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REVIEW – CLINICAL ONCOLOGY

Safety and efficacy of aspirin for primary prevention of cancer: a meta-analysis of randomized controlled trials

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Abstract

Background In the United States, cancer is the second leading cause of mortality, and millions more battle cancer worldwide. As such, primary prevention of cancer is a major interest globally. Aspirin has been studied as a primary prevention method for multiple diseases, mainly cardiovascular disease and various forms of cancer. The role of aspirin as a primary prevention of cancer is still controversial and may be more beneficial in certain cancers over others. With rapidly surfacing large randomized controlled trials (RCTs) studying this subject, we aimed to evaluate the efficacy and safety of aspirin as a primary prophylaxis for cancer.

Methods A comprehensive electronic database search was conducted for all RCTs that compared aspirin versus placebo for the prevention of any type of disease, and where cancer incidence or mortality was reported. The primary outcome was cancerrelated mortality. Secondary outcomes were cancer incidence, all-cause mortality, major bleeding, any bleeding and gastrointestinal (GI) bleeding. We calculated risk ratios (RRs) and 95% confidence intervals (CIs) using a random-effects model at the longest follow-up period.

Results We included 16 RCTs with 104,018 total patients, mean age of 60.51 years, mean follow-up of 5.48 years, and a male percentage of 38.72%. We found that aspirin was not associated with a significant reduction of cancer-related mortality compared with placebo (RR 0.99; 95% CI: 0.87–1.12; $P = 0.85$: $I^2 = 41\%$). Compared with placebo, aspirin was not associated with significant reduction of all-cause mortality (RR 0.97; 95% CI: 0.92–1.02; $P = 0.19$; $I^2 = 13\%$) or cancer incidence (RR: 0.98; 95% CI: 0.92–1.04; $P = 0.43$; $I^2 = 16\%$). However, aspirin treatment was associated with significantly increased risks of any bleeding (RR 1.63; 95% CI: 1.31–2.03; $P < 0.01$), major bleeding (RR 1.41; 95% CI: 1.26–1.57; $P < 0.01$), and GI bleeding (RR 1.85; 95% CI: 1.38–2.48; $P < 0.01$) compared with placebo.

Conclusion Our study did not find any significant reductions in cancer-related mortality or cancer incidence when compared aspirin use with placebo or no aspirin. Our study also highlights that the use of aspirin for primary prevention of cancer was found to cause higher rates of bleeding (any bleeding, major bleeding, and GI bleeding) compared to placebo or no aspirin at the longest follow-up period with no significant benefit in cancer primary prevention.

Keywords Aspirin · Cancer · Primary prevention · Bleeding

Introduction

Cancer is the second leading cause of mortality in the United States, and millions more battle cancer worldwide (Chubak et al. 2016). In 2015, there were 17.5 million cancer cases globally, and 8.7 million cancer-related deaths (Fitzmaurice et al. 2017). From 2005 to 2015, the incidence of cancer increased by 33% internationally (Fitzmaurice et al. 2017). As such, the global interest in primary prevention of cancer remains profound (Ilbawi and Anderson 2015).

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Chemoprevention, the use of a molecule or drug to delay, reverse or prevent a carcinogenesis process, is only one of many strategies to be adopted for primary prevention (Krstic et al. 2019). Several major challenges exist regarding chemoprevention, including the challenge of maintaining the balance between risks and benefits (Krstic et al. 2019). Aspirin has been studied as a primary prevention method for multiple diseases, especially cardiovascular disease, diabetes mellitus, and various forms of cancer (Ma and Yu 2006). The role of aspirin as a primary prevention of cancer is still controversial and may be more beneficial in certain cancers over others (Ma and Yu 2006). With rapidly surfacing large randomized controlled trials (RCTs) studying this subject (McNeil et al. 2018; Moher et al. 2015; Okada et al. 2018), we aimed to evaluate the efficacy and safety of aspirin as a means of primary prevention of cancer.

Methods

Data sources

The study was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) Statement 2015 (Rothwell et al. 2011). A comprehensive search of literature using PubMed, Embase, and the Cochrane Collaboration Central Register of Controlled Trials from inception to December 2018 was performed by TH, BK and YZ. Any disagreements were resolved via consensus. The search terms used were: aspirin, primary prevention, mortality, and cancer.

Selection criteria and data extraction

The study inclusion criteria were: (1) all studies are RCTs; (2) aspirin should be used for primary prevention; (3) aspirin should be compared to placebo or no aspirin control; (4) cancer mortality or cancer incidence should be reported. From each eligible study, two authors, TH and MB, extracted the data and a third author, BK, resolved any discrepancies.

Outcomes

Our primary outcome was cancer-related mortality. Secondary outcomes were all-cause mortality, incidence of cancer, any bleeding events, major bleeding, and gastro-intestinal (GI) bleeding.

Quality assessment

The quality of the included studies was assessed independently by two authors, TH and VS, based on the Jadad scoring system (Table 1).

Statistical analysis

We calculated summary risk ratios (RRs) and 95% confidence intervals (CIs) using the Mantel–Haenszel method for dichotomous data. We used a random-effects model to account for the between-study heterogeneity. Heterogeneity was measured by the Cochrane's Q statistic and I^2 statistic test. Publication bias was assessed by visual inspection of the funnel plot. Furthermore, we explained any heterogeneity ($\geq 20\%$) by performing sensitivity and meta-regression

Table 1 Jadad scoring of included studies

Studies	Jadad score
The ASCEND study collaborative group (2018)	4
McNeil et al. (2018)	4
Okada et al. (2018)	4
Cook et al. (2013)	4
Brighton et al. (2012)	4
Belch et al. (2008)	5
Ogawa et al. (2008)	4
Collaborative Group of the Primary Prevention Project (2001)	3
Medical Research Council's General Practice Research Framework (1998)	5
Vane and Meade (1997)	5
Juul-Möller et al. (1992)	4
ETDRS Investigators (1992)	4
The SALT Collaborative Group (1991)	5
Farrell et al. (1991)	5
The DAMAD Study Group (1989)	4
The Persantine-Aspirin Reinfarction Study Research Group (1980)	3

analyses. Sensitivity analyses were performed by removing trials sequentially and by removing trials that compared aspirin with other agents (i.e., not placebo). Meta-regression analyses were conducted based on the study-level covariates (total aspirin dose, age, hypertension, and follow-up duration). Analysis was performed using RevMan v5.3 Windows and Comprehensive Meta-Analysis software v3.

Results

Study selection and trial characteristics

Figure 1 illustrates the study selection process. We included 16 RCTs with 104,018 total patients, mean age of 60.51 years old, mean follow-up period of 5.48 years, and a male percentage of 38.72%. Tables 2 and 3 illustrate the characteristics of the included trials and patient demographics, respectively.

In the 16 included studies, 5 studies explored the role of aspirin as primary prevention for patients with diabetes, 8 assessed aspirin for primary prevention of cardiovascular disease, 1 study assessed aspirin for use in recurrent venous thromboembolism, and 2 studies primarily assessed the role of aspirin for cancer prevention. All studies were randomized controlled trials. Almost all studies were assessed to be of moderate to high quality (Table 1). Aspirin dosing varied from 81 milligrams (mg) daily to 1200 mg, with reported regimens either daily or every other day. Follow-up duration ranged from 2 years to 10.7 years. All studies compared aspirin to placebo or no aspirin with a preventative substance like dipyridamole, or vitamin E.

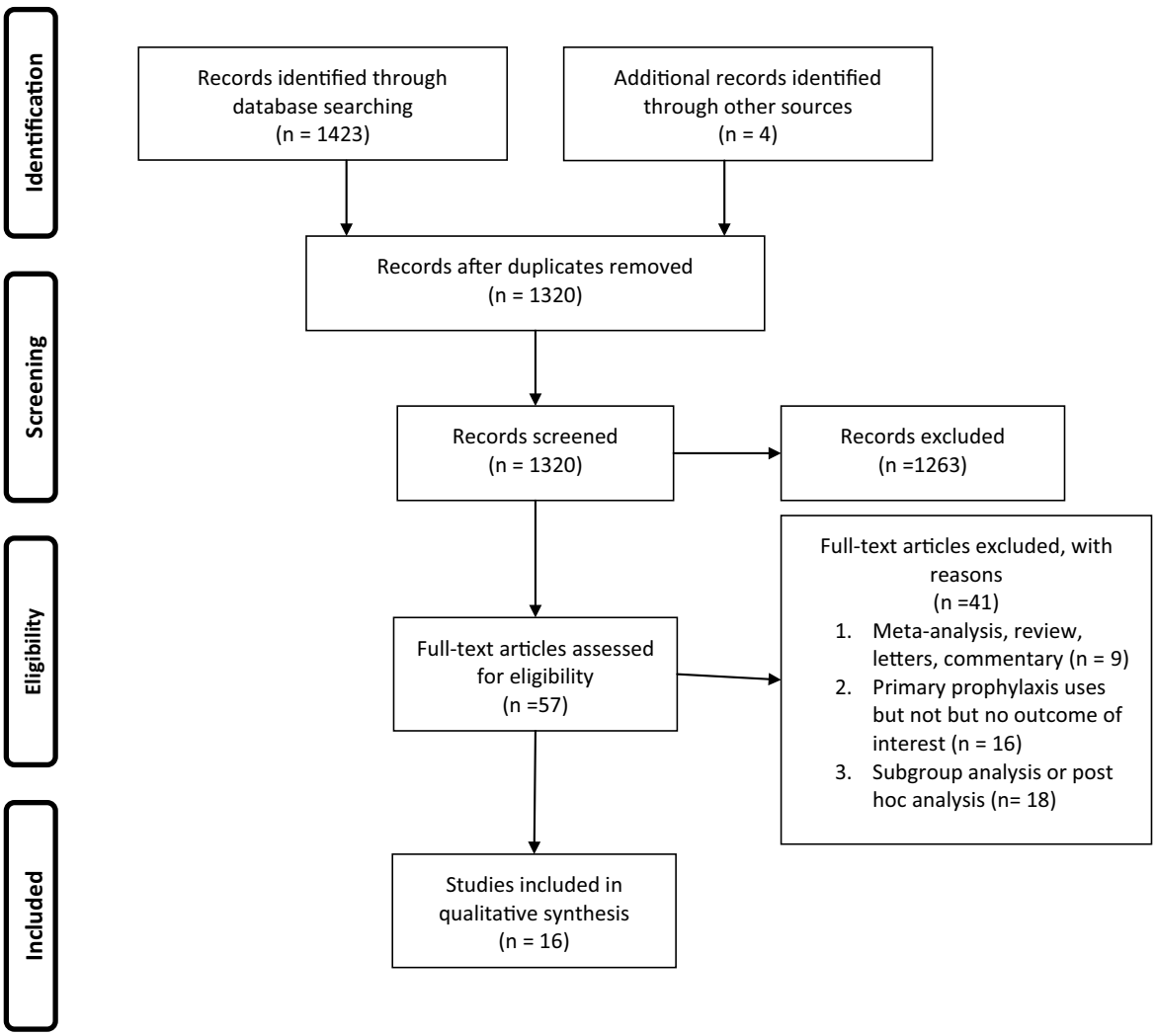

Fig. 1 The preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Table 2 Details of the randomized clinical trials

Studies	Country	Total patients/subgroups	Study subject	Study design	Aspirin dose/duration	Follow-up period	Primary outcomes
The ASCEND study collaborative group (2018)	UK	Total: 15480 Aspirin: 7740 Placebo: 7740	Effect of aspirin for primary prevention in diabetics	RCT	100 mg daily	7.4 years	Primary efficacy outcome: first serious vascular event Primary safety outcome: first major bleeding event
McNeil et al. (2018)	Australia and United States	Total: 19114 Aspirin: 9525 Placebo: 9589	Effect of aspirin on all-cause mortality in the elderly	RCT	100 mg daily	4.7 years	Mortality
Okada et al. (2018)	Japan	Total: 2536 Aspirin: 1259 No aspirin: 1277	Effect of aspirin on cancer prevention in type 2 diabetics	Post-trial JPAD RCT observation	81/100 mg daily	10.7 years	Time to first cancer incidence
Cook et al. (2013)	US	Total: 33682 Aspirin: 16913 Placebo: 16769	Association between alternate day aspirin use and cancer risk	Observational follow-up of RCT	100 mg on alternate days	10 years	Invasive cancer, excluding nonmelanoma skin cancer
Brighton et al. (2012)	International	Total: 822 Aspirin: 411 Placebo: 411	Effect of low-dose aspirin in prevention of recurrent VTE	Randomized double blinded placebo controlled trial	100 mg daily	3.1 years	Recurrence of VTE
Belch et al. (2008)	Scotland	Total: 1276 Aspirin + antioxidant: 320 Aspirin +placebo:318 Antioxidant + placebo: 320 Placebo + placebo: 318	Effect of aspirin and antioxidants in prevention of cardiovascular events in diabetes and arterial disease	RCT, double blinded placebo controlled	100 mg daily	6.7 years	Death from coronary heart disease or stroke Non-fatal myocardial infarction or stroke
Ogawa et al. (2008)	Japan	Total: 2539 Aspirin: 1262 No aspirin:1277	Effect of aspirin in primary prevention atherosclerotic events in type 2 diabetics	Multicenter, prospective, RCT	81//100 mg daily	4.37 years	Atherosclerotic events
Collaborative Group of the Primary Prevention Project (2001)	Italy	Total: 4495 Aspirin: 2226 No aspirin: 2269 Vitamin E: 2231 No vitamin E: 2264	Effect of aspirin and vitamin E in people at cardiovascular risk	Randomized, open label, 2 × 2 factorial trial	100 mg daily	3.6 years	Cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke
Medical Research Council's General Practice Research Framework (1998)	UK	Total: 5499 W + aspirin: 1277 Aspirin + PW: 1268 W + placebo aspirin: 1268 PW +PA: 1272	Effect of low-dose aspirin and warfarin on primary prevention ischemic heart disease in patients at risk	RCT, placebo controlled	75 mg daily	10 years	All ischemic heart disease events

Table 2 (continued)

Studies	Country	Total patients/subgroups	Study subject	Study design	Aspirin dose/duration	Follow-up period	Primary outcomes
Vane and Meade (1997)	UK	Total: 6602 DP + ASA: 1650 DP: 1654 ASA: 1649 Placebo: 1649	Effect of DP or aspirin or combined drugs on stroke prevention	Randomized double blinded placebo controlled	75 mg daily	2 years	Death and/or stroke
Juul-Möller et al. (1992)	Sweden	Total: 2035 Aspirin + sotalol: 1009 Placebo + sotalol: 1026	Aspirin in primary prevention of MI in patients with stable angina	Randomized double blinded placebo controlled	75 mg daily	4.16 years	First occurrence of non-fatal MI or sudden death
ETDRS Investigators (1992)	United States	Total: 3711 Aspirin: 1856 Placebo: 1855	Effect of aspirin on mortality, cardiovascular events in diabetics	Randomized placebo controlled	650 mg daily	5 years	Mortality from any cause
The SALT Collaborative Group (1991)	Sweden	Total 1360 Aspirin: 676 Placebo: 684	Effect of low-dose aspirin on secondary prophylaxis after cerebrovascular events	Randomized placebo controlled	75 mg daily	2.66 years	Stroke and death
Farrell et al. (1991)	UK	Total: 2435 1200 mg aspirin: 815 300 mg aspirin: 806 Placebo: 814	Effect of aspirin on vascular events and deaths	Randomized placebo controlled	1200 mg or 300 mg daily	7 years	Serious vascular events or death
The DAMAD Study Group (1989)	France and UK	Total: 475 ASA + DP: 145 ASA: 150 Placebo: 139	Effect of aspirin and dipyridamole on diabetic retinopathy	Randomized double blinded, placebo controlled trial	330 mg tid	3 years	Microaneurysms per year
The Persantine-Aspirin Reinfarction Study Research Group (1980)	International	Total: 2026 Persantine + aspirin:810 Aspirin: 810 Placebo: 406	Effect of persantine and aspirin on mortality and morbidity in persons with previous MI	RCT double blinded	324 mg tid	3.41 years	Mortality from any cause

US United States, *mg* milligram, *RCT* randomized controlled trial, *VTE* venous thromboembolism, *DP* dipyridamole, *MI* myocardial infarction, *tid* three times daily, *PW* placebo Warfarin, *PA* placebo aspirin, *W* active warfarin; ASA: aspirin; UK: United Kingdom

Table 3 Patients demographics

Studies	Age	Male sex	Race	BMI (Kg/m^2)	Current smoking	Past smoking	HTN	DM	DL	Cardiac disease	Alcohol use	FH of cancer
The ASCEND study collaborative group (2018)	Aspirin: 63.2 ± 9.2 Placebo: 63.3 ± 9.2	Aspirin: 4843 pts (62.6%) Placebo: 4841 pts (62.5%)	Aspirin: White, 7467 pts (96.5%) Placebo: White, 7468 pts (96.5%)	Aspirin mean: 30 ± 6.2 < 25–1080 pts (14.0%) 25 to < 30–2753 (35.6%) ≥ 30–3665 pts (47.4%) Unknown: 242 (3.1%) Placebo mean: 30.6 ± 6.3 < 25–1169 pts (15.1%) 25 to < 30–2776 (35.9%) ≥ 30–3536 pts (45.7%) Unknown: 259 (3.3%)	Aspirin: 639 pts (8.3%) Placebo: 640 pts (8.3%)	Aspirin: 3526 pts (45.6%) Placebo: 3523 pts (45.5)	Aspirin: 4799 pts (61.6%) Placebo: 4767 pts (61.6%)	Aspirin: 7282 pts (94.1%) Placebo: 7287 pts (94.1%)	NA	NA	NA	NA
McNeil et al. (2018)	65–73 y, 9542 pts (49.9%) ≥ 74 y, 9572 pts (50.1%)	*P* value 0.46 M: 8331 pts (43.6%) F: 10,783 pts (56.4%)	White *Australia: 16,362 pts (85.6%) *US: 1088 pts (5.7%) Black: 901 pts (4.7%) Hispanic: 488 pts (2.6%) Other: 275 pts (1.4%)	*P* value 0.22 < 20–352 pts (1.8%) 20–24–4526 pts (23.7%) 25–29–8480 pts (44.4%) ≥30–5677 pts (29.7%)	Current smokers: 735 pts (3.8%)		*P* value 0.94 Yes: 14,195 pts (74.3%) No: 4919 pts (25.7%)	*P* value 0.31 Yes: 2057 pts (10.8%) No: 17,057 pts (89.2%)	*P* value 0.78 Yes: 5979 pts (31.3%) No: 13,135 pts (68.8%)	NA	NA	NA
Okada et al. (2018)	Aspirin: 65 ± 10 No aspirin: 64 ± 10	Aspirin: 705 pts (56%) No aspirin: 681 pts (53%)	Japanese: 2536 pts (100%)	Aspirin mean: 24.4 ± 3.6 No aspirin mean: 24.3 ± 3.7	Aspirin: 289 pts (23%) No aspirin: 248 pts (19%)	Aspirin: 274 pts (22%) No aspirin: 246 pts (19%)	Aspirin: 739 pts (59%) No aspirin: 731 pts (57%)	Aspirin mean A1c: 7.5 ± 1.5 No aspirin mean A1c: 7.4 ± 1.2	Aspirin: 679 pts (54%) No aspirin: 665 pts (52%)	NA	NA	NA

Table 3 (continued)

Studies	Age	Male sex	Race	BMI (Kg/m^2)	Current smoking	Past smoking	HTN	DM	DL	Cardiac disease	Alcohol use	FH of cancer
Cook et al. (2013)	Aspirin: 45–54 y, 12,010 pts (60.2%) 55–64 y, 5876 pts (29.5%) ≥ 65 y, 2048 pts (10.3%) Placebo: 45–54 y, 12,015 Pts (60.2%) 55–64 y, 5878 Pts (29.5%) ≥ 65 y, 2049 Pts (10.3%)	Male: zero pts (0%) Female: 39,876 pts (100%)	NA	Aspirin: < 25–10,094 pts (50.6%) 25 to < 30–6158 (30.9%) ≥ 30–3674 pts (18.5%) Placebo: < 25–10,069 pts (50.7%) 25 to < 30–6193 (31.1%) ≥ 30–3633 pts (18.2%)	Aspirin: 2580 pts (12.9%) Placebo: 2655 pts (13.3%)	Aspirin: 7167 pts (36.0%) Placebo: 7098 pts (35.6%)	NA	NA	NA	NA	Aspirin: < 1 drink/week, 11,627 pts (58.3%) ≥ 2 drink/week, 8302 (41.7) Placebo: <1 drink/week, 11,599 pts (58.2%) ≥ 2 drink/week, 8338 (41.8%)	Aspirin, yes: 3529 (17.7%) Placebo, yes: 3517 pts (17.6%)
Brighton et al. (2012)	Aspirin: 55 ± 16.0 Placebo: 54 ± 15.8	Aspirin: 226 pts (55%) Placebo: 221 pts (54%)	NA	Aspirin: < 30–249 (61%) ≥ 30–160 pts (39%) Placebo: < 30–271 (66%) ≥ 30–140 pts (34%)	NA	NA	NA	NA	NA	NA	NA	NA
Belch et al. (2008)	Aspirin–antioxidant: 61.0 ± 10.0 Aspirin: 60.0 ± 10.1 Antioxidant: 60.0 ± 10.3 Placebo: 60.1 ± 9.7	Aspirin–antioxidant: 151 pts (47%) Aspirin: 135 pts (42%) Antioxidant: 133 pts (43%) Placebo: 138 pts (43%)	NA	Aspirin–antioxidant: 29.7 ± 3.4 Aspirin: 28.7 ± 4.3 Antioxidant: 9.4 ± 4.1 Placebo: 29.2 ± 4.0	Aspirin–antioxidant: 105 pts (33%) Aspirin: 99 pts (31%) Antioxidant: 106 pts (33%) Placebo: 87 pts (27%)	Aspirin–antioxidant: 113 pts (35%) Aspirin: 107 pts (34%) Antioxidant: 111 pts (35%) Placebo: 116% (36%)	Mean systolic Aspirin–antioxidant: 146 ± 22 Aspirin: 143 ± 21 Antioxidant: 144 ± 20 Placebo: 147 ± 21	Total: 1276 pts (100%) Mean A1c Aspirin–antioxidant: 8 ± 1.8 Aspirin: 8.0 ± 1.7 Antioxidant: 7.9 ± 1.8 Placebo: 7.9 ± 1.7	Mean LDL Aspirin–antioxidant: 3.1 ± 0.6 Aspirin: 3.1 ± 0.6 Antioxidant: 3.2 ± 0.6 Placebo: 3.1 ± 0.6	NA	NA	NA
Ogawa et al. (2008)	Aspirin: 65 ± 10 No aspirin: 64 ± 10	Aspirin: 706 pts (56%) No aspirin: 681 pts (52%)	Japanese: 2539 pts (100%)	Aspirin mean: 24 ± 4 No aspirin mean: 24 ± 4	Aspirin: 289 pts (23%) No aspirin: 248 pts (19%)	Aspirin: 274 pts (22%) No aspirin: 246 pts (19%)	Aspirin: 742 pts (59%) No aspirin: 731 pts (57%)	Aspirin mean A1c: 7.1 ± 1.4 No aspirin mean A1c: 7.0 ± 1.2	Aspirin: 680 pts (54%) No aspirin: 665 pts (52%)	NA	NA	NA

Table 3 (continued)

Studies	Age	Male sex	Race	BMI (Kg/m^2)	Current smoking	Past smoking	HTN	DM	DL	Cardiac disease	Alcohol use	FH of cancer
Collaborative Group of the Primary Prevention Project (2001)	Aspirin: 64.5 ± 7.7 No aspirin: 64.3 ± 7.6 Vit-E: 64.4 ± 7.6 No Vit-E: 64.4 ± 7.6	Aspirin: 949 pts (43%) No aspirin: 963 pts (42%) Vit-E: 937 pts (42%) No Vit-E: 975 pts (43%)	NA	Aspirin mean: 27 × 5 ± 4 × 5 No aspirin mean: 27 × 7 ± 4 × 8 Vit-E mean: 27 × 5 ± 4 × 6 No Vit-E mean: 27 × 8 ± 4 × 7	Aspirin: 328 pts (15%) No aspirin: 339 pts (15%) Vit-E: 342 pts (15%) No Vit-E: 325 pts (14%)	Aspirin: 533 pts (24%) No aspirin: 547 pts (24%) Vit-E: 517 pts (23%) No Vit-E: 563 pts (25%)	Aspirin: 1527 pts (69%) No aspirin: 1538 pts (68%) Vit-E: 1500 pts (67%) No Vit-E: 1565 pts (69%)	Aspirin: 377 pts (17%) No aspirin: 365 pts (16%) Vit-E: 360 pts (16%) No Vit-E: 382 pts (17%)	Aspirin: 921 pts (41%) No aspirin: 821 pts (36%) Vit-E: 850 pts (38%) No Vit-E: 892 pts (39%)	NA	NA	NA
Medical Research Council's General Practice Research Framework (1998)	Warfarin–aspirin: 57.4 ± 6 × 9 Warfarin: 57.6 ± 6 × 8 Aspirin: 57.7 ± 6 × 7 Placebo: 57.3 ± 6 × 6	Total no. of males: 5499 pts (100%)	NA	Warfarin–aspirin: 27.4 ± 3.7 Warfarin: 27.4 ± 3.5 Aspirin: 27.3 ± 3.4 Placebo: 27.5 ± 3.8	Warfarin–aspirin: 41.0% Warfarin: 41.3% Aspirin: 41.0% Placebo: 41.6%	NA	Mean systolic Warfarin–aspirin: 139 ± 18 Warfarin: 139 ± 18 Aspirin: 139 ± 18 Placebo: 139 ± 18	NA	Cholesterol Warfarin–aspirin: 6.4 ± 1 Warfarin: 6.4 ± 1 Aspirin: 6.4 ± 1 Placebo: 6.4 ± 1	Total: zero pts (0%)	NA	NA
Vane and Meade (1997)	Aspirin: ≥ 65 y, 1236 pts (75%) DP: ≥ 65 y, 1236 pts (75%) DP-aspirin: ≥ 65 y, 1236 Pts (75%) Placebo: ≥ 65 y, 1244 pts (75%)	NA	NA	NA	Aspirin: 938 pts (57%) DP: 934 pts (56%) DP-aspirin: 965 pts (58%) Placebo: 934 pts (57%)	NA	NA	Aspirin: 240 pts (15%) DP: 278 pts (17%) DP-aspirin: 254 pts (15%) Placebo: 239 pts (14%)	NA	*P* value 0.01 Aspirin: 571 pts (35%) DP: 598 pts (36%) DP-aspirin: 573 pts (35%) Placebo: 577 pts (35%)	*P* value 0.05 > 5 units/day Aspirin: 87 pts (5%) DP: 100 pts (6%) DP-aspirin: 84 pts (5%) Placebo: 96 pts (6%)	NA
Juul-Möller et al. (1992)	Aspirin + sotalol: 67 ± 8 Placebo + sotalol: 67 ± 8	Aspirin + sotalol: 514 pts (51%) Placebo + sotalol: 543 pts (53%)	NA	NA	Aspirin + sotalol: 171 pts (17%) Placebo + sotalol: 164 pts (16%)	NA	Aspirin + sotalol: 433 pts (43%) Placebo + sotalol: 410 pts (40%)	Aspirin + sotalol: 60 pts (6%) Placebo + sotalol: 71 pts (7%)	Median cholesterol Aspirin + sotalol: 6.7 ± 1.3 (mmol/l) Placebo + sotalol: 6.8 ± 1.5 (mmol/l)	NA	NA	NA

Table 3 (continued)

Studies	Age	Male sex	Race	BMI (Kg/m^2)	Current smoking	Past smoking	HTN	DM	DL	Cardiac disease	Alcohol use	FH of cancer
ETDRS Investigators (1992)	Aspirin: < 30 y, 324 pts (17.5%) 30–49 y, 572 pts (30.8) ≥ 50 y, 960 pts (51.7%) Placebo: < 30 y, 302 pts (16.3%) 30–49 y, 596 pts (32.1%) ≥ 50 y, 957 pts (51.6%)	Aspirin: 1031 pts 55.5%) Placebo: 1065 pts (57.4%)	Aspirin White: 1420 pts (76.5%) Placebo White: 1414 pts (76.2%)	NA	Aspirin: ≥ 6 cig/day, 819 pts (44.1%) Placebo: ≥6 cig/day, 822 pts (44.3%)	NA	Aspirin: 840 pts (45.3%) Placebo: 806 pts (43.4%)	Aspirin: 1856 pts (100%) Type 1: 559 pts (30.1%) Type 2: 587 pts (31.6%) Mixed: 710 pts (38.3%) Placebo: 1855 pts (100%) Type 1: 571 pts (30.8%) Type 2: 565 pts (30.5%) Mixed: 719 pts (38.9%)	LDL ≥ 4.15 Aspirin: 336 pts (26.4%) Placebo: 328 pts (25%)	Aspirin: 912 pts (49.1%) Placebo: 900 pts (48.5%)	NA	NA
The SALT Collaborative Group (1991)	Aspirin: 67.1 ± 7.1 Placebo: 66.8 ± 7.2	Aspirin: 442 pts (65.4%) Placebo: 452 pts (66.2%)	NA	NA	Aspirin: 175 pts (26%) Placebo: 168 pts (24.7%)	Aspirin: 143 pts (21.3%) Placebo: 168 pts (24.7%)	Aspirin: 309 pts (45.8%) Placebo: 332 pts (48.6%)	Aspirin: 87 pts (12.9%) Placebo: 87 pts (12.8%)	NA	Aspirin—angina: 116 pts (17.3%) MI: 81 pts (12%) CHF: 41 pts (6.2%) Placebo—Angina: 121 pts (17.8%) MI: 73 pts (10.7%) CHF: 28 pts (4.2%)	NA	NA
Farrell et al. (1991)	Aspirin 1200 mg: 59.9 ± 9.16 Aspirin 300 mg: 60.0 ± 8.92 Placebo: 59.5 ± 9.04	Aspirin 1200 mg: 601 pts (74%) Aspirin 300 mg: 603 pts (75%) Placebo: 575 pts (71%)	NA	Aspirin 1200 mg: 25.3 ± 3.39 Aspirin 300 mg: 25.5 ± 3.82 Placebo: 25.1 ± 3.43	Aspirin 1200 mg: 444 pts (54%) Aspirin 300 mg: 431 pts (53%) Placebo: 417 pts (51%)	NA	Aspirin 1200 mg: 214 pts (26%) Aspirin 300 mg: 225 pts (28%) Placebo: 221 pts (27%)	Aspirin 1200 mg: 30 pts (4%) Aspirin 300 mg: 29 pts (4%) Placebo: 31 pts (4%)	Aspirin 1200 mg: 17 pts (2%) Aspirin 300 mg: 24 pts (3%) Placebo: 14 pts (2%)	Aspirin 1200: 146 pts (18%) Aspirin 300 mg: 164 pts (20%) Placebo: 165 pts (20%)	NA	NA

Table 3 (continued)

Studies	Age	Male sex	Race	BMI (Kg/m^2)	Current smoking	Past smoking	HTN	DM	DL	Cardiac disease	Alcohol use	FH of cancer
The DAMAD Study Group (1989)	Non-insulin tx Aspirin: 53 ± 8 Aspirin + dipyridamole: 55 ± 8 Placebo: 53 ± 8 Insulin tx Aspirin: 53 ± 8 Aspirin + dipyridamole: 55 ± 8 Placebo: 53 ± 8	Non-insulin tx Aspirin: 42 pts (71%) Aspirin + dipyridamole: 37 pts (63%) Placebo: 38 pts (66%) Insulin tx Aspirin: 61 pts (62%) Aspirin + dipyridamole: 65 pts (64%) Placebo: 62 pts (63%)	NA	Non-insulin tx Aspirin: 25 ± 4 Aspirin + dipyridamole: 25 ± 3 Placebo: 26 ± 4 Insulin tx Aspirin: 24 ± 3 Aspirin + dipyridamole: 24 ± 3 Placebo: 24 ± 3	Non-insulin tx Aspirin: 25 pts (42%) Aspirin + dipyridamole: 24 pts (41%) Placebo: 22 pts (37%) Insulin tx Aspirin: 42 pts (42%) Aspirin + dipyridamole: 57 pts (41%) Placebo: 38 pts (37%)	NA	Systolic BP: non-insulin tx Aspirin: 146 ± 18 Aspirin + dipyridamole: 148 ± 22 Placebo: 145 ± 19 Insulin tx Aspirin: 139 ± 18 Aspirin + dipyridamole: 136 ± 20 Placebo: 137 ± 17	A1c non-insulin tx Aspirin: 10 ± 2.5 Aspirin + dipyridamole: 9.8 ± 2.2 Placebo: 9.8 ± 2.2 Insulin tx Aspirin: 10.7 ± 2.2 Aspirin + dipyridamole: 10.4 ± 2.4 Placebo: 10.6 ± 2.3	Mean cholesterol: non-insulin tx Aspirin: 2.3 ± 0.52 Aspirin + dipyridamole: 2.27 ± 0.37 Placebo: 2.24 ± 0.49 Insulin tx Aspirin: 2.19 ± 0.47 Aspirin + dipyridamole: 2.19 ± 0.47 Placebo: 2.24 ± 0.45	NA	NA	NA
The Persantine-Aspirin Reinfarction Study Research Group (1980)	Persantine + aspirin: ≥ 55 y, 480 pts (59.3%) Aspirin: ≥ 55 y, 465 pts (57.5%) Placebo: ≥ 55 y, 228 pts (56.2%)	Males: 1759 pts (86.3%) Females: 267 pts (13.7%)	Persantine + aspirin—White: 776 pts (95.9%) Non-White: 34 pts (4.1%) Aspirin—White: 784 pts (96.9%) Non-White: 26 pts (3.1%) Placebo—White: 399 pts (98.3%) Non-White: 7 pts (1.7%)	BMI > 30.0 kg/m^2 Persantine + aspirin—males: (10.7%); females: (16.8%) Aspirin—males: (9.1%); females: (6.3%) Placebo—males: (12.7%); females: (12.1%)	NA	NA	NA	Use of insulin Persantine + aspirin: 17 pts (2.1%) Aspirin: 7 pts (0.9%) Placebo: 7 Pts (1.7%)	NA	Total: 2026 pts (100%)	NA	NA

Pts patients, *HTN* hypertension, *DM* diabetes mellitus, *DL* dyslipidemia, *Y* years, *NA* not applicable; *FH* family history, *tx* treatment, *BMI* body mass index, *DP* dipyridamole, *mg* milligram, *Vit-E* vitamin E, *Cig* cigarette

Primary outcome

Aspirin was not associated with a significant reduction of cancer-related mortality compared with placebo or no aspirin (RR 0.99; 95% CI: 0.87–1.12; $P = 0.85$: $I^2 = 41\%$) (Fig. 2). Examination of the funnel plot did not suggest any publication bias (Fig. 3). Sensitivity analysis by removing each trial sequentially demonstrated consistent results.

Meta-regression analysis showed a non-significant trend towards more cancer-related survivals with higher aspirin doses ($b < -0.001$; SE< 0.001; $P = 0.07$) and explained 32% of the heterogeneity ($R^2 = 0.32$; $I^2 = 33.7\%$) (Fig. 4). Meta-regression analysis based on age, BMI, and follow-up duration showed non-significant modifier effects on cancer-related mortality.

Secondary outcomes

Compared with placebo, aspirin was not associated with significant reduction in all-cause mortality (RR 0.97; 95% CI: 0.92–1.02; $P = 0.19$; $I^2 = 13\%$) or cancer incidence (RR: 0.98; 95% CI: 0.92–1.04; $P = 0.43$; $I^2 = 16\%$) (Figs. 5, 6). However, aspirin treatment was associated with significantly increased risks of any bleeding (RR 1.63; 95% CI: 1.31–2.03; $P < 0.01$), major bleeding (RR 1.41; 95% CI: 1.26–1.57; $P < 0.01$), and GI bleeding (RR 1.85; 95% CI: 1.38–2.48; $P < 0.01$) compared with placebo or non-aspirin (Figs. 7, 8, 9).

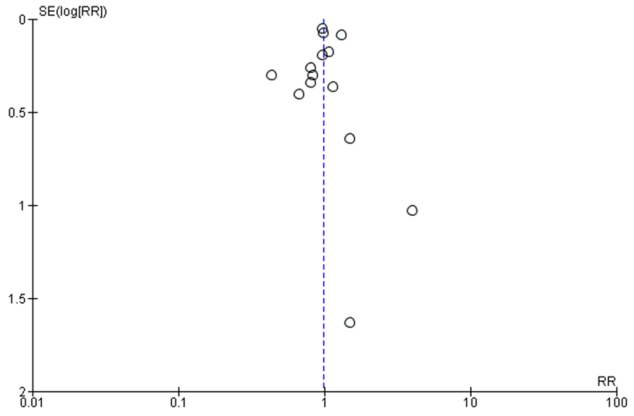

Fig. 3 Funnel plot for primary outcome (cancer-related mortality)

Discussion

In this meta-analysis of 16 RCTs, aspirin was compared to placebo or non-aspirin with other various preventative methods including dipyridamole or Vitamin E. Despite the addition of the three most recent large RCTs studying aspirin in primary prevention (McNeil et al. 2018; Moher et al. 2015; Okada et al. 2018), aspirin did not prove to have a significant reduction in cancer-related mortality, cancer incidence, or all-cause mortality in this large population of studied patients. However, aspirin was associated with significant risks, showing significantly increased risks of any bleeding, major bleeding, and GI bleeding.

Several retrospective studies, large RCTs and meta-analyses have evaluated the role of aspirin in cancer primary

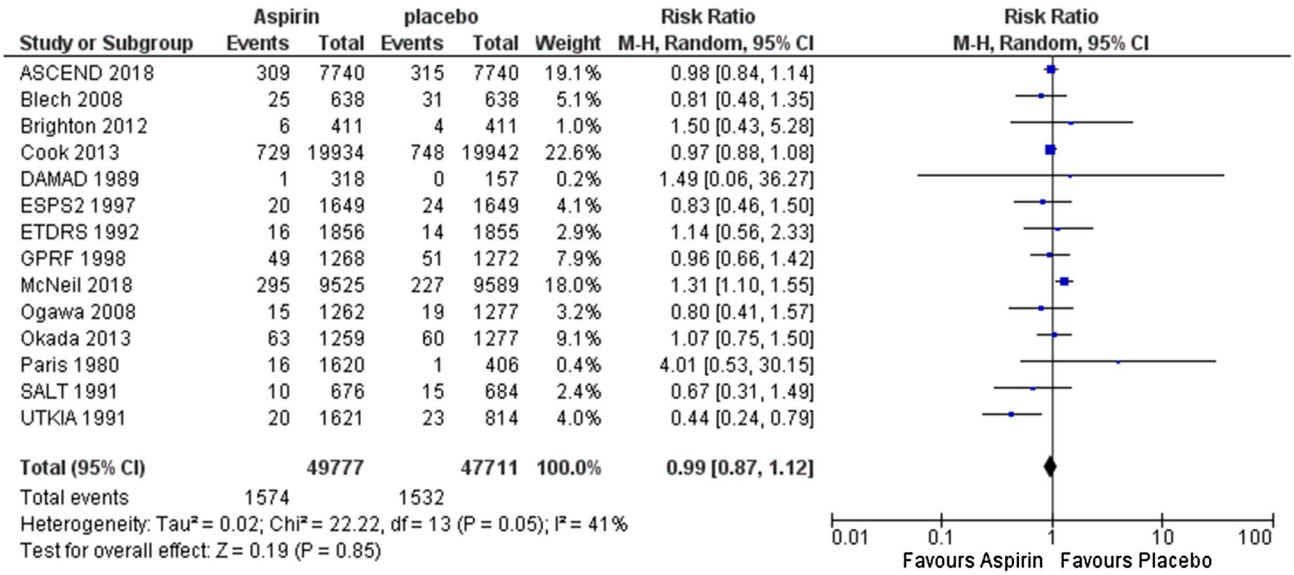

Fig. 2 Forest plot of primary outcome (cancer-related mortality)

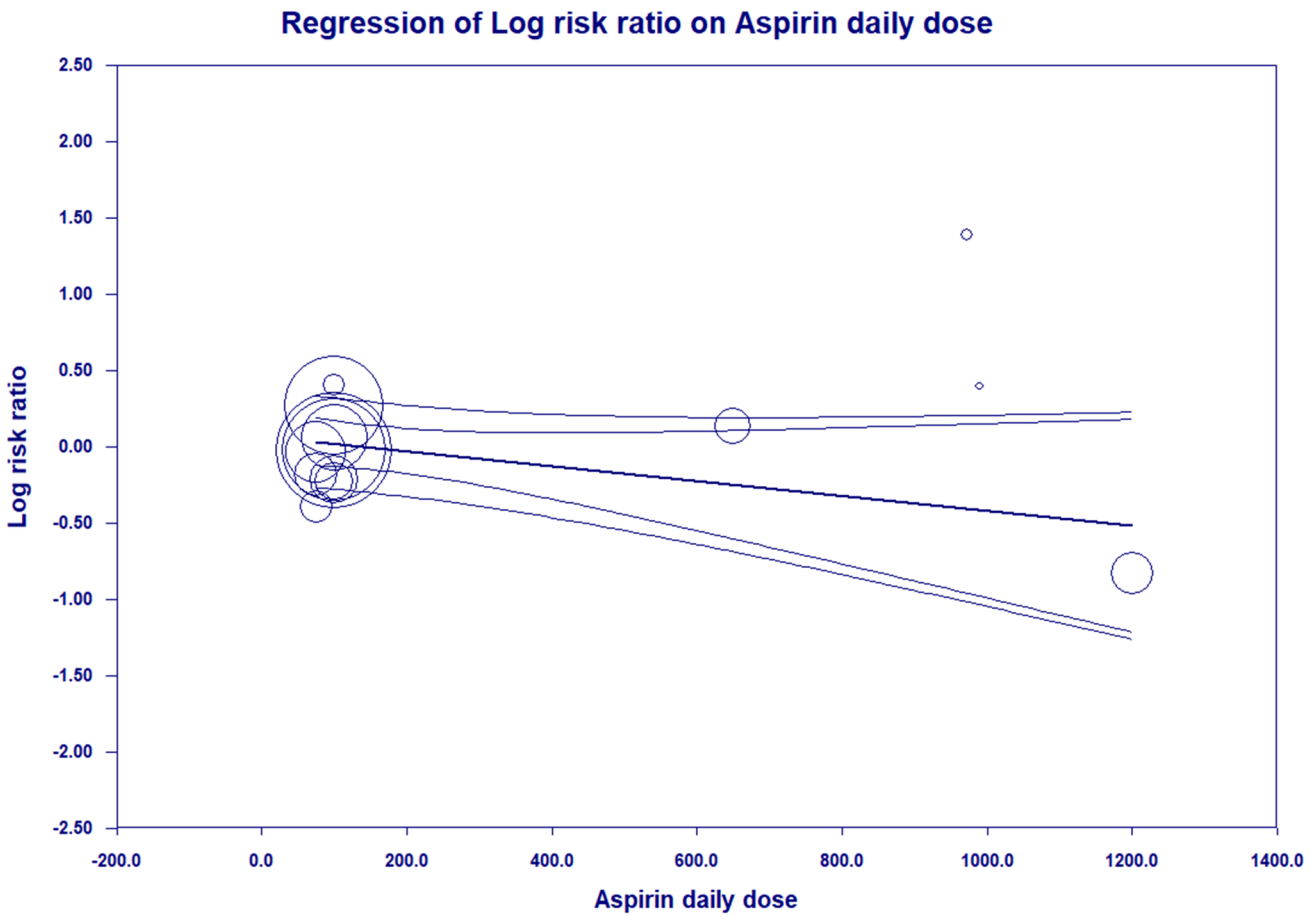

Fig. 4 Meta-regression for cancer-related mortality

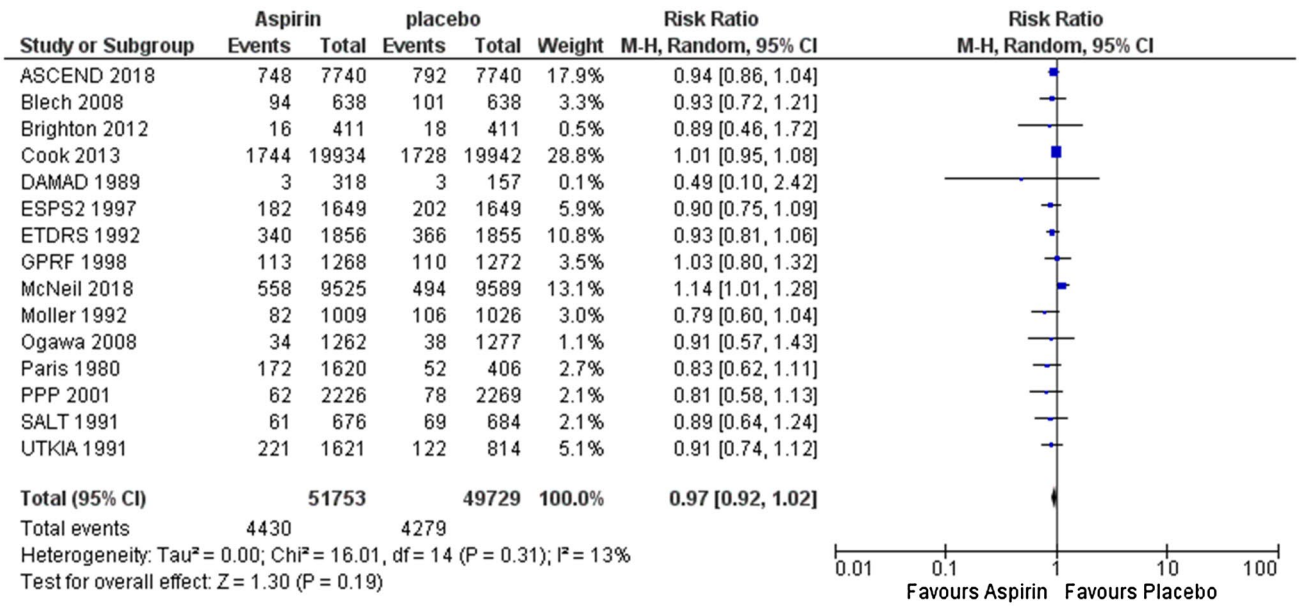

Fig. 5 Forest plot of all-cause mortality

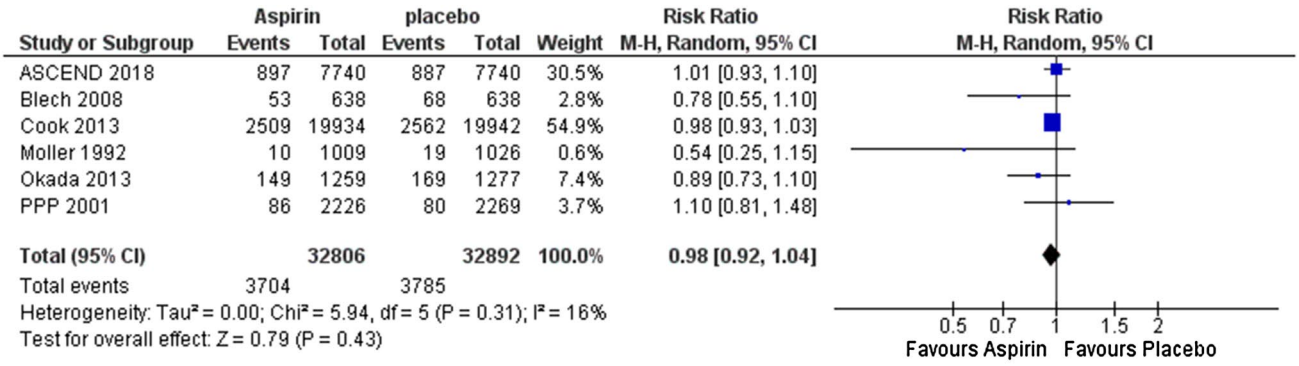

Fig. 6 Forest plot for cancer incidence

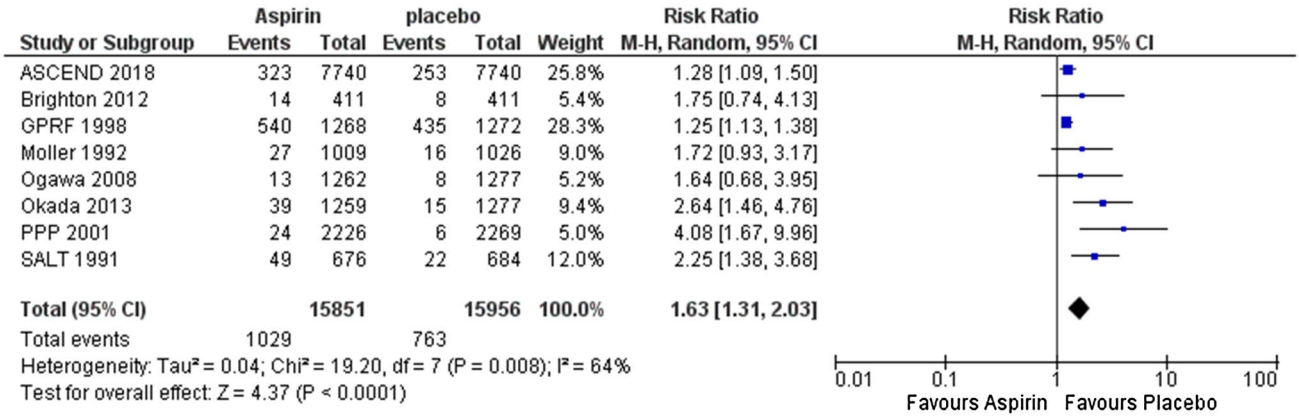

Fig. 7 Forest plot of any bleeding events

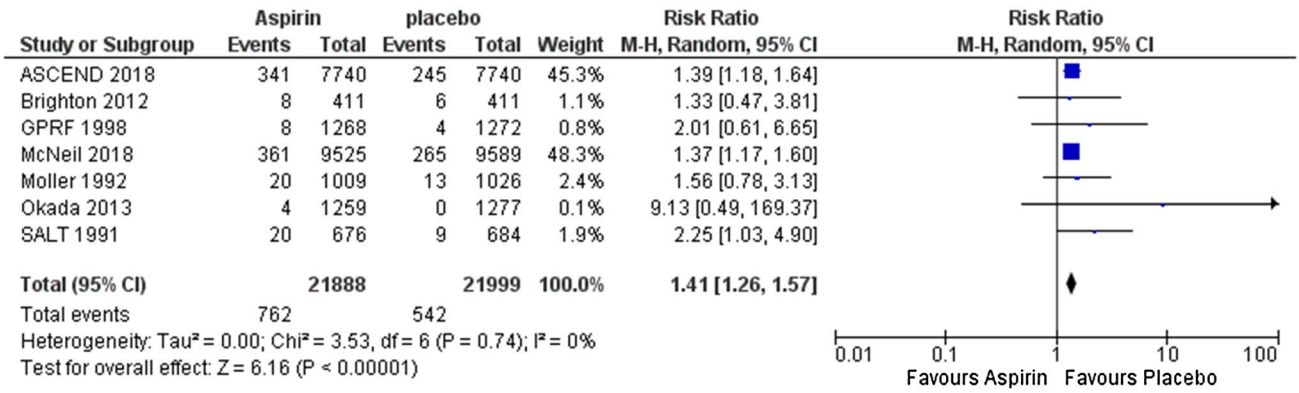

Fig. 8 Forest plot of major bleeding events

prevention. In 2011, Rothwell et al., found that low-dose aspirin use for ≥ 4 years demonstrated a reduced rate of cancer deaths. These findings were based on a meta-analysis that included trials that used aspirin for at least 4 years. The study did not, however, focus on the risks of aspirin use (Seshasai et al. 2012).

According to a recent systematic evidence review done for the United States Preventive Services Task Force (USPSTF), low-dose aspirin may hold modest cancer mortality benefits, but effects are not established clearly since estimates may be imprecise and relatively unstable (Stegeman et al. 2015). The review also found that the percentage of

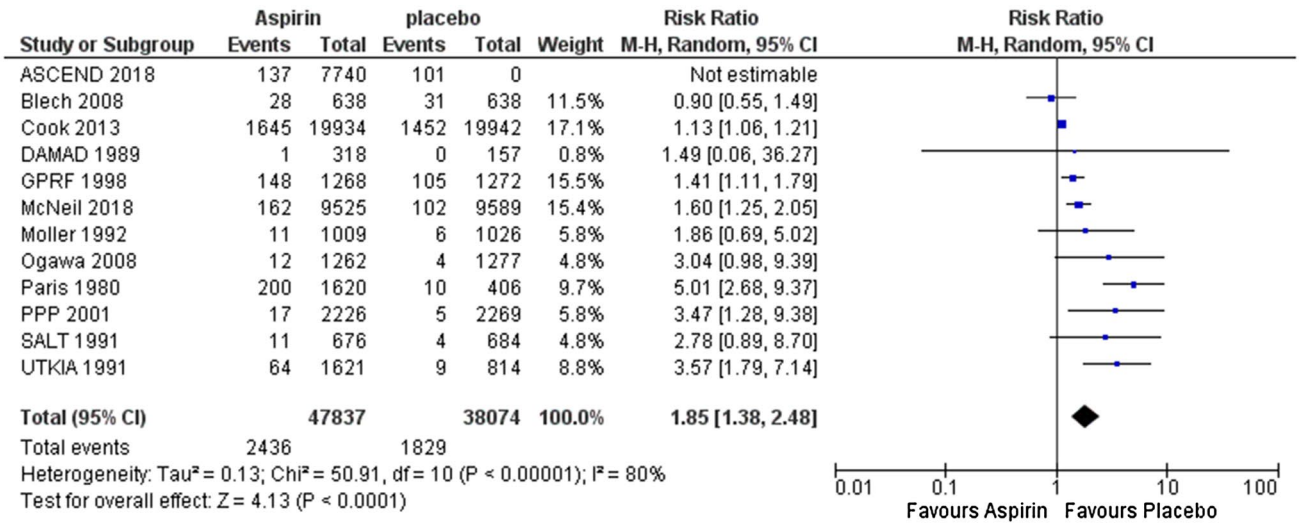

Fig. 9 Forest plot of gastro-intestinal bleeding events

serious bleeding events is higher than suggested by previous clinical trials, and is a critical consideration when assessing benefit of low-dose aspirin use, whether used for cancer prevention or otherwise (Stegeman et al. 2015).

In their last updated 2016 report, the USPSTF found that aspirin use reduced 20-year colorectal cancer mortality rates by 33%, however, aspirin had no effect on all-cause mortality. In addition, aspirin increased the risk of major gastrointestinal bleeding by 58%, and risk of hemorrhagic stroke by 27% (The ASCEND study collaborative group 2018). The data also suggested that the cardiovascular benefits of aspirin started within the first 5 years of aspirin use, whereas the decrease in colorectal cancer mortality was not seen until after 10 years of therapy. Based on these findings, the USPSTF suggested a class B recommendation about "aspirin use for primary prevention of cardiovascular disease and colorectal cancer in adults aged 50–59 years who have a 10% or greater 10-year CVD risk, are at very low risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years" (The ASCEND study collaborative group 2018).

In 2012, Seshasai et al. mentioned in their review that aspirin did show increased bleeding risk when used for primary or secondary prevention of cardiovascular disease, however, it was referred to as trivial bleeding (Tsoi et al. 2019).

In a recent large cohort population study in Hong Kong, it was found that long-term use of low-dose aspirin was associated with the reduction in risk of various cancers, but not breast cancer. No real comments on the risks of aspirin use or its bleeding risks were made in that population (Whitlock EP, Williams SB, Burda BU, Feightner A, Beil T. Aspirin use in adults: cancer, all-cause mortality, and harms. A Systematic Evidence Review for the U.S. Preventive Services Task Force. Evidence Synthesis No. 132. AHRQ Publication No. 13-05193-EF-1. Rockville, MD: Agency for Healthcare Research and Quality and September 2015).

The strengths of our meta-analysis include an extensive search of the available literature. Furthermore, we included only RCTs, which help eliminate the likelihood of confounding bias from nonrandomized studies. However, there are several limitations in the included clinical trials. First, almost all included trials were not primarily studying aspirin in the intent of preventing cancer and rather all the results were obtained by examining other reported primary outcomes. Second, due to various trial designs and protocols, there were major differences in the aspirin dosing and the different control methods used. Third, only a few clinical trials reported all the predetermined outcomes of our study, and some trials reported only one or two of these primary or secondary outcomes either directly or indirectly.

Conclusion

Among patients with cancer, aspirin was not associated with reduced cancer-related mortality, all-cause mortality, or cancer incidence. However, aspirin was associated with increased risk of bleeding events.

This meta-analysis showed that the use of aspirin for primary prevention of cancer was found to cause more bleeding (any bleeding, major bleeding, and GI bleeding) compared to no aspirin at the longest follow-up period, and had no significant benefit with regard to cancer primary prevention (cancer-related mortality and cancer incidence).

Compliance with ethical standards

Conflict of interest Authors declare that they have no conflict of interest.

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