

Electronic Supplementary Material

**Effects of chemopreventive agents on the incidence of recurrent colorectal adenomas:
A systematic review with network meta-analysis of randomized controlled trials**

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Search strategies

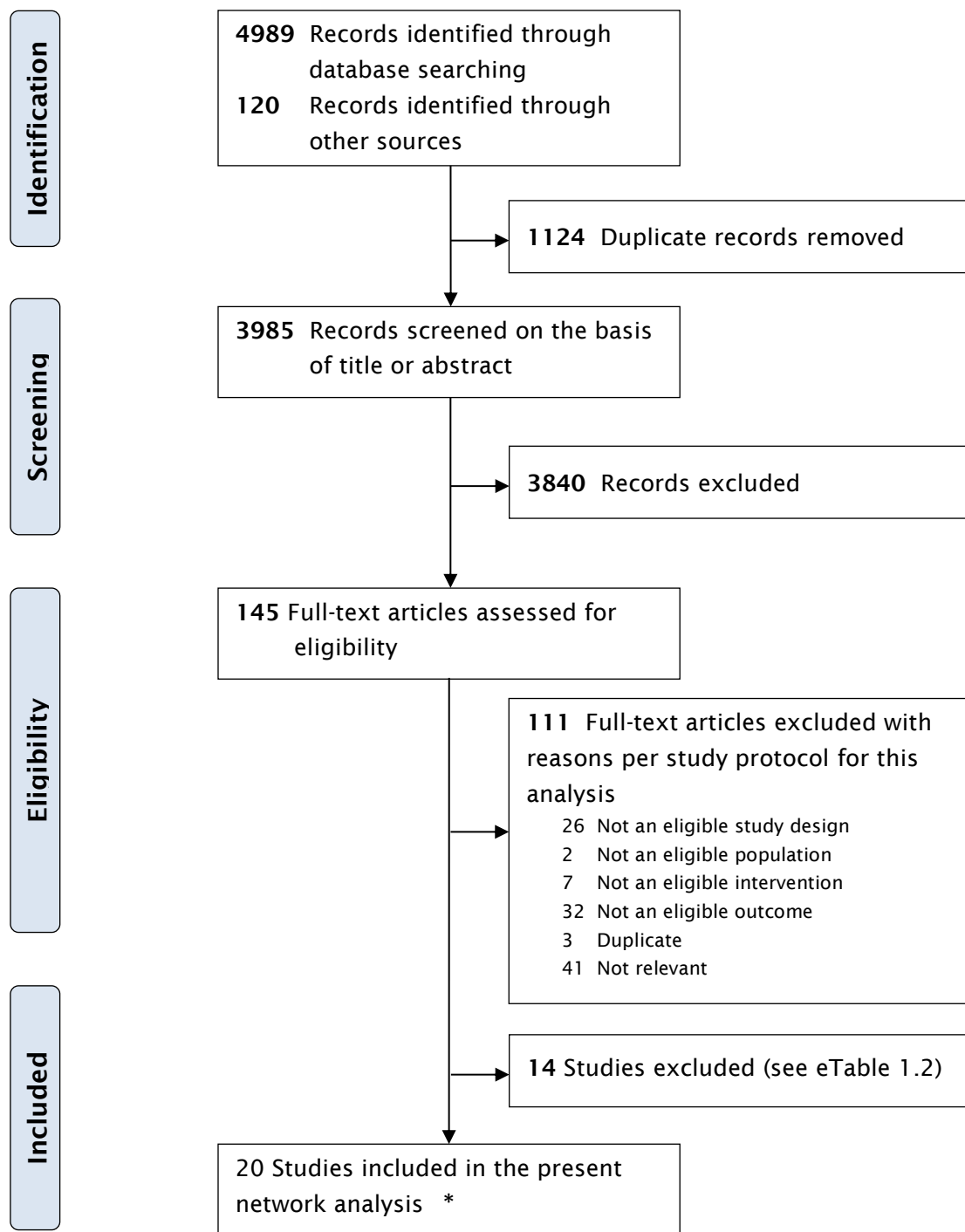
Table S1 Search algorithms as per the parent study design

#1	Adenoma
#2	Adenoma\$
#3	Adenocarcinoma
#4	Adenomatous\$
#5	Adenomatous polyps
#6	Colon cancer\$
#7	Colon neoplas\$
#8	Colon tumor\$
#9	Colonic cancer\$
#10	Colonic neoplas\$
#11	Colonic neoplasms
#12	Colonic polyps
#13	Colonic tumor\$
#14	Colorectal cancer\$
#15	Colorectal neoplas\$
#16	Colorectal neoplasms
#17	Colorectal tumor\$
#18	Intestinal polyps
#19	Polyp\$
#20	Rectal cancer\$
#21	Rectal neoplas\$
#22	Rectal neoplasms
#23	Rectal tumor\$
#24	Rectum cancer\$
#25	Rectum neoplas\$
#26	Rectum tumor\$
#27	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #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
#28	Aspirin
#29	Acetylsalicylic acid
#30	COX-1 inhibitor\$
#31	COX-2 inhibitor\$
#32	COX-2 selective inhibitor\$
#33	Coxib\$
#34	Cyclooxygenase 1 inhibitor\$
#35	Cyclooxygenase 2 inhibitor\$
#36	Cyclooxygenase 2 inhibitors
#37	Cyclooxygenase inhibitor\$
#38	Cyclo-oxygenase inhibitor\$

#39	Cyclooxygenase inhibitors
#40	Nonsteroidal antiinflammatory\$
#41	Non-steroidal antiinflammatory\$
#42	Nonsteroidal anti-inflammatory\$
#43	Non-steroidal anti-inflammatory\$
#44	Anti-inflammatory agents, non-steroidal
#45	NSAID\$
#46	#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45
#47	Folate\$
#48	Folic\$
#49	Folic acid
#50	#47 OR #48 OR #49
#51	Calcium
#52	Calcium\$
#53	Calcium, dietary
#54	#51 OR #52 OR #53
#55	Cholecalciferol
#56	Cholecalciferol\$
#57	Ergocalciferol\$
#58	Ergocalciferols
#59	Vitamin D
#60	#55 OR #56 OR #57 OR #58 OR #59
#61	Antioxidant\$
#62	Anti-oxidant\$
#63	Antioxidants
#64	Ascorbic acid
#65	Vitamin C
#66	Vitamin A
#67	Beta-carotene
#68	Carotenoid\$
#69	Carotenoids
#70	Selenium
#71	Tocopherol\$
#72	Tocopherols
#73	Tocotrienol\$
#74	Tocotrienols
#75	Alpha-tocopherol\$
#76	Vitamin E
#77	#61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76
#78	Clinical trial
#79	Controlled clinical trial
#80	Single blind method

#81	Double blind method
#82	Placebo
#83	Placebo\$
#84	Random\$
#85	Random allocation
#86	Randomized controlled trial
#87	Randomized controlled trials
#88	#78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87
#89	#46 OR #50 OR #54 OR #60 OR #77
#90	#27 AND #88 AND #89
<p>This search strategy (include search terms for both adenomas and colorectal cancer (CRC)) was developed for parent study: a systematic review and network meta-analysis of CPAs for CRC, which has been registered (registration number: CRD42015025849) with PROSPERO, previously.</p>	

Figure S1 Flow diagram and references of included studies



*This flow diagram represent the results based on search strategy given in eTable 1.1 (parent study). Among 20 eligible RCTs (reported adenoma incidence), one RCT Baron et al. (2015) presented two sets of data (provided by the author on request). In this trial, subjects randomized separately into 2 arms; factorial arm (both male and female) and 2-arm (only female). Hence, we analyzed the data separately for two arms (as 2 studies, Baron 2015a and Baron 2015b).

Table S2 Reasons for exclusion of studies

Authors (citation)	Reasons for exclusion
Ladenheim et al. (Gastroenterology. 1995;108(4):1083-7.)	Randomized placebo trial. Interventions and participants: sulindac 300mg/day (n=44); placebo (n=40). Primary outcome is percentage of patients for whom all polyps either disappeared or regressed. Incidence of adenoma not reported.
Baron et al. (Ann N Y Acad Sci. 1999;889:138-45.)	Duplicate of Baron et al., 1999 study (N Engl J Med. 1999;340(2):101-7.).
Baron et al. (N Engl J Med 2003; 348:891-9.)	Aspirin/Folate Polyp Prevention Study (AFPPS): three by-two factorial design RCT, comparing 81 mg and 325 mg of aspirin per day with placebo and comparing 1 mg of folic acid per day with placebo, reported in two papers (Baron et al. 2003 and Cole et al. 2007). Baron et al. 2003 reported only aspirin arm results compared to no intervention. Cole et al. 2007 (JAMA 2007; 297:2351-9.), reported the event rates of all the arms (including aspirin and folic acid).
Benamouzig et al. (Gastroenterology. 2003;125(2):328-36.)	The latest 4-year results of this study available; we used the results from Benamouzig et al., 2012 (Gut. 2012;61(2):255-61.) for our analysis.
Baron et al. (Gastroenterology. 2006;131(6):1674-82.)	Randomized, double-blind, placebo-controlled trial. Interventions and participants: rofecoxib 25 mg/day (n=1,277); Placebo (n=1,293). Rofecoxib was withdrawn from the market; and therefore excluded.
Jaszewski et al. (World J Gastroenterol. 2008;14(28):4492-8.)	Did not report event data (only mean number of adenoma).
Meyskens et al. (Cancer Prev Res Phila Pa. 2008;1(1):32-8.)	Randomized placebo-controlled, double-blind trial. Interventions and participants: difluoromethylornithine (DFMO) 500 mg and sulindac 150 mg (n=191); placebo (n=184) No separate arm for sulindac. DFMO itself a chemopreventive agent; hence the results from this RCT cannot assign only to sulindac.
Bertagnolli et al. (Cancer Prev Res Phila Pa. 2009;2(4):310-21.)	Post-trial results of the Adenoma Prevention with Celecoxib (APC) trial.
Grau et al. (J Natl Cancer Inst. 2009;101(4):267-76.)	Post-trial results of Aspirin/Folate Polyp Prevention Study (AFPPS).
Benamouzig et al. (Curr Colorectal Cancer Rep. 2010;7(1):33-41.)	Duplicate of Benamouzig et al., 2012 study (Gut. 2012;61(2):255-61.).
Arber et al. (Am J Gastroenterol. 2011;106(6):1135-46.)	Post-trial results of the Prevention of Colorectal Sporadic Adenomatous Polypos (Pre SAP) study.
Li et al. (Chinese J Med Guide. 2011;13:89.)	This study was identified from the reference list of Zhao et al. review (Asian Pac J Cancer Prev. 2016;17(5):2711-7.). As per their description, this paper retrieved from "Chinese biomedical literature service system (SinoMed) database"; it's a Chinese study written in Chinese language; and graded as low quality. We searched "Chinese biomedical literature service system (SinoMed) database" to retrieve this article. Unfortunately, we were not able to identify the full text of this study. Hence, we

Authors (citation)	Reasons for exclusion
	communicated with the authors for getting full text/descriptions of this study. However, we didn't received any reply. Moreover, the data obtained from Zhao et al. review for this study showed a control event rate (adenoma incidence) of 80% (39/49), which is too higher than what we saw in other trials (27% to a maximum of 47%). We think that, this study is only a comparative clinical study not an RCT.
Takayama et al. (Clin Cancer Res Off J Am Assoc Cancer Res. 2011;17(11):3803-11.)	Duration of treatment is only 2 months and follow-up \approx 1 year. Interventions and participants: sulindac 300 mg/day (n=60); etodolac 400 mg/day (n=61); placebo (n=58).
Bonelli et al. (J Gastroenterol. 2013;48(6):698-705.)	The latest report of the study is available (Bonelli et al. J Gastroenterol 2013; 48:698-705.).

Description of included studies, interventions, and outcomes

Table S3 Characteristics of eligible randomized controlled trials

Authors (year)	Location	Intervention (No. of patients randomized)	Study size (total No. of patients)	Age (years)	% Male	Remarks	% of randomized participants excluded from main analyses
McKeown-Eyssen et al. (1988)[1]	Canada	Vitamin C 400 mg/day + vitamin E 400 mg/day (n = 96) Placebo (n = 89)	185	(mean 58)	65	Participants with history of adenomas (post-polypectomy – not clear).	26% excluded from analysis as no follow-up colonoscopy.
Roncucci et al. (1993)[2]	Italy	Vitamin A 30,000 IU + vitamin C 1 g + vitamin E 70 mg/day (n = 70) Lactulose 20 g/day (n = 61) No intervention (n = 78)	209	(mean 59)	62	Participants with history of adenomas; and documented clean colon post-polypectomy.	10% had no follow-up colonoscopy and 28% had no follow-up beyond 1 year, but these patients were included in the analysis; presumably assumed no polyps for these patients.
Greenberg et al. (1994)[3]	United States	Beta-carotene (n = 217) Vitamin C + vitamin E (n = 225) Beta-carotene + vitamin C + vitamin E (n = 208) Placebo (n = 214)	864	< 80 (mean 61)	79	Participants with history of adenomas; and documented clean colon post-polypectomy.	13% excluded from 4-year analysis as no follow-up colonoscopy.
MacLennan et al. (1995)[4]	Australia	Beta-carotene (n = 53) Beta-carotene + bran (n = 47) Beta-carotene + LFD (n = 51) Beta-carotene + LFD + bran (n = 50) Normal eating + placebo (n = 48) Bran + placebo (n=50) LFD + placebo (n = 48)	395	30–74	67	Documented polyp free colon.	26% excluded from analysis as no follow-up colonoscopy.

Authors (year)	Location	Intervention (No. of patients randomized)	Study size (total No. of patients)	Age (years)	% Male	Remarks	% of randomized participants excluded from main analyses
		LFD + bran + placebo (n = 48)					
Ponz de Leon et al. (1997)[5]	Italy	Vitamin A 30,000 IU + vitamin C 1 g + vitamin E 70 mg, all given every other day (n = 36) N-acetylcysteine 600 mg/day (n = 33) Placebo (n = 34)	140	NA	NA	Participants with history of adenomas (post-polypectomy - not clear).	26%) not evaluated yet but only preliminary analysis reported.
Hofstad et al. (1998)[6]	Norway	Calcium (elemental calcium) 1,600 mg/day + beta-carotene 15 mg/day + vitamin C 150 mg/day + vitamin E 75 mg/day + selenium 101 µg/day (n = 42) Placebo (n = 51)	116	50-76 (median 67)	51	Participants with history of adenomas (polyps of 1-9 mm in diameter were removed; remaining polyps left in situ).	20% excluded from analysis.
Baron et al. (1999)[7]	United States	Calcium (elemental calcium) 1,200 mg/day (n = 464) Placebo (n = 466)	930	≤ 80 (mean 61)	72	Participants with history of adenomas; and all polyps removed and pathologically examined before study.	11% excluded from analysis as no follow-up colonoscopy.
Bonithon-Kopp et al. (2000)[8]	Multi-national	Calcium (elemental calcium) 2,000 mg/day (n = 218) Placebo (n = 221)	439	35-75 (mean 59)	63	Participants with history of adenomas; and documented clean colon post-polypectomy.	15% excluded from analysis as no follow-up colonoscopy.
Baron et al. (2003)[9]/ Cole et al. (2007)[10]	United States	ASA 81 mg/day (n=169) ASA 325 mg/day (n=167) ASA 81 mg/day + folic acid 1 mg/day (n=175) ASA 325 mg/day + folic acid 1 mg/day (n=171) Folic acid 1 mg/day (n=170) Placebo (n=169)	1,021	21-81 (mean 57)	64	Participants with history of adenomas; and documented clean colon post-polypectomy.	3% excluded from analysis as no follow-up colonoscopy.

Authors (year)	Location	Intervention (No. of patients randomized)	Study size (total No. of patients)	Age (years)	% Male	Remarks	% of randomized participants excluded from main analyses
Sandler et al. (2003)[11]	United States	ASA 325 mg/day (n=317) Placebo (n=318)	635	30-80	52	Participants with of histologically documented colon or rectal cancer with a low risk of recurrent disease; and documented clean colon post-polypectomy.	19% excluded from analysis as no follow-up colonoscopy.
Arber et al. (2006)[12]	Multi-national	Cele 400 mg/day (n=933) Placebo (n=628)	1,561	30-92 (mean 61)	66	Participants with history of adenomas; and documented clean colon post-polypectomy.	11% excluded from analysis as no follow-up colonoscopy at year 1 or year 3.
Bertagnolli et al. (2006)[13]	Multi-national	Cele 400 mg/day (n=685) Cele800 mg/day (n=671) Placebo (n=679)	2,035	31-88 (median 59)	68	Participants with history of adenomas; and documented clean colon post-polypectomy.	10% excluded from analysis as no follow-up colonoscopy at year 1 or year 3.
Logan et al. (2008)[14]	UK,Denmark	ASA 300 mg/day (n=236) Folic acid 0.5 mg/day(n=234) ASA 300 mg/day + folic acid 0.5 mg/day (n=236) Placebo (n=233)	939	28-75 (mean 58)	56	Participants with history of colorectal adenoma ≥ 0.5 cm; and documented clean colon post-polypectomy.	10% excluded from analysis as no follow-up colonoscopy.
Wu et al. (2009)[15]	United States	Folic acid 1 mg/day (n=338) Placebo (n=334)	672	50 -78 (mean 57)	38	Participants with history of adenomas (polyps left in situ) from among participants of 2 large prospective cohorts, the Health Professionals Follow-Up Study and the Nurses' Health Study.	29% excluded from analysis.
Chu et al. (2011)[16]	United States	Calcium carbonate 1,800 mg (n=95) Placebo (n=99)	220	≥ 18 (median 68)	63	Participants with history of stage 0, I or II colorectal cancer.	12% excluded from analysis.

Authors (year)	Location	Intervention (No. of patients randomized)	Study size (total No. of patients)	Age (years)	% Male	Remarks	% of randomized participants excluded from main analyses
Benamouziget al. (2012)[17]	France	ASA 160 mg/day (n=73) ASA 300 mg/day (n=67) Placebo (n=132)	272	18-75	70	Participants with history of at least 3 adenomas irrespective of size, or at least one measuring 6 mm in diameter or more; and documented clean colon post-polypectomy.	32% excluded from analysis as no follow-up colonoscopy at year 4.
Bonelliet al. (2013)[18]	Italy	Selenium 200 µg, zinc 30 mg, vitamin A 2 mg, vitamin C 180 mg, vitamin E 30 mg/day (n=200) Placebo (n=211)	411	25-75 (mean 57)	62	Participants with history of adenomas; and documented clean colon post-polypectomy.	19% excluded from analysis as no follow-up colonoscopy.
Ishikawa et al. (2014)[19]	Japan	ASA 100 mg/day (n=191) Placebo (n=198)	389	40-70	79	Participants with history of single/multiple colorectal adenomas and/or adenocarcinomas with invasions confined to the mucosa; and documented clean colon post-polypectomy.	20% excluded from analysis as no follow-up colonoscopy.
Baron et al. (2015)a[20]	United States	Calcium (elemental calcium) 1,200 mg/day (n=419) Vitamin D3 1,000 IU/day (n=420) Calcium (elemental calcium) 1200 mg + vitamin D3 1,000 IU/day (n=421) Placebo (n=415) [factorial arm]	1,675	45-75 (mean 59)	41	Participants with history of adenomas; and documented clean colon post-polypectomy.	9% excluded from analysis.
Baron et al. (2015)b[20]	United States	Calcium (elemental calcium) 1,200 mg/day (n=295) Calcium (elemental calcium) 1,200 mg + vitamin D3 1,000 IU/day (n=289) [2 arms]	584	45-75 (mean 57)	0	Participants with history of adenomas; and documented clean colon post-polypectomy.	8% excluded from analysis.

Authors (year)	Location	Intervention (No. of patients randomized)	Study size (total No. of patients)	Age (years)	% Male	Remarks	% of randomized participants excluded from main analyses
Pommegaard et al.2016)[21]	Multi-national	ASA 75 mg/day + calcium carbonate 1250 mg/day + calcitriol 0.5 µg/day (n=557) Placebo (n=550)	1107	45-75 (mean 59)	58	Participants with history of adenomas; and documented clean colon post-polypectomy.	38.5% excluded from analysis.

Abbreviations: ASA, aspirin; Cele, celecoxib; LFD, low-fat diet.

Table S4 Primary and secondary outcomes of each study

Authors (year)	Primary outcome(s)	Secondary outcome(s)	Duration of treatment (follow-up schedule)
McKeown-Eyssen et al. (1988)[1]	Recurrent colorectal adenomas.		2 years (2 years).
Roncucci et al. (1993)[2]	Recurrent colorectal adenomas and advanced adenomas.		≈1.5 years (≈ 1.5 years after the baseline examination).
Greenberg et al. (1994)[3]	Recurrent colorectal adenomas.		4 years (4 years after the baseline examination).
MacLennan et al. (1995)[4]	Recurrent colorectal adenomas.		2 years (4 years after the baseline examination).
Ponz de Leon et al. (1997)[5]	Recurrent colorectal adenomas.		Not reported (<2 years).
Hofstad et al. (1998)[6]	Recurrent colorectal adenomas.		3 years (3 years).
Baron et al. (1999)[7]	Recurrent colorectal adenomas.	One or more advanced adenomas.	4 years (analyzed from end year 1 to end year 4).
Bonithon-Kopp et al. (2000)[8]	Recurrent colorectal adenoma at 3 year examination.	One or more advanced adenomas.	3 years (3 years after the baseline examination).
Baron et al. (2003)[9]/ Cole et al. (2007)[10]	Recurrent colorectal adenomas.	Numbers of colorectal adenomas and advanced adenomas.	≈3 years (3 years after the baseline examination).
Sandler et al. (2003)[11]	Incidence of adenoma.	The size of the adenoma; the time to the detection of a first adenoma, and the proportion of patients with advanced adenomas.	≈3 years (participants with early-stage disease at 4 years and all other participants at 3 years after the baseline examination).
Arber et al. (2006)[12]	Recurrent colorectal adenomas at year 1, 3, or both.	Advanced adenomas at year 1, 3, or both; cardiovascular outcomes and adverse events.	≈3 years (1 and 3 years after the baseline examination).
Bertagnolli et al. (2006)[13]	Recurrent colorectal adenomas.	Advanced adenomas at year 1, 3, or both; number of adenomas; size of largest adenoma; adenoma burden; cardiovascular outcomes and adverse events.	3 years (1 and 3 years after the baseline examination).

Authors (year)	Primary outcome(s)	Secondary outcome(s)	Duration of treatment (follow-up schedule)
Logan et al. (2008)[14]	Recurrent colorectal adenomas or adenocarcinomas.	Number of colorectal adenomas detected during follow-up evaluation and recurrent advanced colorectal neoplasia.	3 years (3 years after the baseline examination).
Wu et al. (2009)[15]	Recurrent of colorectal adenomas.		5-6.5 years (≥ 3 months after initiation of trial and ≤ 12 months after completion of the trial).
Chu et al. (2011)[16]	Compliance to drugs and colonoscopies; drop-out rate; adverse effects.	Rate of new adenomas or advanced adenomas.	5 years (5 years after the baseline examination).
Benamouziget al. (2012)[17]	Recurrent colorectal adenomas, the size of new adenomas, and the adenomatous polyp burden.	Numbers of recurrent adenomas and numbers of recurrent advanced adenomas.	4 years (4 years after the baseline examination).
Bonelliet al. (2013)[18]	Recurrent colorectal adenomas.	Recurrent advanced adenomas.	5 years (median follow-up was 4 years; range 1–15 years after the baseline examination).
Ishikawa et al. (2014)[19]	Recurrent colorectal adenomas or adenocarcinomas.	Recurring tumor number, size and histology, and the frequency of adverse effects.	2 years (2 years after the baseline examination).
Baron et al. (2015)[20]	Recurrent adenomas at least 1 year after randomization and up to 6 months after the anticipated 3-year or 5-year colonoscopic examination.	One or more advanced adenomas.	5 years (follow-up examination at year 3 or 5).
Pommergaard et al. 2016)[21]	Recurrent colorectal adenomas.	Advanced adenomas, total number of colorectal adenomas, pathologic classification of the adenomas, the degree of dysplasia, and adenoma size.	≈ 3 years (3 years after the baseline examination).

Table S5 Definition of advanced adenomas in each study

Authors (year)	Definition of advanced adenomas
Roncucci et al. (1993)[2]	Tubule-villous adenomas, large adenomas (≥ 1 cm in diameter).
Baron et al. (1999)[7]	Advanced adenomas not defined in the original article.
Bonithon-Kopp et al. (2000)[8]	Villous or tubule-villous features , or an estimated diameter of at least 1cm.
Baron et al.(2003)[9]/ Cole et al. (2007)[10]	Tubule-villous adenomas (25-75% villous features), villous adenomas (more than 75% villous), large adenomas (at least 1 cm in diameter), severe dysplasia, or invasive cancer.
Sandler et al. (2003)[11]	Adenomas at least 1 cm in diameter or had villous components.
Arber et al. (2006)[12]	Adenoma ≥ 1.0 cm (villous or tubule-villous histology); high-grade dysplasia; intra-mucosal carcinoma or invasive cancer.
Bertagnolli et al. (2006)[13]	Adenoma ≥ 1.0 cm (villous or tubule-villous histology); high-grade dysplasia; Intra-mucosal carcinoma or invasive cancer.
Logan et al. (2008)[14]	Adenomas that were either 1 cm or larger in diameter, villous or tubule-villous, or showed severe dysplasia or invasive cancer.
Chu et al. (2011)[16]	Villous or tubule-villous features , or an estimated diameter of at least 1cm.
Benamouziget al. (2012)[17]	Adenomas with a maximum diameter of at least 10 mm, at least 25% villous elements or evidence of high-grade dysplasia.
Bonelliet al. (2013)[18]	Villous adenomas ($\geq 20\%$ villous features), large adenomas (≥ 1 cm in diameter), adenomas with high-grade dysplasia.
Ishikawa et al. (2014)[19]	Adenomas with high grade dysplasia.
Baron et al. (2015)[20]	Adenomas with cancer, high-grade dysplasia, more than 25% villous features, or an estimated diameter of at least 1cm.
Pommergaard et al. 2016)[21]	Definition was unclear

Risk of bias assessments

Table S6 Summarized risk of bias of included randomized controlled trials

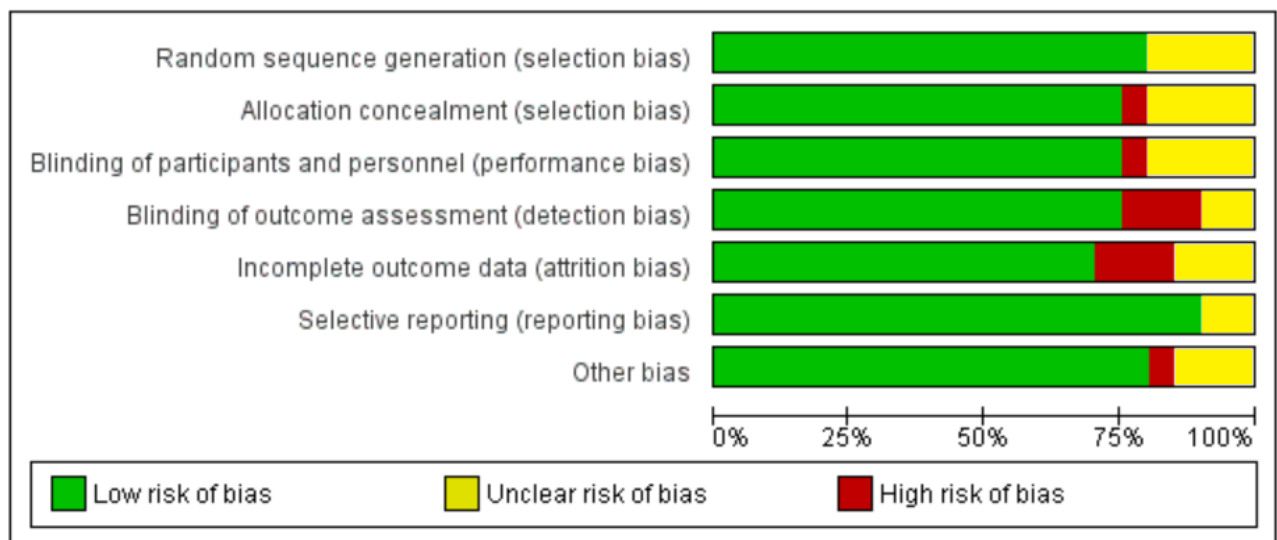
Authors (year)	Adequate sequence generation	Allocation concealment	Blinding participants and personnel	Blinding assessor	Incomplete outcome data	Selective outcome reporting	Other sources of bias
McKeown-Eyssen et al. (1988)[1]	?	+	+	+	-	+	+
Roncucci et al. (1993)[2]	+	?	?	+	+	+	+
Greenberg et al. (1994)[3]	+	+	+	+	+	+	+
MacLennan et al. (1995)[4]	+	+	+	+	?	+	+
Ponz de Leon et al. (1997)[5]	?	?	?	?	-	?	+
Hofstad et al. (1998)[6]	?	?	?	-	+	+	?
Baron et al. (1999)[7]	+	+	+	+	+	+	+
Bonithon-Kopp et al. (2000)[8]	+	+	+	+	+	+	+
Sandler et al. (2003)[11]	+	+	+	+	+	+	+
Arber et al. (2006)[12]	+	+	+	+	+	+	+
Bertagnolli et al. (2006)[13]	+	+	+	+	+	+	+
Cole et al. (2007)[10]	+	+	+	+	+	+	+
Logan et al. (2008)[14]	+	+	+	+	+	+	+
Wu et al. (2009)[15]	+	+	+	-	-	?	?
Chu et al. (2011)[16]	?	-	?	-	+	+	-
Benamouzig et al. (2012)[17]	+	+	+	+	?	+	?
Bonelli et al. (2013)[18]	+	?	+	?	+	+	+
Ishikawa et al. (2014)[19]	+	+	-	+	+	+	+
Baron et al. (2015)[20]	+	+	+	+	+	+	+
Pommergaard et al. (2016)[21]	+	+	+	+	?	+	+

low risk (+); unclear risk (?); high risk (-)

Justifications for other sources of bias:

- Hofstad et al. (1998): Control event rate is too high compared to large/good quality RCTs.
- Wu et al. (2009): 197 of 672 (29%) excluded from analysis as no-follow-up colonoscopy; follow-up of participants of 2 large prospective cohorts; no colonoscopy before randomization (baseline adenoma not resected).
- Chu et al. (2011): Used participants with history of colorectal cancer stage 0, I or II; control event rate is too high compared to large-high quality RCTs on subjects with history of only adenomas.
- Benamouzig et al. (2012): 87 of 272 (32%) excluded from analysis as no-follow-up colonoscopy at year 4. Possibility of lack of statistical power due to 32% exclusion rate. However, missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; Reviewers think that, plausible bias unlikely to seriously alter the results. Moreover, this is the most update results from APACC trail and the only trail with a long duration of follow-up of 4 years; hence review authors agree to use the most updated results (Not 1-year results from APACC study – Benamouzig et al. (2003)).

Figure S2 Summarized risk of bias of included randomized controlled trials

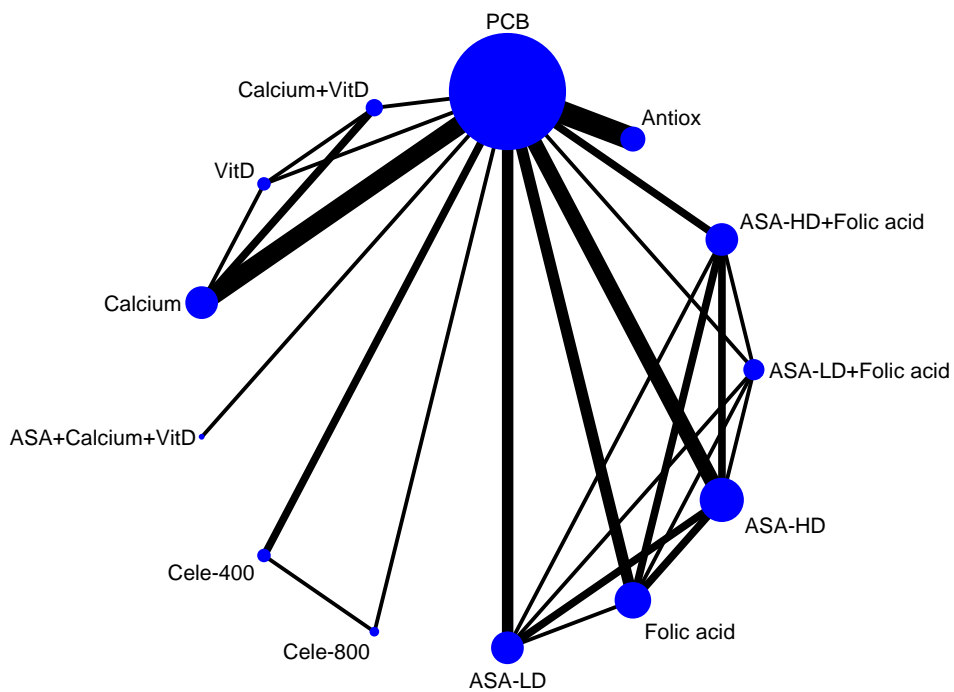


This report followed the recommended approach for assessing risk of bias in randomized controlled trials included in Cochrane reviews. This tool addresses specific bias domains including methods for generating the random sequence, allocation concealment, blinding of participants and investigators, blinding of outcome assessment, incompleteness of outcome data and selective outcome reporting. Each item is adjudicated within each study and the results are represented in a risk of bias table. The adjudication of the risk of bias is achieved by answering pre-specified questions about the methods reported by each study in relation to the risk domain, such that the conclusion is either low risk of bias, unclear risk of bias or high risk of bias.

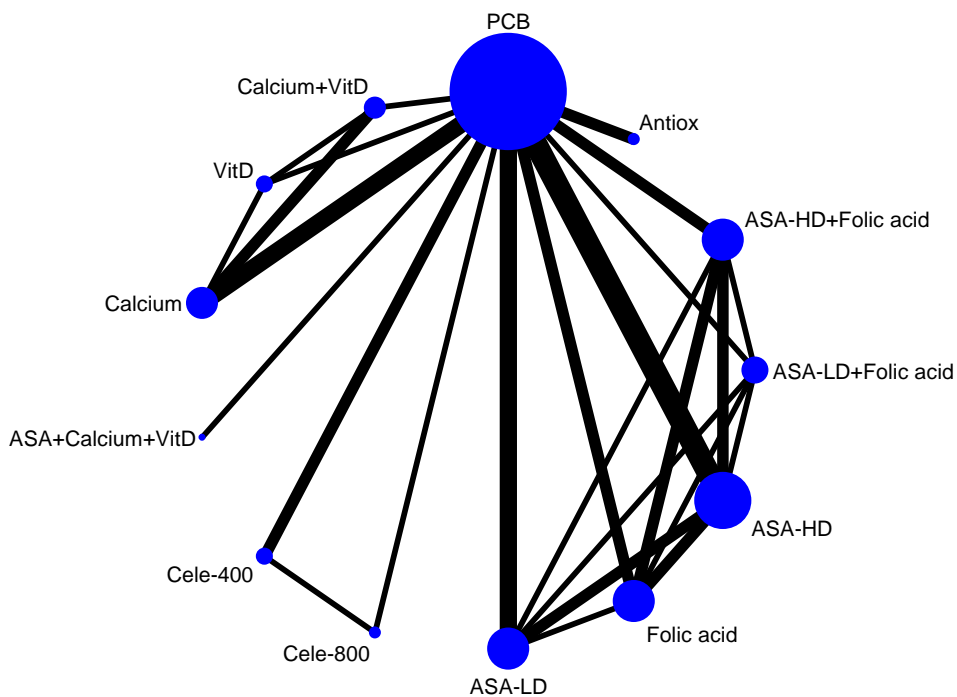
Network of comparisons

Figure S3 Network plot of all intervention comparisons for incidence of any adenomas

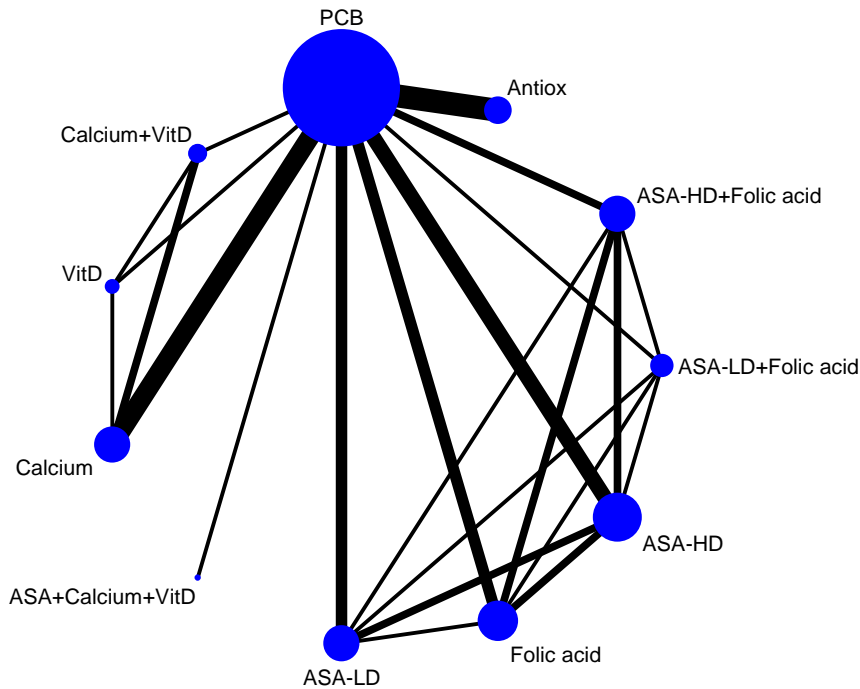
i. All studies



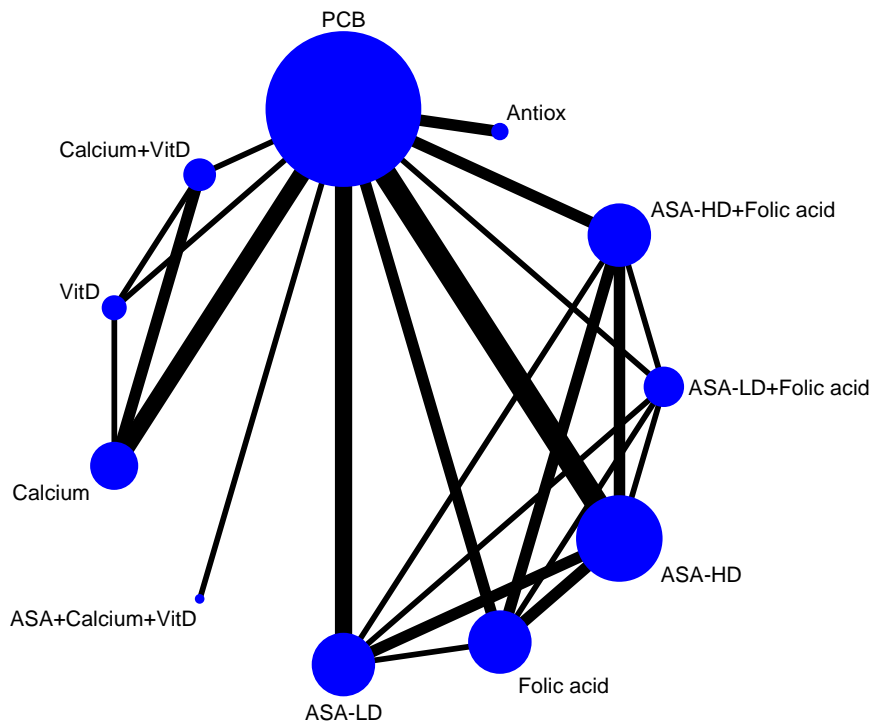
ii. Low ROB studies including celecoxib



iii. Low ROB + High ROB studies excluding celecoxib



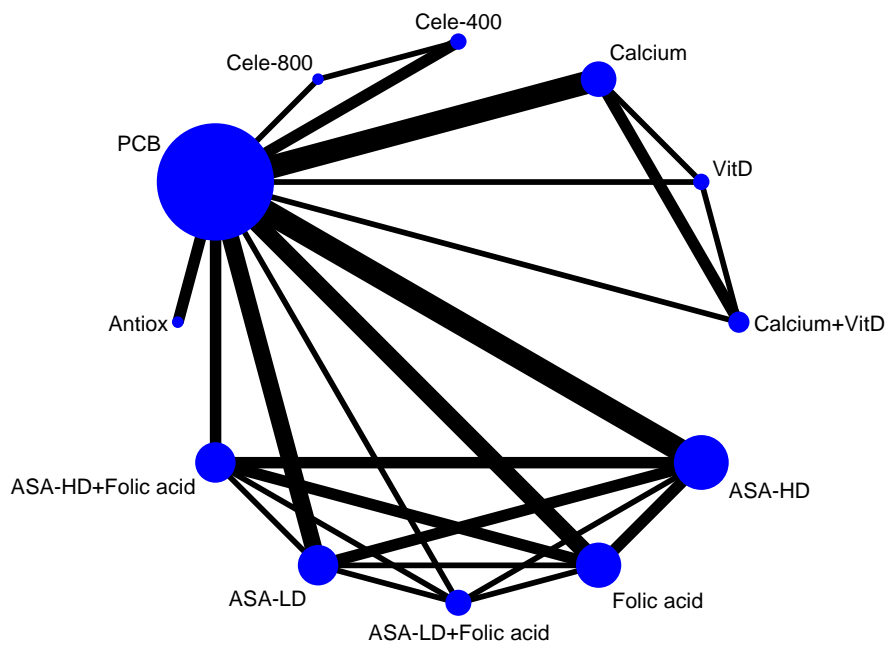
iv. Low ROB studies excluding celecoxib



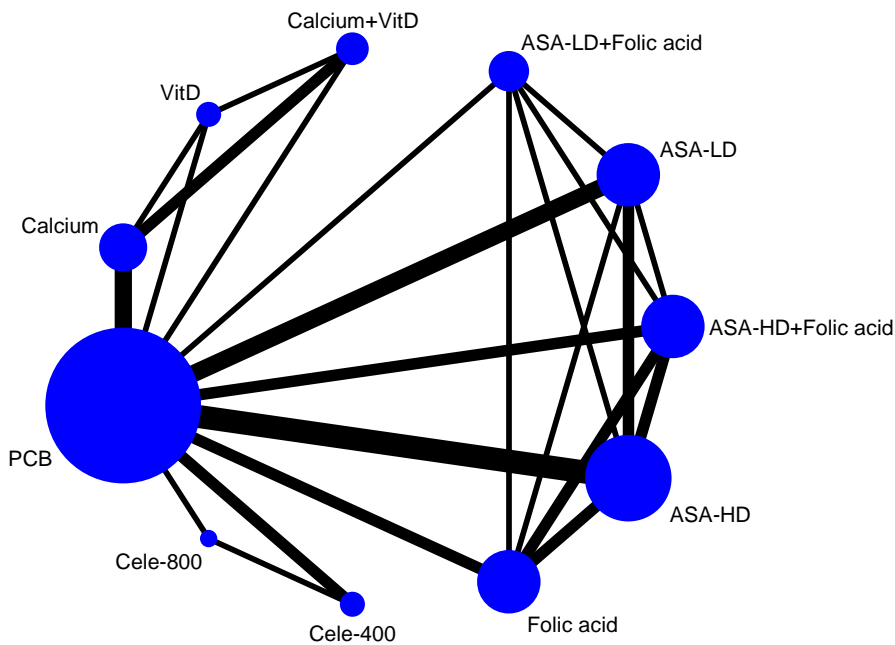
Size of the node corresponds to the number of individual studies that studied the treatment. The directly compared treatments are linked with a line, the thickness of which corresponds to the number of studies that assessed this comparison. Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

Figure S4 Network plot of all intervention comparisons for incidence of advanced adenomas

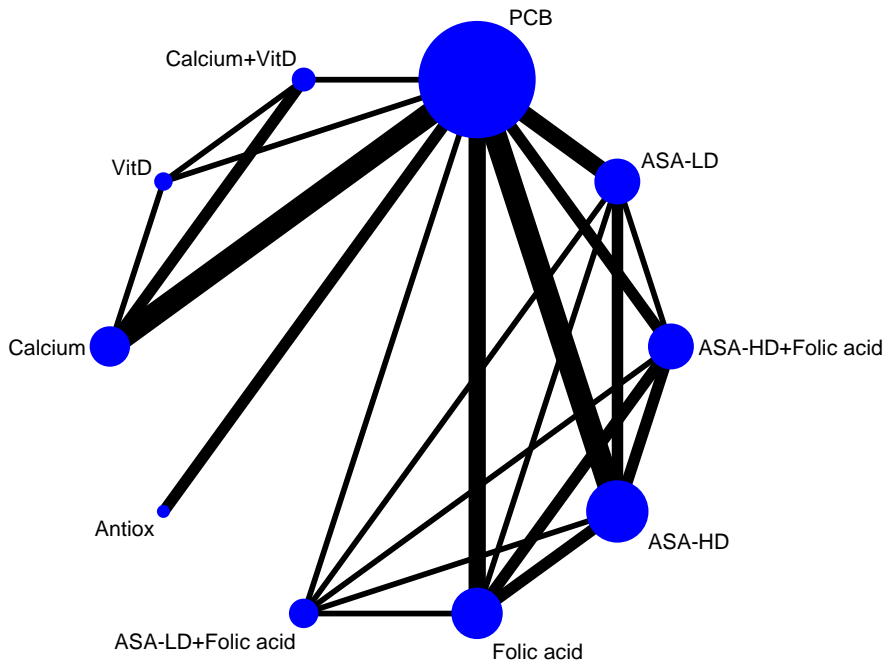
i. All studies



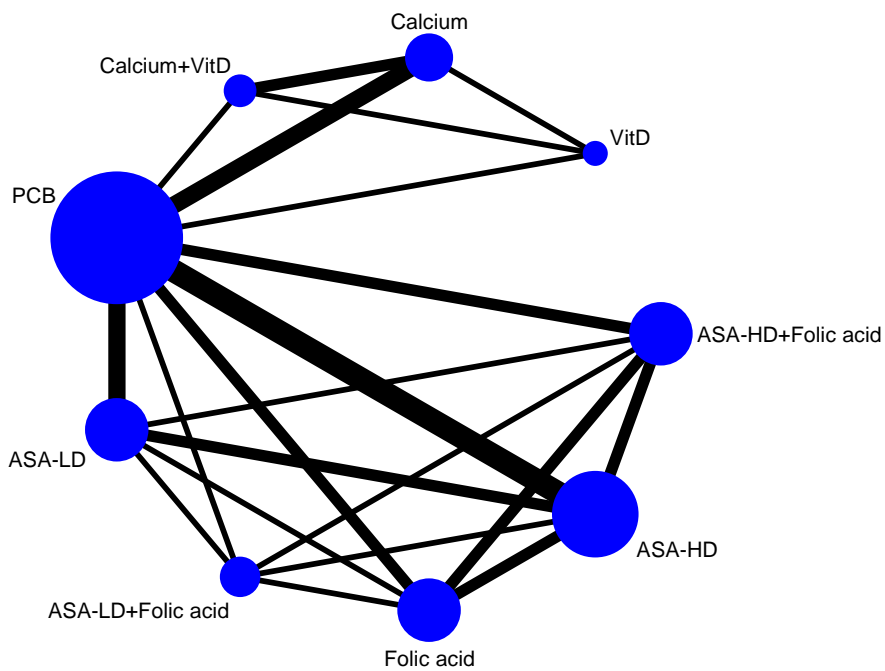
ii. Low ROB studies including celecoxib



iii. Low ROB + High ROB studies excluding celecoxib



iv. Low ROB studies excluding celecoxib



Size of the node corresponds to the number of individual studies that studied the treatment. The directly compared treatments are linked with a line, the thickness of which corresponds to the number of studies that assessed this comparison. Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

Assessment of inconsistency in intervention triangular or quadratic loops for each outcome network

Table S7 Assessment of global inconsistency in networks using the ‘design-by-treatment’ interaction model (all studies)

Network outcome	Chi-square	P value for test of global inconsistency
Incidence of any adenomas	7.57	0.751
Incidence of advanced adenomas	7.34	0.771

Difference between direct and indirect loops

We estimated inconsistency as the difference between direct and indirect estimates (called inconsistency factor, IF) and the corresponding 95% CI for each IF in each closed triangular or quadratic loop. Inconsistent loops are those that present inconsistency factors with 95% confidence intervals incompatible with zero.

Table S8 Assessment of loop inconsistency in networks (all studies)

Loop	IF [95% CI]	P value	Loop heterogeneity τ^2
Incidence of any adenomas			
ASA(HD) – ASA(LD) – Folic	0.66 [0.08,1.24]	0.027	0.000
ASA(HD) – ASA(LD) – ASA(LD)+Folic	0.61 [0.00,1.24]	0.060	0.000
ASA(HD) – ASA(LD) – PCB	0.47 [0.00,1.01]	0.088	0.022
ASA(HD)+Folic – Folic – PCB	0.29 [0.00,0.69]	0.143	0.000
ASA(HD)+Folic – ASA(LD)+Folic – PCB	0.24 [0.00,0.74]	0.353	0.000
ASA(LD)+Folic – Folic – PCB	0.21 [0.00,0.64]	0.333	0.000
Calcium – Calcium+VitD – PCB	0.19 [0.00,0.43]	0.126	0.000
Calcium – PCB – VitD	0.19 [0.00,0.44]	0.149	0.000
ASA(HD) – ASA(LD)+Folic – PCB	0.17 [0.00,0.60]	0.450	0.000
ASA(LD) – ASA(LD)+Folic – PCB	0.16 [0.00,0.61]	0.505	0.000
ASA(HD)+Folic – ASA(LD) – Folic	0.15 [0.00,0.62]	0.519	0.000
ASA(HD)+Folic – ASA(LD)+Folic – Folic	0.15 [0.00,0.64]	0.533	0.000
ASA(HD) – ASA(LD)+Folic – Folic	0.15 [0.00,0.64]	0.548	0.000
ASA(LD) – Folic – PCB	0.13 [0.00,0.49]	0.495	0.000
ASA(HD) – ASA(HD)+Folic – ASA(LD)	0.12 [0.00,0.61]	0.618	0.000
ASA(HD) – Folic – PCB	0.09 [0.00,0.82]	0.801	0.072
ASA(HD)+Folic – ASA(LD) – PCB	0.07 [0.00,0.47]	0.720	0.000

Loop	IF [95% CI]	P value	Loop heterogeneity tau ²
Incidence of any adenomas			
Celecoxib(400) - Celecoxib(800) - PCB	0.04 [0.00,0.25]	0.710	0.000
Calcium - Calcium+VitD - VitD	0.01 [0.00,0.33]	0.965	0.000
ASA(HD) - ASA(HD)+Folic - ASA(LD)+Folic	0.01 [0.00,0.52]	0.986	0.000
ASA(HD) - ASA(HD)+Folic - PCB	0.00 [0.00,0.86]	0.995	0.096
ASA(HD) - ASA(HD)+Folic - Folic	**	**	0.000
ASA(HD)+Folic - ASA(LD) - ASA(LD)+Folic	**	**	0.000
Calcium+VitD - PCB - VitD	**	**	0.000
ASA(LD) - ASA(LD)+Folic - Folic	**	**	0.000
Incidence of advanced adenomas			
ASA(HD) - ASA(HD)+Folic - ASA(LD)	0.97 [0.00,2.44]	0.198	0.000
ASA(HD)+Folic - ASA(LD) - PCB	0.95 [0.00,2.23]	0.142	0.000
ASA(HD) - ASA(LD) - ASA(LD)+Folic	0.89 [0.00,2.51]	0.287	0.000
ASA(HD)+Folic - ASA(LD)+Folic - PCB	0.81 [0.00,1.98]	0.178	0.000
ASA(LD) - Folic - PCB	0.80 [0.00,1.79]	0.115	0.000
ASA(LD)+Folic - Folic - PCB	0.61 [0.00,1.68]	0.271	0.000
ASA(HD) - ASA(LD)+Folic - PCB	0.58 [0.00,1.70]	0.317	0.000
ASA(HD) - ASA(LD) - PCB	0.57 [0.00,1.56]	0.256	0.000
ASA(LD) - ASA(LD)+Folic - PCB	0.48 [0.00,1.95]	0.527	0.000
Calcium - PCB - VitD	0.36 [0.00,1.05]	0.299	0.000
ASA(HD)+Folic - Folic - PCB	0.30 [0.00,1.17]	0.495	0.000
Calcium - Calcium+VitD - PCB	0.29 [0.00,0.95]	0.391	0.000
Calcium - Calcium+VitD - VitD	0.23 [0.00,1.07]	0.590	0.000
ASA(HD)+Folic - ASA(LD) - Folic	0.23 [0.00,1.37]	0.696	0.000
ASA(HD)+Folic - ASA(LD)+FA - Folic	0.23 [0.00,1.34]	0.688	0.000
ASA(HD) - ASA(LD) - Folic	0.17 [0.00,1.24]	0.750	0.000
ASA(HD) - ASA(HD)+Folic - ASA(LD)+Folic	0.16 [0.00,1.32]	0.792	0.000
Celecoxib(400) - Celecoxib(800) - PCB	0.11 [0.00,0.74]	0.722	0.000
ASA(HD) - ASA(LD)+Folic - Folic	0.07 [0.00,1.17]	0.900	0.000
ASA(HD) - Folic - PCB	0.05 [0.00,0.95]	0.907	0.000
ASA(HD) - ASA(HD)+Folic - PCB	0.05 [0.00,1.14]	0.931	0.048
ASA(HD) - ASA(HD)+Folic - Folic	**	**	0.000
ASA(HD)+Folic - ASA(LD) - ASA(LD)+Folic	**	**	0.000
ASA(LD) - ASA(LD)+Folic - Folic	**	**	0.000
Calcium+VitD - PCB - VitD	**	**	0.000

Note **Loop is formed only by multi-arm trial(s) - Consistent by definition.

Table S9 Assessment of loop inconsistency in networks by node-splitting model (all studies)

Tests of inconsistency by node-splitting method fitted the nod-splitting model of Dias et al. (Stat Med 2010;29:932-44.). The results reported the estimated direct and indirect treatment effects and their differences; the P-value for the difference is the test of consistency.

Comparisons		Direct		Indirect		Difference			tau ²
		RR	SE	RR	SE	RR	SE	P value	
Incidence of any adenomas									
ASA+Calcium+VitD	PCB	-	-	-	-	-	-	-	-
ASA-HD	PCB	0.93	0.11	0.76	0.37	0.47	0.39	0.608	0.162
ASA-HD+Folic acid	PCB	0.96	0.15	0.74	0.30	0.48	0.34	0.441	0.158
ASA-LD	PCB	0.84	0.11	0.39	0.28	0.68	0.29	0.008	0.095
ASA-LD+Folic acid	PCB	0.80	0.21	0.53	0.31	0.59	0.37	0.268	0.152
ASA-HD	Folic acid	0.81	0.15	1.10	0.26	0.74	0.30	0.310	0.157
ASA-HD+Folic acid	Folic acid	0.83	0.14	1.43	0.48	0.58	0.50	0.279	0.151
ASA-LD	Folic acid	0.75	0.21	0.68	0.23	1.10	0.31	0.745	0.170
ASA-LD+Folic acid	Folic acid	0.67	0.21	0.71	0.40	0.94	0.44	0.887	0.170
ASA-HD+Folic acid	ASA-HD	1.02	0.16	0.81	0.40	1.26	0.43	0.594	0.166
ASA-LD+Folic acid	ASA-LD	0.88	0.22	1.25	0.45	0.71	0.49	0.485	0.165
ASA-LD+Folic acid	ASA-HD+Folic acid	0.75	0.21	0.94	0.47	0.80	0.51	0.653	0.165
ASA-LD+Folic acid	ASA-HD	0.77	0.22	0.78	0.37	0.98	0.42	0.969	0.169
ASA-LD	ASA-HD	0.70	0.16	1.17	0.24	0.60	0.29	0.074	0.141
ASA-LD	ASA-HD+Folic acid	0.85	0.21	0.79	0.27	1.06	0.34	0.854	0.169
Antiox	PCB	-	-	-	-	-	-	-	-
Calcium	PCB	0.80	0.10	0.95	0.54	0.39	0.54	0.761	0.171

Comparisons		Direct		Indirect		Difference			tau ²
		RR	SE	RR	SE	RR	SE	P value	
Calcium+VitD	PCB	0.95	0.18	0.74	0.22	0.48	0.28	0.371	0.158
Cele-400	PCB	-	-	-	-	-	-	-	-
Cele-800	PCB	0.62	0.19	0.57	0.49	0.57	0.53	0.879	0.177
Cele-800	Cele-400	0.87	0.19	0.94	0.49	0.92	0.53	0.879	0.177
Folic acid	PCB	1.05	0.13	1.02	0.36	0.36	0.38	0.945	0.168
VitD	PCB	0.98	0.17	0.65	0.35	1.51	0.39	0.293	0.154
Calcium	VitD	0.95	0.18	0.73	0.33	1.32	0.38	0.478	0.164
Calcium+VitD	VitD	0.97	0.19	0.83	0.51	1.18	0.54	0.762	0.171
Calcium	Calcium+VitD	0.99	0.13	0.65	0.37	1.52	0.39	0.293	0.154
Incidence of advanced adenomas									
ASA-HD	PCB	0.87	0.18	0.48	0.71	1.82	0.73	0.410	0.000
ASA-HD+Folic acid	PCB	0.81	0.21	0.78	0.55	1.05	0.58	0.934	0.000
ASA-LD	PCB	0.85	0.31	0.23	0.54	3.70	0.59	0.027	0.000
ASA-LD+Folic acid	PCB	0.76	0.39	0.26	0.54	2.94	0.64	0.091	0.000
ASA-HD	Folic acid	0.68	0.19	0.81	0.50	0.83	0.53	0.730	0.000
ASA-HD+Folic acid	Folic acid	0.65	0.19	1.19	0.75	0.54	0.76	0.421	0.000
ASA-LD	Folic acid	0.41	0.34	0.74	0.40	0.56	0.48	0.219	0.000
ASA-LD+Folic acid	Folic acid	0.41	0.34	0.60	0.56	0.68	0.56	0.486	0.026
ASA-HD+Folic acid	ASA-HD	0.94	0.21	1.25	0.80	0.75	0.83	0.732	0.000
ASA-LD+Folic acid	ASA-LD	1.09	0.42	0.21	1.03	5.29	1.12	0.136	0.000
ASA-LD+Folic acid	ASA-HD+Folic acid	0.57	0.36	1.26	0.65	0.45	0.69	0.249	0.000
ASA-LD+Folic acid	ASA-HD	0.57	0.37	0.88	0.58	0.65	0.64	0.498	0.000

Comparisons		Direct		Indirect		Difference			tau ²
		RR	SE	RR	SE	RR	SE	P value	
ASA-LD	ASA-HD	0.71	0.32	0.93	0.54	0.76	0.60	0.653	0.000
ASA-LD	ASA-HD+Folic acid	0.55	0.37	1.43	0.46	0.38	0.57	0.089	0.000
Antiox	PCB	-	-	-	-	-	-	-	-
Calcium	PCB	1.00	0.14	0.76	0.74	1.32	0.75	0.707	0.028
Calcium+VitD	PCB	1.03	0.22	0.79	0.34	1.32	0.41	0.503	0.000
Cele-400	PCB	-	-	-	-	-	-	-	-
Cele-800	PCB	0.37	0.20	0.46	0.55	0.79	0.56	0.682	0.099
Cele-800	Cele-400	0.81	0.22	0.64	0.52	1.26	0.56	0.682	0.099
Folic acid	PCB	1.18	0.16	2.04	0.74	0.58	0.77	0.480	0.000
VitD	PCB	1.19	0.22	0.61	0.50	1.93	0.55	0.234	0.000
Calcium	VitD	1.04	0.20	0.55	0.45	1.89	0.49	0.192	0.000
Calcium+VitD	VitD	0.88	0.22	1.16	0.71	0.76	0.75	0.707	0.028
Calcium	Calcium+VitD	1.11	0.17	0.57	0.53	1.92	0.55	0.234	0.000

Results of meta-analyses of direct comparisons

Table S10 Results of pairwise meta-analyses

Comparisons		No. of studies (all RCTs)	Pairwise meta-analysis relative risk [95% CI]	Heterogeneity, I ²	No. of studies (RCTs withlow ROB including celecoxib)	Pairwise meta-analysis relative risk [95% CI]	Heterogeneity, I ²
Incidence of any adenomas							
ASA+Calcium+VitD	PCB	1	0.94 [0.68, 1.29]	NA	1	0.94 [0.68, 1.29]	NA
ASA-HD	PCB	4	0.93 [0.67, 1.29]	76.7%	4	0.93 [0.67, 1.29]	76.7%
ASA-HD+Folic acid	PCB	2	0.97 [0.77, 1.22]	23.7%	2	0.97 [0.77, 1.22]	23.7%
ASA-LD	PCB	3	0.83 [0.70, 0.99]	0.0%	3	0.83 [0.70, 0.99]	0.0%
ASA-LD+Folic acid	PCB	1	0.80 [0.61, 1.05]	NA	1	0.80 [0.61, 1.05]	NA
ASA-HD	Folic acid	2	0.83 [0.68, 0.99]	0.0%	2	0.83 [0.68, 0.99]	0.0%
ASA-HD+Folic acid	Folic acid	2	0.85 [0.70, 1.01]	0.0%	2	0.85 [0.70, 1.01]	0.0%
ASA-LD	Folic acid	1	0.76 [0.60, 0.96]	NA	1	0.76 [0.60, 0.96]	NA
ASA-LD+Folic acid	Folic acid	1	0.67 [0.52, 0.86]	NA	1	0.67 [0.52, 0.86]	NA
ASA-HD+Folic acid	ASA-HD	2	1.02 [0.84, 1.25]	0.0%	2	1.02 [0.84, 1.25]	0.0%
ASA-LD+Folic acid	ASA-LD	1	0.88 [0.67, 1.17]	NA	1	0.88 [0.67, 1.17]	NA
ASA-LD+Folic acid	ASA-HD+Folic acid	1	0.75 [0.58, 0.98]	NA	1	0.75 [0.58, 0.98]	NA
ASA-LD+Folic acid	ASA-HD	1	0.77 [0.59, 1.01]	NA	1	0.77 [0.59, 1.01]	NA
ASA-LD	ASA-HD	2	0.67 [0.37, 1.21]	77.9%	2	0.67 [0.37, 1.21]	77.9%
ASA-LD	ASA-HD+Folic acid	1	0.85 [0.66, 1.09]	NA	1	0.85 [0.66, 1.09]	NA

Comparisons		No. of studies (all RCTs)	Pairwise meta-analysis relative risk [95% CI]	Heterogeneity, I ²	No. of studies (RCTs with low ROB including celecoxib)	Pairwise meta-analysis relative risk [95% CI]	Heterogeneity, I ²
Antiox	PCB	6	0.77 [0.54, 1.11]	77.0%	2	1.09 [0.91, 1.32]	2.4%
Calcium	PCB	5	0.83 [0.75, 0.93]	8.5%	3	0.88 [0.79, 0.99]	0.0%
Calcium-VitD	PCB	1	0.95 [0.82, 1.10]	NA	1	0.95 [0.82, 1.10]	NA
Cele-400	PCB	2	0.70 [0.64, 0.76]	0.0%	2	0.70 [0.64, 0.76]	0.0%
Cele-800	PCB	1	0.62 [0.55, 0.69]	NA	1	0.62 [0.55, 0.69]	NA
Cele-800	Cele-400	1	0.87 [0.76, 0.99]	NA	1	0.87 [0.76, 0.99]	NA
Folic acid	PCB	3	1.06 [0.87, 1.28]	35.0%	2	1.16 [0.97, 1.40]	0.0%
VitD	PCB	1	0.98 [0.84, 1.13]	NA	1	0.98 [0.84, 1.13]	NA
Calcium	VitD	1	0.95 [0.82, 1.11]	NA	1	0.95 [0.82, 1.11]	NA
Calcium-VitD	VitD	1	0.97 [0.83, 1.14]	NA	1	0.97 [0.83, 1.14]	NA
Calcium	Calcium-VitD	2	0.98 [0.86, 1.12]	0.0%	2	0.98 [0.86, 1.12]	0.0%
Incidence of advanced adenomas							
ASA-HD	PCB	4	0.88 [0.61, 1.25]	0.0%	4	0.88 [0.61, 1.25]	0.0%
ASA-HD+Folic acid	PCB	2	0.87 [0.40, 1.92]	71.0%	2	0.87 [0.40, 1.92]	71.0%
ASA-LD	PCB	3	0.84 [0.46, 1.55]	0.0%	3	0.84 [0.46, 1.55]	0.0%
ASA-LD+Folic acid	PCB	1	0.76 [0.35, 1.62]	NA	1	0.76 [0.35, 1.62]	NA
ASA-HD	Folic acid	2	0.68 [0.47, 0.99]	0.0%	2	0.68 [0.47, 0.99]	0.0%
ASA-HD+Folic acid	Folic acid	2	0.64 [0.44, 0.93]	0.0%	2	0.64 [0.44, 0.93]	0.0%
ASA-LD	Folic acid	1	0.37 [0.19, 0.75]	NA	1	0.37 [0.19, 0.75]	NA

Comparisons		No. of studies (all RCTs)	Pairwise meta-analysis relative risk [95% CI]	Heterogeneity, I ²	No. of studies (RCTs with low ROB including celecoxib)	Pairwise meta-analysis relative risk [95% CI]	Heterogeneity, I ²
ASA-LD+Folic acid	Folic acid	1	0.41 [0.21, 0.79]	NA	1	0.41 [0.21, 0.79]	NA
ASA-HD+Folic acid	ASA-HD	2	0.93 [0.61, 1.42]	0.0%	2	0.93 [0.61, 1.42]	0.0%
ASA-LD+Folic acid	ASA-LD	1	1.09 [0.47, 2.49]	NA	1	1.09 [0.47, 2.49]	NA
ASA-LD+Folic acid	ASA-HD+Folic acid	1	0.57 [0.28, 1.16]	NA	1	0.57 [0.28, 1.16]	NA
ASA-LD+Folic acid	ASA-HD	1	0.58 [0.28, 1.18]	NA	1	0.58 [0.28, 1.18]	NA
ASA-LD	ASA-HD	2	0.72 [0.32, 1.65]	33.6%	2	0.72 [0.32, 1.65]	33.6%
ASA-LD	ASA-HD+Folic acid	1	0.52 [0.25, 1.09]	NA	1	0.52 [0.25, 1.09]	NA
Antiox	PCB	2	0.45 [0.16, 1.23]	25.8%	-	-	-
Calcium	PCB	4	1.01 [0.74, 1.38]	17.5%	3	1.02 [0.67, 1.55]	44.9%
Calcium-VitD	PCB	1	1.04 [0.67, 1.61]	NA	1	1.04 [0.67, 1.61]	NA
Cele-400	PCB	2	0.48 [0.38, 0.60]	0.0%	2	0.48 [0.38, 0.60]	0.0%
Cele-800	PCB	1	0.37 [0.26, 0.51]	NA	1	0.37 [0.26, 0.51]	NA
Cele-800	Cele-400	1	0.81 [0.55, 1.20]	NA	1	0.81 [0.55, 1.20]	NA
Folic acid	PCB	3	1.21 [0.82, 1.78]	28.6%	2	1.34 [0.77, 2.36]	54.9%
VitD	PCB	1	1.19 [0.78, 1.82]	NA	1	1.19 [0.78, 1.82]	NA
Calcium	VitD	1	1.04 [0.70, 1.55]	NA	1	1.04 [0.70, 1.55]	NA
Calcium-VitD	VitD	1	0.87 [0.58, 1.33]	NA	1	0.87 [0.58, 1.33]	NA
Calcium	Calcium-VitD	2	1.11 [0.79, 1.56]	0.0%	2	1.11 [0.79, 1.56]	0.0%

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

Results of network meta-analysis

Table S11 Results of network meta-analysis for incidence of any adenomas

Intervention	All studies	
	RR [95% CI]	SUCRArank
Cele-800	<u>0.61 [0.45, 0.83]</u>	1
Cele-400	<u>0.70 [0.55, 0.87]</u>	2
ASA-LD+Folic acid	0.71 [0.50, 1.00]	3
ASA-LD	<u>0.75 [0.59, 0.96]</u>	4
Calcium	<u>0.81 [0.68, 0.97]</u>	5
Antiox	0.86 [0.68, 1.07]	6
Calcium+VitD	0.86 [0.66, 1.12]	7
VitD	0.90 [0.67, 1.22]	8
ASA-HD+Folic acid	0.91 [0.70, 1.19]	9
ASA+Calcium+VitD	0.94 [0.60, 1.45]	10
ASA-HD	0.92 [0.75, 1.13]	11
PCB	reference	12
Folic acid	1.05 [0.84, 1.31]	13
Overall inconsistency Chi-square (p value)	7.57 (0.751)	
Number of studies	21	

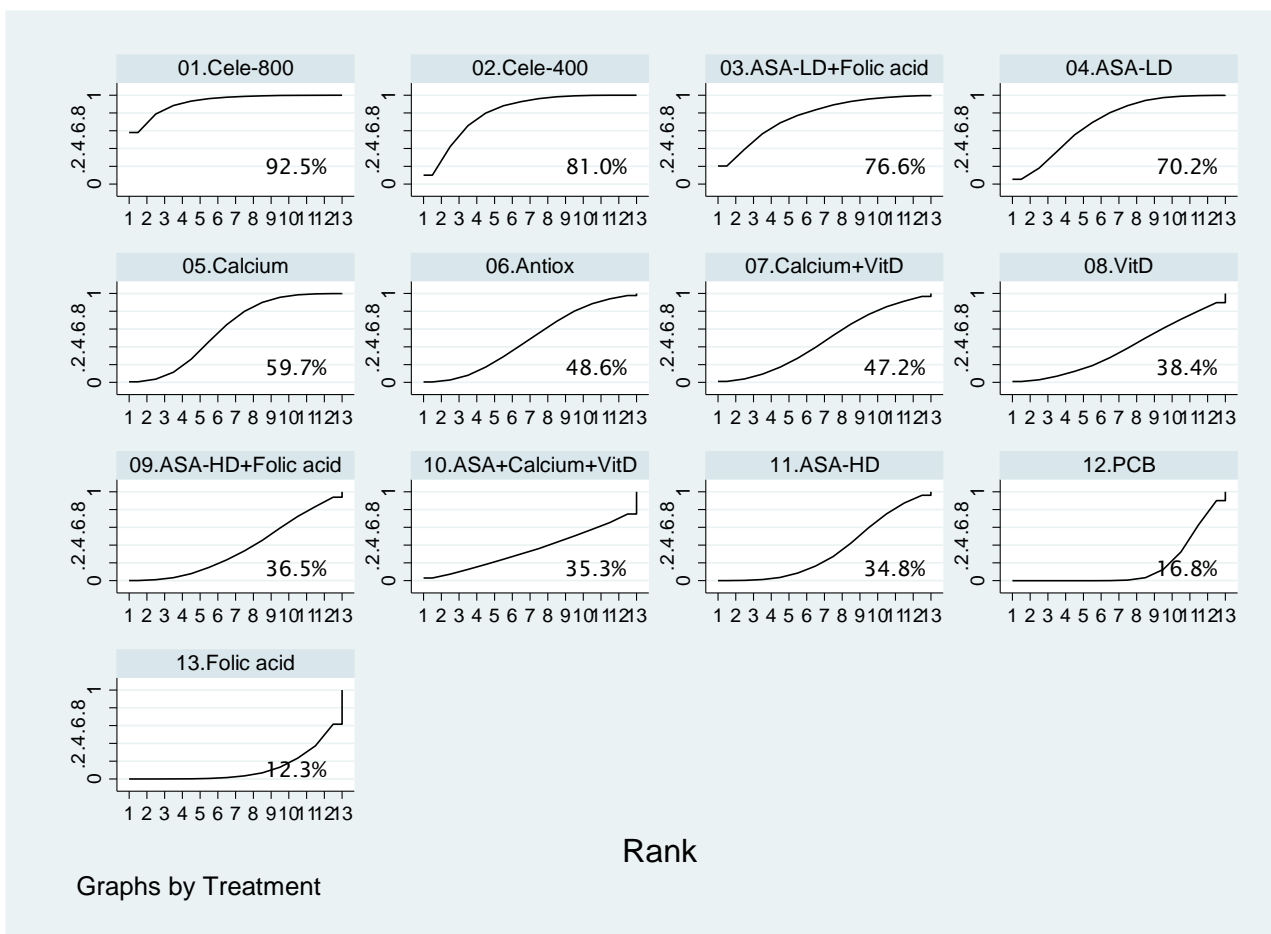
Figure S5 Network estimated relative risk (95% confidence interval) of chemopreventive agents for incidence of any adenomas (all studies)

ASA+Calcium+VitD														
1.02 (0.62,1.66)	ASA-HD													
1.02 (0.61,1.71)	1.01 (0.76,1.32)	ASA-HD+Folic acid												
1.24 (0.75,2.05)	1.22 (0.93,1.60)	1.21 (0.89,1.65)	ASA-LD											
1.32 (0.75,2.31)	1.29 (0.91,1.85)	1.29 (0.89,1.87)	1.06 (0.73,1.55)	ASA-LD+Folic acid										
1.09 (0.67,1.79)	1.07 (0.79,1.46)	1.07 (0.76,1.50)	0.88 (0.64,1.22)	0.83 (0.55,1.25)	Antiox									
1.15 (0.72,1.86)	1.13 (0.86,1.49)	1.13 (0.82,1.55)	0.93 (0.69,1.26)	0.88 (0.59,1.29)	1.06 (0.80,1.40)	Calcium								
1.09 (0.65,1.82)	1.07 (0.76,1.50)	1.06 (0.73,1.54)	0.88 (0.61,1.25)	0.82 (0.53,1.28)	1.00 (0.71,1.40)	0.94 (0.74,1.20)	Calcium+VitD							
1.34 (0.82,2.21)	1.32 (0.97,1.80)	1.31 (0.93,1.86)	1.08 (0.78,1.51)	1.02 (0.67,1.54)	1.23 (0.89,1.69)	1.16 (0.87,1.55)	1.24 (0.87,1.75)	Cele-400						
1.53 (0.90,2.62)	1.50 (1.04,2.18)	1.49 (1.00,2.23)	1.24 (0.84,1.82)	1.16 (0.73,1.84)	1.40 (0.96,2.04)	1.33 (0.93,1.89)	1.41 (0.94,2.11)	1.14 (0.84,1.55)	Cele-800					
0.89 (0.54,1.46)	0.87 (0.68,1.12)	0.87 (0.66,1.14)	0.72 (0.54,0.96)	0.68 (0.47,0.97)	0.82 (0.60,1.11)	0.77 (0.58,1.02)	0.82 (0.58,1.15)	0.66 (0.48,0.91)	0.58 (0.40,0.85)	Folic acid				
1.04 (0.61,1.77)	1.02 (0.70,1.47)	1.01 (0.68,1.51)	0.84 (0.57,1.23)	0.79 (0.50,1.25)	0.95 (0.65,1.38)	0.90 (0.67,1.21)	0.95 (0.69,1.31)	0.77 (0.53,1.13)	0.68 (0.44,1.04)	1.16 (0.80,1.69)	VitD			
0.94 (0.60,1.45)	0.92 (0.75,1.13)	0.91 (0.70,1.19)	0.75 (0.59,0.96)	0.71 (0.50,1.00)	0.86 (0.68,1.07)	0.81 (0.68,0.97)	0.86 (0.66,1.12)	0.70 (0.55,0.87)	0.61 (0.45,0.83)	1.05 (0.84,1.31)	0.90 (0.67,1.22)	PCB		

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

*Comparison between treatments should be read from column to row for each outcome (row treatment is reference).

Figure S6 SUCRA ranking curve for incidence of any adenomas (all studies)



Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

Table S12 Results of network meta-analysis for incidence of advanced adenomas

Intervention	All studies	
	RR [95% CI]	SUCRArank
Cele-800	0.37 [0.27, 0.52]	1
Cele-400	0.48 [0.38, 0.60]	2
Antiox	0.51 [0.27, 0.97]	3
ASA-LD+Folic acid	0.54 [0.28, 1.02]	4
ASA-LD	0.63 [0.37, 1.09]	5
ASA-HD+Folic acid	0.81 [0.55, 1.19]	6
ASA-HD	0.84 [0.59, 1.19]	7
Calcium+VitD	0.95 [0.66, 1.37]	8
Calcium	0.99 [0.76, 1.30]	9
PCB	reference	10
VitD	1.06 [0.72, 1.56]	11
Folic acid	1.22 [0.89, 1.65]	12
Overall inconsistency Chi-square(p value)	7.34 (0.771)	
Number of studies	15	

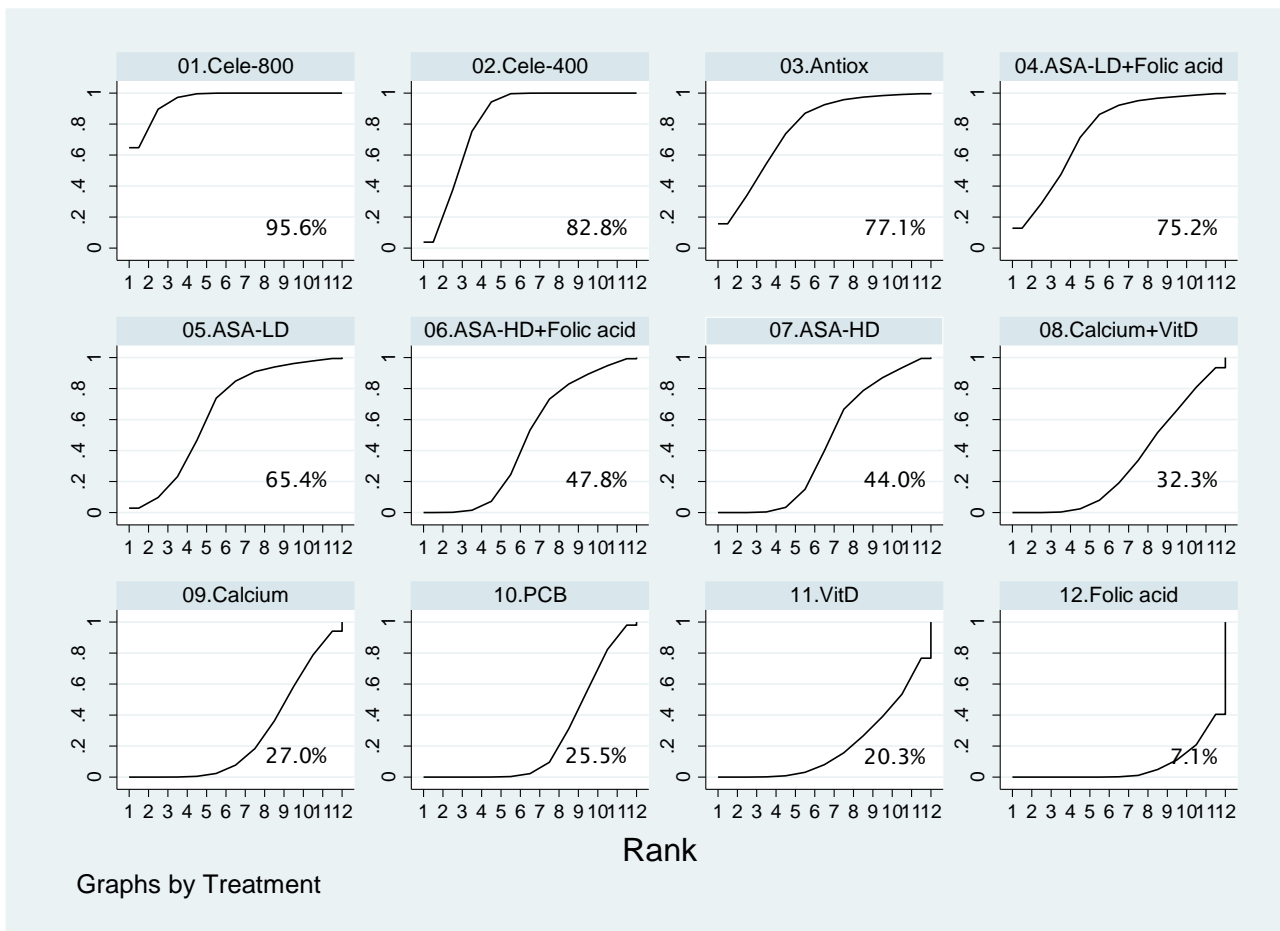
Figure S7 Network estimated relative risk (95% confidence interval) of chemopreventive agents for incidence of advanced adenomas (all studies)

ASA-HD												
1.04 (0.69,1.56)	ASA-HD+ Folic acid											
1.33 (0.76,2.32)	1.27 (0.71,2.30)	ASA-LD										
1.57 (0.82,3.00)	1.51 (0.78,2.91)	1.18 (0.55,2.53)	ASA-LD+ Folic acid									
1.64 (0.79,3.41)	1.58 (0.75,3.34)	1.24 (0.53,2.88)	1.05 (0.42,2.60)	Antiox								
0.84 (0.54,1.31)	0.81 (0.51,1.30)	0.64 (0.35,1.17)	0.54 (0.27,1.08)	0.51 (0.26,1.03)	Calcium							
0.88 (0.53,1.46)	0.85 (0.50,1.44)	0.67 (0.35,1.28)	0.56 (0.27,1.18)	0.54 (0.26,1.12)	1.04 (0.75,1.45)	Calcium+Vit D						
1.77 (1.16,2.68)	1.70 (1.08,2.67)	1.33 (0.74,2.41)	1.13 (0.57,2.24)	1.07 (0.54,2.13)	2.09 (1.47,2.99)	2.00 (1.30,3.09)	Cele-400					
2.26 (1.40,3.65)	2.17 (1.30,3.61)	1.70 (0.90,3.22)	1.44 (0.70,2.97)	1.37 (0.67,2.83)	2.68 (1.75,4.10)	2.56 (1.56,4.20)	1.28 (0.89,1.84)	Cele-800				
0.69 (0.49,0.98)	0.66 (0.46,0.96)	0.52 (0.30,0.90)	0.44 (0.23,0.83)	0.42 (0.21,0.86)	0.82 (0.54,1.23)	0.78 (0.49,1.26)	0.39 (0.27,0.57)	0.31 (0.19,0.48)	Folic acid			
0.79 (0.47,1.32)	0.76 (0.44,1.31)	0.60 (0.31,1.16)	0.50 (0.24,1.07)	0.48 (0.23,1.02)	0.94 (0.65,1.35)	0.90 (0.60,1.33)	0.45 (0.29,0.70)	0.35 (0.21,0.58)	1.14 (0.70,1.87)	VitD		
0.84 (0.59,1.19)	0.81 (0.55,1.19)	0.63 (0.37,1.09)	0.54 (0.28,1.02)	0.51 (0.27,0.97)	0.99 (0.76,1.30)	0.95 (0.66,1.37)	0.48 (0.38,0.60)	0.37 (0.27,0.52)	1.22 (0.89,1.65)	1.06 (0.72,1.56)	PCB	

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

*Comparison between treatments should be read from column to row for each outcome (row treatment is reference).

Figure S8 SUCRA ranking curve for incidence of advanced adenomas (all studies)



Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

Sensitivity analyses of network meta-analysis

Table S13 Results of sensitivity analyses of network meta-analysis for incidence of any adenomas

Intervention	All studies		Low ROB studies including celecoxib		Low ROB + High ROB excluding celecoxib		Low ROB studies excluding celecoxib*	
	RR [95% CI]	SUCRA rank	RR [95% CI]	SUCRA rank	RR [95% CI]	SUCRA rank	RR [95% CI]	SUCRA rank
Cele-800	0.61 [0.45, 0.83]	1	0.61 [0.55, 0.69]	1	-	-	-	-
Cele-400	0.70 [0.55, 0.87]	2	0.70 [0.64, 0.75]	2	-	-	-	-
ASA-LD+Folic acid	0.71 [0.50, 1.00]	3	0.74 [0.58, 0.94]	3	0.71 [0.49, 1.03]	1	0.80 [0.61, 1.05]	1
ASA-LD	0.75 [0.59, 0.96]	4	0.79 [0.67, 0.94]	4	0.75 [0.58, 0.97]	2	0.91 [0.70, 1.17]	2
Calcium	0.81 [0.68, 0.97]	5	0.88 [0.79, 0.99]	5	0.81 [0.66, 0.98]	3	0.93 [0.80, 1.09]	3
Antiox	0.86 [0.68, 1.07]	6	1.09 [0.91, 1.31]	12	0.85 [0.67, 1.07]	4	1.09 [0.91, 1.31]	10
Calcium+VitD	0.86 [0.66, 1.12]	7	0.92 [0.80, 1.05]	6	0.86 [0.64, 1.15]	5	0.95 [0.82, 1.10]	4
VitD	0.90 [0.67, 1.22]	8	0.95 [0.82, 1.09]	9	0.90 [0.64, 1.26]	6	0.98 [0.84, 1.13]	6
ASA-HD+Folic acid	0.91 [0.70, 1.19]	9	0.96 [0.80, 1.15]	10	0.91 [0.69, 1.21]	7	1.07 [0.84, 1.36]	9
ASA+Calcium+VitD	0.94 [0.60, 1.45]	10	0.94 [0.68, 1.29]	7	0.94 [0.58, 1.50]	8	0.94 [0.68, 1.29]	5
ASA-HD	0.92 [0.75, 1.13]	11	0.94 [0.81, 1.10]	8	0.92 [0.73, 1.15]	9	1.04 [0.81, 1.33]	8
PCB	reference	12	reference	11	reference	10	reference	7
Folic acid	1.05 [0.84, 1.31]	13	1.13 [0.96, 1.34]	13	1.05 [0.83, 1.33]	11	1.20 [0.95, 1.51]	11
Overall inconsistency Chi-square (p value)	7.57 (0.751)		17.97 (0.055)		7.56 (0.672)		17.73 (0.039)	
Number of studies	21		14		19		12	

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

*The finding under inconsistency model.

Figure S9 Network estimated relative risk (95% confidence interval) of chemopreventive agents for incidence of any adenomas

i. Low ROB studies including celecoxib

ASA+Calcium+VitD															
0.99 (0.70,1.42)	ASA-HD														
0.98 (0.68,1.41)	0.98 (0.82,1.18)	ASA-HD+Folic acid													
1.18 (0.82,1.69)	1.19 (0.98,1.43)	1.21 (0.98,1.48)	ASA-LD												
1.26 (0.84,1.89)	1.27 (1.00,1.63)	1.29 (1.01,1.67)	1.07 (0.83,1.39)	ASA-LD+Folic acid											
0.86 (0.59,1.24)	0.86 (0.68,1.09)	0.88 (0.68,1.13)	0.73 (0.57,0.93)	0.68 (0.50,0.92)	Antiox										
1.06 (0.75,1.49)	1.07 (0.88,1.29)	1.08 (0.88,1.34)	0.90 (0.73,1.10)	0.84 (0.64,1.09)	1.24 (1.00,1.53)	Calcium									
1.02 (0.72,1.44)	1.03 (0.84,1.26)	1.04 (0.83,1.31)	0.86 (0.70,1.07)	0.81 (0.61,1.06)	1.19 (0.95,1.49)	0.96 (0.85,1.09)	Calcium+VitD								
1.34 (0.96,1.87)	1.35 (1.14,1.60)	1.37 (1.13,1.67)	1.14 (0.95,1.37)	1.06 (0.82,1.37)	1.57 (1.28,1.91)	1.27 (1.11,1.45)	1.32 (1.13,1.54)	Cele-400							
1.53 (1.08,2.15)	1.54 (1.27,1.86)	1.56 (1.26,1.93)	1.29 (1.06,1.58)	1.21 (0.92,1.58)	1.78 (1.44,2.21)	1.44 (1.23,1.69)	1.50 (1.26,1.79)	1.14 (1.01,1.29)	Cele-800						
0.83 (0.57,1.19)	0.83 (0.70,0.99)	0.85 (0.71,1.01)	0.70 (0.58,0.85)	0.65 (0.51,0.83)	0.97 (0.75,1.24)	0.78 (0.64,0.95)	0.81 (0.65,1.00)	0.62 (0.51,0.74)	0.54 (0.44,0.66)	Folic acid					
0.98 (0.69,1.40)	0.99 (0.81,1.22)	1.01 (0.80,1.27)	0.84 (0.67,1.04)	0.78 (0.59,1.03)	1.15 (0.91,1.45)	0.93 (0.81,1.07)	0.97 (0.83,1.12)	0.73 (0.62,0.86)	0.65 (0.54,0.77)	1.19 (0.96,1.48)	VitD				
0.94 (0.68,1.29)	0.94 (0.81,1.10)	0.96 (0.80,1.15)	0.79 (0.67,0.94)	0.74 (0.58,0.94)	1.09 (0.91,1.31)	0.88 (0.79,0.99)	0.92 (0.80,1.05)	0.70 (0.64,0.75)	0.61 (0.55,0.69)	1.13 (0.96,1.34)	0.95 (0.82,1.09)	PCB			

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

*Comparison between treatments should be read from column to row for each outcome (row treatment is reference).

ii. Low ROB + High ROB studies excluding celecoxib

ASA+Calcium+ VitD										
1.02 (0.60,1.72)	ASA-HD									
1.03 (0.59,1.78)	1.01 (0.75,1.36)	ASA-HD+ Folic acid								
1.25 (0.73,2.14)	1.22 (0.91,1.64)	1.21 (0.87,1.69)	ASA-LD							
1.32 (0.72,2.41)	1.30 (0.88,1.91)	1.29 (0.86,1.92)	1.06 (0.71,1.59)	ASA-LD+ Folic acid						
1.11 (0.65,1.88)	1.09 (0.78,1.51)	1.08 (0.75,1.56)	0.89 (0.63,1.26)	0.84 (0.54,1.30)	Antiox					
1.16 (0.69,1.93)	1.14 (0.85,1.53)	1.13 (0.80,1.59)	0.93 (0.67,1.29)	0.88 (0.58,1.34)	1.05 (0.77,1.42)	Calcium				
1.09 (0.63,1.90)	1.07 (0.74,1.55)	1.06 (0.71,1.60)	0.88 (0.59,1.29)	0.83 (0.51,1.33)	0.99 (0.68,1.43)	0.94 (0.72,1.23)	Calcium+VitD			
0.89 (0.52,1.51)	0.88 (0.67,1.15)	0.87 (0.65,1.17)	0.72 (0.53,0.97)	0.68 (0.46,1.00)	0.81 (0.58,1.13)	0.77 (0.57,1.05)	0.82 (0.56,1.19)	Folic acid		
1.04 (0.58,1.86)	1.02 (0.68,1.53)	1.01 (0.65,1.57)	0.83 (0.55,1.28)	0.79 (0.48,1.30)	0.94 (0.62,1.42)	0.90 (0.64,1.25)	0.95 (0.67,1.36)	1.17 (0.77,1.76)	VitD	
0.94 (0.58,1.50)	0.92 (0.73,1.15)	0.91 (0.69,1.21)	0.75 (0.58,0.97)	0.71 (0.49,1.03)	0.85 (0.67,1.07)	0.81 (0.66,0.98)	0.86 (0.64,1.15)	1.05 (0.83,1.33)	0.90 (0.64,1.26)	PCB

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; PCB, placebo; VitD, vitamin D.

*Comparison between treatments should be read from column to row for each outcome (row treatment is reference).

iii. Low ROB studies excluding celecoxib**

ASA+Calcium+ VitD										
0.90 (0.60,1.35)	ASA-HD									
0.88 (0.59,1.31)	0.98 (0.77,1.24)	ASA-HD+ Folic acid								
1.03 (0.68,1.56)	1.15 (0.89,1.48)	1.18 (0.91,1.51)	ASA-LD							
1.17 (0.77,1.79)	1.30 (0.99,1.71)	1.33 (1.02,1.74)	1.13 (0.86,1.50)	ASA-LD+ Folic acid						
0.86 (0.59,1.24)	0.95 (0.70,1.29)	0.98 (0.72,1.32)	0.83 (0.60,1.14)	0.73 (0.53,1.02)	Antiox					
1.00 (0.70,1.43)	1.12 (0.83,1.49)	1.14 (0.86,1.52)	0.97 (0.72,1.31)	0.86 (0.63,1.17)	1.17 (0.92,1.49)	Calcium				
0.99 (0.69,1.41)	1.10 (0.82,1.46)	1.12 (0.85,1.49)	0.96 (0.71,1.29)	0.84 (0.62,1.15)	1.15 (0.91,1.46)	0.99 (0.77,1.27)	Calcium+VitD			
0.73 (0.53,1.16)	0.87 (0.69,1.09)	0.89 (0.71,1.11)	0.76 (0.60,0.96)	0.67 (0.52,0.86)	0.91 (0.68,1.22)	0.78 (0.59,1.02)	0.79 (0.60,1.04)	Folic acid		
0.96 (0.67,1.37)	1.07 (0.80,1.42)	1.09 (0.82,1.45)	0.93 (0.69,1.25)	0.82 (0.60,1.12)	1.12 (0.88,1.42)	0.96 (0.82,1.11)	0.97 (0.83,1.13)	1.23 (0.93,1.61)	VitD	
0.94 (0.68,1.29)	1.04 (0.81,1.33)	1.07 (0.84,1.36)	0.91 (0.70,1.17)	0.80 (0.61,1.05)	1.09 (0.91,1.31)	0.93 (0.80,1.09)	0.95 (0.82,1.10)	1.20 (0.95,1.51)	0.98 (0.84,1.13)	PCB

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; PCB, placebo; VitD, vitamin D.

*Comparison between treatments should be read from column to row for each outcome (row treatment is reference).

**The finding under inconsistency model.

Table S14 Results of sensitivity analyses of network meta-analysis for incidence of advanced adenomas

Intervention	All studies		Low ROB studies including celecoxib		Low ROB + High ROB excluding celecoxib		Low ROB studies excluding celecoxib	
	RR [95% CI]	SUCRA rank	RR [95% CI]	SUCRA rank	RR [95% CI]	SUCRA rank	RR [95% CI]	SUCRA rank
Cele-800	0.37 [0.27, 0.52]	1	0.37 [0.26, 0.53]	1	-	-	-	-
Cele-400	0.48 [0.38, 0.60]	2	0.48 [0.37, 0.61]	2	-	-	-	-
Antiox	0.51 [0.27, 0.97]	3	-	-	0.51 [0.26, 0.99]	1	-	-
ASA-LD+Folic acid	0.54 [0.28, 1.02]	4	0.56 [0.29, 1.09]	3	0.54 [0.28, 1.06]	2	0.57 [0.28, 1.16]	1
ASA-LD	0.63 [0.37, 1.09]	5	0.66 [0.37, 1.15]	4	0.64 [0.36, 1.12]	3	0.67 [0.37, 1.20]	2
ASA-HD+Folic acid	0.81 [0.55, 1.19]	6	0.84 [0.56, 1.27]	5	0.81 [0.54, 1.23]	4	0.85 [0.54, 1.34]	3
ASA-HD	0.84 [0.59, 1.19]	7	0.87 [0.60, 1.25]	6	0.84 [0.59, 1.22]	5	0.88 [0.59, 1.31]	4
Calcium+VitD	0.95 [0.66, 1.37]	8	0.95 [0.65, 1.40]	7	0.96 [0.64, 1.43]	6	0.96 [0.62, 1.49]	5
Calcium	0.99 [0.76, 1.30]	9	0.99 [0.74, 1.33]	8	1.00 [0.75, 1.33]	7	0.99 [0.71, 1.40]	6
PCB	reference	10	reference	9	reference	8	reference	7
VitD	1.06 [0.72, 1.56]	11	1.06 [0.71, 1.59]	10	1.07 [0.70, 1.63]	9	1.07 [0.67, 1.72]	8
Folic acid	1.22 [0.89, 1.65]	12	1.31 [0.91, 1.88]	11	1.22 [0.88, 1.70]	10	1.33 [0.88, 2.00]	9
Overall inconsistency Chi-square (p value)	7.34 (0.771)		4.15 (0.940)		7.21 (0.706)		4.10 (0.905)	
Number of studies	15		11		13		9	

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

Figure S10 Network estimated relative risk (95% confidence interval) of chemopreventive agents for incidence of advanced adenomas

i. Low ROB studies including celecoxib

ASA-HD											
1.03 (0.68,1.57)	ASA-HD+ Folic acid										
1.33 (0.75,2.34)	1.28 (0.71,2.33)	ASA-LD									
1.55 (0.80,3.00)	1.50 (0.77,2.93)	1.17 (0.54,2.52)	ASA-LD+ Folic acid								
0.88 (0.55,1.41)	0.85 (0.51,1.41)	0.66 (0.35,1.25)	0.57 (0.27,1.17)	Calcium							
0.92 (0.54,1.55)	0.88 (0.51,1.55)	0.69 (0.35,1.36)	0.59 (0.27,1.27)	1.04 (0.74,1.47)	Calcium+VitD						
1.83 (1.18,2.84)	1.77 (1.09,2.85)	1.38 (0.75,2.54)	1.18 (0.58,2.39)	2.08 (1.41,3.06)	2.00 (1.26,3.16)	Cele-400					
2.34 (1.41,3.87)	2.26 (1.32,3.87)	1.76 (0.91,3.40)	1.50 (0.71,3.18)	2.66 (1.68,4.20)	2.55 (1.52,4.29)	1.28 (0.87,1.87)	Cele-800				
0.67 (0.46,0.96)	0.64 (0.44,0.95)	0.50 (0.28,0.88)	0.43 (0.23,0.82)	0.76 (0.47,1.21)	0.73 (0.43,1.23)	0.36 (0.23,0.57)	0.29 (0.17,0.47)	Folic acid			
0.82 (0.48,1.41)	0.79 (0.45,1.41)	0.62 (0.31,1.23)	0.53 (0.24,1.15)	0.93 (0.64,1.37)	0.90 (0.59,1.35)	0.45 (0.28,0.72)	0.35 (0.21,0.60)	1.23 (0.72,2.11)	VitD		
0.87 (0.60,1.25)	0.84 (0.56,1.27)	0.66 (0.37,1.15)	0.56 (0.29,1.09)	0.99 (0.74,1.33)	0.95 (0.65,1.40)	0.48 (0.37,0.61)	0.37 (0.26,0.53)	1.31 (0.91,1.88)	1.06 (0.71,1.59)	PCB	

Abbreviations: ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; Cele-400, celecoxib 400 mg/day; Cele-800, celecoxib 800 mg/day; PCB, placebo; VitD, vitamin D.

*Comparison between treatments should be read from column to row for each outcome (row treatment is reference).

ii. Low ROB + High ROB studies excluding celecoxib

ASA-HD									
1.04 (0.68,1.59)	ASA-HD+Folic acid								
1.32 (0.74,2.35)	1.27 (0.69,2.33)	ASA-LD							
1.56 (0.80,3.06)	1.50 (0.76,2.97)	1.18 (0.54,2.58)	ASA-LD+Folic acid						
1.67 (0.77,3.59)	1.60 (0.73,3.54)	1.26 (0.52,3.04)	1.07 (0.41,2.76)	Antiox					
0.85 (0.53,1.35)	0.82 (0.49,1.35)	0.64 (0.34,1.21)	0.54 (0.26,1.12)	0.51 (0.24,1.06)	Calcium				
0.88 (0.52,1.51)	0.85 (0.48,1.50)	0.67 (0.34,1.32)	0.56 (0.26,1.23)	0.53 (0.24,1.16)	1.04 (0.73,1.49)	Calcium+VitD			
0.69 (0.48,1.00)	0.66 (0.45,0.99)	0.52 (0.30,0.93)	0.44 (0.23,0.85)	0.41 (0.20,0.88)	0.82 (0.53,1.26)	0.78 (0.47,1.31)	Folic acid		
0.79 (0.45,1.38)	0.76 (0.42,1.37)	0.60 (0.30,1.21)	0.51 (0.23,1.12)	0.47 (0.21,1.05)	0.93 (0.62,1.40)	0.90 (0.58,1.39)	1.15 (0.67,1.95)	VitD	
0.84 (0.59,1.22)	0.81 (0.54,1.23)	0.64 (0.36,1.12)	0.54 (0.28,1.06)	0.51 (0.26,0.99)	1.00 (0.75,1.33)	0.96 (0.64,1.43)	1.22 (0.88,1.70)	1.07 (0.70,1.63)	PCB

Abbreviations: Antiox, antioxidants; ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements; PCB, placebo; VitD, vitamin D.

*Comparison between treatments should be read from column to row for each outcome (row treatment is reference).

iii. Low ROB studies excluding celecoxib

ASA-HD								
1.03 (0.66,1.62)	ASA-HD+Folic acid							
1.32 (0.73,2.40)	1.28 (0.68,2.40)	ASA-LD						
1.54 (0.77,3.11)	1.50 (0.74,3.05)	1.17 (0.52,2.62)	ASA-LD+Folic acid					
0.89 (0.53,1.49)	0.86 (0.49,1.51)	0.67 (0.34,1.32)	0.57 (0.26,1.25)	Calcium				
0.92 (0.51,1.66)	0.89 (0.48,1.67)	0.70 (0.34,1.45)	0.59 (0.26,1.36)	1.04 (0.70,1.53)	Calcium+VitD			
0.66 (0.44,1.00)	0.64 (0.42,0.99)	0.50 (0.28,0.92)	0.43 (0.22,0.85)	0.75 (0.44,1.27)	0.72 (0.40,1.31)	Folic acid		
0.82 (0.45,1.53)	0.80 (0.42,1.53)	0.63 (0.30,1.32)	0.53 (0.23,1.24)	0.93 (0.59,1.46)	0.90 (0.55,1.46)	1.24 (0.67,2.32)	VitD	
0.88 (0.59,1.31)	0.85 (0.54,1.34)	0.67 (0.37,1.20)	0.57 (0.28,1.16)	0.99 (0.71,1.40)	0.96 (0.62,1.49)	1.33 (0.88,2.00)	1.07 (0.67,1.72)	PCB

Abbreviations:ASA-HD, high-dose aspirin; ASA-LD, low-dose aspirin; Calcium, calcium supplements;PCB, placebo; VitD, vitamin D.

*Comparison between treatments should be read from column to row for each outcome (row treatment is reference).

Supplementary 10
GRADE summary of evidence

Table S15 GRADE Summary of evidence (all studies)

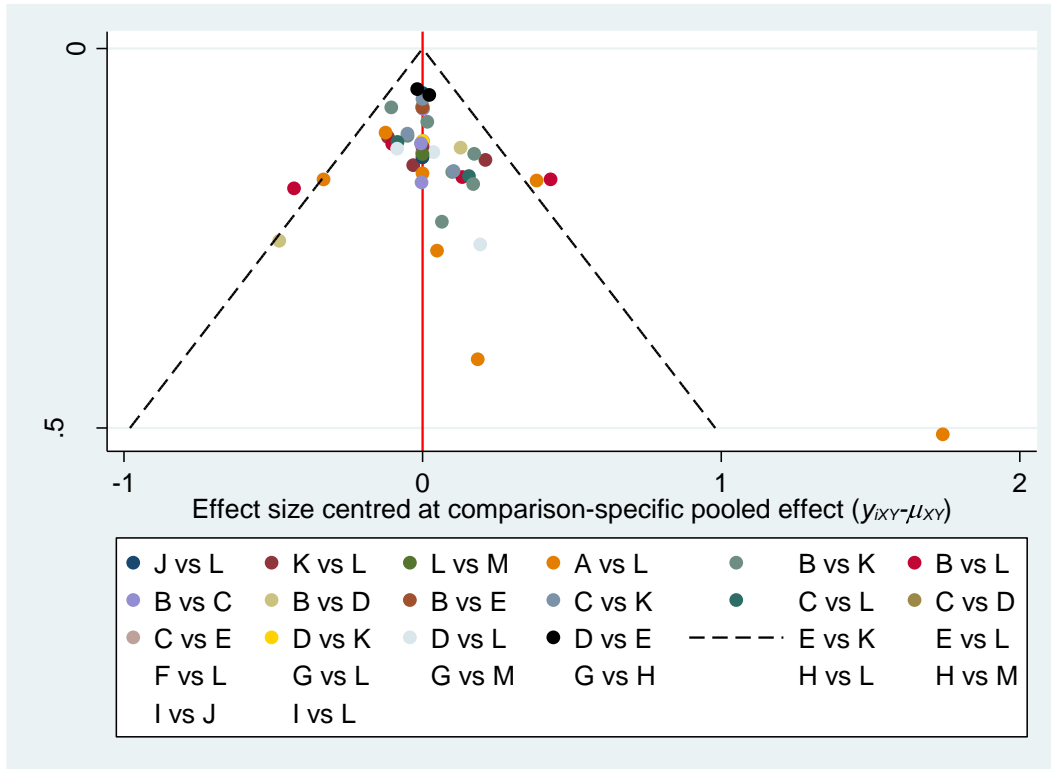
Comparisons	Direct evidence (from pairwise meta-analysis)		Indirect evidence (from node-splitting)		Network meta-analysis	
	RR [95% CI]	Quality of evidence	RR [95% CI]	Quality of evidence	RR [95% CI]	Quality of evidence
Any adenomas						
Celecoxib 400mg/day versus Placebo	0.70 [0.64, 0.76]	High	0.71 [0.54, 0.89]	High	0.70 [0.55, 0.87]	High
Celecoxib 800mg/day versus Placebo	0.62 [0.55, 0.69]	High	0.57 [0.22, 1.50]	High	0.61 [0.45, 0.83]	High
Low-dose aspirin versus Placebo	0.83 [0.70, 0.99]	Moderate ^a	0.39 [0.23, 0.67]	Low ^b	0.75 [0.59, 0.96]	Moderate
Calcium versus Placebo	0.83 [0.75, 0.93]	Low ^{c, d}	0.95 [0.33, 2.70]	Low ^e	0.81 [0.68, 0.97]	Low
Celecoxib 800mg/day versus Celecoxib 400 mg/day	0.87 [0.76, 0.99]	High	0.94 [0.36, 2.47]	High	0.88 [0.65, 1.19]	High
Celecoxib 400 mg/day versus Low-dose aspirin	NA	-	0.93 [0.66, 1.28]	Moderate ^f	0.93 [0.66, 1.28]	Moderate
Celecoxib 400mg/day versus Calcium	NA	-	0.86 [0.65, 1.15]	Moderate ^f	0.86 [0.65, 1.15]	Moderate
Low-dose aspirin versus Calcium	NA	-	0.93 [0.69, 1.26]	Low ^f	0.93 [0.69, 1.26]	Low
Low-dose aspirin versus High-dose aspirin	0.67 [0.37, 1.21]	Low ^{g, h}	1.17 [0.74, 1.87]	Low ⁱ	0.82 [0.63, 1.08]	Low

^a Imprecision (the optimal information size criterion is not achieved (addressed by Trial Sequential Analysis)); ^b Contributing direct evidence of moderate quality and intransitivity (time difference in outcome measures and dose variations); ^c Limitations (risk of bias) and ^d indirectness (interventions were delivered in different doses and the duration of follow-up varied among these studies); ^e Contributing direct evidence of low quality and intransitivity; ^f Intransitivity; ^g Inconsistency explained by I² statistic; ^h Indirectness (time difference in outcome measures and dose variations, difference in population in one study); ⁱ Contributing direct evidence of low quality and intransitivity.
NA: not available.

Comparison-adjusted funnel plot for each outcome from the network meta-analyses

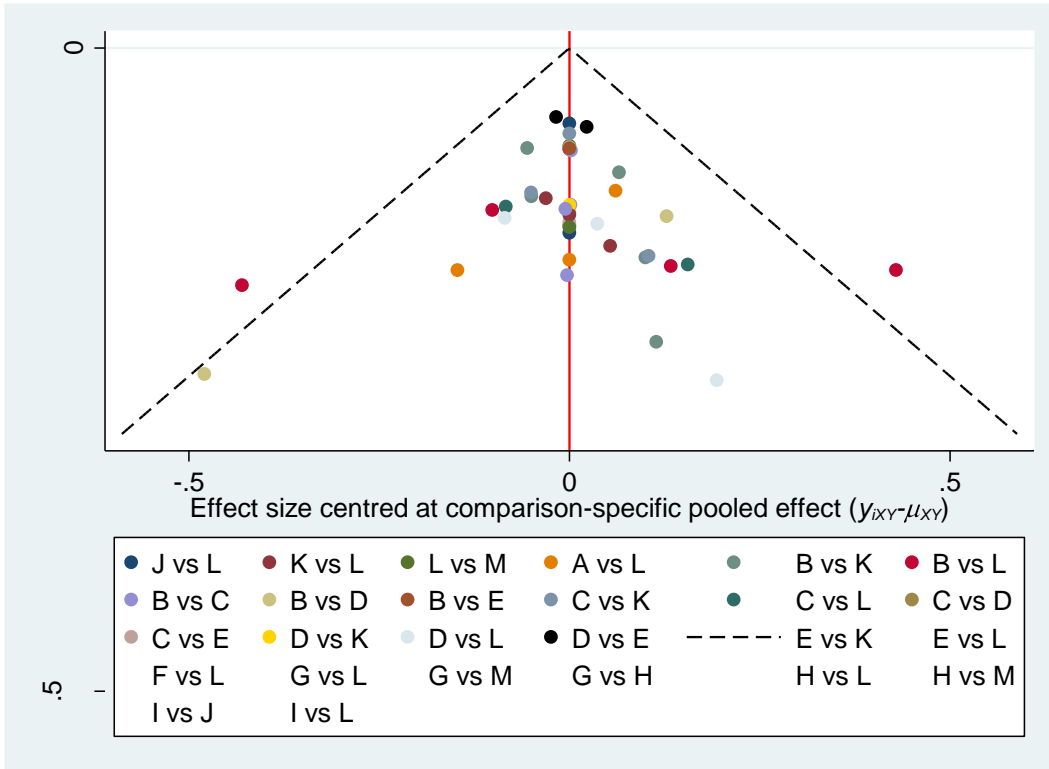
Figure S11 Comparison-adjusted funnel plot for the network of incidence of any adenomas in all comparison

i. All studies



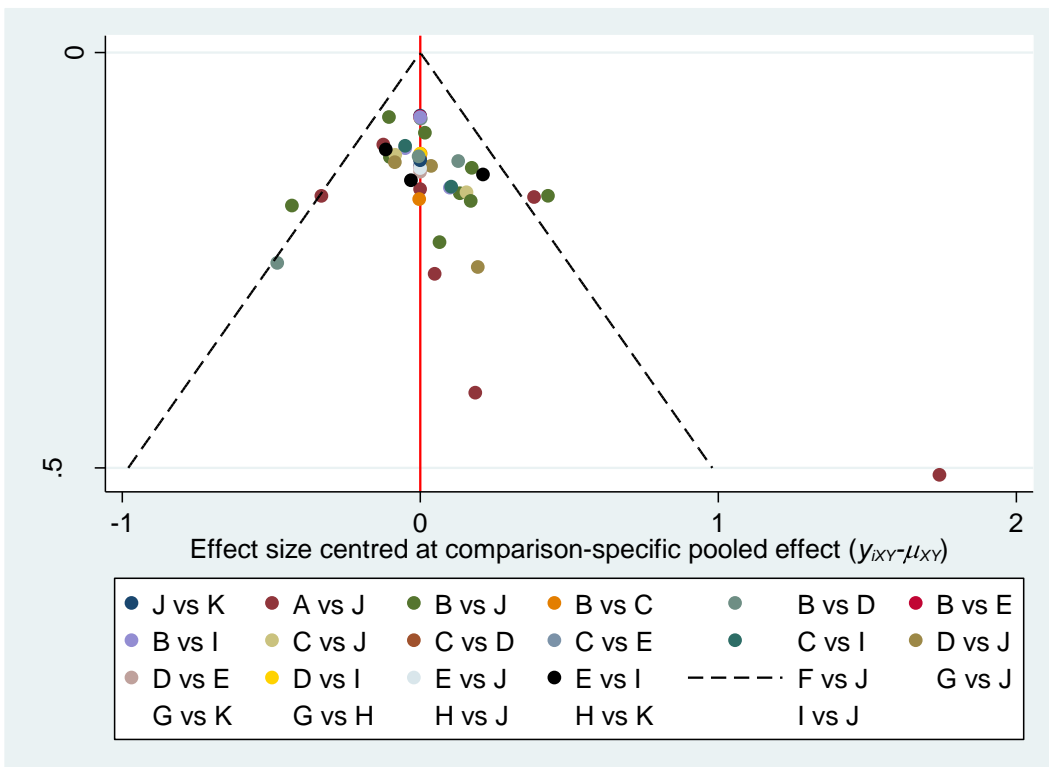
A, ASA+Calcium+VitD; B, ASA-HD; C, ASA-HD+Folic acid; D, ASA-LD; E, ASA-LD+Folic acid; F, Antiox; G, Calcium; H, Calcium+VitD; I, Cele-400; J, Cele-800; K, Folic acid; L, PCB; M, VitD.

ii. Low ROB studies including celecoxib



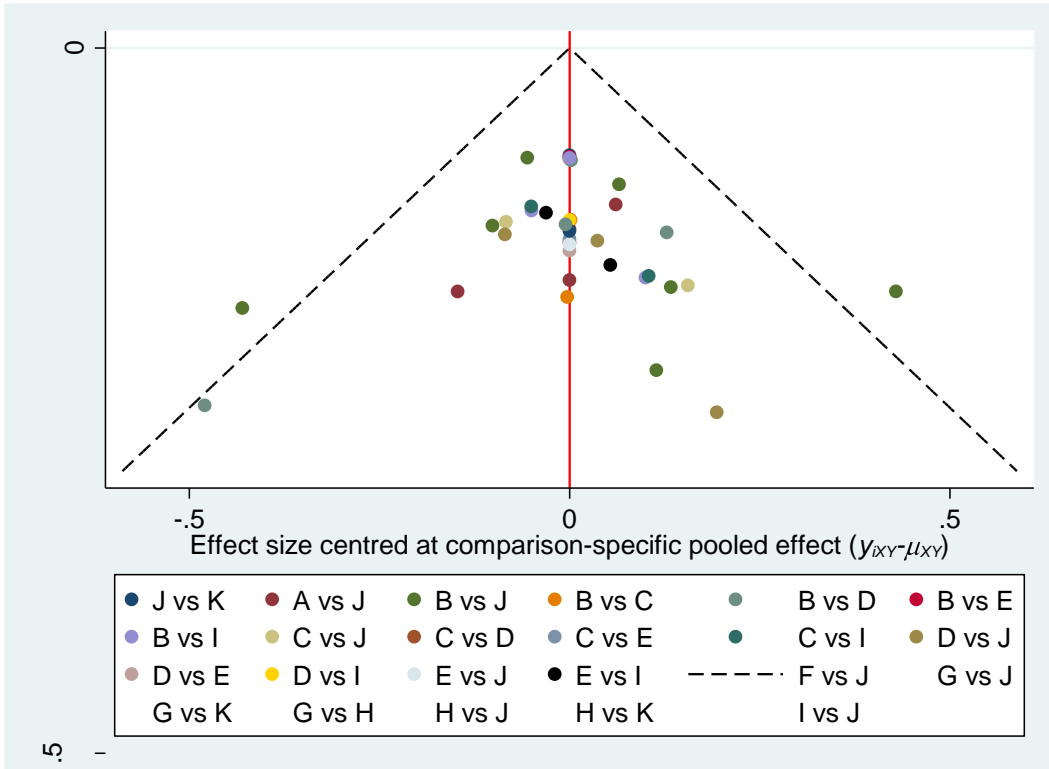
A, ASA+Calcium+VitD; B, ASA-HD; C, ASA-HD+Folic acid; D, ASA-LD; E, ASA-LD+Folic acid; F, Antiox; G, Calcium; H, Calcium+VitD; I, Cele-400; J, Cele-800; K, Folic acid; L, PCB; M, VitD.

iii. Low ROB + High ROB studies excluding celecoxib



A, ASA+Calcium+VitD; B, ASA-HD; C, ASA-HD+Folic acid; D, ASA-LD; E, ASA-LD+Folic acid; F, Antiox; G, Calcium; H, Calcium+VitD; I, Folic acid; J, PCB; K, VitD.

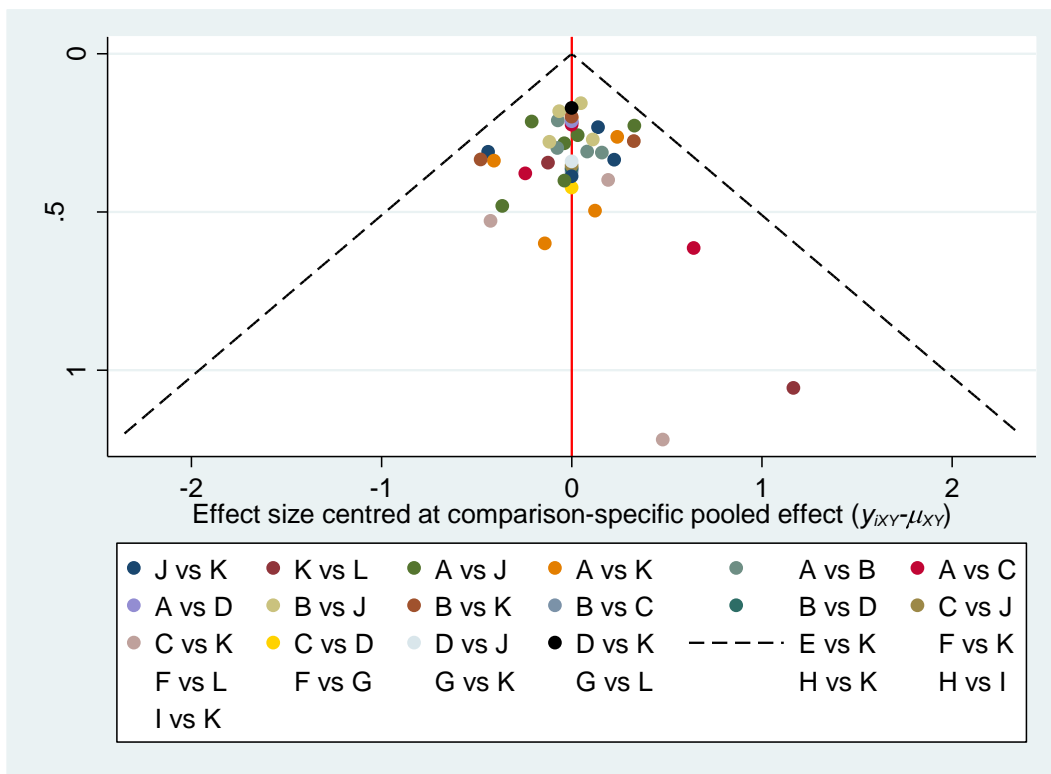
iv. LowROB studies excluding celecoxib



A, ASA+Calcium+VitD; B, ASA-HD; C, ASA-HD+Folic acid; D, ASA-LD; E, ASA-LD+Folic acid; F, Antiox;
 G, Calcium; H, Calcium+VitD; I, Folic acid; J, PCB; K, VitD.

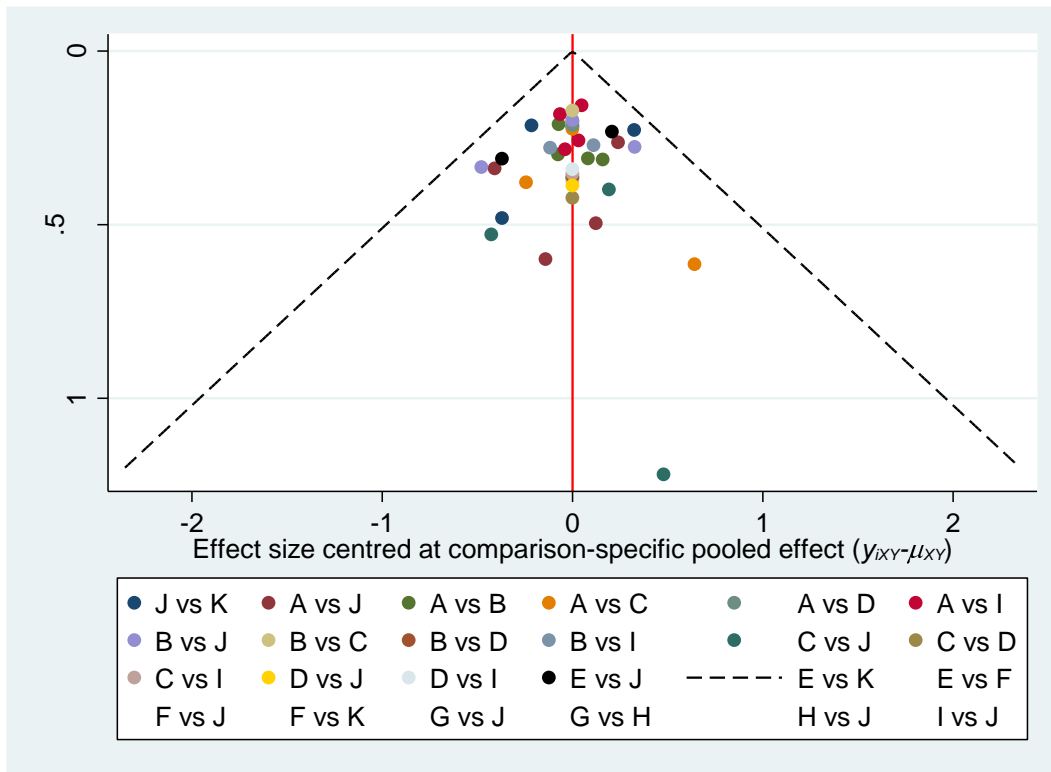
Figure S12 Comparison-adjusted funnel plot for the network of incidence of advanced adenomas in all comparison

i. All studies



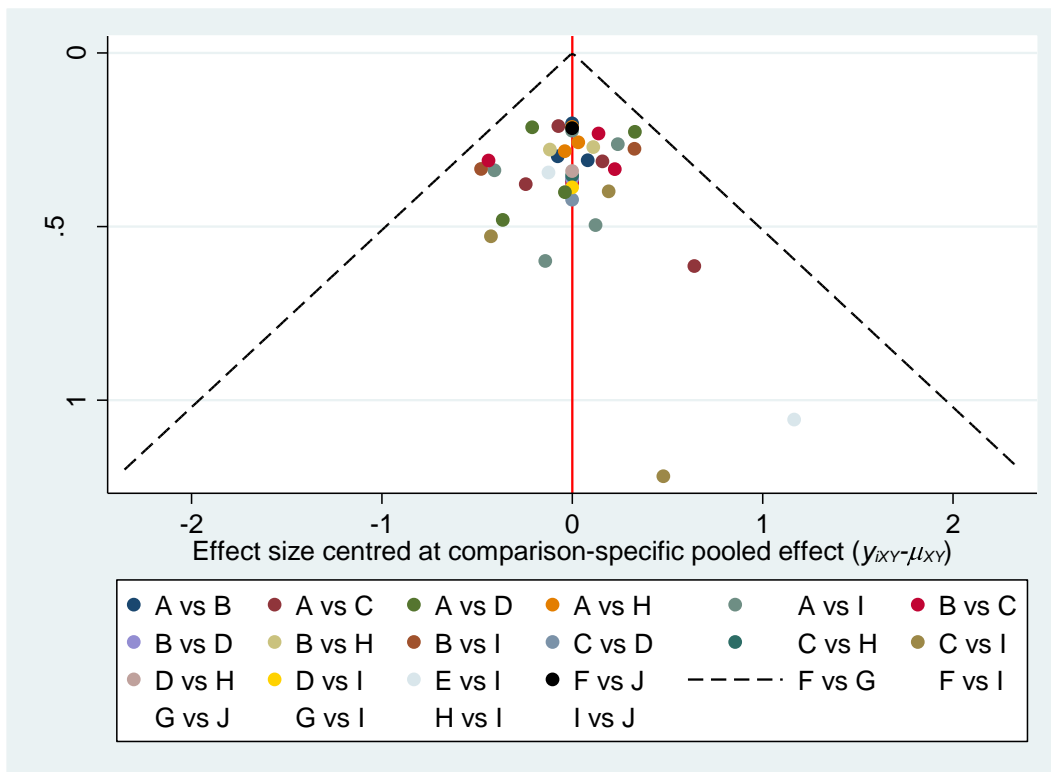
A, ASA-HD; B, ASA-HD+Folic acid; C, ASA-LD; D, ASA-LD+Folic acid; E, Antiox; F, Calcium; G, Calcium+VitD; H, Cele-400; I, Cele-800; J, Folic acid; K, PCB; L, VitD.

ii. Low ROB studies including celecoxib



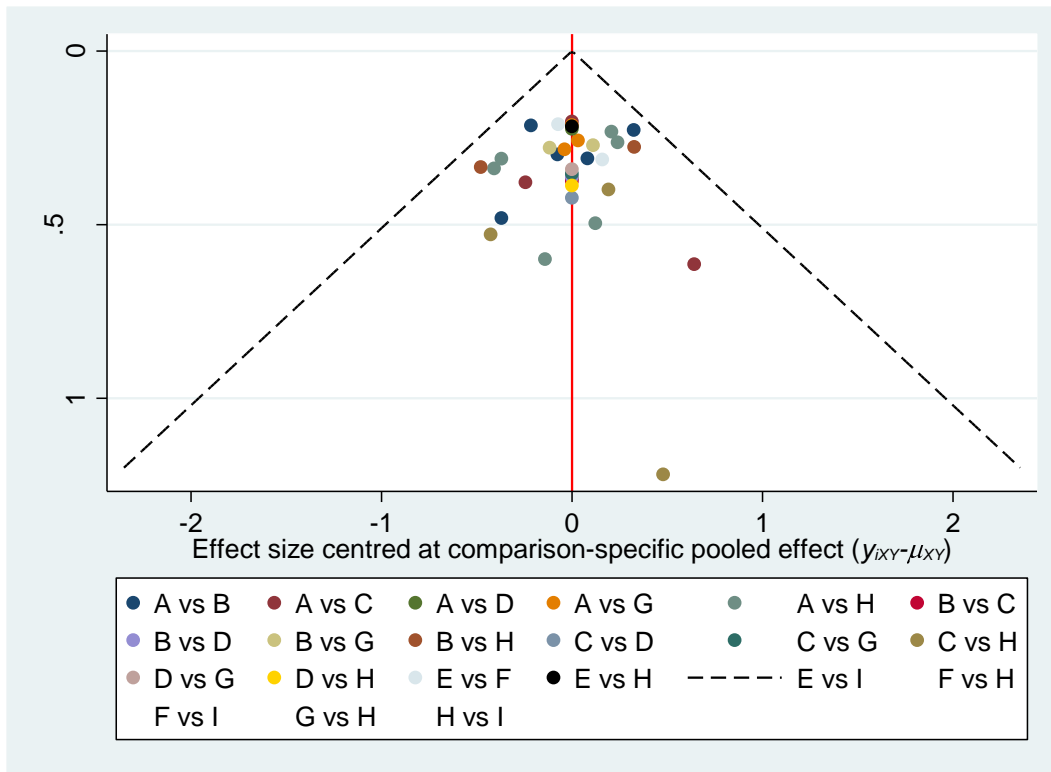
A, ASA-HD; B, ASA-HD+Folic acid; C, ASA-LD; D, ASA-LD+Folic acid; E, Calcium; F, Calcium+VitD; G, Cele-400; H, Cele-800; I, Folic acid; J, PCB; K, VitD.

iii. Low ROB + High ROB studies excluding celecoxib



A, ASA-HD; B, ASA-HD+Folic acid; C, ASA-LD; D, ASA-LD+Folic acid; E, Antiox; F, Calcium; G, Calcium+VitD; H, Folic acid; I, PCB; J, VitD.

iv. Low ROB studies excluding celecoxib



A, ASA-HD; B, ASA-HD+Folic acid; C, ASA-LD; D, ASA-LD+Folic acid; E, Calcium; F, Calcium+VitD; G, Folic acid; H, PCB; I, VitD.

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