidence of major events)									
	Cancer	Men	9.70	0.92 (0.65)	15.20	1.52 (1.07)	20.75	2.09 (1.45)	25.39	2.51 (1.75)
		Women	10.41	0.72 (0.48)	13.19	1.03 (0.67)	15.78	1.26 (0.85)	18.08	1.48 (1.03)
	Myocardial Infarction	Men	5.13	0.52	6.75	0.68	8.72	0.89	10.92	1.15
		Women	1.62	0.15	2.59	0.23	4.22	0.37	6.69	0.61
	Stroke	Men	2.14	0.06	3.16	0.08	4.66	0.12	6.66	0.18
		Women	1.71	0.05	2.54	0.07	3.84	0.10	5.75	0.15
	Adverse Events *Harms due to major extracranial bleeding after 10 years of aspirin use by age and gender*	Men	1.12	0.320.42	1.58	0.49 (0.64)	2.00	0.66 (0.85)	2.37	0.81 (1.05)
		Women	0.57	0.160.21	0.81	0.25 (0.32)	1.05	0.34 (0.44)	1.30	0.43 (0.55)
	Net Benefit *Reduction in major events verse adverse events*	Men	18.09	**1.18 (0.81)**	26.70	**1.80 (1.19)**	36.13	**2.44 (1.62)**	45.34	**3.03 (2.03)**
		Women	14.31	**0.79 (0.47)**	19.13	**1.07 (0.65)**	24.88	**1.39 (0.88)**	31.83	**1.82 (1.24)**
	Mortality *Benefits of 10 years aspirin use on mortality by age and gender*	Men	12.53	**1.05 (0.86)**	19.64	**1.60 (1.30)**	28.19	**2.24 (1.82)**	35.66	2.72 (2.22)
		Women	7.92	**0.55 (0.40)**	12.24	**0.82 (0.61)**	18.06	**1.16 (0.89)**	24.60	1.53 (1.20)
	Subgroup analysis (mortality due to major events)									
	Cancer	Men	7.45	0.99 (0.80)	11.59	1.48 (1.19)	16.40	2.04 (1.62)	20.53	2.41 (1.91)
		Women	6.12	0.53 (0.39)	8.80	0.78 (0.58)	12.04	1.09 (0.82)	15.26	1.39 (1.06)
	Myocardial Infarction	Men	5.08	0.07	8.05	0.12	11.80	0.20	15.13	0.31
		Women	1.08	0.02	3.44	0.04	6.02	0.08	9.33	0.14
	Adverse events *Harms of 10 years of aspirin use on mortality by age and gender*	Men	1.29	**0.11 (0.12)**	2.31	**0.17 (0.18)**	3.93	**0.28 (0.30)**	5.73	**0.54 (0.58)**
		Women	0.93	**0.09 (0.09)**	1.79	**0.11 (0.12)**	3.42	**0.19 (0.21)**	5.86	**0.41 (0.44)**
	Subgroup analysis (mortality due to adverse events)									
	Stroke	Men	1.03	0.06	1.85	0.09	3.21	0.17	4.83	0.32
		Women	0.74	0.04	1.47	0.06	2.90	0.11	5.12	0.26
	GI bleeding	Men	0.19	0.04 (0.04)	0.34	0.05 (0.06)	0.57	0.08 (0.09)	0.74	0.17 (0.19)
		Women	0.12	0.02 (0.03)	0.22	0.03 (0.04)	0.39	0.05 (0.06)	0.59	0.11 (0.13)
	Peptic ulcer	Men	0.08	0.02 (0.02)	0.12	0.03 (0.03)	0.15	0.03 (0.04)	0.17	0.05 (0.06)
		Women	0.07	0.02 (0.02)	0.10	0.02 (0.02)	0.13	0.03 0.03)	0.16	0.04 (0.05)
	All-cause mortality	Men	18.02	0.94 (0.74)	0.27	**1.43 (1.12)**	41.99	**1.96 (1.52)**	58.74	**2.18 (1.64)**
		Women	11.82	0.47 (0.31)	18.55	**0.70 (0.49)**	29.86	**0.97 (0.69)**	47.45	**1.12 (0.76)**

Baseline probabilities of an event and aspirin-related reductions (per 100 individuals in 15 years) using best (and conservative) estimates for prophylactic use of aspirin for 10 years on the incidence of major events namely cancer, myocardial infarction, stroke and major bleeding according to sex and age at starting use. All estimates are adjusted for inter-current mortality. Baseline '20-year' event-specific mortality probabilities and aspirin-related reductions (per 100 individuals) using best (and conservative) estimates for prophylactic use of aspirin for 10 years on mortality due to cancer, myocardial infarction, stroke and aspirin-related adverse events (peptic ulcer and gastrointestinal bleeding) according to sex and age at starting use. Effects on cardiovascular and bleeding events are assumed to occur only during active treatment (10 years) and those for cancer do not start until

after 3-5 years of use but persist for an additional 5 years after treatment completion. Baseline rates are for the entire 15-20 year period. Figures in parentheses are conservative estimates. The figures in bold represent overall benefits, overall harms and net balance of benefit and harm.

Table 22: Results of studies examining effects of Aspirin on colorectal cancer outcomes in high risk populations

Study	Outcome			N actual	Aspirin % (n)	Placebo % (n)	Size of effect	CI (95%)	p-value[a]	Follow up (median)
Cole 2009 (UK) AFPPS CALGB ukCAP APACC	**Adenoma incidence** *Random-effect risk ratio of adenoma incidence comparing any aspirin dose verse placebo in pooled analysis of AFPPS, CALGB, ukCAP, APACC trials*			2698	32.9 (507) N=1542	36.7 (424) N=1156	RR=0.83	0.72-0.96	**0.012**	35.1 months
	Adenoma incidence *Random-effect risk ratio of adenoma incidence comparing lower-dose aspirin (81 or 160 mg/day) verse placebo in pooled analysis of AFPPS and APACC trials*			913	39.6 (172) N=434	48.6 (233) N=479	RR=0.83	0.71-0.96	**0.012**	24.2 months
	Adenoma incidence *Random-effect risk ratio of adenoma incidence comparing higher dose aspirin (300 or 325 mg/day) verse placebo in pooled analysis of AFPPS, CALGB, ukCAP, APACC trials*			2264	30.2 (335) N=1108	36.7 N=1156	RR=0.85	0.70-1.03	0.099	29.5 months
	Subgroup analysis (Effect of aspirin on risk of adenoma in high risk populations in RCTs)									
	RCT trials	AFPPS	any aspirin dose vs placebo	1084	41.6 (300) N=721	47.1 (171) N=363	RR=0.88	0.77-1.02	NS	32.2 months
			81 mg/day aspirin vs placebo	729	38.3 (140) N=366	47.1 (171) N=363	RR=0.81	**0.69-0.96**	SSD	
			325 mg/day aspirin vs placebo	718	45.1 (160) N=355	47.1 (171) N=363	RR=0.96	0.82-1.12	NS	
		CALGB	325 mg/day aspirin vs placebo	517	16.6 (43) N=259	27.1 (70) N=258	RR=0.61	**0.44-0.86**	SSD	31.3 months
		ukCAP	300 mg/day aspirin vs placebo	853	22.8 (99) N=434	28.9 (121) N=419	RR=0.79	**0.63-0.99**	SSD	37.5 months
		APACC	any aspirin dose vs placebo	244	50.8 (65) N=128	53.4 (62) N=116	RR=0.95	0.75-1.21	NS	47.2 months
			160 mg/day aspirin vs placebo	184	47.1 (32) N=68	53.4 (62) N=116	RR=0.88	0.65-1.19	NS	
			300 mg/day aspirin vs placebo	176	55.0 (33) N=60	53.4 (62) N=116	RR=1.03	0.77-1.37	NS	
	Age		≤54 years	990	28.9 (166) N=574	32.5 (135) N=416	RR=0.84	0.66-1.06	NS	35.1 months
			55-63 years	846	35.0 (175) N=500	34.7 (120) N=346	RR=0.98	0.67-1.42	NS	
			≥64 years	862	35.5 (166) N=468	42.9 (169) N=394	RR=0.73	0.54-1.00	NS	
	Gender		Male	1609	37.2 (348) N=935	41.8 (282) N=674	RR=0.84	**0.73-0.98**	SSD	
			Female	1089	26.2 (159) N=607	29.5 (142) N=482	RR=0.82	**0.68-0.99**	SSD	
	Body Mass Index (kg/m^2)		<25.0	791	29.2 (129)	33.8 (118)	RR=0.78	0.51-1.18	NS	

			N=442	N=349			
	25.0 to 29.9	1070	36.3 (228) N=628	39.6 (175) N=442	RR=0.86	0.74-1.00	NS
	≥30.0	522	37.1 (111) N=299	39.5 (88) N=223	RR=0.84	0.68-1.04	NS
Family history of colorectal cancer	Yes	591	40.4 (148) N=366	45.3 (102) N=225	RR=0.86	0.71-1.04	NS
	No	1124	35.7 (230) N=644	37.3 (179) N=480	RR=0.89	0.76-1.03	NS
No. of lifetime adenomas at baseline	1	1170	29.1 (199) N=685	30.5 (148) N=485	RR=0.91	0.75-1.09	NS
	≥2	1007	44.3 (264) N=596	49.9 (205) N=411	RR=0.86	**0.76-0.98**	SSD
Advanced lesion at baseline	Yes	1062	34.2 (203) N=594	35.5 (166) N=468	RR=0.91	0.74-1.12	NS
	No	952	39.5 (234) N=593	44.3 (159) N=359	RR=0.86	0.72-1.03	NS

AS = Aspirin; PI = Placebo; N = number of participants; CI = confidence interval; RR = Relative risk ratio; NR = not reported; NS= not statistically significantly different; SSD = statistically significantly different; AFPPS = Aspirin/Folate Polyp Prevention Study; CALGB = Colorectal Adenoma Prevention Study [Cancer and Leukemia Group B]; ukCAP = United Kingdom Colorectal Adenoma Prevention Study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal [a] *P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.*

Table 23: Results of studies examining effects of Aspirin on colorectal cancer outcomes in high risk populations

Study	Outcome			N actual	Aspirin % (n)	Placebo % (n)	Size of effect	CI (95%)	p-value[a]	Follow up
Cole 2009 (UK) AFPPS CALGB ukCAP APACC	**Adenoma incidence** *Random-effect risk ratio of adenoma incidence for any aspirin dose verse placebo in pooled analysis of CALGB, ukCAP, APACC trials 0-12 months after randomisation*			463	23.2 (51) N=220	37.4 (91) N=243	RR=0.62	**0.48-0.81**	SSD	0-12 months
	Adenoma incidence *Random-effect risk ratio of adenoma incidence for any aspirin dose verse placebo in pooled analysis of AFPPS, CALGB, ukCAP, APACC 12-24 months after randomisation*			411	25.6 (56) N=219	27.6 (53) N=192	RR=0.86	0.55-1.33	NS	12-24 months
	Adenoma incidence *Random-effect risk ratio of adenoma incidence for any aspirin dose verse placebo in pooled analysis of AFPPS, CALGB, ukCAP, APACC trials 24-38 months after randomisation*			1659	32.3 (327) N=1012	34.8 (225) N=647	RR=0.84	**0.74-0.96**	SSD	24-38 months
	Adenoma incidence *Random-effect risk ratio of adenoma incidence for any aspirin dose verse placebo in pooled analysis of AFPPS, CALGB, ukCAP, APACC trials ≥38 months after randomisation*			700	27.9 (100) N=359	26.4 (90) N=341	RR=0.99	0.78-1.26	NS	≥38 months
	Subgroup analysis (Effect of aspirin on risk of adenoma in high risk populations in RCTs)									
	Time interval after randomisation	0-12 months[b]	CALGB	252	12.8 (15) N=117	23.0 (31) N=135	RR=0.56	**0.32-0.98**	SSD	0-12 months
			ukCAP	78	47.2 (17) N=36	71.4 (30) N=42	RR=0.66	**0.45-0.98**	SSD	
			APACC	133	28.4 (19) N=67	45.5 (30) N=66	RR=0.62	**0.39-0.99**	SSD	
		12-24 months	AFPPS	51	41.7 (15) N=36	20.0 (3) N=15	RR=2.08	0.71-6.16	NS	12-24 months
			CALGB	185	13.3 (12) N=90	16.8 (16) N=95	RR=0.79	0.40-1.58	NS	
			ukCAP	68	25.7 (9) N=35	48.5 (16) N=33	RR=0.53	0.27-1.03	NS	
			APACC	107	34.5 (20) N=58	36.7 (18) N=49	RR=0.94	0.56-1.56	NS	
		24-38 months[c]	AFPPS	1007	40.5 (271) N=669	46.7 (158) N=338	RR=0.87	0.75-1.00	NS	24-38 months
			CALGB	309	11.8 (18) N=152	17.8 (28) N=157	RR=0.66	0.38-1.15	NS	
			ukCAP	343	19.9 (38) N=191	25.7 (39) N=152	RR=0.78	0.52-1.15	NS	
		≥ 38 months	AFPPS	65	47.6 (20) N=42	47.8 (11) N=23	RR=1.00	0.59-1.69	NS	≥38 months
			CALGB	60	15.6 (5) N=32	17.9 (5) N=28	RR=0.88	0.28-2.71	NS	
			ukCAP	400	19.9 (38) N=191	20.6 (43) N=209	RR=0.97	0.65-1.43	NS	
			APACC	175	39.4 (37) N=94	38.3 (31) N=81	RR=1.03	0.71-1.49	NS	

AS = Aspirin; PI = Placebo; N = number of participants; CI = confidence interval; RR = Relative risk ratio; NR = not reported; NS= not statistically significantly different; SSD = statistically significantly different; AFPPS = Aspirin/Folate Polyp Prevention Study; CALGB = Colorectal Adenoma Prevention Study [Cancer and Leukemia Group B]; ukCAP = United Kingdom Colorectal

Adenoma Prevention Study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal [a] *P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.* [b]*The AFPPS trial had no examinations during the 0- to 12-month interval;* [c]*The APACC trial had only two examinations during the 24- to 38- month interval.*

Table 24: Results of studies examining effects of Aspirin on colorectal cancer outcomes in high risk populations

Study	Outcome			N actual	Aspirin % (n)	Placebo % (n)	Size of effect	CI (95%)	p-value[a]	Follow up (median)
Cole 2009 (UK) AFPPS CALGB ukCAP APACC	**Advanced lesion incidence** *Random-effect risk ratio of advanced lesion incidence comparing any aspirin dose verse placebo in pooled analysis of AFPPS, CALGB, ukCAP, APACC trials*			2698	8.7 (134) N=1542	11.9 (137) N=1156	RR=0.72	0.57-0.90	**0.0046**	35.1 months
	Advanced lesion incidence *Random-effect risk ratio of advanced lesion incidence comparing lower-dose aspirin (81 or 160 mg/day) verse placebo in pooled analysis of AFPPS and APACC trials*			913	9.7 (42) N=434	13.6 (65) N=479	RR=0.83	0.44-1.58	0.57	24.2 months
	Advanced lesion incidence *Random-effect risk ratio of advanced lesion incidence comparing higher dose aspirin (300 or 325 mg/day) verse placebo in pooled analysis of AFPPS, CALGB, ukCAP, APACC trials*			2264	8.3 (92) N=1108	11.9 (137) N=1156	RR=0.71	0.56-0.92	**0.0089**	29.5 months
	Subgroup analysis (Effect of aspirin on risk of advanced lesion in high risk populations in RCTs)									
	RCT trials	AFPPS	any aspirin dose vs placebo	1084	9.2 (66) N=721	12.4 (45) N=363	RR=0.74	0.52-1.06	NS	32.2 months
			81 mg/day aspirin vs placebo	729	7.7 (28) N=366	12.4 (45) N=363	RR=0.62	**0.39-0.97**	SSD	
			325 mg/day aspirin vs placebo	718	10.7 (38) N=355	12.4 (45) N=363	RR=0.86	0.58-1.30	NS	
		CALGB	(325 mg/day aspirin)	517	2.7 (7) N=259	3.5 (9) N=258	RR=0.77	0.29-2.05	NS	31.3 months
		ukCAP	(300 mg/day aspirin)	853	9.4 (41) N=434	15.0 (63) N=419	RR=0.63	**0.43-0.91**	SSD	37.5 months
		APACC	any aspirin dose vs placebo	244	15.6 (20) N=128	17.2 (20) N=116	RR=0.91	0.51-1.60	NS	47.2 months
			(160 mg/day aspirin)	184	20.6 (14) N=68	17.2 (20) N=116	RR=1.19	0.65-2.21	NS	
			(300 mg/day aspirin)	176	10.0 (6) N=60	17.2 (20) N=116	RR=0.58	0.25-1.37	NS	
	Age		≤54 years	990	6.6 (38) N=574	10.3 (43) N=416	RR=0.58	**0.38-0.89**	SSD	35.1 months
			55-63 years	846	9.2 (46) N=500	10.4 (36) N=346	RR=0.84	0.55-1.27	NS	
			≥64 years	862	10.7 (50) N=468	14.7 (58) N=394	RR=0.74	0.51-1.07	NS	
	Gender		Male	1609	10.5 (98) N=935	13.4 (90) N=674	RR=0.78	0.56-1.08	NS	
			Female	1089	5.9 (36) N=607	9.8 (47) N=482	RR=0.62	0.41-0.95	NS	
	Body Mass Index (kg/m^2)		<25.0	791	7.9 (35)	10.6 (37)	RR=0.83	0.53-1.31	NS	

			N=442	N=349			
	25.0 to 29.9	1070	9.7 (61) N=628	13.3 (59) N=442	RR=0.71	0.44-1.14	NS
	≥30.0	522	8.0 (24) N=299	9.4 (21) N=223	RR=0.69	0.39-1.22	NS
Family history of colorectal cancer	Yes	591	8.2 (30) N=366	16.4 (37) N=225	RR=0.53	**0.33-0.83**	SSD
	No	1124	11.3 (73) N=644	12.7 (61) N=480	RR=0.92	0.67-1.28	NS
No. of lifetime adenomas at baseline	1	1170	7.6 (52) N=685	12.6 (61) N=485	RR=0.62	**0.43-0.88**	SSD
	≥2	1007	12.6 (75) N=596	16.3 (67) N=411	RR=0.81	0.60-1.11	NS
Advanced lesion at baseline	Yes	1062	12.3 (73) N=594	16.7 (78) N=468	RR=0.72	**0.54-0.98**	SSD
	No	952	7.9 (47) N=593	11.4 (41) N=359	RR=0.71	0.48-1.07	NS
Time interval after randomisation	0-12 months	-	-	-	Pooled RR=0.47	**0.24-0.90**	SSD
	12-24 months	-	-	-	Pooled RR=0.91	0.42-2.00	NS
	23-38 months	-	-	-	Pooled RR=0.72	0.52-1.00	NS
	≥38 months	-	-	-	Pooled RR=0.71	0.37-1.35	NS

AS = Aspirin; PI = Placebo; N = number of participants; CI = confidence interval; RR = Relative risk ratio; NR = not reported; NS= not statistically significantly different; SSD = statistically significantly different; RCT = randomized controlled trial; AFPPS = Aspirin/Folate Polyp Prevention Study; CALGB = Colorectal Adenoma Prevention Study [Cancer and Leukemia Group B]; ukCAP = United Kingdom Colorectal Adenoma Prevention Study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal [a] *P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant. Subgroup p-value significance was based on confidence interval ranges.*

Table 25: Results of studies examining effects of Aspirin on colorectal cancer outcomes in high risk populations

Study	Outcome		N actual	Aspirin % (n)	Placebo % (n)	Size of effect	CI (95%)	p-value[a]	Follow up
Cole 2009 (UK) AFPPS CALGB ukCAP APACC	**Adverse events** *Number of participants (%) comparing any aspirin dose verse placebo in combined AFPPS, CALGB, ukCAP, APACC trials*	Death	2967	0.95 (16) N=1678	0.85 (11) N=1289	NR	NR	0.85	NR
		Myocardial infarction	2967	0.48 (8) N=1678	0.31 (4) N=1289	NR	NR	0.57	
		Stroke	2967	0.00 (0) N=1678	0.66 (12) N=1289	NR	NR	**0.002**	
		Major bleeding	2967	2.79 (36) N=1678	2.5 (42) N=1289	NR	NR	0.64	
		Invasive cancer	2967	2.62 (44) N=1678	1.86 (24) N=1289	NR	NR	0.18	
		Colorectal cancer	2967	0.54 (9) N=1678	0.62 (8) N=1289	NR	NR	0.81	
		Any event above	2967	6.20 (104) N=1678	5.51 (71) N=1289	NR	NR	0.48	

AS = Aspirin; PI = Placebo; N = number of participants; CI = confidence interval; NR = not reported; AFPPS = Aspirin/Folate Polyp Prevention Study; CALGB = Colorectal Adenoma Prevention Study [Cancer and Leukemia Group B]; ukCAP = United Kingdom Colorectal Adenoma Prevention Study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal [a] P-values (two-sided) are from Fisher's exact test comparing placebo vs aspirin in any dose.

2.6 Body of Evidence

Effects of interventions on relevant outcomes are described in Tables 26-40.

I Incidence of colorectal cancer

Table 26. Body of evidence examining the effect of aspirin on colorectal cancer incidence

Name of study	Study type	Level of evidence [a]	Risk of bias	N	Results summary %	Size of effect rating[a]	p value[b]	CI (95%)	Relevance of evidence[a]
Aspirin vs Placebo (600 mg aspirin or placebo + 30 g resistant starch or placebo starch after mean follow up period of 29 months)									
Burn 2008 **Burn 2011** CAPP2 Trial **Mean age**:46 years (25-79) **Gender (%):** F/M = 55/45 **Follow up mean** (range): 29.0 months (7-74) **Mean duration of receipt of study drug** (range): 26.5 months (1-67)	RCT (multi-centre)	II	Low	 693 693 693 693 693	**Neoplasm incidence:** AS: 18.9 Pl: 19.0 **<u>Subgroup analysis:</u>** **Neoplasm type (incidence):** Adenoma only: AS:16 Pl:16.0 CRC only: AS:1.4 PI:2.0 Adenoma and CRC AS:1.4 PI:0.9 Advanced neoplasms AS:7.4 PI:9.9	 RR=1.0 NR NR NR NR	 NS 0.96 0.54 0.45 0.33	 0.71-1.4 NR NR NR NR	 1 1 1 1 1
Aspirin vs Placebo (600 mg aspirin or placebo only after mean follow up period of 29 months)									
Burn 2008 **Burn 2011** CAPP2 Trial **Mean age**:46 years (25-79) **Gender (%):** F/M = 55/45 **Follow up mean** (range): 29.0 months (7-74) **Mean duration of receipt of study drug** (range): 26.5 months (1-67)	RCT (multi-centre)	II	Low	 19 19 19 19 19	**Neoplasm incidence:** AS: 44.4 Pl: 20.0 **<u>Subgroup analysis:</u>** **Neoplasm type (incidence):** Adenoma only: AS:33.3 Pl: 20 CRC only: AS:11.1 PI:0 Adenoma and CRC AS:0 PI:0 Advanced neoplasms AS:11.1 PI:10	 NR NR NR NR NR	 NR NR NR NR NR	 NR NR NR NR NR	 1 1 1 1 1

Neoplasm incidence from all colonoscopies within 4 time groups after mean follow up period of 29 months									
Burn 2008 **Burn 2011** CAPP2 Trial **Mean age**:46 years (25-79) **Gender (%):** F/M = 55/45 **Follow up mean** (range): 29.0 months (7-74) **Mean duration of receipt of study drug** (range): 26.5 months (1-67)	RCT (multi-centre)	II	Low	1,094 300 546 130 118	**Neoplasm incidence:** AS: 13.3 Pl: 12.7 **<u>Subgroup analysis:</u>** **Time on study** 6-18 mths AS: 8.2 PI:13.6 19-30 mths AS:15.8 PI:13.8 31-42 mths AS:11.7 PI:10.0 <u>≥</u> 43 mths AS:16.3 PI: 8.7	NR RR=0.6 RR=1.1 RR=1.2 RR=1.9	NR NS NS NS NS	NR 0.3–1.2 0.8–1.7 0.4–3.1 0.7–5.1	1 1 1 1 1
Incidence of colorectal cancer measured from the date of randomisation with long term follow up (66.1 mths)									
Burn 2008 **Burn 2011** CAPP2 Trial **Mean age** (range): 46 years (25-79) **Gender (%):** F/M = 55.0/45.0 **Follow up mean** (range): 29.0 months (7-74) **Mean duration of receipt of study drug** (range): 26.5 months (1-67)	RCT (multi-centre)	II	Low	671 NR NR NR	**CRC incidence:** AS: 3.8 Pl: 8.2 **<u>Subgroup analysis:</u>** **Effect of time** <u>≥</u>2 yrs AS vs ≥2 yrs Pl AS:NR PI:NR <2 yrs AS vs ≥2 yrs Pl AS:NR PI:NR <2 yrs Pl vs ≥2 yrs Pl AS:NR PI:NR	HR=0.63 HR=0.41 HR=1.07 HR=0.62	0.12 0.02 0.87 0.30	0.35–1.13 0.19–0.86 0.47–2.41 0.25–1.52	1 1 1 1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; F = female; M = male; CI = confidence interval; NR = not reported; SD = standard deviation; SSD = statistically significantly different, NS = not statistically significantly different; RR = relative risk ratio; HR = hazards ratio; RCT = randomized controlled trial; mths = months; CAPP2 = Colorectal Adenoma/Carcinoma Prevention Programme 2. [a] Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 27. Body of evidence examining the effect of aspirin on colorectal cancer incidence

Name of study	Study type	Level of evidence[a]	Risk of bias	N	Results summary %	Size of effect rating[a]	p value[b]	CI (95%)	Relevance of evidence[a]
100 mg aspirin vs placebo and 600 IU Vitamin E vs placebo on alternate days									
Cook 2005 **Cook 2013** **van Kruijsdijk 2015** WHS Trial **Gender:** all females **Mean Age** (SD): 54.6 (7.0) **Mean BMI** (SD): 26.0 (5.1) **Smoking status** (n/%)**:** Current: 5235/13.1% Past: 14,265/35.8% Never: 20,340/51.1% **Alcohol use (**drks/wk): <1: 23,226/58.3% ≥1: 16,640/41.7% **Physical activity** (Kcal/wk)**:** <1000: 25,994/66.0% ≥1000: 13,383/34.0% **Mean follow up:** 10.1 years	RCT	II	Low	39,876	**CRC incidence (mean FU 10.1 yrs):** AS: 0.67 PI: 0.69	RR=0.97	0.83	0.77–1.24	1
					Subgroup analysis: **CRC incidence after FU of 10.1 yrs:**				
				39,876	Colon AS:0.52 PI: 0.56	RR=0.92	0.57	0.71–1.21	1
				39,876	Rectal AS: 0.15 PI: 0.13	RR=1.20	0.50	0.70–2.04	1
				39,876	**CRC incidence after FU of 16 yrs:** AS: 1.0 PI: 1.2	HR=0.80	0.021	0.67–0.97	1
					Subgroup analysis: **Sites of CRC after 18 yrs follow up:**				
				39,876	Colon: AS: 0.8 PI: 1.0	HR=0.79	0.026	0.64–0.97	1
				39,876	Proximal cancers: AS: 0.4 PI: 0.6	HR=0.73	0.022	0.55–0.95	1
				39,876	Distal cancers: AS: 0.3 PI: 0.3	HR=0.87	0.45	0.62–1.24	1
				39,876	Rectal: AS: 0.2 PI: 0.3	HR=0.86	0.46	0.58–1.28	1
					Stages of CRC after 18 yrs follow up:				
				39,876	Dukes stage C/D AS: 0.4 PI 0.5	HR=0.80	0.126	0.60–1.07	1
				39,876	Dukes stage A/B AS: 0.6 PI: 0.7	HR=0.82	0.10	0.64–1.04	1
					CRC Risk of total population:		**NNT**		
				27,939	Absolute risk (10yr) AS:0.60% Pl:0.61%	ARR=0.01%	>1000	0.00%-32.05%	1
				27,939	Absolute risk (15yr) AS:0.86% Pl:1.01%	ARR=0.14%	709	0.02%-0.59%	1
					Subgroup analysis: **CRC Risk of women <65 years:**				
				24,971	Absolute risk (10yr) AS:0.47% Pl:0.51%	ARR=0.05%	NNT= >1000	0.00% to 0.96%	1
				24,971	Absolute risk (15yr) AS:0.71% Pl:0.88%	ARR=0.17%	NNT= 581	0.04% to 0.55%	1
					CRC Risk of women ≥65 years:				
				2,968	Absolute risk (10yr) AS:1.71% Pl:1.43%	ARR= -0.27%	NNH=369	-1.17% to 0.63%	1
				2,968	Absolute risk (15yr) AS:2.17% Pl:2.06%	ARR= -0.11%	NNH=924	-1.15% to 0.93%	1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; F = female; M = male; CI = confidence interval; NR = not reported; SD = standard deviation; NNT = number needed to treat; NNH = number needed to harm; SSD = statistically significantly different, NS = not statistically significantly different; RR = relative risk ratio; HR =

hazards ratio; ARR = absolute risk reduction; RCT = randomized controlled trial; FU = follow up; Kcal = kilocalorie; yrs = years; wk = week; WHS = Women's Health Study. [a] *Refer to appendix B for detailed explanations of rating scores;* [b] *P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.*

Table 28. Body of evidence examining the effect of aspirin on colorectal cancer incidence

Name of study	Study type	Level of evidence [a]	Risk of bias	N	Results summary %	Size of effect rating[a]	p value[b]	CI (95%)	Relevance of evidence[a]
Incidence of colorectal cancer measured from the date of randomisation with long term follow up									
Peto 1988 **Flossman 2007** BDAT Trial **Gender:** All male **Mean Age** (SD): 61.7 years (7.0) **Smoking status** (n/%): Never: 1254/24.4 Past: 2288/44.6 Current (<20/day):347/6.8 Current (≥20/day):314/6.1 Other/mixed: 932/18.1 **Mean trial duration** (range): 5.7 years (5–6) **Median follow up:** 23 yrs	RCT	II	At risk	5,139 5,139 5,139	**CRC incidence after mean follow up period of ≥ 20 yrs:** AS: 2.68 C: 3.74 **Subgroup analysis:** **Incidence of CRC measured from the date of randomisation:** 0 - 9 yrs AS: 0.81 C: 0.99 10 – 19 yrs AS: 1.46 C: 2.22	HR=0.70 HR=0.82 HR=0.64	0.04 0.52 0.05	0.51–0.97 0.45–1.49 0.42–0.97	1 1 1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; F = female; M = male; CI = confidence interval; NR = not reported; SD = standard deviation; HR = hazards ratio; RCT = randomized controlled trial; yrs = years; BDAT = British Doctors Aspirin Trial. [a] Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 29. Body of evidence examining the effect of aspirin on colorectal cancer incidence

Name of study	Study type	Level of evidence [a]	Risk of bias	N	Results summary %	Size of effect rating[a]	p value[b]	CI (95%)	Relevance of evidence[a]
Incidence of colorectal cancer measured from the date of randomisation with long term follow up									
UK-TIA study group 1988 **Farrell 1991** **Flossman 2007** UK-TIA Trial **Mean Age**(SD): 59.8 yrs (9.0) **Gender (%):** F:27 / M:73 **Obesity index (kg/m^2)**(mean/SD): 1200 mg aspirin: 25.3/3.39 300 mg aspirin: 25.5/3.82 Control: 25.1/3.43 **Regular Smokers (n/%):** 1200 mg aspirin: 444/54 300 mg aspirin: 431/53 Control: 417/51 **Trial duration** (mean/range) 4.4 yrs/1.0 – 7.1 yrs **Follow up** (range) 21 - 27 yrs	RCT (multi-centre)	II	Low	2,449 2,449 2,449	**CRC incidence after mean follow up period of <u>></u> 20 yrs:** AS: 2.68 C: 3.74 **<u>Subgroup analysis:</u>** **Incidence of CRC measured from the date of randomisation:** 0 - 9 yrs AS: 1.1 PI: 1.0 10 – 19 yrs AS: 0.9 PI: 1.8	HR=0.82 HR=1.14 HR=0.51	0.41 0.78 0.05	0.49-1.38 0.49-2.61 0.25-1.00	1 1 1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; F = female; M = male; CI = confidence interval; SD = standard deviation; HR = hazards ratio; RCT = randomized controlled trial; yrs = years; UK-TIA = The United Kingdom Transient Ischaemic Attack Trial. [a] Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 30. Body of evidence examining the effect of aspirin on colorectal cancer incidence

Name of study	Study type	Level of evidence [a]	Risk of bias	N	Results summary %	Size of effect rating[a]	p value[b]	CI (95%)	Relevance of evidence[a]
Effect of randomisation to a period of treatment with aspirin on the incidence of colorectal cancer during a median of 23 years of follow up Pooled analysis of data from 2 RCT's [BDAT and UK-TIA]									
Flossmann 2007 (UK) BDAT Trial and UK-TIA Trial	Meta-analysis of 2 RCTs	I	High	7,588	**Incidence of CRC during a median of 23 years of follow up** AS: 2.5 PI: 3.4	HR=0.74	0.02	0.56–0.97	1
					<u>Subgroup analysis:</u> **Incidence of CRC stratified into treatment periods**				
				6,076	≥ 5 years AS: 2.5 PI: 3.8	HR=0.63	0.002	0.47–0.85	1
				7,588	0-9 years AS: 0.9 PI: 0.9	HR=0.92	0.73	0.56–1.49	1
				7,588	10-19 years AS: 1.3 PI: 2.1	HR=0.60	0.007	0.42–0.87	1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; F = female; M = male; CI = confidence interval; NR = not reported; SD = standard deviation; SSD = statistically significantly different, NS = not statistically significantly different; RR = relative risk ratio; HR = hazards ratio; RCT = randomized controlled trial; BDAT = British Doctors Aspirin Trial; UK-TIA = The United Kingdom Transient Ischaemic Attack Trial. [a] Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 31. Body of evidence examining the effect of aspirin on colorectal cancer incidence

Name of study	Study type	Level of evidence [a]	Risk of bias	N	Results summary %	Size of effect rating[a]	p-value[b]	CI (95%)	Relevance of evidence[a]
Meta-analysis of colorectal cancer incidence in RCTs comparing Aspirin to placebo after a median follow up period of 18.3 yrs (Pooled data of 4 RCT's [BDAT, SALT, TPT, UK-TIA])									
Rothwell 2010 (UK) BDAT SALT TPT UK-TIA	Meta-analysis of 4 RCTs	I	Moderate		**Effect of low dose Aspirin (75 – 300 mg) vs control on incidence of colorectal cancer** **Subgroup analysis:** **Scheduled treatment**				
				8,073	All patients: AS: NR PI: NR	HR=0.75	0.02	0.56-0.97	1
				7,383	≥ 2.5 yrs: AS: NR PI: NR	HR=0.69	0.003	0.51-0.93	1
				5,077	≥ 5 yrs: AS: NR PI: NR	HR=0.62	0.003	0.43-0.94	1
					Effect of low dose Aspirin (75 – 1200 mg) vs control on incidence of colorectal cancer **Subgroup analysis:** **Sites of CRC**				
				14,033	All Colon cancer: AS: NR PI: NR	HR=0.76	0.02	0.60-0.96	1
				14,033	Proximal cancer: AS: NR PI: NR	HR=0.45	0.001	0.28-0.74	1
				14,033	Distal cancer: AS: NR PI: NR	HR=1.10	0.66	0.73-1.64	1
				14,033	Site unspecified AS: NR PI: NR	HR=0.74	0.11	0.51-1.07	1
				14,033	Rectal cancer: AS: NR PI: NR	HR=0.90	0.58	0.63-1.30	1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; mg = milligrams; F = female; M = male; CI = confidence interval; NR = not reported; HR = hazards ratio; RCT = randomized controlled trial; yrs = years; CAPP2 = Colorectal Adenoma/Carcinoma Prevention Programme 2; WHS = Women's Health Study; BDAT = British Doctors Aspirin Trial; UK-TIA = The United Kingdom Transient Ischaemic Attack Trial; TPT = Thrombosis Prevention Trial; SALT = Swedish Aspirin Low Dose Trial. [a] Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 32. Body of evidence examining the effect of aspirin on colorectal cancer incidence

Name of study	Study type	Level of evidence [a]	Risk of bias	N	Results summary %	Size of effect rating[a]	p value [b]	CI (95%)	Relevance of evidence[a]
Any adenoma: Aspirin vs Placebo									
Cole 2009 (UK) AFPPS CALGB ukCAP APACC	Meta-analysis of 4 RCTs	I	Low		**Incidence of adenoma stratified into Aspirin dose** Any aspirin dose (AFPPS, CALGB, ukCAP, APACC)				
				2698	AS: 32.9 Pl: 36.7	RR=0.83	**0.012**	0.72-0.96	1
					81 or 160 mg/day (AFPPS and APACC)				
				913	AS: 39.6 Pl: 48.6	RR=0.83	**0.012**	0.71-0.96	1
					300 or 325 mg/day (AFPPS, CALGB, ukCAP, APACC)				
				2264	AS: 30.2 Pl: 36.7	RR=0.85	0.099	0.70-1.03	1
					Effect of aspirin on risk of adenoma **Subgroup analysis:** **Incidence of adenoma stratified by RCT trial**				
				1084	AFPPS: Any aspirin dose AS: 41.6 Pl: 47.1	RR=0.88	NS	0.77-1.02	1
				729	AFPPS: 81 mg/day AS: 38.3 Pl: 47.1	RR=0.81	SSD	**0.69-0.96**	1
				718	AFPPS: 325 mg/day AS: 45.1 Pl: 47.1	RR=0.96	NS	0.82-1.12	1
				517	CALGB: 325 mg/day AS: 16.6 Pl: 27.1	RR=0.61	SSD	**0.44-0.86**	1
				853	ukCAP: 300 mg/day AS: 22.8 Pl: 28.9	RR=0.79	SSD	**0.63-0.99**	1
				244	APACC: Any aspirin dose AS: 50.8 Pl: 53.4	RR=0.95	NS	0.75-1.21	1
				184	APACC: 81 mg/day AS: 47.1 Pl: 53.4	RR=0.88	NS	0.65-1.19	1
				176	APACC: 300 mg/day AS: 55.0 Pl: 53.4	RR=1.03	NS	0.77-1.37	1
					Incidence of adenoma stratified by age				
				990	≤54 years AS: 28.9 Pl: 32.5	RR=0.84	NS	0.66-1.06	1
				846	55-63 years AS: 35.0 Pl: 34.7	RR=0.98	NS	0.67-1.42	1
				862	≥64 years AS: 35.5 Pl: 42.9	RR=0.73	NS	0.54-1.00	1
					Incidence of adenoma stratified by gender				
				1609	Male: AS: 37.2 Pl: 41.8	RR=0.84	SSD	**0.73-0.98**	1
				1089	Female: AS: 26.2 Pl: 29.5	RR=0.82	SSD	**0.68-0.99**	1
					Incidence of adenoma stratified by BMI (kg/m^2)				
				791	<25.0 AS: 29.2 Pl: 33.8	RR=0.78	NS	0.51-1.18	1
				1070	25.0 to 29.9 AS: 36.3 Pl: 39.6	RR=0.86	NS	0.74-1.00	1
				522	≥30.0 AS: 37.1 Pl: 39.5	RR=0.84	NS	0.68-1.04	1

					Incidence of adenoma stratified by family history of CRC				
				591	Yes AS: 40.4 Pl: 45.3	RR=0.86	NS	0.71-1.04	1
				1124	No AS: 35.7 Pl: 37.3	RR=0.89	NS	0.76-1.03	1
					Incidence of adenoma by no. of lifetime adenomas at baseline				
				1170	1 AS: 29.1 Pl: 30.5	RR=0.91	NS	0.75-1.09	1
				1007	≥2 AS: 44.3 Pl: 49.9	RR=0.86	SSD	**0.76-0.98**	1
					Incidence of adenoma stratified by advanced lesion at baseline				
				1062	Yes AS: 34.2 Pl: 35.5	RR=0.91	NS	0.74-1.12	1
				952	No AS: 39.5 Pl: 44.3	RR=0.86	NS	0.72-1.03	1
					Incidence of adenoma by time interval after randomisation				
					0-12 months				
				252	CALGB AS: 12.8 Pl 23.0	RR=0.56	SSD	**0.32-0.98**	1
				78	ukCAP AS: 47.2 Pl: 71.4	RR=0.66	SSD	**0.45-0.98**	1
				133	APACC AS: 28.4 Pl: 45.5	RR=0.62	SSD	**0.39-0.99**	1
				463	Total AS: 23.2 Pl: 37.4	RR=0.62	SSD	**0.48-0.81**	1
					12-24 months				
				51	AFPPS AS: 41.7 Pl: 20.0	RR=2.08	NS	0.71-6.16	1
				185	CALGB AS: 13.3 Pl: 16.8	RR=0.79	NS	0.40-1.58	1
				68	ukCAP AS: 25.7 Pl: 48.5	RR=0.53	NS	0.27-1.03	1
				107	APACC AS: 34.5 Pl: 36.7	RR=0.94	NS	0.56-1.56	1
				411	Total AS: 25.6 Pl: 27.6	RR=0.86	NS	0.55-1.33	1
					24-38 months				
				1007	AFPPS AS: 40.5 Pl: 46.7	RR=0.87	NS	0.75-1.00	1
				309	CALGB AS: 11.8 Pl: 17.8	RR=0.66	NS	0.38-1.15	1
				343	ukCAP AS: 19.9 Pl: 25.7	RR=0.78	NS	0.52-1.15	1
				1659	Total AS: 32.3 Pl: 34.8	RR=0.84	SSD	**0.74-0.96**	1
					≥ 38 months				
				65	AFPPS AS: 47.6 Pl: 47.8	RR=1.00	NS	0.59-1.69	1
				60	CALGB AS: 15.6 Pl: 17.9	RR=0.88	NS	0.28-2.71	1
				400	ukCAP AS: 19.9 Pl: 20.6	RR=0.97	NS	0.65-1.43	1
				175	APACC AS: 39.4 Pl: 38.3	RR=1.03	NS	0.71-1.49	1
				700	Total AS: 27.9 Pl: 26.4	RR=0.99	NS	0.78-1.26	1

AS = Aspirin; PI = Placebo; N = number of participants; mg = milligrams; kg = kilograms; m = metres; F = female; M = male; CI = confidence interval; SSD = statistically significantly different, NS = not statistically significantly different; RR = risk ratio; RCT = randomised controlled trial; AFPPS = Aspirin/Folate Polyp Prevention Study; CALGB = Colorectal Adenoma Prevention Study [Cancer and Leukemia Group B]; ukCAP = United Kingdom Colorectal Adenoma Prevention Study; APACC =Association pour la Prevention par l'Aspirine du Cancer Colorectal. [a]Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 33. Body of evidence examining the effect of aspirin on colorectal cancer incidence

Name of study	Study type	Level of evidence[a]	Risk of bias	N	Results summary %	Size of effect rating[a]	p value [b]	CI (95%)	Relevance of evidence[a]
Advanced lesion: Aspirin vs Placebo									
Cole 2009 (UK) AFPPS CALGB ukCAP APACC	Meta-analysis of 4 RCTs	I	Low		**Incidence of advanced lesion stratified into Aspirin dose**				
					Any aspirin dose (AFPPS, CALGB, ukCAP, APACC)				
				2698	AS: 8.7 Pl: 11.9	RR=0.72	**0.0046**	0.57-0.90	1
					81 or 160 mg/day (AFPPS and APACC)				
				913	AS: 9.7 Pl: 13.6	RR=0.83	0.57	0.44-1.58	1
					300 or 325 mg/day (AFPPS, CALGB, ukCAP, APACC)				
				2264	AS: 8.3 Pl: 11.9	RR=0.71	0.0089	0.56-1.92	1
					Aspirin on risk of advanced lesion in high risk populations				
					<u>Subgroup analysis:</u> **Incidence of advanced lesion stratified by RCT trial**				
					AFPPS: Any aspirin dose				
				1084	AS: 9.2 Pl: 12.4	RR=0.74	NS	0.52-1.06	1
					AFPPS: 81 mg/day				
				729	AS: 7.7 Pl: 12.4	RR=0.62	SSD	**0.39-0.97**	1
					AFPPS: 325 mg/day				
				718	AS: 10.7 Pl: 12.4	RR=0.86	NS	0.58-1.30	1
					CALGB: 325 mg/day				
				517	AS: 2.7 Pl: 3.5	RR=0.77	NS	0.29-2.05	1
					ukCAP: 300 mg/day				
				853	AS: 9.4 Pl: 15.0	RR=0.63	SSD	**0.43-0.91**	1
					APACC: Any aspirin dose				
				244	AS: 15.6 Pl: 17.2	RR=0.91	NS	0.51-1.60	1
					APACC: 81 mg/day				
				184	AS: 20.6 Pl: 17.2	RR=1.19	NS	0.65-2.21	1
					APACC: 300 mg/day				
				176	AS: 10.0 Pl: 17.2	RR=0.58	NS	0.25-1.37	1
					Incidence of advanced lesion stratified by age				

				990	≤54 years AS: 28.9 Pl: 32.5	RR=0.58	SSD	**0.38-0.89**	1
				846	55-63 years AS: 35.0 Pl: 34.7	RR=1.84		0.55-1.27	1
				862	≥64 years AS: 35.5 Pl: 42.9	RR=0.74	NS	0.51-1.07	1
							NS		
					Incidence of advanced lesion stratified by gender				
				1609	Male: AS: 10.5 Pl: 13.4	RR=0.78		0.56-1.08	1
				1089	Female: AS: 5.9 Pl: 9.8	RR=0.62	NS	0.41-0.95	1
							NS		
					Incidence of advanced lesion stratified by Body Mass Index (kg/m^2)				1
				791	<25.0 AS: 7.9 Pl: 10.6	RR=0.83		0.53-1.31	1
				1070	25.0 to 29.9 AS: 9.7 Pl: 13.3	RR=0.71	NS	0.44-1.14	1
				522	≥30.0 AS: 8.0 Pl: 9.4	RR=0.69	NS	0.39-1.22	
							NS		
					Incidence of advanced lesion stratified by family history of colorectal cancer				
				591	Yes AS: 8.2 Pl: 16.4	RR=0.53		**0.33-0.83**	1
				1124	No AS: 11.3 Pl: 12.7	RR=0.92	SSD	0.67-1.28	1
							NS		
					Incidence of advanced lesion stratified by no. of lifetime adenomas at baseline				
				1170	1 AS: 7.6 Pl: 12.6	RR=0.62		**0.43-0.88**	1
				1007	≥2 AS: 12.6 Pl: 16.3	RR=0.81	SSD	0.60-1.11	1
							NS		
					Incidence of advanced lesion stratified by advanced lesion at baseline				
				1062	Yes AS: 12.3 Pl: 16.7	RR=0.72		**0.54-0.98**	1
				952	No AS: 7.9 Pl: 11.4	RR=0.71	SSD	0.48-1.07	1
							NS		
					Incidence of advanced lesion stratified by time interval after randomisation (pooled data)				
				NR	0-12 months	RR=0.47		**0.24-0.90**	1
				NR	12-24 months	RR=0.91	SSD	0.42-2.00	1
				NR	24-38 months	RR=0.72	NS	0.52-1.00	1
				NR	≥ 38 months	RR=0.71	NS	0.37-1.35	1
							NS		

AS = Aspirin; PI = Placebo; N = number of participants; mg = milligrams; kg = kilograms; m = metres; F = female; M = male; CI = confidence interval; NR = not reported; SSD = statistically significantly different, NS = not statistically significantly different; RR = risk ratio; RCT = randomised controlled trial; AFPPS = Aspirin/Folate Polyp Prevention Study; CALGB = Colorectal Adenoma Prevention Study [Cancer and Leukemia Group B]; ukCAP = United Kingdom Colorectal Adenoma Prevention Study; APACC =Association pour la Prevention par l'Aspirine du Cancer Colorectal. [a]Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

II Colorectal cancer mortality

Table 34. Body of evidence examining the effect of aspirin on colorectal cancer mortality

Name of study	Study type	Level of evidence [a]	Risk of bias	N	Results summary	Size of effect rating[a]	p value[b]	CI (95%)	Relevance of evidence[a]
Effect of 500 mg aspirin on CRC mortality after a mean follow up period of 22-23 years									
Peto 1988 **Flossman 2007** BDAT Trial **Gender:** All male **Mean Age** (SD): 61.7 yrs (7.0) **Smoking status** (n/%): Never: 1254/24.4 Past: 2288/44.6 Current (<20/day): 347/ 6.8 Current (≥20/day): 314/ 6.1 Other/mixed: 932/18.1 **Mean trial duration** (range): 5.7 years (5–6) **Median follow up:** 23 years	RCT	II	At risk	5,139	**Effect of 500 mg aspirin on long term risk of death due to colorectal cancer** AS: 1.72 PI: 2.34	OR=0.73	NS	0.49-1.10	1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; mg = milligrams; F = female; M = male; CI = confidence interval; NR = not reported; SD = standard deviation; SSD = statistically significantly different, NS = not statistically significantly different; OR = odds ratio; ARR = absolute risk reduction; RCT = randomized controlled trial; BDAT = British Doctors Aspirin Trial; [a]Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 35. Body of evidence examining the effect of aspirin on colorectal cancer mortality

Name of study	Study type	Level of evidence[a]	Risk of bias	N	Results summary	Size of effect rating[a]	p value[b]	(95% CI)	Relevance of evidence[a]
Effect of 75 mg aspirin on CRC mortality after a mean follow up period of 18-23 years									
Norrving 1991 **Rothwell 2010** (Sweden) SALT **Age range:** 50-79 yrs **Gender (%)** F:34.2 M:65.8 **Smoking Status** Current AS: 26.0 PI: 27.9 Ex-smoker AS: 21.3 PI: 24.7 Never Smoked AS: 52.7 PI: 47.4 **Duration of study drug (months):** AS: 30.6 PI: 27.5 **Trial duration** (median/range) 2.7 yrs/1.0 – 5.3 yrs **Follow up range** 18 - 23 yrs	RCT	II	Low	1360 912	**Effect of 75 mg aspirin on long term risk of death due to CRC** AS: 1.04 PI: 1.46 **Effect of 75 mg aspirin on long term risk of death due to CRC excluding patients with scheduled duration of trial treatment < 2.5 yrs** AS: 0.45 PI: 1.50	OR = 0.71 OR = 0.30	NS NS	0.27-1.86 0.06-1.44	1 1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; mg = milligrams; F = female; M = male; CI = confidence interval; NR = not reported; SD = standard deviation; NS = not statistically significantly different; OR = odds ratio; RCT = randomized controlled trial; yrs = years; mths = months; [a]Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 36. Body of evidence examining the effect of aspirin on colorectal cancer mortality

Name of study	Study type	Level of evidence [a]	Risk of bias	N	Results summary	Size of effect rating[a]	p value[b]	(95% CI)	Relevance of evidence[a]
Effect of 75 mg aspirin on CRC mortality after a mean follow up period of 17-20 years									
Meade 1998 **Rothwell 2010** (UK) TPT **Mean Age** (SD): 57.5 yrs (6.7 yrs) **Trial duration** (mean/range) 6.9 yrs/4.3-8.6 yrs **Follow up range:** 17-20 yrs	RCT	II	Low	5085 5085	**Effect of 75 mg aspirin on long term risk of death due to CRC** AS: 1.34 PI: 2.16 **Effect of 75 mg aspirin on long term risk of death due to CRC excluding patients with scheduled duration of trial treatment < 2.5 yrs** AS: 1.34 PI: 2.16	OR=0.61 OR=0.61	NR NR	0.40–0.94 0.40–0.94	1 1
Effect of aspirin on CRC mortality after a mean follow up period of 21-27 years									
UK-TIA study group 1988 **Farrell 1991** **Flossman 2007** UK-TIA Trial **Mean Age** (SD): 59.8 yrs(9.0) **Gender (%)** F: 27 M: 73 **Trial duration** (mean/range) 4.4 yrs/1.0 – 7.1 yrs **Follow up range:** 21 - 27 yrs	RCT	II	Low	1628 1638	**Effect of 300 mg aspirin on long term risk of death due to CRC** AS: 0.99 PI: 1.96 **Effect of 1200 mg aspirin on long term risk of death due to CRC** AS: 1.34 PI: 1.96	OR=0.50 OR=0.68	NS NS	0.21–1.17 0.31–1.47	1 1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; mg = milligrams; F = female; M = male; CI = confidence interval; NR = not reported; SD = standard deviation; NS = not statistically significantly different; OR = odds ratio; RCT = randomized controlled trial; yrs = years; UK-TIA = The United Kingdom Transient Ischaemic Attack Trial; TPT = Thrombosis Prevention Trial; [a]Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 37. Body of evidence examining the effect of aspirin on colorectal cancer mortality

Name of study	Study type	Level of evidence[a]	Risk of bias[c]	N	Results summary	Size of effect rating[a]	p value[b]	(95% CI)	Relevance of evidence[a]
Meta-analysis of colorectal cancer mortality in RCTs after a median follow up of 18.3 yrs [4 RCTs: BDAT, SALT, TPT, UK-TIA]									
Rothwell 2010 (UK) BDAT SALT TPT UK-TIA	Meta-analysis of RCTs	I	Moderate		**Effect of aspirin (75-1200 mg) on long-term risk of death due to colorectal cancer in 4 RCTs (BDAT, SALT, TPT, UK-TIA)**				
				14,033	AS: 1.44 PI: 2.10	OR=0.66	0.002	0.51–0.85	1
					Effect of aspirin on long-term risk of mortality due to colorectal cancer in 4 RCTs				
					<u>Subgroup analysis:</u> **Doses of Aspirin**				
					500 – 1200 mg daily (BDAT, UK-TIA)				
				6,777	AS: 1.65 PI: 2.22	OR=0.72	NS	0.50–1.03	1
					75 – 300 mg daily (UK-TIA, TPT, SALT)				
				8,073	AS: 1.22 PI: 2.00	OR=0.60	SSD	0.42–0.86	1
					Effect of low dose 75 – 300 mg Aspirin vs control on long term mortality due to CRC **<u>Subgroup analysis:</u>** **Scheduled treatment**				
				8,073	All patients; AS: NR PI: NR	HR=0.61	0.005	0.43 – 0.87	1
				7,383	≥ 2.5 yrs; AS: NR PI: NR	HR=0.54	0.001	0.36 – 0.80	1
				5,077	≥ 5 yrs; AS: NR PI: NR	HR=0.48	0.001	0.30 – 0.77	1
					Effect of Aspirin (75 – 1200 mg) vs control on mortality due to CRC				
					<u>Subgroup analysis:</u> **Sites of CRC**				
				14,033	All Colon cancer; AS: NR PI: NR	HR=0.65	0.005	0.48 – 0.88	1
				14,033	Proximal cancer; AS: NR PI: NR	HR=0.34	0.001	0.18 – 0.66	1
				14,033	Distal cancer; AS: NR PI: NR	HR=1.21	0.54	0.66 – 2.24	1
				14,033	Site unspecified AS: NR PI: NR	HR=0.61	0.02	0.40 – 0.94	1
				14,033	Rectal cancer AS: NR PI: NR	HR=0.80	0.35	0.50 – 1.28	1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; mg = milligrams; F = female; M = male; CI = confidence interval; NR = not reported; SD = standard deviation; SSD = statistically significantly different, NS = not statistically significantly different; HR = hazards ratio; OR = odds ratio; RCT = randomized controlled trial; yrs = years; mths = months; BDAT

= British Doctors Aspirin Trial; UK-TIA = The United Kingdom Transient Ischaemic Attack Trial; TPT = Thrombosis Prevention Trial; SALT = Swedish Aspirin Low Dose Trial .[a]Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant. [c] see tables 8 and 9 for risk of bias assessments.

III Adverse Effects

Table 38. Body of evidence examining the effect of aspirin on adverse effects

Name of study	Study type	Level of evidence [a]	Risk of bias	N	Results summary (%)	Size of effect rating[a]	p value[b]	(95% CI)	Relevance of evidence[a]
Adverse effects reported after mean follow up period of 18 years									
Cook 2005 **Cook 2013** WHS Trial **Gender:** all females **Mean Age** (SD): 54.6 yrs (7.0) **Mean BMI** (SD): 26.0 (5.1) **Smoking status** (n/%)**:** Current: 5235/13.1% Past: 14,265/35.8% Never: 20,340/51.1% **Alcohol use** (drinks/wk)(n/%): <1: 23,226/58.3% ≥1: 16,640/41.7% **Physical activity** (Kcal/wk)**:** <1000: 25,994/66.0% ≥1000: 13,383/34.0% **Mean follow up:** 10.1 years	RCT	II	Low	39,876 39,876 39,876	**Subgroup analysis:** Gastrointestinal bleeding: AS: 8.3 PI: 7.3 Peptic Ulcer AS: 7.3 PI: 6.2 Colon Polyp AS:26.0 PI:25.8	HR=1.14 HR=1.17 HR=1.00	< 0.001 < 0.001 0.94	1.06–1.22 1.09–1.27 0.96–1.04	1 1 1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; CI = confidence interval; NR = not reported; SD = standard deviation; HR = hazards ratio; RCT = randomized controlled trial; wk = week; Kcal = kilocalorie; WHS = Women's Health Study .[a]Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant.

Table 39. Body of evidence examining the effect of aspirin on adverse effects

Name of study	Study type	Level of evidence[a]	Risk of bias[c]	N	Results summary	Size of effect rating[a]	p value[b]	(95% CI)	Relevance of evidence[a]
Adverse events reported during follow up (1-8 years) measured from the date of randomization to 30/9/1986. For each type of adverse effect patients were only counted once.									
UK-TIA study group 1988 **Farrell 1991** **Flossman 2007** **Rothwell 2010**	RCT (multi-centre)	II	Low		**Subgroup analysis:** **Upper gastrointestinal symptoms (nausea, abdominal pain, heartburn, vomiting)**				
UK-TIA Trial				1622	300 mg AS: 31 PI: 26	OR=1.32	SSD	1.06–1.65	1
Age ≥ 40 yrs				1621	1200mg AS: 41 300mg AS: 31	OR=1.54	SSD	1.25–1.89	1
Gender (%) F: 27 M: 73				2435	**Constipation** 1200mg+300mg AS: 6 PI: 2	OR=2.72	SSD	1.68–4.40	1
Trial duration (mean/range) 4.4 yrs/1.0 – 7.1 yrs					**Any gastrointestinal bleeding**				
Follow up (range) 21 - 27 yrs				1620	300mg AS: 3 PI: 1	OR=2.57	SSD	1.20–5.53	1
				1621	1200mg AS: 5 300mg AS: 3	OR=1.62	NS	0.94–2.79	1

AS = Aspirin; PI = Placebo; C = control group; CRC = Colorectal cancer; N = number of participants; mg = milligrams; F = female; M = male; CI = confidence interval; SSD = statistically significantly different, NS = not statistically significantly different; OR = odds ratio; ARR = absolute risk reduction; RCT = randomized controlled trial; WHS = Women's Health Study; UK-TIA = The United Kingdom Transient Ischaemic Attack Trial; Z = Z score; [a] Refer to appendix B for detailed explanations of rating scores; [b] P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant; [c]see tables 8 and 9 for risk of bias assessments.

Table 40. Body of evidence examining the effect of aspirin on adverse effects

Name of study	Study type	Level of evidence[a]	Risk of bias	N	Results summary (%)	Size of effect rating[a]	p value[b]	CI (95%)	Relevance of evidence[a]
Adverse events reported									
Cole 2009 (UK) AFPPS CALGB ukCAP APACC	Meta-analysis of 4 RCTs	I	Low		**Adverse events for any aspirin dose verse placebo** **Death** 2967 **Myocardial infarction** 2967 **Stroke** 2967 **Major bleeding** 2967 Invasive cancer 2967 Colorectal cancer 2967 Any event above 2967	 AS: 0.95 PI: 0.85 AS: 0.48 PI: 0.31 AS: 0.00 PI: 0.66 AS: 2.79 PI: 2.5 AS: 2.62 PI: 1.86 AS: 0.54 PI: 0.62 AS: 6.20 PI: 5.51	 NR NR NR NR NR NR NR	 0.85 0.57 **0.002** 0.64 0.18 0.81 0.48	 NR NR NR NR NR NR NR	 1 1 1 1 1 1 1

AS = Aspirin; PI = Placebo; N = number of participants; CI = confidence interval; NR = not reported; RCT = randomized controlled trial; AFPPS = Aspirin/Folate Polyp Prevention Study; CALGB = Colorectal Adenoma Prevention Study [Cancer and Leukemia Group B]; ukCAP = United Kingdom Colorectal Adenoma Prevention Study; APACC = Association pour la Prevention par l'Aspirine du Cancer Colorectal [a]Refer to appendix B for detailed explanations of rating scores; [b]P-values derived from two-sided tests, p-value <0.05 was considered to be statistically significant;

References: Included studies

1. Baron JA, Cole BF, Sandler RS, Haile RW, Ahnen D, Bresalier R, et al. *A randomized trial of aspirin to prevent colorectal adenomas. The New England journal of medicine.* 2003;348(10):891-9.

2. Benamouzig R, Deyra J, Martin A, Girard B, Jullian E, Piednoir B, et al. *Daily soluble aspirin and prevention of colorectal adenoma recurrence: one-year results of the APACC trial*. Gastroenterology. 2003;125(2):328-36.

3. Burn J, Bishop DT, Mecklin JP, Macrae F, Möslein G, Olschwang S, et al. *Effect of aspirin or resistant starch on colorectal neoplasia in the Lynch syndrome.* N Engl J Med 2008 Dec 11;359(24):2567-78.

4. Burn J, Gerdes AM, Macrae F, Mecklin JP, Moeslein G, Olschwang S, et al. *Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial.* Lancet 2011 Dec 17;378(9809):2081-7.

5. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, et al. *Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials*. Journal of the National Cancer Institute. 2009;101(4):256-66.

6. Cook NR, Lee IM, Gaziano JM, Gordon D, Ridker PM, Manson JE, et al. *Low-dose aspirin in the primary prevention of cancer: the Women's Health Study: a randomized controlled trial.* JAMA 2005 Jul 6;294(1):47-55.

7. 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 Jul 16;159(2):77-85.

8. Farrell B, Godwin J, Richards S, Warlow C. *The United Kingdom Transient Ischemic Attach (UK-TIA) Aspirin Trial – Final Results*: Journal of Neurology Neurosurgery and Psychiatry 1991 Dec 54;(12):1044-1054.

9. Flossmann E, Rothwell PM, British Doctors Aspirin Trial and the UK-TIA Aspirin Trial. *Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies.* Lancet 2007 May 12;369(9573):1603-13.

10. van Kruijsdijk RC, Visseren FL, Ridker PM, Dorresteijn JA, Buring JE, van der Graaf Y, Cook NR. *Individualised prediction of alternate-day aspirin treatment effects on the combined risk of cancer, cardiovascular disease and gastrointestinal bleeding in healthy women.* Heart. 2015 101(5):369-76.

11. Logan RF, Grainge MJ, Shepherd VC, Armitage NC, Muir KR. *Aspirin and folic acid for the prevention of recurrent colorectal adenomas*. Gastroenterology. 2008;134(1):29-38.

12. Meade TW, Wilkes HC, Kelleher CC, Roderick PJ, Brennan PJ, Wilson CW, Howarth DJ, Stirling Y, Garrow K, Dickinson CJ, Rose G, Miller GJ, Peart WS, Breckenridge AM, Grahame-Smith DG, Pocock SJ, Zuhrie SR. *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*. Lancet 1998 Jan 351;(9098):233-241

13. Norrving B, Elwin CE, Peterson B, Blomstrand C, Olsson JE, Nilsson B, Vonarbin M, Britton M, Helmers C, Rosen A, Samuelsson K, Strandberg K, Wahlgren NG, Garde A Svensson J, Huitfeldt B, Lundberg PO, Wilhelmsen L, Melander H, Selinus I, Carlsson A. *Swedish aspirin low dose trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischemic events*. Lancet 1991 Nov 338;(8779):1345-1349

14. Peto R, Gray R, Collins R, Wheatley K, et al. *Randomised trial of prophylactic daily aspirin in British male doctors*. BMJ 1988 Jan 296;(6618):313-316.

15. Rothwell PM, Wilson M, Elwin CE, Norrving B, Algra A, Warlow CP, et al. *Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials.* Lancet 2010 Nov 20;376(9754):1741-50.

16. Sandler RS, Halabi S, Baron JA, Budinger S, Paskett E, Keresztes R, et al. *A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer*. The New England journal of medicine. 2003;348(10):883-90.

17. UK-TIA study group. *United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: interim results.* BMJ 1988 Jan 296;(6618):316-320.

APPENDICES

Appendix A: Search strategies used

For PubMed database:

#	Searches
1	Colorect* [title/abstract] or colon* [title/abstract] or rectal* [title/abstract] or rectum* [title/abstract] or Anus* [title/abstract] or bowel* [title/abstract]
2	Cancer* [title/abstract] or neoplas* [title/abstract] or oncolog* [title/abstract] or malignan* [title/abstract] or tumor* [title/abstract] or tumour* [title/abstract] or carcinoma* [title/abstract] or adenocarcinoma* [title/abstract]
3	1 AND 2
4	Colorectal neoplasms [MeSH terms]
5	Colonic neoplasms [MeSH terms]
6	Rectal neoplasms [MeSH terms]
7	4 or 5 or 6
8	3 or 7
9	Aspirin [title/abstract]
10	Acetylsalicylic Acid [title/abstract]
11	Aspirin [MeSH Terms]
12	9 or 10 or 11
13	8 AND 12
14	English[la] AND 2004:3000[dp]
15	13 AND 14

ATSI search terms used in PubMed database:

#	Searches
1	australia[mh] OR Australia*[tiab]
2	ancestry group, oceanic[mh] OR ancestry groups, oceanic[mh] OR aborigine, australian[mh] OR aborigines, australian[mh] OR australian aborigine[mh] OR australian aborigines[mh] OR aborigin*[tiab] OR indigenous[tiab]
3	1 AND 2
4	torres strait islander*[tiab]
5	3 OR 4
6	colorect*[tiab] OR colon*[tiab] OR rectal*[tiab] OR rectum*[tiab] OR anus*[tiab] OR bowel*[tiab]
7	(cancer*[tiab] OR neoplas*[tiab] OR oncolog*[tiab] OR malignan*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR colorectal neoplasms[mh] OR colonic neoplasms[mh] OR rectal neoplasms[mh])
8	6 AND 7
9	5 AND 8
10	english[la] AND 2004:3000[dp]
11	9 AND 10

For Embase database:

#	Search
1	aspirin.mp. or exp acetylsalicylic acid/
2	aspirin.ti,ab. OR acetylsalicylic acid.ti,ab.
3	1 OR 2
4	(colorect$ or colon$ or rectal$ or rectum$ or anus$ or bowel$).ti,ab.
5	(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adeno).ti,ab.
6	4 AND 5
7	hereditary nonpolyposis colorectal cancer/ or colorectal polyp/ or colorectal tumor/ or colorectal cancer/ or colorectal anastomosis/ or colorectal carcinoma/ or colorectal adenoma/ or colorectal.mp. or hereditary colorectal cancer/
8	colon anastomosis/ or colon carcinoma/ or colon polyposis/ or colon adenocarcinoma/ or colon tumor/ or colon.mp. or colon cancer/ or colon adenoma/ or colon carcinogenesis/ or colon polyp/ or familial colon polyposis/
9	rectum cancer/ or rectum tumor/ or rectum anastomosis/ or rectum carcinoma/ or rectum adenoma/ or rectum/ or rectum polyp/ or rectum.mp.
10	7 OR 8 OR 9
11	6 OR 10
12	Clinical trial/
13	Randomized controlled trial/
14	Randomization/
15	Single blind procedure/
16	Double blind procedure/
17	Crossover procedure/
18	Placebo/
19	Randomi?ed controlled trial$.tw.
20	Rct.tw.
21	Random allocation.tw.
22	Randomly allocated.tw
23	Allocated randomly.tw
24	(allocated adj2 random).tw.
25	Single blind$.tw.
26	Double blind$.tw.
27	((treble or triple) adj blind$).tw.
28	Placebo$.tw.
29	Prospective study/
30	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29
31	3 AND 11 AND 30
32	limit 31 to english language
33	limit 32 to yr="2004-Current"
34	animal/ not human/
35	33 NOT 34

*Used the SIGN filter for identifying randomized controlled trials (*www.sign.ac.uk/methodology/filters.html#systematic *accessed 20/02/2013)*

ATSI search terms used in Embase database:

#	**Searches**
1	exp Australia/ OR Australia$.ti,ab
2	Oceanic ancestry group/ OR aborigin$.ti,ab. OR indigenous.mp.
3	1 AND 2
4	torres strait$ islander$.ti,ab
5	3 OR 4
6	(colorect$ or colon$ or rectal$ or rectum$ or anus$ or bowel$).ti,ab.
7	(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adeno).ti,ab.
8	6 AND 7
9	hereditary nonpolyposis colorectal cancer/ or colorectal polyp/ or colorectal tumor/ or colorectal cancer/ or colorectal anastomosis/ or colorectal carcinoma/ or colorectal adenoma/ or colorectal.mp. or hereditary colorectal cancer/
10	colon anastomosis/ or colon carcinoma/ or colon polyposis/ or colon adenocarcinoma/ or colon tumor/ or colon.mp. or colon cancer/ or colon adenoma/ or colon carcinogenesis/ or colon polyp/ or familial colon polyposis/
11	rectum cancer/ or rectum tumor/ or rectum anastomosis/ or rectum carcinoma/ or rectum adenoma/ or rectum/ or rectum polyp/ or rectum.mp.
12	9 OR 10 OR 11
13	8 OR 12
14	5 AND 13
15	limit 14 to english language
16	limit 15 to yr="2004-Current"

For Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment database and PsycINFO:

#	**Searches**
1	aspirin.mp. or exp acetylsalicylic acid/
2	aspirin.ti,ab. OR acetylsalicylic acid.ti,ab.
3	1 OR 2
4	(colorect$ or colon$ or rectal$ or rectum$ or anus$ or bowel$).ti,ab.
5	(cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adeno).ti,ab.
6	4 AND 5
7	hereditary nonpolyposis colorectal cancer/ or colorectal polyp/ or colorectal tumor/ or colorectal cancer/ or colorectal anastomosis/ or colorectal carcinoma/ or colorectal adenoma/ or colorectal.mp. or hereditary colorectal cancer/
8	colon anastomosis/ or colon carcinoma/ or colon polyposis/ or colon adenocarcinoma/ or colon tumor/ or colon.mp. or colon cancer/ or colon adenoma/ or colon carcinogenesis/ or colon polyp/ or familial colon polyposis/
9	rectum cancer/ or rectum tumor/ or rectum anastomosis/ or rectum carcinoma/ or rectum adenoma/ or rectum/ or rectum polyp/ or rectum.mp.
10	7 OR 8 OR 9
11	6 OR 10
12	3 AND 10
13	limit 12 to english language
14	limit 13 to yr="2004-Current"

For CINAHL database:

#	Searches
1	Colorectal (TX All Text)
2	cancer (TX All Text)
3	aspirin (TX All Text)
4	2004-2016 (Publication Date)
5	1 AND 2 AND 3 AND 4

Appendix B:

Level of Evidence rating criteria – Intervention studies

Level	Study type
I	Meta-analysis or a systematic review of level II studies
II	Randomised controlled trial or a phase III/IV clinical trial
III-1	Pseudo-randomised controlled trial or a meta-analysis/systematic review of level III-1 studies
III-2	Comparative study with concurrent controls: - Phase II clinical trial - Non-randomised, experimental trial9 - Controlled pre test/post test study - Adjusted indirect comparisons - Interrupted time series with a control group - Cohort study - Case-control study or a meta-analysis/systematic review of level III-2 studies
III-3	A comparative study without concurrent controls: - Phase I clinical trial - Historical control study - Two or more single arm study10 - Unadjusted indirect comparisons - Interrupted time series without a parallel control group or a meta-analysis/systematic review of level III-3 studies
IV	Case series with either post-test or pre-test/post-test outcomes or a meta-analysis/systematic review of level IV studies

According to the standards of the National Health and Medical Research Council

Level of Evidence rating criteria – Diagnostic accuracy studies

Level	Study type
I	Meta-analysis or a systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation

III-2	A comparison with reference standard that does not meet the criteria required for level II and III-1 evidence
III-3	Diagnostic case-control study
IV	Study of diagnostic yield (no reference standard)

According to the standards of the National Health and Medical Research Council

Level of Evidence rating criteria – Risk factor studies

Level	Study type
I	Meta-analysis or a systematic review of level II studies
II	Prospective cohort studies
III-1	All or none
III-2	Retrospective cohort studies
III-3	Case-control studies
IV	Cross-sectional studies or case series

According to the standards of the National Health and Medical Research Council

Relevance of the evidence

Rating	Relevance
1	Evidence of an effect on patient-relevant clinical outcomes including benefits and harms, quality of life and survival.
2	Evidence of an effect on a surrogate outcome* that has been shown to be predictive of patient-relevant outcomes for the same intervention.
3	Evidence of an effect on proven surrogate outcomes but for a different intervention.
4	Evidence of an effect on proven surrogate outcomes but for a different intervention and population.
5	Evidence confined to unproven surrogate outcomes.

**'surrogate outcome' refers to reasonable indicators of whether there has been some effect (e.g. blood pressure measurements or levels of serum cholesterol)*

Points for considering patient-relevant outcomes:
i) The goal of decision making in health care is to choose the intervention(s) (which may include doing nothing) that is (are) most likely to deliver the outcomes that patients find desirable.
ii) Surrogate outcomes (such as blood pressure measurements or levels of serum cholesterol) may be reasonable indicators of whether there has been some effect. However, they should not be the basis for clinical decisions unless they reliably predict an effect on the way the patient feels, otherwise they will not be of interest to the patient or their carers.
iii) All possible outcomes that are of most interest to patients (particularly harms) should be identified and evaluated.

Adapted from table 1.10 of: National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra: NHMRC; 2000. http://www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/cp69.pdf

Appendix C:
Potentially relevant guidelines identified and reason why not adopted

Year	Organisation	Title of Guideline	Reason why not adopted
2016	U.S. Preventive Services Task Force	Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer	Included studies that did not meet our inclusion criteria
2015	National Institute for Health and Care Excellence (NICE)	Suspected Cancer: recognition and referral	No relevant content to this PICO
2015	NCCN	Colon Cancer	No relevant content to this PICO
2014	Victoria Government	Optimal care pathway for people with colorectal cancer	Not based on a systematic review
2014	National Institute for Health and Care Excellence (NICE)	Colorectal Cancer: the diagnosis and management of colorectal cancer	No relevant content to this PICO
2013	ESMO Guidelines Working Group	Early colon cancer: ESMO Clinical Practise Guidelines for diagnosis, treatment and follow-up	No relevant content to this PICO
2013	ESMO Guidelines Working Group	Rectal cancer: ESMO Clinical Practise Guidelines for diagnosis, treatment and follow-up	No relevant content to this PICO
2011	National Institute for Health and Care Excellence (NICE)	Colorectal Cancer: the Diagnosis and management of colorectal cancer	No relevant content to this PICO
2009	Gastroenterological Society of Australia	Early Detection, Screening and Surveillance for Bowel Cancer	No relevant content to this PICO
2008	WA Cancer & Palliative Care Network	Colorectal cancer model of care	No relevant content to this PICO
2007	U.S. Preventive Services Task Force	The Use of Aspirin for Primary Prevention of Colorectal Cancer	Included studies that did not meet our inclusion criteria. Outdated guideline

Excluded studies

Study	Reason for Exclusion
Ait Ouakrim 2015	Inappropriate study design
Algra 2012	Relevant data published previously
Allison 2006	Inappropriate study design
Arber 2005a	Unable to collect
Arber 2005b	Unable to collect
Asano 2004a	Relevant data published previously
Asano 2004b	Inappropriate study design and population
Avivi 2012	Review article
Baron 2009	Unable to collect
Barry 2009	Inappropriate study design
Benamouzig 2005	No relevant outcome
Bosetti 2006	Review article
Bosetti 2012	Review article
Burn 2012	Unable to collect
Burn 2013a	Unable to collect
Burn 2013b	Relevant data published previously
Chan 2005	Inappropriate study design
Chan 2008	Inappropriate study design
Chan 2010	Review article
Chan 2012	Review article
Cole 2009	Inappropriate population
Cooper 2010	Relevant data published previously
Courtney 2004	Review article
Cuzick 2009	Review article
Das 2007	Review article
Di Francesco 2015	Unable to collect
Diehl 2012	Review article
Din 2010	Inappropriate study design
Dovizio 2012	Review article
Dube 2007	Relevant data published previously
Fedirko 2015	Inappropriate population
Ferrandez 2012	Review article
Friis 2009	Inappropriate study design
Friis 2015	Inappropriate study design
Gracia-Albeniz 2011	Review article
Gasche 2004	Review article
Gill 2005	Unable to collect
Half 2009	Review article
Harris 2005	Unable to collect
Harris 2008	Inappropriate study design
Hawk 2005	Review article
Herszenyi 2008	Unable to collect
Hoffmeister 2006	Inappropriate study design
Hoffmeister 2007	Inappropriate study design
Hollestein 2014	Inappropriate study design
Huang 2013	Inappropriate study design
Huang 2015	Unable to collect

Ishikawa 2013	Inappropriate population
Jacobs 2007	Inappropriate study design
Jacobs 2010	Review article
Jankowski 2008	Review article
Kanik 2004	Inappropriate population
Kim 2006	Inappropriate population
Komiya 2013	Review article
Koretz 2011	Unable to collect
Kothari 2015	Inappropriate study design
Kraus 2015	Unable to collect
Larsson 2006	Inappropriate study design
Lee 2012a	Unable to collect
Lee 2012b	Inappropriate study design
Leshno 2008	Review article
Manzano 2012	Review article
Massat 2013	Review article
Morgan 2004	Review article
Movahedi 2015	No relevant outcomes
Murra 2005	Review article
Nan 2013	Inappropriate study design
Nan 2015	Inappropriate study design
Patrono 2013	Relevant data published previously
Peek 2004	Review article
Rao 2004	Unable to collect
Reddy 2007	Unable to collect
Rennert 2007	Unable to collect
Rothwell 2011	No relevant outcome
Ruder 2011	Inappropriate study design
Sehdev 2015	Review article
Serrano 2004	Review article
Stanojevic-Bakic 2004	Review article
Steffen 2014	Inappropriate study design
Sturmer 2007	Unable to collect
Sutcliffe 2013a	Relevant data published previously/no relevant outcome
Sutcliffe 2013b	Relevant data published previously/no relevant outcome
Thiagarajan 2012	Review article
Thun 2012	Review article
Tougeron 2014	Review article
Ulrich 2006	Review article
USPSTF Aspirin Guideline 2007	Outdated guideline
Vinogradova 2007	Inappropriate study design
Wickham 2012	Review article
Yasuda 2008	Review article
Ye 2013	Inappropriate study design
Yeomans 2011	Review article
Zhang 2011	Inappropriate study design

References: Excluded Studies

1. Ait Ouakrim D, Dashti SG, Chau R, Buchanan DD, Clendenning M, Rosty C, et al. *Aspirin, Ibuprofen, and the Risk of Colorectal Cancer in Lynch Syndrome.* J Natl Cancer Inst 2015 Sep;107(9): published online.

2. 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 May;13(5):518-27.

3. Allison M, Garland C, Chlebowski R, Criqui M, Langer R, Wu L, et al. *The association between aspirin use and the incidence of colorectal cancer in women.* Am J Epidemiol 2006 Sep 15;164(6):567-75.

4. Arber N, Levin B. *Chemoprevention of colorectal cancer: ready for routine use?* Curr Top Med Chem 2005a;5(5):517-25.

5. Arber N, Levin B. *Chemoprevention of colorectal cancer: ready for routine use?* Recent Results Cancer Res 2005b;166:213-30.

6. Asano TK, McLeod RS. *Non steroidal anti-inflammatory drugs (NSAID) and Aspirin for preventing colorectal adenomas and carcinomas.* Cochrane Database Syst Rev 2004a;(2):CD004079.

7. Asano TK, McLeod RS. *Nonsteroidal anti-inflammatory drugs and aspirin for the prevention of colorectal adenomas and cancer: a systematic review.* Dis Colon Rectum 2004b May;47(5):665-73.

8. Avivi D, Moshkowitz M, Detering E, Arber N. *The role of low-dose aspirin in the prevention of colorectal cancer.* Expert Opin Ther Targets 2012 Mar;16 Suppl 1:S51-62.

9. Baron JA. *Aspirin and NSAIDs for the prevention of colorectal cancer.* Recent Results Cancer Res 2009;181:223-9.

10. Barry EL, Sansbury LB, Grau MV, Ali IU, Tsang S, Munroe DJ, et al. *Cyclooxygenase-2 polymorphisms, aspirin treatment, and risk for colorectal adenoma recurrence--data from a randomized clinical trial.* Cancer Epidemiol Biomarkers Prev 2009 Oct;18(10):2726-33.

11. Benamouzig R, Uzzan B, Little J, Chaussade S. *Low dose aspirin, COX-inhibition and chemoprevention of colorectal cancer.* Curr Top Med Chem 2005;5(5):493-503.

12. Bosetti C, Gallus S, La Vecchia C. *Aspirin and cancer risk: an updated quantitative review to 2005.* Cancer Causes Control 2006 Sep;17(7):871-88.

13. Bosetti C, Rosato V, Gallus S, Cuzick J, La Vecchia C. *Aspirin and cancer risk: a quantitative review to 2011.* Ann Oncol 2012 Jun;23(6):1403-15.

14. Burn J, Mathers J, Bishop DT. *Lynch syndrome: history, causes, diagnosis, treatment and prevention (CAPP2 trial).* Dig Dis 2012;30 Suppl 2:39-47.

15. Burn J, Mathers J, Bishop DT. *Genetics, inheritance and strategies for prevention in populations at high risk of colorectal cancer (CRC).* Recent Results Cancer Res 2013a;191:157-83.

16. Burn J, Mathers JC, Bishop DT. *Chemoprevention in Lynch syndrome.* Fam Cancer 2013b Dec;12(4):707-18.

17. 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 Aug 24;294(8):914-23.

18. 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 Jan;134(1):21-8.

19. Chan AT, Giovannucci EL. *Primary prevention of colorectal cancer.* Gastroenterology 2010 Jun;138(6):2029-2043.e10.

20. Chan AT, Arber N, Burn J, Chia WK, Elwood P, Hull MA, et al. *Aspirin in the chemoprevention of colorectal neoplasia: an overview.* Cancer Prev Res (Phila) 2012 Feb;5(2):164-78.

21. Cole BF, Logan RF, Halabi S, Benamouzig R, Sandler RS, Grainge MJ, et al. *Aspirin for the chemoprevention of colorectal adenomas: meta-analysis of the randomized trials.* J Natl Cancer Inst 2009 Feb 18;101(4):256-66.

22. Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, et al. *Chemoprevention of colorectal cancer: systematic review and economic evaluation.* Health Technol Assess 2010 Jun;14(32):1-206.

23. Courtney ED, Melville DM, Leicester RJ. *Review article: chemoprevention of colorectal cancer.* Aliment Pharmacol Ther 2004 Jan 1;19(1):1-24.

24. Cuzick J, Otto F, Baron JA, Brown PH, Burn J, Greenwald P, et al. *Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement.* Lancet Oncol 2009 May;10(5):501-7.

25. Das D, Arber N, Jankowski JA. *Chemoprevention of colorectal cancer.* Digestion 2007;76(1):51-67.

26. Di Francesco L, López Contreras LA, Sacco A, Patrignani P. *New insights into the mechanism of action of aspirin in the prevention of colorectal neoplasia.* Curr Pharm Des 2015 Sep;21(35): 5116-26.

27. Diehl AK, *Review: Daily aspirin reduces short term risk for cancer and cancer mortality* Ann Intern Med 2012 157(2): p. JC2-2.

28. Din FV, Theodoratou E, Farrington SM, Tenesa A, Barnetson RA, Cetnarskyj R, et al. *Effect of aspirin and NSAIDs on risk and survival from colorectal cancer.* Gut 2010 Dec;59(12):1670-9.

29. Dovizio M, Tacconelli S, Sostres C, Ricciotti E, Patrignani P. *Mechanistic and pharmacological issues of aspirin as an anticancer agent.* Pharmaceuticals (Basel) 2012 Dec 5;5(12):1346-71.

30. Dubé C, Rostom A, Lewin G, Tsertsvadze A, Barrowman N, Code C, et al. *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 Mar 6;146(5):365-75.

31. Fedirko V, Bradshaw PT, Figueiredo JC, Sandler RS, Barry EL, Ahnen DJ, et al. *Urinary Metabolites of Prostanoids and Risk of Recurrent Colorectal Adenomas in the Aspirin/Folate Polyp Prevention Study (AFPPS).* Cancer Prev Res (Phila) 2015 Nov;8(11):1061-8.

32. Ferrández A, Piazuelo E, Castells A. *Aspirin and the prevention of colorectal cancer.* Best Pract Res Clin Gastroenterol 2012 Apr;26(2):185-95.

33. Friis S, Poulsen AH, Sørensen HT, Tjønneland A, Overvad K, Vogel U, et al. *Aspirin and other non-steroidal anti-inflammatory drugs and risk of colorectal cancer: a Danish cohort study.* Cancer Causes Control 2009 Jul;20(5):731-40.

34. Friis S, Riis AH, Erichsen R, Baron JA, Sørensen HT. *Low-Dose Aspirin or Nonsteroidal Anti-inflammatory Drug Use and Colorectal Cancer Risk: A Population-Based, Case-Control Study.* Ann Intern Med 2015 Sep 1;163(5):347-55.

35. Garcia-Albeniz X, Chan AT. *Aspirin for the prevention of colorectal cancer.* Best Practice and Research Clinical Gastroenterology 2011 Aug;25(4-5):461-72.

36. Gasche C. *Review article: the chemoprevention of colorectal carcinoma.* Aliment Pharmacol Ther 2004 Oct;20 Suppl 4:31-5.

37. Gill S, Sinicrope FA. *Colorectal cancer prevention: is an ounce of prevention worth a pound of cure?* Semin Oncol 2005 Feb;32(1):24-34.

38. Half E, Arber N. *Colon cancer: preventive agents and the present status of chemoprevention.* Expert Opin Pharmacother 2009 Feb;10(2):211-9.

39. Harris RE, Beebe-Donk J, Doss H, Burr Doss D. *Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade (review).* Oncol Rep 2005 Apr;13(4):559-83.

40. Harris RE, Beebe-Donk J, Alshafie GA. *Similar reductions in the risk of human colon cancer by selective and nonselective cyclooxygenase-2 (COX-2) inhibitors.* BMC Cancer 2008 Aug 14;8:237.

41. Hawk ET, Levin B. *Colorectal cancer prevention.* J Clin Oncol 2005 Jan 10;23(2):378-91.

42. Herszényi L, Farinati F, Miheller P, Tulassay Z. *Chemoprevention of colorectal cancer: feasibility in everyday practice?* Eur J Cancer Prev 2008 Nov;17(6):502-14.

43. Hoffmeister M, Chang-Claude J, Brenner H. *Do older adults using NSAIDs have a reduced risk of colorectal cancer?* Drugs Aging 2006;23(6):513-23.

44. Hoffmeister M, Chang-Claude J, Brenner H. *Individual and joint use of statins and low-dose aspirin and risk of colorectal cancer: a population-based case-control study.* Int J Cancer 2007 Sep 15;121(6):1325-30.

45. Hollestein LM, van Herk-Sukel MP, Ruiter R, de Vries E, Mathijssen RH, Wiemer EA, et al. *Incident cancer risk after the start of aspirin use: results from a Dutch population-based cohort study of low dose aspirin users.* Int J Cancer 2014 Jul 1;135(1):157-65.

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

47. Huang WK, Tu HT, See LC. *Aspirin use on incidence and mortality of gastrointestinal cancers: current state of epidemiological evidence.* Curr Pharm Des 2015;21(35):5108-15.

48. Ishikawa H, Wakabayashi K, Suzuki S, Mutoh M, Hirata K, Nakamura T, et al. *Preventive effects of low-dose aspirin on colorectal adenoma growth in patients with familial adenomatous polyposis: double-blind, randomized clinical trial.* Cancer Med 2013 Feb;2(1):50-6.

49. 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 Apr 18;99(8):608-15.

50. Jacobs RJ, Kodach LL, Hardwick JCH. *Chemoprevention of colorectal cancer: Progress or Pipedream?* Curr Cancer Ther Rev 2010 6(2):143-156.

51. Jankowski J, Hunt R. *Cyclooxygenase-2 inhibitors in colorectal cancer prevention: counterpoint.* Cancer Epidemiol Biomarkers Prev 2008 Aug;17(8):1858-61.

52. Kanik EA, Canbaz H, Colak T, Aydin S. *Chemopreventive effect of nonsteroidal anti-inflammatory drugs on the development of a new colorectal polyp or adenoma in a high-risk population: a meta-analysis.* Curr Ther Res Clin Exp 2004 Jul;65(4):345-52.

53. Kim S, Baron JA, Mott LA, Burke CA, Church TR, McKeown-Eyssen GE, et al. *Aspirin may be more effective in preventing colorectal adenomas in patients with higher BMI (United States).* Cancer Causes Control 2006 Dec;17(10):1299-304.

54. Komiya M, Fujii G, Takahashi M, Iigo M, Mutoh M. *Prevention and intervention trials for colorectal cancer.* Jpn J Clin Oncol 2013 Jul;43(7):685-94.

55. Koretz R. *ACP Journal Club. Meta-analysis: aspirin reduces risk for colon cancer and related mortality at 20 years, particularly when taken for ≥ 5 years.* Ann Intern Med 2011 Mar 15;154(6):JC3-3.

56. Kothari N, Kim R, Jorissen RN, Desai J, Tie J, Wong HL, et al. *Impact of regular aspirin use on overall and cancer-specific survival in patients with colorectal cancer harboring a PIK3CA mutation.* Acta Oncol 2015 Apr;54(4):487-92.

57. Kraus S, Sion D, Arber N. *Can we select patients for colorectal cancer prevention with aspirin?* Curr Pharm Des 2015;21(35):5127-34.

58. Larsson SC, Giovannucci E, Wolk A. *Long-term aspirin use and colorectal cancer risk: a cohort study in Sweden.* Br J Cancer 2006 Nov 6;95(9):1277-9.

59. Lee CS, McNamara D, O'Morain CA. *Aspirin as a chemoprevention agent for colorectal cancer.* Curr Drug Metab 2012a Nov;13(9):1313-22.

60. Lee TJ, Hull MA, Rajasekhar PT, Clifford GM, Ritchie M, James P, et al. *Aspirin users attending for NHS bowel cancer screening have less colorectal neoplasia: chemoprevention or false-positive faecal occult blood testing?* Digestion 2012b;85(4):278-81.

61. Leshno M, Moshkowitz M, Arber N. *Point/Counterpoint: Aspirin is clinically effective in chemoprevention of colorectal neoplasia: point.* Cancer Epidemiol Biomarkers Prev 2008 Jul;17(7):1558-61.

62. Manzano A, Pérez-Segura P. *Colorectal cancer chemoprevention: is this the future of colorectal cancer prevention?* Scientific World Journal 2012;2012:327341.

63. Massat NJ, Moss SM, Halloran SP, Duffy SW. *Screening and primary prevention of colorectal cancer: a review of sex-specific and site-specific differences.* J Med Screen 2013;20(3):125-48.

64. Morgan G. *Aspirin and colorectal cancer?* Eur J Public Health 2004 Mar;14(1):105-6.

65. Movahedi M, Bishop DT, Macrae F, Mecklin JP, Moeslein G, Olschwang S, et al. *Obesity, Aspirin, and Risk of Colorectal Cancer in Carriers of Hereditary Colorectal Cancer: A Prospective Investigation in the CAPP2 Study.* J Clin Oncol 2015 Nov 1;33(31):3591-7.

66. Murra S. *Do ASA and NSAIDs reduce the risk of colorectal cancer?* Cmaj 2005 173(10):1159-1160.

67. Nan H, Morikawa T, Suuriniemi M, Imamura Y, Werner L, Kuchiba A, et al. *Aspirin use, 8q24 single nucleotide polymorphism rs6983267, and colorectal cancer according to CTNNB1 alterations.* J Natl Cancer Inst 2013 Dec 18;105(24):1852-61.

68. Nan H, Hutter CM, Lin Y, Jacobs EJ, Ulrich CM, White E, et al. *Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants.* JAMA 2015 Mar 17;313(11):1133-42.

69. Patrono C. *Low dose aspirin in primary prevention: Cardioprotection, chemoprevention, both, or neither?* European Heart Journal 2013 34(44):3403-3411.

70. Peek RM Jr. *Prevention of colorectal cancer through the use of COX-2 selective inhibitors.* Cancer Chemother Pharmacol 2004 Sep;54 Suppl 1:S50-6.

71. Rao CV, Reddy BS. *NSAIDs and chemoprevention.* Curr Cancer Drug Targets 2004 Feb;4(1):29-42.

72. Reddy BS. *Strategies for colon cancer prevention: combination of chemopreventive agents.* Subcell Biochem 2007;42:213-25.

73. Rennert G. *Prevention and early detection of colorectal cancer--new horizons.* Recent Results Cancer Res 2007;174:179-87.

74. Rothwell PM, Fowkes FG, Belch JF, 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 Jan 1;377(9759):31-41.

75. Ruder EH, Laiyemo AO, Graubard BI, Hollenbeck AR, Schatzkin A, Cross AJ. *Non-steroidal anti-inflammatory drugs and colorectal cancer risk in a large, prospective cohort.* Am J Gastroenterol 2011 Jul;106(7):1340-50.

76. Sehdev A, O'Neil BH. *The Role of Aspirin, Vitamin D, Exercise, Diet, Statins, and Metformin in the Prevention and Treatment of Colorectal Cancer.* Curr Treat Options Oncol 2015 Sep;16(9):43.

77. Serrano D, Lazzeroni M, Decensi A. *Chemoprevention of colorectal cancer: an update.* Tech Coloproctol 2004 Dec;8 Suppl 2:s248-52.

78. Stanojevic-Bakic N. *Cyclooxygenase inhibitors in the chemoprevention of colorectal cancer.* J of BUON 2004 9(2):139-145.

79. Steffen A, Weber MF, Roder DM, Banks E. *Colorectal cancer screening and subsequent incidence of colorectal cancer: results from the 45 and Up Study.* Med J Aust 2014 Nov 3;201(9):523-7.

80. Stürmer 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 Nov 6;147(9):674.

81. Sutcliffe P, Connock M, Gurung T, Freeman K, Johnson S, Kandala NB, et al. *Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview of reviews.* Health Technol Assess 2013a Sep;17(43):1-253.

82. Sutcliffe P, Connock M, Gurung T, Freeman K, Johnson S, Ngianga-Bakwin K, et al. *Aspirin in primary prevention of cardiovascular disease and cancer: a systematic review of the balance of evidence from reviews of randomized trials.* PLoS One 2013b;8(12):e81970.

83. Thiagarajan P, Jankowski JA. *Aspirin and NSAIDs; benefits and harms for the gut.* Best Pract Res Clin Gastroenterol 2012 Apr;26(2):197-206].

84. Thun MJ, Jacobs EJ, Patrono C. *The role of aspirin in cancer prevention.* Nat Rev Clin Oncol 2012 Apr 3;9(5):259-67.

85. Tougeron D, Sha D, Manthravadi S, Sinicrope FA. *Aspirin and colorectal cancer: back to the future.* Clin Cancer Res 2014 Mar 1;20(5):1087-94.

86. Ulrich CM, Bigler J, Potter JD. *Non-steroidal anti-inflammatory drugs for cancer prevention: promise, perils and pharmacogenetics.* Nat Rev Cancer 2006 Feb;6(2):130-40.

87. 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 Mar 6;146(5):361-4.

88. Vinogradova Y, Hippisley-Cox J, Coupland C, Logan RF. *Risk of colorectal cancer in patients prescribed statins, nonsteroidal anti-inflammatory drugs, and cyclooxygenase-2 inhibitors: nested case-control study.* Gastroenterology 2007 Aug;133(2):393-402.

89. Wickham R. *Aspirin and decreased colon cancer risk: challenges interpreting a large prospective trial.* J Adv Pract Oncol 2012 Nov;3(6):399-405.

90. Yasuda O, Takemura Y, Kawamoto H, Rakugi H. *Aspirin: recent developments.* Cell Mol Life Sci 2008 Feb;65(3):354-8.

91. 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.

92. Yeomans ND. *Aspirin: old drug, new uses and challenges.* J Gastroenterol Hepatol 2011 Mar;26(3):426-31.

93. Zhang X, Smith-Warner SA, Chan AT, Wu K, Spiegelman D, Fuchs CS, et al. *Aspirin use, body mass index, physical activity, plasma C-peptide, and colon cancer risk in US health professionals.* Am J Epidemiol 2011 Aug 15;174(4):459-67.