Supplementary Material

Supplementary Methods

Search strategy

MOOSE checklist for meta-analysis of observational study

Supplementary Tables

Supplementary Figures

Supplementary Methods

Search strategy

PubMed (from inception to 25 April)

#1 "colorectal neoplasms"[MeSH Terms] 198667

#2 "colorectal neoplas*"[Title/Abstract] OR "colorectal tumo*"[Title/Abstract] OR "colorectal cancer*"[Title/Abstract] OR "colorectal carcinoma*"[Title/Abstract] OR "colorectal adenocarcinoma*"[Title/Abstract] OR "colorectal malign*"[Title/Abstract] 119424

#3 "colon tumor"[Title/Abstract] OR "colon cancer"[Title/Abstract] OR "colon carcinoma"[Title/Abstract] OR "colon adenocarcinoma"[Title/Abstract] 59736

#4 "rectal tumor"[Title/Abstract] OR "rectal cancer"[Title/Abstract] OR "rectal carcinoma"[Title/Abstract] OR "rectal adenocarcinoma"[Title/Abstract] OR "rectum tumor"[Title/Abstract] OR "rectum cancer"[Title/Abstract] OR "rectum carcinoma"[Title/Abstract] OR "rectum adenocarcinoma"[Title/Abstract] 26968

#5 #1 OR #2 OR #3 OR #4 253563

#6 "aspirin"[Title/Abstract] 48471

#7 "acetylsalicylic acid"[Title/Abstract] 9509

#8 "NSAIDs"[Title/Abstract] 19379

#9 "nonsteroidal anti-inflammatory drugs"[Title/Abstract] 11864

#10 #6 OR #7 OR #8 OR #9 77567

#11 "death"[Title/Abstract] 700655

#12 "mortality"[Title/Abstract] 747496

#13 "survival"[Title/Abstract] 926214

#14 #11 OR #12 OR #13 2027380

#15 #5 AND #10 AND #14 538

Embase

#1 'colorectal cancer'/exp 176652

#2 'colorectal neoplas*':ti,ab 5780

#3 'colorectal tumo*':ti,ab 9569

#4 'colorectal carcinoma*':ti,ab 21898

#5 'colorectal adenocarcinoma*':ti,ab 6247

#6 'colorectal malign*':ti,ab 1152

#7 #2 OR #3 OR #4 OR #5 OR #6 41116

#8 'colon tumor':ti,ab 3105

#9 'colon cancer':ti,ab 65730

#10 'colon carcinoma':ti,ab 13230

#11 'colon adenocarcinoma':ti,ab 5553

#12 #8 OR #9 OR #10 OR #11 81982

#13 'rectal tumor':ti,ab 986

#14 'rectal cancer':ti,ab 35025

#15 'rectal carcinoma':ti,ab 4709

#16 'rectal adenocarcinoma':ti,ab 3205

#17 'rectum tumor':ti,ab 62

#18 'rectum cancer':ti,ab 837

#19 'rectum carcinoma':ti,ab 378

#20 'rectum adenocarcinoma':ti,ab 119

#21 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 40,954

#22 #1 OR #7 OR #12 OR #21 287095

#23 'aspirin':ti,ab 73464

#24 'acetylsalicylic acid':ti,ab 12681

#25 'nsaids':ti,ab 32325

#26 'nonsteroidal anti-inflammatory drugs':ti,ab 14024

#27 #23 OR #24 OR #25 OR #26 117914

#28 'death':ti,ab 980289

#29 'mortality':ti,ab 1086766

#30 'survival':ti,ab 1363439

#31 #28 OR #29 OR #30 2890894

#32 #22 AND #27 AND #31 798

Cochrane Library

#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees 7912

#2 (colorectal neoplas*):ti,ab,kw 7595

#3 (colorectal tumo*):ti,ab,kw 4637

#4 (colorectal cancer*):ti,ab,kw 13779

#5 (colorectal carcinoma*):ti,ab,kw 2035

#6 (colorectal adenocarcinoma*):ti,ab,kw 1176

#7 (colorectal malign*):ti,ab,kw 1043

#8 #2 or #3 or #4 or #5 or #6 or #7 15414

#9 (colon tumor):ti,ab,kw 1865

#10 (colon cancer):ti,ab,kw 5249

#11 (colon carcinoma):ti,ab,kw 925

#12 colon adenocarcinoma 839

#13 #9 or #10 or #11 or #12 5896

#14 (rectal tumor):ti,ab,kw 1788

#15 (rectal cancer):ti,ab,kw 4797

#16 (rectal carcinoma):ti,ab,kw 956

#17 (rectal adenocarcinoma):ti,ab,kw 801

#18 (rectum tumor):ti,ab,kw 1440

#19 (rectum cancer):ti,ab,kw 3365

#20 (rectum carcinoma):ti,ab,kw 822

#21 (rectum adenocarcinoma):ti,ab,kw 697

#22 #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 6613

#23 #1 or #8 or #13 or #22 22882

#24 (aspirin):ti,ab,kw 13464

#25 (acetylsalicylic acid):ti,ab,kw 5176

#26 (NSAIDs):ti,ab,kw 4423

#27 (nonsteroidal anti-inflammatory drugs):ti,ab,kw 4628

#28 #24 or #25 or #26 or #2722274

#29 (death):ti,ab,kw 59156

#30 (mortality):ti,ab,kw 86384

#31 (survival):ti,ab,kw 99941

#32 #29 or #30 or #31 185225

#33 #23 and #28 and #32 124

MOOSE checklist for meta-analysis of observational study

Category	Reported on
Reporting of background should include	
Problem definition	Introduction
Hypothesis statement	
Description of study outcome(s)	
Type of exposure or intervention used	
Type of study designs used	
Study population	
Reporting of search strategy should include	
Qualifications of searchers (eg, librarians and investigators)	search
Search strategy, including time period included in the synthesis and keywords	strategy and selection criteria
Effort to include all available studies, including contact with authors	
Databases and registries searched Search software used, name and version, including special features used (eg, explosion)	
Use of hand searching (eg, reference lists of obtained articles)	
List of citations located and those excluded, including justification	
Method of addressing articles published in languages other than English	
Method of handling abstracts and unpublished studies	
Description of any contact with authors	
Reporting of methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	data analysis
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	
Assessment of heterogeneity	
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	
Provision of appropriate tables and graphics	
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Results,

Table giving descriptive information for each study included	Table 1, Table 2, Figure 1, Figure 2, Supplementary Table 2-4, Supplementary Figure 2-3
Results of sensitivity testing (eg, subgroup analysis)	
Indication of statistical uncertainty of findings	
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	Discussion
Justification for exclusion (eg, exclusion of non–English-language citations)	
Assessment of quality of included studies	
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Conclusions, Disclosures
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	
Guidelines for future research	
Disclosure of funding source	

Supplementary Table 1. Ongoing clinical trials of aspirin as adjuvant agent in CRC treatment

Trail name[a]	Trail number	Starting time	Design	Patients	Country	Dose and duration	Primary outcome	Secondary outcome
ASCOLT	NCT00565708	2007	Double-blind, placebo controlled, multicenter RCT	Duke B and high risk Duke C CRC	Australia	200mg once daily for 3 years	DFS	OS
ASPIRIN	NCT02301286	2015	Double-blind, placebo controlled RCT	Stage II-III colon cancer patients aged⩾45 years old	Netherlands	80mg once daily for 5 years	5-year OS	DFS, time to treatment failure
APREMEC	NCT02607072	2015	Double-blind, placebo controlled, multicenter RCT	Postsurgical non-metastasized colorectal cancer patients	China	200mg daily, 100mg daily	3-year DFS	—
ADD-Aspirin	NCT02804815	2015	Double-blind, placebo controlled RCT	Non-metastatic common solid tumors (colorectal cancer, breast cancer, prostate cancer, gastro-oesophageal cancer) aged⩾ 16 years old	UK	100mg, 300mg daily for at least 5 years	OS of all cohorts combined, invasive DFS in breast cancer cohort, DFS in colorectal cancer cohort, OS in gastro-oesophageal cancer cohort, biochemical RFS in prostate cancer cohort	Adherence, Number of participants with serious hemorrhage, Number of participants with treatment-related cardiovascular events, Number of participants with second malignancies as assessed by case report form, Number of participants that show a decline in cognition and extent of decline
Adjuvant Aspirin Treatment for Colon Cancer Patients	NCT02467582	2016	Double-blind, placebo controlled, multicenter RCT	*PIK3CA* mutated colon cancer patients aged ⩾ 18 years old	Belgium, Germany, Hungary, Switzerland	100mg daily for 3 years	DFS	time to recurrence, OS, cancer-specific survival, adverse events

ALASCCA	NCT02647099	2016	Double-blind, placebo controlled, biomarker-based RCT	*PIK3CA* mutated colorectal cancer patients aged ⩾ 18 years old	Sweden	160mg daily for 3 years	Time to recurrence	DFS, OS, frequency and severity of adverse events
ASAMET	NCT03047837	2017	Double-blind, placebo controlled, multicenter RCT with 2×2 factorial design biomarker	Stage I-III colorectal cancer patients aged⩾18 years old	Italy	Aspirin 100mg daily for 12 months, Metformin 850mg daily for 12 months	*NF-κB* in colonic tissues	*Ps6k*, *p53*, beta-catenin, *PI3K* in colonic tissues; IL-6, CRP, VEGF and HOMA index in blood; gene expression levels of candidate genes and pathways; metformin concentration in tissue and blood
ASAC	NCT03326791	2017	Double-blind, placebo controlled, multicenter RCT	patients (aged⩾18 years old) treated with resection for colorectal cancer liver metastases	Denmark, Norway, Sweden	160mg once daily for 3 years or till disease recurrence	DFS	Time to recurrence, OS, health-related quality of life, cost-effectiveness analyses
ICAR	NCT03170115	2017	RCT	High risk locally advanced rectal cancer	Brazil	100mg daily during the chemoradiotherapy	Tumor downstaging after induction chemotherapy	Radiological Tumor response rate after induction chemotherapy, Pathological Tumor response rate, Pathologic complete response, DFS, OS
ASPIRIN Trial Belgium	NCT03464305	2018	Double-blind, placebo controlled RCT	Stage II-III colon cancer patients aged⩾45 years old	Antwerp	80mg once daily for 5 years	5-year OS	DFS, time to treatment failure
ASPIK French	NCT02945033	2018	Double-blind, placebo controlled RCT	*PIK3CA* mutated stage III or II high risk colon cancer patients aged⩾18 years old	France	100mg once daily for 3 years	Number of patient with local or distant recurrence or second colorectal cancer or death from any cause,	Number of patient with local or distant recurrence or second colorectal cancer or death from any cause, whichever occurred first; Number of alive patient;

		whichever occurred first	Number of pills taken by the patient for compliance evaluation; Number of severe bleeding grade 3-4 events; Number of participants with treatment-related adverse events

[a]All of these trials are ongoing studies, relevant data or papers are not published now. CRC = colorectal cancer, RCT = randomized clinical trial, DFS = disease free survival, OS = overall survival, NF-κB = nuclear factor kappa B, CRP = c-reactive protein, VEGF = vascular endothelial growth factor, HOMA index = homeostasis model assessment (fasting blood glucose (mmol/L)*insulin (mU/L))/22.5.

Supplementary Table 2. The risk estimate in individual study

Study	Country	Aspirin use and the prognosis of patients				Adjustments
		Timing of Aspirin use[a]	Molecular marker	Site of primary tumor	Tumor stage	
Chan AT, et al. 2009 (1)	The USA	HR(95%CI) Timing 4 CSS 0.89 (0.59-1.35) OS 0.95 (0.71-1.28) Timing 5 CSS 0.53 (0.33-0.86) OS 0.68 (0.51-0.92) Timing 6 CSS 0.71 (0.53-0.95) OS e0.79 (0.65-0.97)	HR(95%CI) COX2 High Timing 4 CSS 0.56 (0.23-1.33) Timing 5 CSS 0.22 (0.07-0.74) Timing 6 CSS 0.39 (0.20-0.76) OS 0.62 (0.42-0.93) Low Timing 6 CSS 1.22 (0.36-4.18) OS 1.05 (0.55-2.02)	—	I-III	age, sex, date of diagnosis of cancer, stage, tumor site, histological grade, time from diagnosis to first measurement of postdiagnosis aspirin use, smoking, metabolic equivalent tasks per week after diagnosis, BMI, family history in a first-degree relative, use of aspirin prediagnosis
Zell JA, et al. 2009 (2)	The USA	HR(95%CI) Timing 2 CSS 0.62 (0.41-0.94) OS 0.74 (0.54-1.01)	—	—	—	age, tumor site, stage, time from NSAIDs assessment to CRC diagnosis, surgery, family history in a first-degree relative
Din FV, et al. 2010 (3)	The UK	OR(95%CI) Timing 2 CSS 1.03 (0.80-1.31) OS 1.12 (0.90-1.39)	—	—	—	age, sex, stage, family history
Case-control						
Coghill AE, et al. 2011 (4)	The USA	HR(95%CI) Timing 2 CSS 0.76 (0.61-0.95)	—	HR(95%CI) Colon Timing 2 CSS 0.62 (0.40-0.94) Rectal Timing 2 CSS 1.03 (0.72-1.47)	—	age, sex, stage, BMI, screening, smoking, diabetes and prior inflammatory conditions, first-course treatment
Bastiaannet E, et al. 2012 (5)	The Netherland	RR(95%CI) Timing 4 OS 0.88 (0.83-0.94) Timing 5 OS 0.77 (0.63-0.95)	—	RR(95%CI) Colon Timing 3 OS 1.5 (1.2-1.8) Timing 4	—	sex, age, comorbidity, year of incidence, grade, stage, chemotherapy (colon cancer), radiotherapy (rectal cancer), surgery

				OS 0.89 (0.82-0.96) Timing 5 OS 0.65 (0.50-0.84) Rectal Timing 3 OS 1.4 (1.0-2.0) Timing 4 OS 0.87(0.78-0.97) Timing 5 OS 1.10 (0.79-1.54)		
Liao X, et al. 2012 (6)	The USA	—	HR(95%CI) *PIK3CA* Timing 4 Wild type CSS 0.92 (0.56-1.51) OS 0.85 (0.60-1.21) Mutation CSS 0.18 (0.04-0.92) OS 0.60 (0.26-1.40) Timing 5 Wild type CSS 0.90 (0.53-1.54) OS 0.97 (0.68-1.37) Mutation CSS 0.28 (0.04-2.10) OS 0.59 (0.24-1.41) Timing 6 Wild type CSS 0.96 (0.69-1.32) OS 0.94 (0.75-1.17) Mutation CSS 0.18 (0.06-0.61) OS 0.54 (0.31-0.94)	—	—	age, sex, year of diagnosis, stage, time from diagnosis to first measurement of aspirin use after diagnosis, regular use or nonuse of aspirin before diagnosis, tumor site, tumor differentiation, BMI, microsatellite instability status, CpG island methylator phenotype, *KRAS* mutation, *BRAF* mutation, *LINE-1* methylation, and the presence or absence of *COX2* expression.
Reimers MS, et al. 2012 (7)	The Netherland	RR(95%CI) Timing 5 OS 0.59 (0.44-0.81)	—	—	—	age, sex, stage, year of diagnosis, grade, adjuvant chemotherapy, surgery, comorbidity
Walker AJ, et al. 2012 (8)	The UK	HR(95%CI) Timing 4	—	—	—	age, gender, smoking, BMI, alcohol use and comorbidity

		OS 0.86 (0.76-0.98) Timing 5 OS 0.99 (0.84-1.16) Timing 6 OS 0.91(0.82-1.00)				
Chae YK, et al. 2013 (9) Conference abstract	The USA	HR(95%CI) Timing 1 OS 1.37 (0.80-2.35)	HR(95%CI) *PIK3CA* Timing 1 Wild type OS 1.80 (1.01-3.23) Mutation OS 0.75 (0.17-3.20)	—	—	NA
Domingo E, et al. 2013 (10)	The UK	—	HR(95%CI) *PIK3CA* Timing 6 Wild type OS 0.95 (0.56-1.61) RFS 0.94 (0.59-1.49) Mutation OS 0.29(0.04-2.33) RFS 0.11 (0.001-0.832) *COX-2* Timing 6 High RFS 0.55 (0.16-1.91) Low RFS 0.76 (0.45-1.29)	—	II-III	age, sex, stage, tumor site, tumor grade, microsatellite instability, prior chemotherapy or radiotherapy
McCowan C, et al. 2013 (11)	The UK	HR(95%CI) Timing 2 CSS 0.96 (0.84-1.11) OS 0.99 (0.90-1.09) Timing 6 CSS 0.58 (0.45-0.75) OS 0.67 (0.57-0.79)	—	HR(95%CI) Colon Timing 6 OS 0.72 (0.57-0.91) Rectal Timing 6 OS 0.80 (0.58-1.11)	—	age, sex, stage, aspirin use pre-diagnosis, socio-economic status
Sun R, et al. 2013 (12)	The USA	—	HR(95%CI) *β-catenin*	—	—	NA

Conference abstract			Timing 6 Positive CSS 0.53 (0.30-0.95) OS 0.65 (0.53-0.80) Negative CSS 1.06 (0.62-1.83) OS 0.84 (0.70-1.01)			
Cardwell CR, et al. 2014 (13) Case-control	The UK	OR(95%CI) Timing 2 CSS 1.03 (0.91-1.17) Timing 4 CSS 0.72 (0.44-1.18) Timing 5 CSS 0.95 (0.69-1.32) Timing 6 CSS 1.06 (0.92-1.24) OS 1.06 (0.94-1.19)	—	OR(95%CI) Colon Timing 2 CSS 0.99 (0.84-1.17) Timing 4 CSS 0.88 (0.49-1.59) Timing 5 CSS 0.93 (0.59-1.47) Timing 6 CSS 1.02 (0.83-1.25) OS 1.10 (0.86-1.18) Rectal Timing 2 CSS 1.11 (0.91-1.35) Timing 4 CSS 0.43 (0.16-1.13) Timing 5 CSS 1.00 (0.61-1.65) Timing 6 CSS 1.10 (0.88-1.38) OS 1.12 (0.93-1.36)	—	stage, grade, surgery within 6 months of diagnosis, chemotherapy within 6 months, radiotherapy within 6 months, statin use, metformin use, comorbidities, smoking
Goh CH, et al. 2014 (14)	Singapore	unadjusted HR(95%CI) Timing 1 CSS 1.06 (0.71-1.58) RFS 1.04 (0.72-1.48) Timing 3 CSS 1.76 (1.09-2.83) RFS 1.56 (1.01-2.43) Timing 5 CSS 0.81 (0.51-1.28) RFS 0.86 (0.58-1.27)	—	—	I-III	NA

Reimers MS, et al. 2014 (15) Colon cancer only	The Netherland	—	—	HR(95%CI) Colon Timing 6 OS 0.64（0.49-0.83） *PIK3CA* Timing 6 Mutation OS 0.73 (0.33-1.63) Wild type OS 0.55 (0.40-0.75) *COX2* Timing 6 High OS 0.68(0.48-0.97) Low OS 0.59(0.38-0.97) *HLA* Timing 6 Positive OS 0.53 (0.38-0.74) Negative OS 1.03 (0.66-1.61)	—	sex, age, comorbidity, year of incidence, histologic grade, stage, and chemotherapy
Kothari N, et al. 2015 (16)	Australia	—	Unadjusted HR(95%CI) *PIK3CA* Timing 2 Mutation CSS 0.60 (0.34-1.16) OS 0.96 (0.58-1.57)	—	—	NA
Ng K, et al. 2015 (17) Colon cancer only	The USA	—	—	HR(95%CI) Colon Timing 1 OS 0.63 (0.35-1.12) RFS 0.51 (0.28-0.95) DFS 0.68 (0.42-1.11)	III	age, sex, race, adjuvant treatment arm, family history, baseline performance status, depth of invasion, number of positive lymph nodes, grade, BMI, physical activity

Restivo A, et al. 2015 (18) Rectal cancer only	Italy	—	—	HR(95%CI) Rectal Timing 5 OS 0.21 (0.05-0.89) PFS 0.2 (0.07-0.60) Risk of metastasis 0.30 (0.10-0.86) Local recurrence 0.6 (0.06-4.5)	II-III	NA
Zanders MM, et al. 2015 (19)	The Netherland	HR(95%CI) Timing 1 OS 0.96 (0.73-1.26)	—	HR(95%CI) Colon Timing 1 OS 0.76 (0.55-1.06) Rectal Timing1 OS 1.49 (0.86-2.60)	HR(95%CI) Stage I-III Timing 1 OS 0.98(0.70-1.37) Stage IV Timing 1 OS 1.20(0.66-2.17)	age, sex, calendar year of CRC diagnosis, tumor site, stage, administration of surgery/ radiotherapy and/or chemotherapy, use of metformin, sulfonylurea derivatives, insulin, other diabetes medication, statins and aspirin after diagnosis as time-dependent cumulative exposure and as time-dependent ever-never terms, the use of these drugs before diagnosis as a dichotomized variable
Babic A, et al. 2016 (20)	The USA	—	HR(95%CI) sTNF-RII Timing 6 High OS 0.52 (0.20-1.33)	—	—	NA
Bains SJ, et al. 2016 (21)	Norway	HR(95%CI) Timing 4 CSS 0.77 (0.71-0.84) OS 0.86 (0.81-0.92) Timing 5 CSS 1.00 (0.87-1.14) OS 1.06 (0.96-1.18) Timing 6 CSS 0.85(0.79-0.92) OS 0.95(0.90-1.01)	—	HR(95%CI) Rectal Timing 6 CSS 0.79 (0.69-0.90) OS 0.91 (0.82-1.02)	HR(95%CI) Stage IV Timing 6 CSS 0.85 (0.74-0.98) OS 0.91 (0.80-1.03)	sex, age, site of disease, tumor differentiation, disease stage, surgery, ACE inhibitor/ARB use, NSAIDs/coxib use, statin use, beta blocker use, metformin use
Frouws MA, et al. 2017 (22)	Netherland	—	—	HR(95%CI) Colon Timing 4 OS 0.55 (0.48-0.63)	—	age, sex, stage, surgery, radiotherapy, chemotherapy, comorbidities

				Timing 5 OS 0.56 (0.43-0.72) Rectal Timing 4 OS 0.63 (0.52-0.75) Timing 5 OS 0.41 (0.27-0.63)		
Frouws MA, et al. 2017 (23)	Netherland	HR(95%CI) Timing 2 OS 0.42 (0.37-0.48)	—	—	—	age, sex, stage, number of comorbidities, treatment: surgery/ radiotherapy / chemotherapy
Frouws MA, et al. 2017 (24)	Netherland	RR(95%CI) Timing 5 OS 0.64 (0.48-0.86)	RR(95%CI) *BRAF* Timing 5 Wild type OS 0.60 (0.44-0.83) Mutation OS 1.11 (0.57-2.16) *KRAS* Timing 5 Wild type OS 0.67 (0.47-0.97) Mutation OS 0.56 (0.34-0.93)	—	—	age, comorbidity, grade, stage and chemotherapy
Giampieri R, et al. 2017 (25)	Italy	HR(95%CI) Timing 5 OS 0.43 (0.26-0.72) PFS 0.48 (0.30-0.79)	—	—	—	NA
Gray RT, et al. 2017 (26) Colon cancer only	Northern Ireland			HR(95%CI) Colon Timing 1 CSS 0.69 (0.47-0.98) OS 0.76 (0.57-1.03) *PIK3CA* Timing 1 Wild type CSS 0.69 (0.46-1.05)	II-III	age, sex, stage, year of diagnosis, grade, MSI status, Eastern Cooperative Oncology Group performance status, family history of colorectal cancer, adjuvant chemotherapy use, Charlson comorbidity score

				OS 0.80 (0.57-1.13) Mutation CSS 0.66 (0.22-2.01) OS 0.79 (0.35-1.78) *COX-2* Timing 1 High CSS 0.55 (0.32-0.96) OS 0.64 (0.42-0.98) Low CSS 1.19 (0.68-2.07) OS 1.28 (0.80-2.03)		
Hamada T, et al. 2017 (27)	The USA	HR(95%CI) Timing 6 CSS 0.65 (0.40-1.07) OS 0.74 (0.50-1.09)	HR(95%CI) *PD-L1* Low Timing 4 CSS 0.09 (0.02-0.32) OS 0.26 (0.11-0.59) Timing 5 CSS 0.17 (0.02-1.41) OS 0.54 (0.22-1.32) Timing 6 CSS 0.16 (0.06-0.41) OS 0.38 (0.23-0.65) High Timing 4 CSS 1.02 (0.49-2.15) OS 0.87 (0.48-1.60) Timing 5 CSS 1.25 (0.61-2.59) OS 1.31 (0.64-2.68) Timing 6 CSS 1.01 (0.61-1.67) OS 0.98 (0.62-1.55)	—	—	age at diagnosis, year of diagnosis, tumor differentiation, disease stage, microsatellite instability status, long interspersed nucleotide element-1 methylation level, and *CDX2* expression status
Hua XW, et al. 2017 (28)	The USA	HR(95%CI) Timing 3 OS 1.05 (0.63-1.74)	—	—	—	sex, body mass index, smoking status, stage at diagnosis, and time between baseline and follow-up survey

		Timing 4 CSS 0.45(0.19-1.08) OS 0.89(0.63-1.26) CVDS 0.98 (0.41-2.32) Timing 5 CSS 0.39 (0.19-0.78) OS 0.63 (0.46-0.85) CVDS 0.52 (0.21-1.28) Timing 6 CSS 0.44 (0.25-0.77) OS 0.74 (0.59-0.94) CVDS 0.68 (0.36-1.29)				
Murphy C, et al. 2017 (29) Colon cancer only	Australia		—	Unadjusted HR(95%CI) Colon Timing 2 OS 1.26 (0.72-2.21) RFS 0.63(0.30-1.32) *PIK3CA* Timing 2 Mutation OS 1.76 (0.51-6.04) RFS 0.45 (0.06-3.70) Wild type OS 2.50 (1.46-4.28) RFS 0.77 (0.34-1.73)	II	NA
Gray RT, et al. 2018 (30)	Northern Ireland	HR(95%CI) Timing 4 CSS 0.80 (0.56-1.13) OS 0.88 (0.67-1.17) Timing 5 CSS 1.51 (1.12-2.05) OS 1.53(1.19-1.95) Timing 6 CSS 1.17 (1.00-1.36) OS 1.21 (1.07-1.37) CVDS 1.63 (1.15-2.29)	—	HR(95%CI) Colon Timing 6 CSS 1.13 (0.94-1.36) Rectal Timing 6 CSS 1.26 (0.94-1.69)	—	age, sex, year of diagnosis, deprivation, tumor site (colon or rectum), stage, grade, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities, statin use

Rouette J, et al. 2018 (31) Conference abstract	Canada	HR(95%CI) Timing 2 OS 1.09 (0.96-1.22)	—	—	—	NA
Tsoi K KF, et al. 2018 (32) Case-control	Hong Kong, China	Unadjusted HR(95%CI) Timing 1 CSS 0.59 (0.56-0.62) OS 1.43(1.42-1.44) GIBS 1.09 (1.00-1.19) CVDS 4.22 (4.11-4.33) CBDS 2.12 (2.06-2.19)	—	Unadjusted HR(95%CI) Colon Timing 1 CSS 0.60 (0.57-0.64) Rectal Timing 1 CSS 0.56 (0.51-0.61)	—	NA
Ventura L, et al. 2018 (33)	Italy	HR(95%CI) Timing 1 CCS 0.71 (0.52-0.97) OS 1.18 (1.12-1.23) Risk of major bleeding 1.11 (0.86-1.44)	—	HR(95%CI) Colon Timing 1 CCS 0.71 (0.50-1.01) Rectal Timing 1 CCS 0.79 (0.39-1.59)	—	sex, age, consumption of drugs linked with metabolic syndrome, socio-economics status
Sung JJY, et al. 2019 (34)	Hong Kong, China	HR(95%CI) Timing 4 CCS 0.70 (0.60-0.82) OS 0.62 (0.56-0.69) CVDS 1.38 (0.89-2.12) CBDS 0.88 (0.52-1.49) Timing 5 CCS 0.87 (0.78-0.96) OS 0.89 (0.83-0.96) CVDS 3.14 (2.32-4.26) CBDS 2.23 (1.47-3.38)	—	Unadjusted HR(95%CI) Colon Timing 4 CCS 0.63 (0.53-0.76) Timing 5 CCS 0.88 (0.78-0.99) Rectal Timing 4 CCS 1.00 (0.72-1.40) Timing 5 CCS 1.00 (0.83-1.23)	—	Cardiovascular and cerebrovascular diseases, NSAIDs, chemotherapy

[a]Timing 1-Ever use, Timing 2- Prediagnosis use, Timing 3- aspirin use only before diagnosis, Timing 4- Continued use, Timing 5- Postdiagnosis use, Timing 6-Aspirin use after diagnosis regardless of its usage before diagnosis. HR = hazard ratio, RR = risk ratio, OR = odds ratio, CI = confidence interval, CSS = cancer-specific survival, OS = overall survival, BMI = body mass index, NSAIDs = non-steroidal anti-inflammatory drugs; CRC = colorectal cancer, LINE-1 = long interspersed nucleotide element-1, COX2 = cyclooxygenase-2, RFS = relapse free survival, DFS = disease free survival, PFS = progression free survival, sTNF-RII = soluble tumor necrosis factor-receptor II.

Supplementary Table 3. Newcastle-Ottawa Scale for Cohort Study Quality[a]

Study	Selection				Comparability[b]	Outcome		
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up cohorts
Chan AT, et al. 2009 (1)	--	☆	--	☆	☆☆	☆	☆	☆
Zell JA, et al. 2009 (2)	--	☆	--	☆	☆☆	☆	--	☆
Coghill AE, et al. 2011 (4)	☆	☆	--	☆	☆☆	☆	☆	☆
Bastiaannet E, et al. 2012 (5)	☆	☆	☆	☆	☆☆	☆	☆	☆
Liao X, et al. 2012 (6)	☆	☆		☆	☆☆	☆	☆	☆
Reimers MS, et al. 2012 (7)	--	☆	☆	☆	☆☆	☆	--	☆
Walker AJ, et al. 2012 (8)	☆	☆	--	☆	☆	☆	☆	☆
Chae YK, et al. 2013 (9)	--	☆	--	☆	--	--	--	☆
Domingo E, et al. 2013 (10)	--	☆	--	☆	☆☆	☆	☆	☆
McCowan C, et al. 2013 (11)	☆	☆	☆	☆	☆☆	☆	☆	☆
Sun R, et al. 2013 (12)	☆	☆	--	☆	--	--	--	☆
Goh CH, et al. 2014 (14)	☆	☆	☆	☆	--	☆	--	☆
Reimers MS, et al. 2014 (15)	☆	☆	☆	☆	☆☆	☆	--	☆
Kothari N et al, 2015 (16)	--	☆	☆	☆	--	--	☆	☆
Ng K, et al. 2015 (17)	--	☆	--	☆	☆	☆	☆	☆
Restivo A, et al. 2015 (18)	--	☆	☆	☆	--	--	☆	☆
Zanders MM, et al. 2015 (19)	--	☆	☆	☆	☆☆	☆	☆	☆
Babic A, et	☆	☆	☆	☆	--	--	--	☆

al. 2016 (20)								
Bains SJ, et al, 2016 (21)	☆	☆	☆	☆	☆☆	☆	☆	☆
Frouws MA, et al. 2017 (22)	☆	☆	☆	☆	--	--	--	☆
Frouws MA, et al. 2017 (23)	☆	☆	☆	☆	☆☆	☆	☆	☆
Frouws MA, et al. 2017 (24)	☆	☆	☆	☆	☆☆	☆	--	☆
Giampieri R, et al. 2017 (25)	--	☆	--	☆	--	--	--	☆
Gray RT, et al. 2017(26)	--	☆	☆	☆	☆☆	☆	☆	☆
Hamada T, et al. 2017 (27)	☆	☆	--	☆	☆☆	☆	☆	☆
Hua XW, et al, 2017 (28)	☆	☆	--	☆	☆☆	☆	☆	☆
Murphy C, et al. 2017 (29)	--	☆	☆	☆	--	☆	--	☆
Gray RT, et al, 2018 (30)	--	☆	☆	☆	☆☆	☆	☆	☆
Rouette J, et al. 2018 (31)	☆	☆	--	☆	--	--	--	☆
Ventura L, et al. 2018 (33)	☆	☆	--	☆	☆	☆	--	☆
Sung JJY, et al. 2019 (34)	☆	☆	☆	☆	--	☆	--	☆

[a] A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

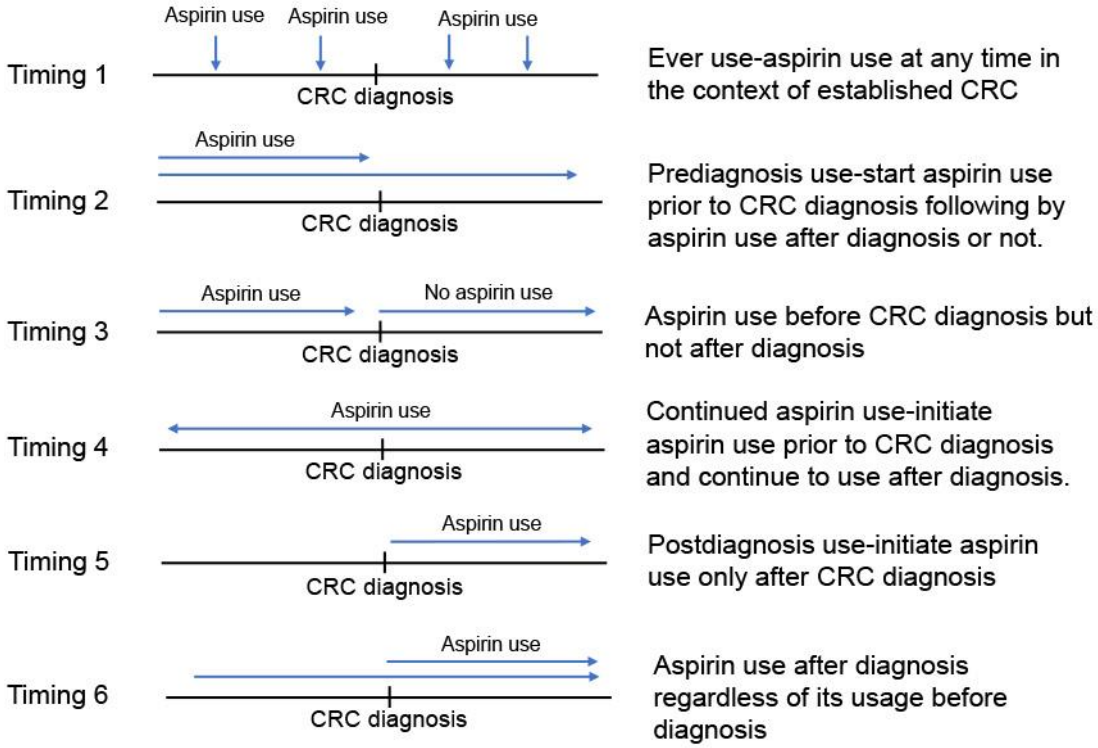
[b]If the study controls for age (the most important factor) or cancer stage (the second important factor), one star can be awarded. If the study controls for both factors, two stars can be awarded.

Supplementary Table 4. Newcastle-Ottawa Scale for Case-Control Study Quality[a]

Study	Selection				Comparability[b]	Exposure		
	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Assessment of exposure	Same method of ascertainment of cases and controls	Non-response rate
Din FV, et al. 2010 (3)	☆	--	☆	☆	☆☆	--	☆	
Cardwell CR, et al. 2014 (13)	☆	☆	☆	☆	☆	--	☆	
Tsoi K KF, et al. 2018 (32)	☆	☆	☆	☆	--	--	☆	

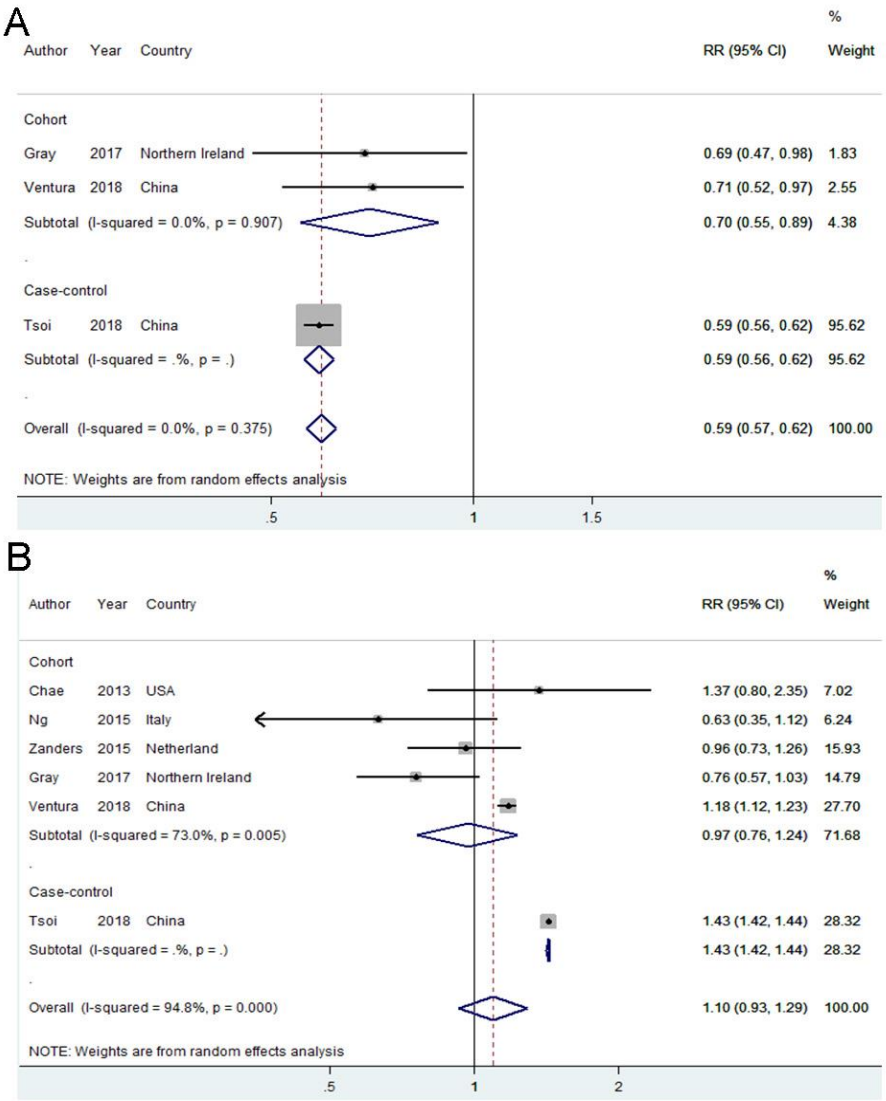
[a] A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.
[b] If the study controls for age (the most important factor) or cancer stage (the second important factor), one star can be awarded. If the study controls for both factors, two stars can be awarded.

Supplementary Figures

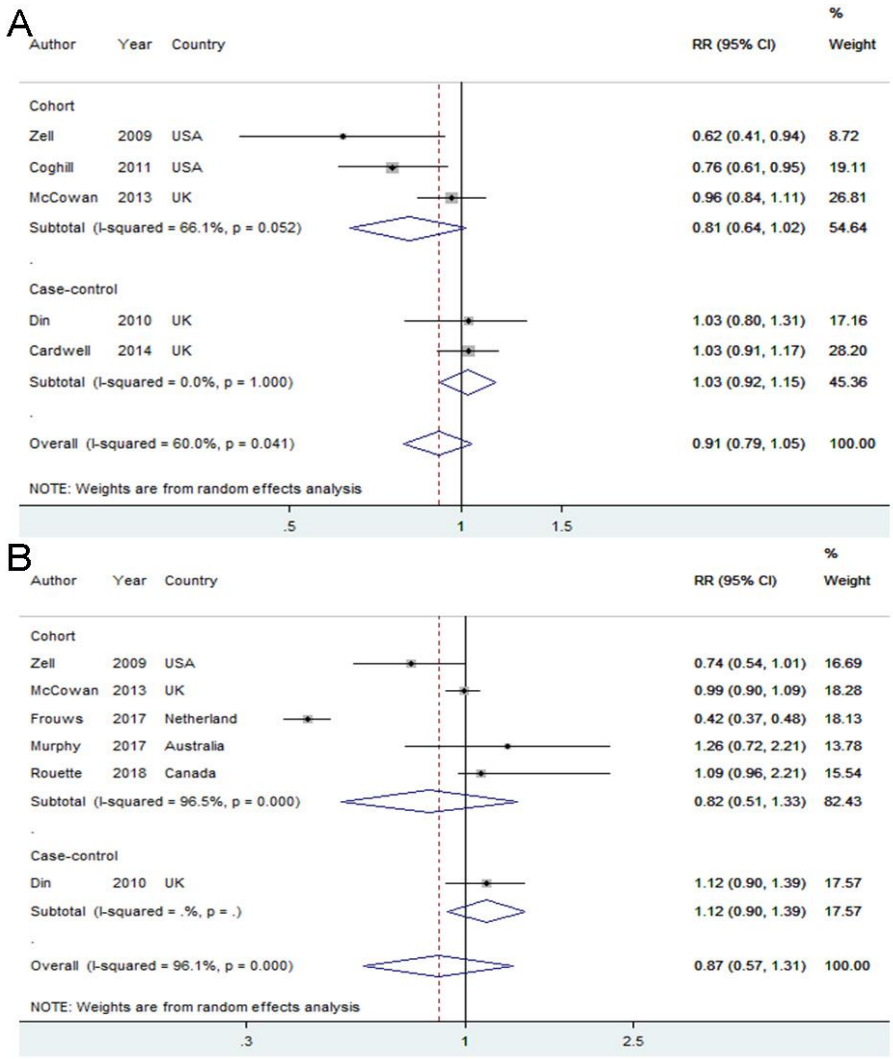


Supplementary Figure 1. Graphical illustration of different timing of aspirin use.

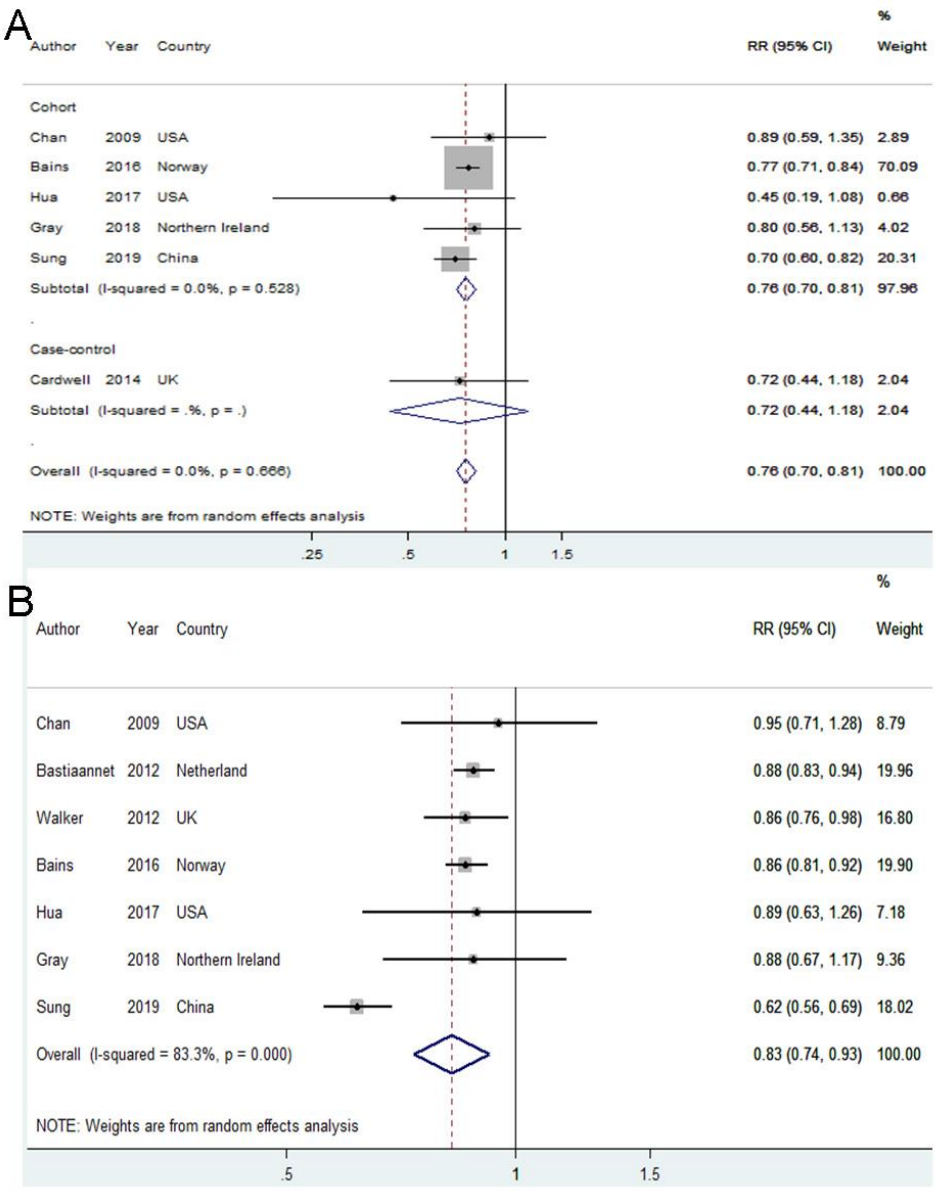
CRC = colorectal cancer.



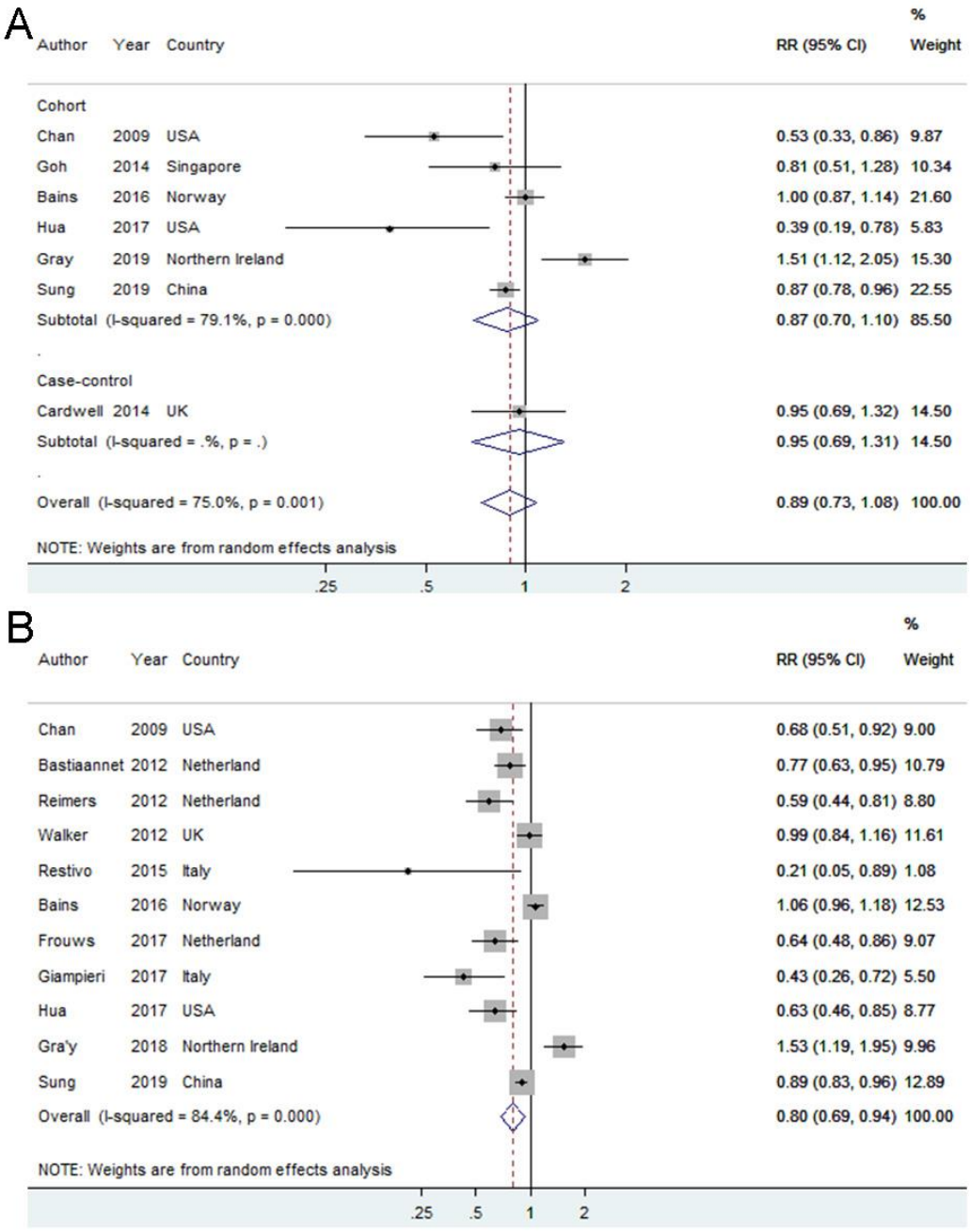
Supplementary Figure 2. Forest plots of ever use of aspirin in relation to CRC mortality. A cancer-specific mortality; B all-cause mortality. RR was calculated using the Mantel-Haenszel random-effects model and P value from the z test to exam whether the pooled effect was statistically significant. All statistical tests were 2-sided. The error bars represents 95%CI of individual study, and the size of the diamonds in grey represents the weight of each study in the pooled estimate. Diamonds in blue represent the pooled effect. RR = risk ratio; CI = confidence interval.



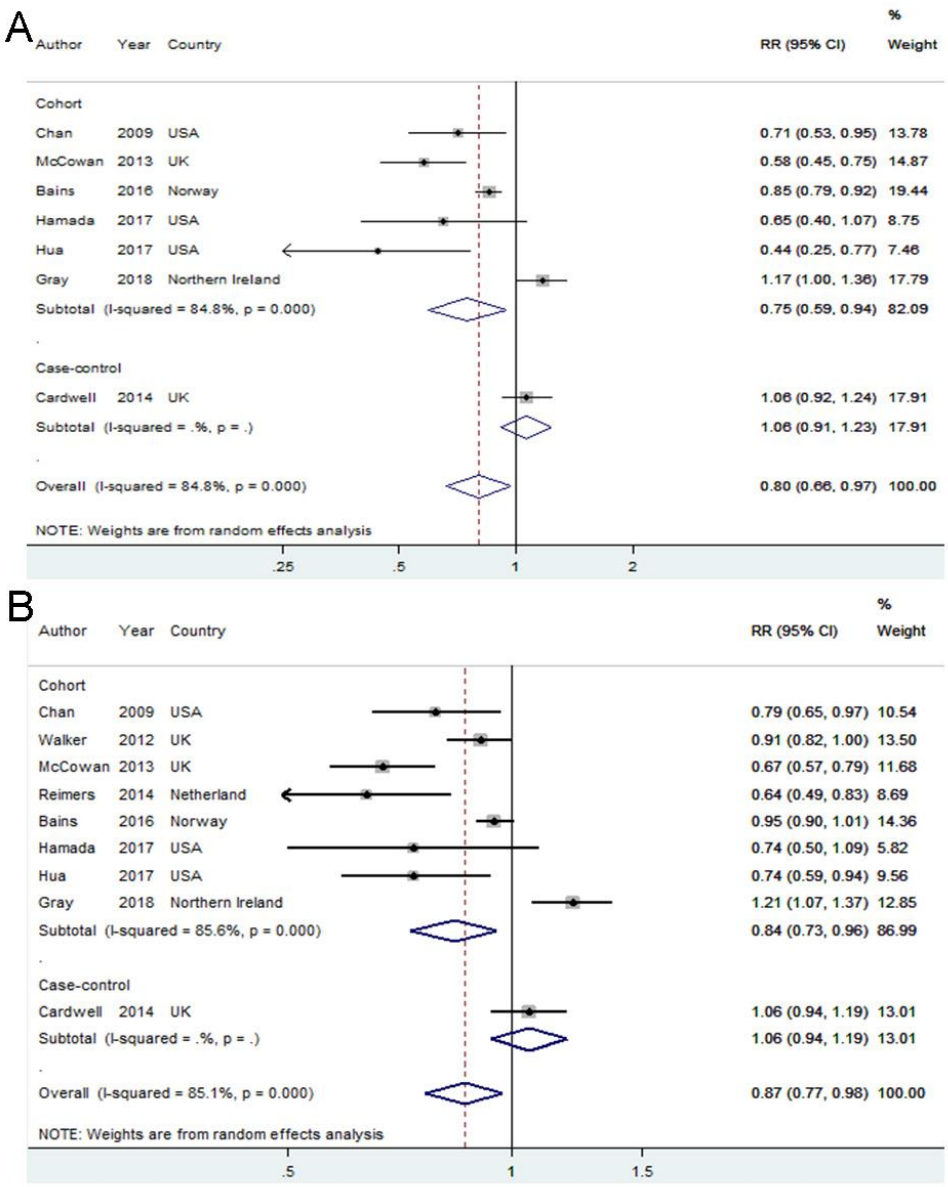
Supplementary Figure 3. Forest plots of prediagnosis use of aspirin use in relation to CRC mortality. A cancer-specific mortality; B all-cause mortality. RR was calculated using the Mantel-Haenszel random-effects model and P value from the z test to exam whether the pooled effect was statistically significant. All statistical tests were 2-sided. The error bars represents 95%CI of individual study, and the size of the diamonds in grey represents the weight of each study in the pooled estimate. Diamonds in blue represent the pooled effect. RR = risk ratio; CI = confidence interval.



Supplementary Figure 4. Forest plots of continued use of aspirin use in relation to CRC mortality. A cancer-specific mortality; B all-cause mortality. RR was calculated using the Mantel-Haenszel random-effects model and P value from the z test to exam whether the pooled effect was statistically significant. All statistical tests were 2-sided. The error bars represents 95%CI of individual study, and the size of the diamonds in grey represents the weight of each study in the pooled estimate. Diamonds in blue represent the pooled effect. RR = risk ratio; CI = confidence interval.



Supplementary Figure 5. Forest plots of postdiagnosis use of aspirin use in relation to CRC mortality. A cancer-specific mortality; B all-cause mortality. RR was calculated using the Mantel-Haenszel random-effects model and P value from the z test to exam whether the pooled effect was statistically significant. All statistical tests were 2-sided. The error bars represents 95%CI of individual study, and the size of the diamonds in grey represents the weight of each study in the pooled estimate. Diamonds in blue represent the pooled effect. RR = risk ratio; CI = confidence interval.



Supplementary Figure 6. Forest plots of CRC mortality regarding aspirin use after diagnosis regardless of its use before diagnosis. A cancer-specific mortality; B all-cause mortality. RR was calculated using the Mantel-Haenszel random-effects model and P value from the z test to exam whether the pooled effect was statistically significant. All statistical tests were 2-sided. The error bars represents 95%CI of individual study, and the size of the diamonds in grey represents the weight of each study in the pooled estimate. Diamonds in blue represent the pooled effect. RR = risk ratio; CI = confidence interval.

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