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ORIGINAL RESEARCH

Efficacy and safety of chemopreventive agents on colorectal cancer incidence and mortality: systematic review and network meta-analysis

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Background: Various interventions have been tested as primary prevention of colorectal cancers (CRC), but comprehensive evidence comparing them is absent. We examined the effects of various chemopreventive agents (CPAs) on CRC incidence and mortality.

Methods: We did a network meta-analysis based on a systematic review of randomized controlled trials (RCTs) that compared at least one CPA (aspirin, antioxidants, folic acid, vitamin B6, vitamin B12, calcium, vitamin D, alone or in combination) to placebo or other CPA in persons without history of CRC. Several databases were searched from inception up to March 2017. Primary outcomes were early and long-term CRC incidence and mortality.

Results: Twenty-one RCTs comprising 281,063 participants, 9 RCTS comprising 160,101 participants, and 7 RCTs comprising 24,001 participants were included in the network meta-analysis for early risk of CRC incidence, long-term risk of CRC incidence and mortality, respectively. For early CRC incidence, no CPAs were found to be effective. For long-term CRC incidence and mortality, aspirin was the only intervention that showed protective effects with potential dose-dependent effects (risk ratio [RR], 0.74 [95% CI, 0.57–0.97] for high-dose [≥325 mg/day] and RR, 0.81 [95% CI, 0.67–0.98] for very-low-dose [≤100 mg/day]). Similar trend was found for mortality (RR, 0.43 [95% CI, 0.23–0.81] for low-dose [>100–325 mg/day] and RR, 0.65 [95% CI, 0.45–0.94] for very-low-dose). However, in net clinical benefit analysis, when combining risk estimates on mortality from CRC, cardiovascular disease, and pooled risk estimates of major gastrointestinal bleeding, low-dose aspirin provided the highest net survival gain (%) of 1.736 [95% CI, 1.010–2.434].

Conclusion: Aspirin at the dose range of 75–325 mg/day is a safe and effective primary prevention for long-term CRC among people at average risk. None of the other CPAs were found to be effective. There may potentially be differential effects among various doses of aspirin that needs further investigation.

Keywords: colorectal cancer, primary chemoprevention, chemopreventive agents, aspirin, network meta-analysis, net clinical benefit analysis

Plain language summary

Aspirin (75–325 mg/day) is a safe and effective intervention to prevent colorectal cancer among people at average risk. The effect may be dose and time-dependent. No other tested interventions were found to be effective. Net clinical benefit analysis combining mortality from CRC, cardiovascular disease, and bleeding indicated that low-dose aspirin (>100–325 mg/day) provided the highest net survival gain. For patients with low risk of bleeding, low-dose aspirin may slightly be more attractive due to a larger reduction in CRC mortality and the best net clinical benefit. For patients at high risk of bleeding, very-low-dose aspirin (≤100 mg/day) may be more appropriate due to its best safety profile especially in cases of GI bleeding. There may potentially be differential effects among various doses of aspirin that needs further investigation.

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Introduction

Colorectal cancer (CRC) is the fourth leading cause of death due to cancer worldwide.[1] The burden of CRC on society with respect to mortality, morbidity, and costs is enormous. Therefore, prevention of CRC is an important public health objective. A number of pharmacological interventions have been investigated in randomized controlled trials (RCTs)[2–32] as chemopreventive agents (CPAs) for CRC in persons at average risk (those without personal or family history of colorectal neoplasia or conditions such as inflammatory bowel disease or hereditary colorectal cancer syndrome)[33] with variable results. A recent meta-analysis of RCTs by the United States Preventive Services Task Force (USPSTF) suggested that aspirin taken for several years could be effective in reducing long-term incidence and mortality due to CRC.[34,35] However, the relative efficacy and safety of aspirin at different doses has not been investigated yet. Moreover, comprehensive evidence comparing different CPAs including aspirin is still lacking. Previous reviews and meta-analyses[27,34,36–40] have focused only on pair-wise comparison of various CPAs.

Hence, we performed a systematic review and network meta-analysis (NMA) to determine the relative efficacy and safety of various CPAs on CRC incidence and mortality in persons at average risk. Since aspirin is recommended by USPSTF for both prevention of cardiovascular disease and colorectal cancer,[35] therefore interested to evaluate the overall impact of various doses of aspirin on CRC mortality, cardiovascular (CV) mortality, and major gastrointestinal (GI) bleeding events through net clinical benefit analysis. This information may uniquely offer an evaluation to the multidimensional impact of a single intervention, which is aspirin in this case.

Methods

Protocol and registration

This study was performed as part of a systematic review which has been previously registered (PROSPERO CRD42015025849)[41] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for NMA.[42]

Search strategy and study selection

We identified relevant studies by a systematic search of Medline, Embase, Cochrane Central Register of Controlled Trials, CINAHL Plus, and International Pharmaceutical Abstracts until March 2017. In addition, we searched the clinical trial registry (www.clinicaltrials.gov) and published systematic reviews. The search was restricted to studies published from 2008 onwards because studies published up to 2007 could be identified from the published high-quality systematic reviews.[36,37,39] Studies included were RCTs and long-term follow-up of RCTs, which reported the efficacy of any CPAs for the primary prevention of CRC in individuals at average risk.[33] Supplement 1 details the search strategies.

Type of interventions

Candidate CPAs were aspirin, any antioxidants (vitamins A, C and E, beta-carotene and selenium alone or in different combinations), folic acid, vitamin B6, vitamin B12, calcium and vitamin D (alone or in combination). The interventions included are those which have been investigated as CPAs for primary prevention of CRC. Comparators were another candidate CPA or placebo. We classified aspirin (ASA) into three groups for the analysis as described by the latest review for the USPSTF[34]: high-dose or HDASA (>325 mg/day), low-dose or LDASA (>100 and ≤325 mg/day), and very-low-dose or VLDASA (≤100 mg/day) aspirin.

Outcomes of interest

Primary efficacy outcomes of interest were incidence and mortality due to CRC. We present primary efficacy outcomes stratified by follow-up period after initiation of CPA as early risk (0–10 years) and long-term risk (0–≥20 years) since previous data showed that timing of intervention might impact outcomes.[34] For safety outcomes, we collected data for interventions with evidence of efficacy in reducing either long-term CRC incidence or mortality (that is aspirin at different doses). Safety outcomes of interest were CV mortality and major GI bleeding events. The study investigators defined GI bleeding events that required hospitalization, transfusion, leading to death, as fatal or major. They also defined CV mortality as deaths due to any CV complications including myocardial infarction (MI), stroke (ischemic and hemorrhagic) or CV deaths (excluding deaths due to GI bleeding events).

Data extraction and quality assessment

Description of data extraction is reported in Supplement 2. Data were extracted independently by two reviewers (S.K.V, S.M.C). The most recent data were included if multiple publications of the same trial were retrieved. The study authors were contacted if required data were not available from publications. (Table S2.1 in Supplement 2). For all outcomes, we used the initial number of participants randomized to each trial arm and performed the analyses irrespective of how the authors of the original trials had analyzed the data (intention-to-treat principle).[43] Participants who were lost to follow-up

were considered survivors, free of CRC or adverse events. Two reviewers (S.K.V, K.G.L) independently assessed the risk of bias (ROB) using the revised Cochrane risk of bias tool (RoB 2.0).[44] Any discrepancies were resolved by consensus. The quality of evidence from NMA was evaluated using GRADEpro® GDT software online.[45] Description of grading of evidence is provided in Methods S2.1 in Supplement 2.

Data synthesis and statistical analysis

A more detailed description of data synthesis and statistical analysis is provided in Methods S2.1 and Table S2.2 in Supplement 2. The relative intervention effects (ie, risk ratio [RR]) were estimated for individual studies. A direct meta-analysis was used to pool RRs using a random-effects model. Heterogeneity was assessed using the Cochran Q test and the I^2 statistic. A random-effects NMA using consistency model was applied to compare all interventions using direct and indirect data.[46,47] Inconsistency assumption was evaluated using the global inconsistency test by fitting design-by-treatment in the inconsistency model. Placebo was used as the common comparator in the network model. In the network meta-analysis, the surface under the cumulative ranking (SUCRA) curves were estimated to rank the intervention hierarchy. Higher SUCRA scores (ranging from 0 to 1) correspond to a higher ranking for prevention of CRC incidence and mortality and lower SUCRA scores correspond to a higher ranking for safety regarding CV mortality and GI bleeding events, compared with other CPAs. Publication bias was examined with a comparison-adjusted funnel plot.[48] For statistical analysis, we used Stata version 14.0 (StataCorp, College Station, TX, USA). To assess the robustness of our primary efficacy outcomes, multiple pre-specified sensitivity analyses were performed by restricting studies with low-risk of bias, follow-up period of 0–≥20 years after CPA initiation and various other assumptions (Table S2.3 in Supplement 2).

Net clinical benefit (NCB) analysis

Similar to approaches used in previous meta-analyses,[53,54] an NCB analysis was performed to assess the balance of benefits from CRC mortality prevention[34] and CV benefits[49,50] with other risks[51,52] of aspirin at different doses. Detailed description of NCB analysis is presented in Methods S2.2 in Supplement 2. Net survival gain (a way to represent the results of NCB) was calculatd by reviewing the estimated absolute effect of aspirin on long-term CRC mortality and CV mortality (the data for CV mortality comprised of mortality due to myocardial infarction [MI], stroke [ischemic and hemorrhagic], and other CV events apart from GI bleeding events) and subtracted the risk of mortality due to major GI bleeding events. With this approach, GI bleeding and hemorrhagic stroke associated with aspirin were comprehensively integrated into the equation. The NCB was calculated according to the formula, Net survival gain (%)= Difference in pooled risk estimates of CRC mortality between reference and intervention + Difference in pooled risk estimates of CV mortality between reference and intervention − Weight x difference in pooled risk estimates of major GI bleeding events between reference and intervention. For interpretation, a higher value of net survival gain corresponds to the more benefit gain for CPAs compared with the placebo. The weighting factor was determined by the proportion of death among patients with GI bleeding. Based on previously published reports (Methods S2.2), fatal GI bleeding event had approximately 6% of the effect of single mortality; therefore a weighting factor of 0.06 was used. Additional sensitivity analyses of NCB were conducted by varying weighting factors from 0.01 to 0.16 (Methods S2.2). The scatter plot between combined risk estimates of mortality from CRC and CV and pooled risk estimates of major GI bleeding was also produced to demonstrate the risk vs. benefit. Pooled risk estimate of the treatment with reference was calculated based on meta-analyses.[55] To obtain the 95% confidence intervals of NCB, 1,000 bootstrap samples of risk estimates were performed for each intervention to calculate the risk differences among groups receiving placebo and various doses of aspirin.[56,57] A series of threshold analyses were also performed by varying the weight for the case-fatality ratio of GI bleeding and by varying the incidence of GI bleeding to evaluate the impact of varying risks of GI bleeding on the NCB.

For NCB analysis, we collected data on CV mortality and major GI bleeding events from fair and good quality (criteria defined by the USPSTF)[58] primary and secondary cardiovascular disease (CVD) prevention trials on aspirin in average-risk individuals for CRC as recently reported by the updated USPSTF reports.[52]

Results

Study selection

A PRISMA flow diagram depicting the search and selection process for the primary outcomes is presented in Figure S1.1 in Supplement 1. Our search identified a total of 4,573 citations after exclusion of duplicates. Among the 145 articles assessed for full text, 112 studies were excluded with reasons. In total, 21 RCTs[2–7,9–13,15–25] reporting the early risk of CRC incidence and 12 RCTs[8,24–31,59–64] reporting the long-term risk of either CRC incidence or mortality were included in our analysis. Another study[65] reporting the early risk of

CRC incidence was identified, but excluded with reasons (Supplement 2). Data on long-term risk of either CRC incidence or mortality from these 12 studies were identified from six post-trial observational studies[8,28–31,59] and two individual participant data (IPD) meta-analyses.[26,27] Additional unpublished relevant information were obtained from the authors of the Women Health Study (WHS), the Women's Antioxidant Cardiovascular Study (WACS), the Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS) and Physicians' Health Study II and used these data in the analysis of early risk of CRC incidence (Table S2.1 Supplement 2).

For safety outcomes, we collected data from 24 RCTs (including 6 RCTs reporting either the long-term risk of CRC incidence and mortality) on aspirin included in the updated USPSTF review[52] (Figure S3.1 in Supplement 3). Safety data from an additional trial (Dutch transient ischemic attack trial.; DTIA),[64] which reported long-term CRC mortality, was also included.

Characteristics of the included studies

Table 1 describes the characteristics of all included studies (a more detailed description is provided in Tables S3.1–S3.12 in Supplement 3). In total, 21 RCTs[2–7,9–13,15–25,32] with 281,063 participants comparing 13 CPAs (Figure 1) were included in the NMA of early risk of CRC. Mean age of the population was 61 years. The length of follow-up from recruitment to study was 3.4–10 years.

Among 12 RCTs reporting the long-term risk of CRC, 9 RCTs[8,24,25,28,30,31,59–61] comparing 9 interventions with 160,101 participants (Figure 2A) treated for 3.2–10 years were included in the NMA of the long-term CRC incidence. Seven RCTs[24,25,60–64] comparing seven interventions (Figure 2B) with 24,001 participants treated for approximately 2.6–10 years were included in the NMA of the long-term CRC mortality. Duration of follow-up among these 12 trials ranged from around six to more than 20 years. Mean age of the population was 60 years. All trials with long-term follow-up data were double-blinded and placebo-controlled, except one (open control design).[24]

Safety outcomes for aspirin at different doses were available from 25 RCTs (Tables S3.9, S3.10 in Supplement 3), including 11 primary and 14 secondary CVD prevention trials in average-risk individuals for CRC with an average follow-up of 1–10 years. Characteristics of all studies reporting safety outcomes are prsented in Table S3.10 in Supplement 3.

Quality of included studies

A detailed description of the risk of bias (ROB) assessment among included RCTs are presented in Tables S3.4 and S3.8 in Supplement 3. Among 21 RCTs reporting early risk of CRC (Table S3.4), 17 trials[4–7,9,10,12,15,16,18–23] had low ROB in most criteria. The remaining four trials were judged to be at high ROB.[2,13,16,17] Among 12 RCTs reporting the long-term risk of CRC (Table S3.8), no studies were judged to be at high risk of bias in any domain. For safety outcomes analyses, we included only fair-to-good quality RCTs (as per the criteria defined by USPSTF[58] from the updated USPSTF review.[52])

Effects on the primary efficacy outcomes

Treatment effects estimated from pairwise meta-analysis are presented in Supplement 4, without evidence of any substantial statistical heterogeneity. Treatment effects estimated from NMA for CPAs on early, long-term CRC incidence, and mortality are presented in Supplements 5, 6 and 7, respectively.

Early risk of CRC incidence

Based on the NMA, there was no effect on the early risk of CRC incidence within approximately 3.4–10 years of initiation of HDASA (RR, 0.91 [95% CI 0.55–1.53]), LDASA (RR, 1.15 [95% CI 0.75–1.74]), VLDASA (RR, 0.89 [95% CI 0.63–1.26]), antioxidants alone (RR, 0.94 [95% CI 0.81–1.10]) or with ASAVLD (RR, 0.97 [95% CI 0.69–1.37]), folic acid alone (RR, 1.00 [95% CI 0.14–7.14]) or with vitamin B12 (RR, 0.94 [95% CI 0.66–1.35]) or with vitamin B12 and B6 (RR, 1.17 [95% CI 0.81–1.70]), calcium (RR, 0.19 [95% CI 0.01–3.60]), and vitamin D (RR, 1.03 [95% CI 0.59–1.82]), compared to placebo (Table S5.1 in Supplement 5). The results of NMA were similar to those obtained using standard pairwise meta-analysis and robust to the changes in sensitivity analyses (Figure S5.3 and Table S5.2 in Supplement 5).

Long-term risk of CRC incidence

NMA based on seven studies,[8,24,25,28,30,31,59] for which the long-term incidence of CRC with a follow-up of more than 10 years suggested that, compared with placebo, HDASA (RR, 0.74 [95% CI 0.57–0.97]) was ranked best for reducing the long-term CRC incidence, followed by VLDASA (RR, 0.81 [95% CI 0.67–0.98]), calcium with vitamin D (RR, 0.96 [95% CI 0.81–1.13]), LDASA (RR, 1.03 [95% CI 0.83–1.27]), and any antioxidants (RR, 1.07 [95% CI 0.89–1.28]) (Table S6.1 in Supplement 6). This is consistent with the pairwise meta-analysis (Figure S6.3 in Supplement 6). When we assessed comparative efficacy among aspirin at different doses, none of the treatments were superior over others (Figure 3). Overall, the results were robust to the changes in sensitivity analyses and HDASA, and VLDASA remained superior to placebo (Table S6.2 in Supplement 6).

Long-term risk of CRC mortality

NMA based on 5 RCTs[24,25,62–64] with follow-up of more than 10 years suggested that, compared with placebo, LDASA (RR, 0.43 [95% CI 0.23–0.81]) was ranked best for reducing long-term mortality due to CRC, followed by VLDASA (RR, 0.65 [95% CI 0.45, 0.94]) and HDASA (RR, 0.71 [0.50–1.01]), respectively (Table S7.1 in Supplement 7). NMA results were consistent with the pairwise meta-analysis, except for LDASA (Figure S7.3 in Supplement 7). When we assessed comparative efficacy, LDASA was not superior to VLDASA (RR, 0.65 [95% CI 0.34–1.25]) and HDASA (RR, 1.66 [95% CI 0.84–3.29]) (Figure 3). The results from multiple sensitivity analyses were justifiably robust to the main analysis (Table S7.2 in Supplement 7).

Safety outcomes

We limited this analysis to the three CPAs (HDASA, LDASA, and VLDASA) with evidence of efficacy in reducing either long-term CRC incidence or mortality (Supplement 8). Results from NMA showed that HDASA ranked the lowest for safety (ie, major GI bleeding events) (RR, 4.04 [95% CI 1.86–8.76]), followed by LDASA (RR, 1.85 [95% CI 1.22–2.81]) and VLDASA (RR, 1.44 [95% CI 1.15–1.81]). For CV mortality, there was no significant effect demonstrated by any doses of aspirin within approximately 1–10 years of initiation.

Network consistency and small study effects

The test of global inconsistency showed no inconsistency for any outcomes (Supplement 9). Comparison-adjusted plots showed no substantial evidence of small study effects, although the number of studies included in each comparison was small (Supplement 10).

GRADE summary of the evidence

Overall, the quality of evidence based on GRADE is generally rated as very-low to moderate. Detailed information on GRADE summary of evidence is presented in Supplement 11.

Net clinical benefit analysis

All 3 doses of aspirin were significantly better than placebo (Table S12.1 in Supplement 12). LDASA provided the highest net survival gain (%) of 1.736 (95% CI 1.010–2.434) followed by VLDASA (1.091 [95% CI 0.614–1.573] and HDASA 0.908 [95% CI 0.416–1.342], respectively). LDASA, VLDASA, and HDASA would result in a NCB of around 17, 11, and 9 deaths saved per 1,000 patients treated. The scatter plot (Figure 4) of combined risk estimates of CRC, CV mortality, and major GI bleeding reveals that LDASA has 0.7% less death compared to VLDASA with additional 0.1% increase in GI bleeding events (Tables S12.1, S12.2 and Method S12.1 in Supplement 12). The number needed to treat (NNT) and number needed to harm (NNH) for LDASA is 143 and 1,000, respectively.

For the sensitivity analysis, the NCB of aspirin declines when the weighting factor for GI bleeding increases (varying from 0.01 to 0.16) (Figure S12.1 in Supplement 12). For the threshold analysis, when the case-fatality ratio of GI bleeding (weight) increases at 1.0, NCB of LDASA is still better than the NCB of VLDASA (Figure S12.2 in Supplement 12). The incidences of GI bleeding need to be as high as 25%, (80 times higher risk of GI bleeding than normal), to demonstrate an equivalent NCB for LDASA and VLDASA (Figure S12.3 in Supplement 12).

Discussion

To the best of our knowledge, this is the first systematic review and network meta-analysis in the field of primary prevention of CRC by CPAs. The present review, combining direct and indirect evidence from 26 RCTs (297,476 participants) reporting either the early or long-term risk of CRC incidence or mortality, is the largest analysis in this field. Moreover, we were able to incorporate data of 4 trials for early risk of CRC incidence that were previously not analyzed (Table S2.2 in Supplement 2) and the DTIA trial (a trial testing different doses of aspirin without control),[64] which was not included in the pairwise meta-analysis of earlier studies reporting the long-term risk of CRC mortality.[27,34,37] Based on this comprehensive dataset and the use of NMA, we were able to conclude that, aspirin, antioxidants, calcium (with or without vitamin D), vitamin B6/12 and folic acid, either alone or in combination did not have appreciable protective effects against CRC within approximately 10 years of initiation. Additionally, our analysis suggests that aspirin at the dose range of 75–325 mg is a safe and effective intervention to reduce long-term CRC mortality and the benefit outweighs the risk of bleeding.

For antioxidants, various trials (Table S3.11 in Supplement 3) along with recent meta-analyses have failed to detect any protective effects despite supportive evidence from in vitro, in vivo, and observational studies.[66] It is important to note however that most antioxidants trials are relatively short in duration and therefore make it difficult to detect any appreciable effects that require long-term follow-up. In addition, antioxidants are a diverse group of compounds. Readers

Table 1 Brief description of included studies in network meta-analysis

Author, year (reference)	Study name	Study design (double blind, placebo controlled, randomized trial)	Population	Number of participants
Randomized controlled trials reported early risk of colorectal cancer incidence				
Gann et al (1993)/ Hennekens et al (1996)[2,3]	PHS[a]	Yes, 2×2 factorial	Male physicians	22,071
Peto et al (1988)[24,26]	BDAT	Open control, parallel	Male physicians	5,139
Farrell et al (1991)[25,26]	UK-TIA	Yes, parallel, 3-arms	History of TIA or minor ischemic stroke	2,449
Omenn et al (1996)[4]	CARET	Yes, parallel	Cigarette smokers, former smokers, and workers exposed to asbestos	18,314
HPS group (2002)[5]	HPS	Yes, 2×2 factorial	History of coronary and other occlusive arterial disease or diabetes	20,536
Duffield-Lillico et al (2002)[6]	NPCT	Yes, parallel	History of non-melanoma skin cancer	1,312
Virtamo et al (2003)[7,8]	ATBC	Yes, 2×2 factorial	Male cigarette smokers	29,133
Trivedi et al (2003)[9]	NA	Yes, parallel	Physicians and the general practice population	2,686
Zhu et al (2003)[13]	NA	Unclear, parallel-4 arms	History of atrophic gastritis	216
Hercberg et al (2004)[10]	SU.VI.MAX	Yes, parallel	General population	13,017
Lonn et al (2005)/ Lonn et al (2006)[11,12]	HOPE[a]	Yes, 2×2 factorial	History of CV diseases or diabetes	9,541
Cook et al (2005)[19]	WHS[a]	Yes, 2×2 factorial	Female health professionals	39,876
Wactawski-Wende et al (2006)[15]	WHI	Yes, parallel	Postmenopausal women	36,282
Lappe et al (2007)[16]	NA	Yes, parallel, 3-arms	Postmenopausal women	1,179
Lin et al (2009)[17]	WACS[a]	Yes, 2×2×2×2 factorial	Female health professionals at high risk of CV disease	2,729[d]
Zhang et al (2008)[18]	WAFACS[a]	Yes, 2×2×2×2 factorial	Female health professionals at high risk of CV disease	5,442[d]
Lippman et al (2009)[20]	SELECT	Yes, 2×2 factorial	General population (men only)	35,533
Gaziano et al (2009)[21]	PHS II	Yes, 2×2×2×2 factorial	Male physicians	14,520[d]
Armitage et al (2010)[22]	SEARCH	Yes, 2×2 factorial	History of MI	12,064
Hankey et al (2012)[23]	VITATOPS	Yes, parallel	History of recent stroke or transient ischemic attack	8,164
Gao et al (2013)[32]	NA	Open-control, parallel	General population	860
Randomized controlled trials reported the long-term risk of either colorectal cancer incidence or mortality				
Peto et al (1988)[24,27]	BDAT	Open control, parallel	Male physicians	5,139
Farrell et al (1991)[25,27]	UK-TIA	Yes, parallel, 3-arms	History of TIA or minor ischemic stroke	2,449
Stürmer et al (1998)[59]	PHS[a]	Yes, 2×2 factorial	Male physicians	22,071
Virtamo et al (2003)[8]	ATBC	Yes, 2×2 factorial	Male cigarette smokers	29,133
Goodman et al (2004)[28]	CARET	Yes, parallel	Cigarette smokers, former smokers, and workers exposed to asbestos	18,314
Ebbing et al (2009)[29,60,61]	NORVIT/ WENBIT[a]	Yes, Combined analysis and extended follow-up of 2 RCTs.	History of ischemic heart disease	6,837 (both trials)
Cook et al (2013)[30]	WHS	Yes, 2×2 factorial	Female health professionals	39,876
Cauley et al (2013)[31]	WHI	Yes, parallel	Postmenopausal women	36,282
Rothwell et al (2010)[27]	TPT[62]	Yes, 2×2 factorial	High risk for IHD	5,085
	SALT[63]	Yes, parallel	History of TIA or stroke	1,360
	DTIA[64]	No placebo, parallel	History of TIA or stroke	3,131

Notes: A more detailed description with efficacy outcomes from all individual studies is reported in Supplement 3.WHS and PHS are alternate-day dose studies (100 mg every other day (defined as ASA-VLD) and 325 mg every other day (ASA-LD), respectively).[34] [a]Detailed description of studies provided in Table S2.2 in Supplement 2. [b]Range. [c]Median. [d]Based on data provided by authors (refer Tables S2.1 and S2.2 in Supplement 2). [e]Long-term data of these trials extracted from an IPD meta-analysis reported by Rothwell 2010.[27]

Abbreviations: ASA, asprin; AO, antioxidant; ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention study; B6, vitamin B6; B12, vitamin B12; BDAT, British Doctors Aspirin Trial; CA, calcium; CARET, carotene and retinol efficacy trial; CTL, control; CV, cardiovascular; DTIA, Dutch Transient Ischaemic Attack Trial; FA, folic acid; FAVB, folic acid with vitamin B6 and B12; GI, gastrointestinal; HD, high-dose; HOPE, Heart Outcomes Prevention Evaluation trial; HPS, Heart Protection Study; IHD, ischemic heart disease; LD, low-dose; MI, myocardial infarction; NPCT, nutritional prevention of cancer trial; NORVIT, Norwegian Vitamin Trial; PHS, Physicians' Health Study; PLB, placebo; SALT, Swedish Aspirin Low Dose Trial; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SELECT, Selenium and Vitamin E Cancer Prevention Trial; SU.VI.MAX, Supplémentation en Vitamines et Minéraux Antioxydants study; TPT, Thrombosis Prevention Trial; TIA, transient ischemic attack; UK-TIA, UK Transient Ischaemic Attack Aspirin Trial;VD, vitamin D, VITATOPS, Vitamins to Prevent Stroke Trial; VLD, very-low-dose; WACS, The Women's Antioxidant Cardiovascular Study; WAFACS, Women's Antioxidant and Folic Acid Cardiovascular Study; WENBIT, Western Norway B Vitamin Intervention Trial; WHI, women's health initiative; WHS, Women's Health Study.

Mean age (years)	Male %	Interventions	Mean intended treatment duration (years)	Mean follow-up (years)	Outcome measures
53	100	ASA-LD; AOs; PLB	5 (ASA-LD); 12 (AO)	5 (ASA-LD); 12 (AO)	CV events, cancers and overall mortality
62	100	ASA-HD; CTL	6	Up to 9 years[b]	CV events and mortality from CV causes
60	73	ASA-LD; ASA-HD; PLB	4.4[c] (1–7 years)	Up to 9 years[b]	CV events, mortality from vascular and non-vascular causes
57	66	AOs; PLB	4	4	Lung cancer, other cancers and overall mortality
40–80[b]	75	AOs; PLB	5	5	Major coronary events, cancers and overall mortality
63	75	AOs; PLB	4.5	7.4	Non-melanoma skin cancer, other cancers and overall mortality
57	100	AOs; PLB	6.1	6.1	Lung cancer, other cancers and overall mortality
75	76	VD; PLB	5	5	Fractures, cancers, CV events and overall mortality
56	63	FA+B12; AOs; PLB	2	6	Stomach cancer and other GI cancers
49	39	AOs; PLB	7.5	7.5	CV events, cancers and overall mortality
66	73	AOs; FA+B6+B12; PLB	4.5	4.5	Cancer incidence, cancer deaths, major CV events and overall mortality
55	0	ASA-VLD; AOs; ASA-VLD+AOs; PLB	10.1	10.1	Cancer or CV events
59	0	CA+VD; PLB	7	7	Fractures and cancers
67	0	CA; CA+VD; PLB	4	4	Fractures and cancers
60	0	AOs; PLB	8[d]	8[d]	CV events, cancers and overall mortality
63	0	AOs; FAVB; FAVB+ AOs; PLB	6.8[d]	6.8[d]	CV events, cancers and overall mortality
62-6[c]	100	AOs; PLB	5.5	5.5	Prostate cancer and other cancers
64	100	AOs; PLB	8	8	CV diseases, prostate and total cancer
64	83	FA+B12; PLB	6.7	6.7	CV events and cancers
62	64	FAVB; PLB	3.4	3.4	CV events, cancers and overall mortality
61	50	FA;CTL	3	3	Colorectal adenomas
62	100	ASA-HD; CTL	6 (at least 5 years for all patients)	up to 23[a]	CV events and mortality from CV causes
60	73	ASA-LD; ASA-HD; PLB	4.4[c] (1–7 years)	up to 21–27 [a]	CV events, mortality from vascular and non-vascular causes
53	100	ASA-LD; PLB	5	12	MI and other CV events; cancer
57.2	100	AOs; PLB	6.1	12	Cancer incidence and mortality
57	66	AOs; PLB	4	10	Lung cancer and other cancers
62	76	FAVB; FA+B12; PLB	3.2	6.4	CV outcomes
55	0	ASA-VLD; CTL	10.1	18	Any invasive cancer
59	0	CA+VD; PLB	7	11	Fractures and colorectal cancer
57.5	100	ASA-VLD; PLB	7 (at least 5 years)	Up to 17–20[b]	Ischemic heart diseases
70	66	ASA-VLD; PLB	2.7 (1–5 years)	Up to 18–23[b]	Composite outcome of stroke or death from any causes
65.3	65	ASA-VLD; ASA-LD	2.6 (1–4 years)	Up to 17[b]	Death from CV causes

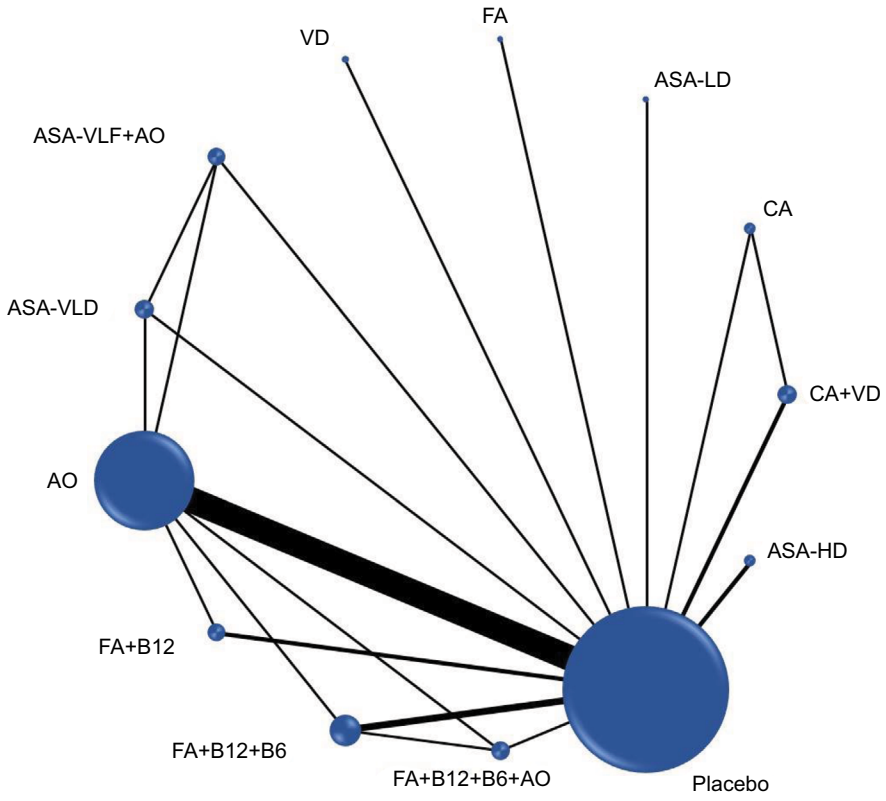

Figure 1 Network plot of chemopreventive agents tested in RCTs for early risk of CRC incidence.
Abbreviations: RCT, randomized controlled trials; CRC, colorectal cancer; ASA, asprin; HD, high-dose; LD, low-dose; VLD, very-low-dose; VitaminB12; B6, vitamin B6; CA, calcium; AO, antioxidants; FA, folic acid; VD, vitamin D.

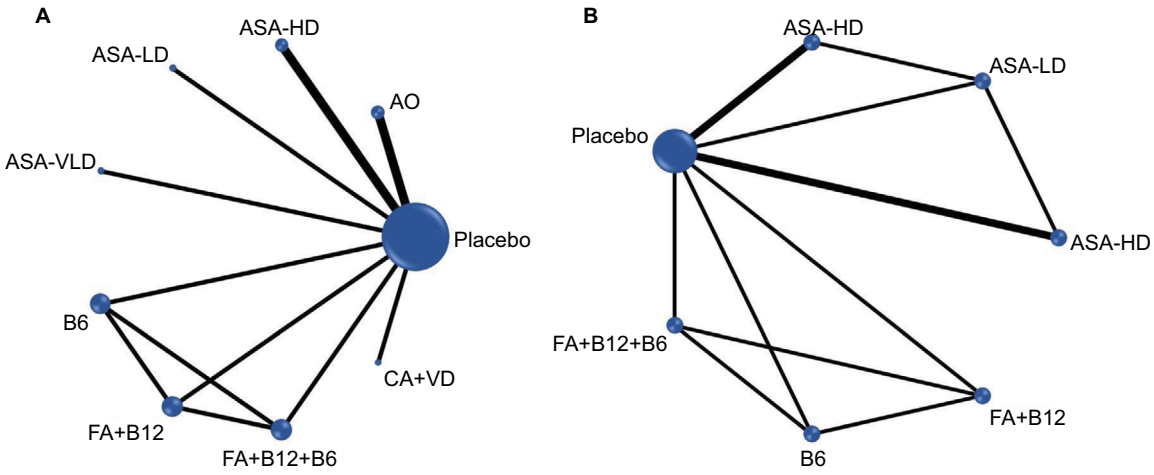

Figure 2 Network plots of chemopreventive agents tested in RCTS (follow-up 0–≥20 years) for (**A**) long-term risk of CRC incidence (**B**) long-term risk of CRC mortality.
Abbreviations: RCT, randomized controlled trials; CRC, colorectal cancer; ASA, asprin; HD, high-dose; LD, low-dose; VLD, very-low-dose; VitaminB12; B6, vitamin B6; CA, calcium; AO, antioxidants; FA, folic acid; VD, vitamin D.

must, therefore, note that the findings of our analysis only applied to beta-carotene, vitamin A, vitamin E, vitamin C, selenium, and zinc.

Observational studies suggested a relationship among calcium and vitamin D levels and CRC.[67,68] A recent meta-analysis suggested that calcium may have a moderate protective effect on CRC recurrence.[69] However, we did not find any effects of calcium (alone or with vitamin D). A recent phase-2 trial showed that high-dose vitamin D3 (loading dose of 8,000 IU/day orally for 2 weeks followed by 4,000 IU/day) significantly improved survival in patients with metastatic CRC.[70] It should be noted that low dose (400 IU/day) of vitamin D was used in

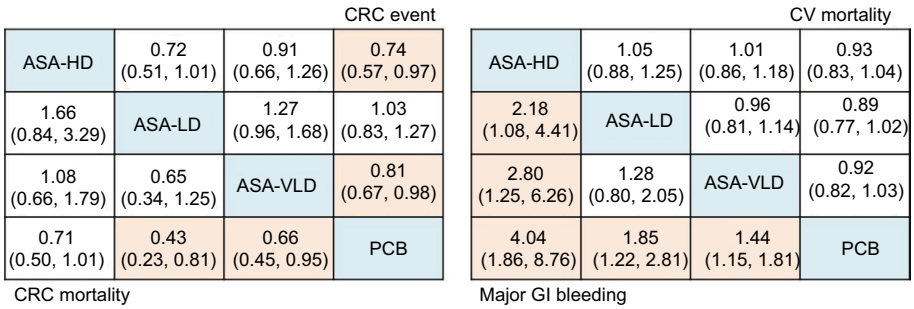

Figure 3 Efficacy and safety of aspirin for colorectal cancer in network meta-analysis.
Notes: Efficacy outcomes are long-term CRC incidence and CRC mortality. Safety outcomes are major GI bleeding events and CV deaths. Risk ratio (95% credible interval) of comparisons for each outcome is in cells in common between column-defining and row-defining treatment. Comparison between treatments should read from row to column for CRC event and CV mortality and column to row for CRC mortality and major GI bleeding events. For risk of CRC event and CV mortality, risk ratio <1 favor row-defining treatment. For risk of CRC mortality and GI bleeding events, risk ratio, <1 favor column-defining treatment. Orange shaded results indicate statistical significance.
Abbreviations: CRC, colorectal cancer; CV, cardiovascular; GI, gastrointestinal; ASA, asprin; HD, high-dose; LD, low-dose; VLD, very-low-dose; PCB, placebo.

all primary prevention trials (and not in the form of vitamin D3).[69,71] As a result, future trials of vitamin D may need to explore both different forms and various dosing of vitamin D.

Previous studies of folic acid supplementation on CRC showed inconsistent results.[40,72,73] We did not find either a decrease or an increase in the risk of CRC in any folic intervention (Table S3.12 in Supplement 3). A recent study suggested that the effect of folic acid may depend upon the existing level of blood folate along with methylenetetrahydrofolate reductase (MTHFR) genotype.[74] Therefore, the effect of folic acid on CRC may require further investigation based on those factors.

Over the past few decades, data concerning aspirin derived from RCTs and meta-analyses generated mostly discouraging findings for CRC prevention after medium-term, in-trial follow-up (≤10 years).[2,19,36,37] However, recent extended follow-up of RCTs has shown remarkably consistent evidence on the protective effect of aspirin against long-term CRC incidence and mortality.[27,30,34] The 2016 USPSTF guideline[35,75] suggested the use of aspirin (<100 mg/day) for primary CRC prevention in people who have a 10% or greater 10-year risk for CVD and who are not at an increased risk of bleeding. This recommendation was derived from pairwise meta-analysis and multi-criteria decision analysis (MCDA) using a microsimulation model to systematically estimate the balance of benefits and harms through the gain in net life years and quality-adjusted life years.[34,50] Our analysis took different approaches. First, we explored the comparative efficacy of different CPAs including aspirin to ensure that all interventions in the landscape were represented and analyzed.[27,34,36–40] Our results lend strong support to USPSTF by showing that, based on the most current data, aspirin is the only effective CPA compared to placebo and other CPAs.

While USPSTF analysis attempted to evaluate the effect of doses and duration of treatment, no meaningful analysis was made due to the limited amount of direct head-to-head trials of different doses of aspirin. To extend beyond USPSTF analysis, we did an NMA to comprehensively compare 3 doses of aspirin and able to show detailed differences in efficacy and safety of aspirin at different doses (Figure 3). We believe that this analysis is useful since aspirin demonstrated a dose-dependent effect relating to the risks of GI bleeding events and hemorrhagic stroke.[76] Therefore, selection of aspirin dose for long-term use requires striking the right balance between benefit and risk. To tackle this issue, we used NCB to simultaneously evaluate effects of aspirin on CRC and CV mortality along with major GI bleeding of different aspirin doses. Based on this comprehensive evaluation investigating the multidimensional effects of aspirin, we were able to show that both LDASA and VLDASA appeared to strike an optimal balance on CV and CRC mortality vs major GI bleeding (Figure 4). Based on analysis with different weighting on major GI bleeding event, LDASA seemed to provide the highest net survival gain among different doses of aspirin. However, we caution readers that this result is far from definite and should be taken as hypothesis generated for further research to try to identify the optimal dose of aspirin for CRC prevention, cardiovascular disease prevention along with acceptable adverse drug reaction. As a result, until more evidence becomes available, it may be prudent to consider both low-dose (100–325 mg/day) and very-low-dose aspirin (75–100 mg/day) as the viable options for both CRC and cardiovascular disease prevention.

Limitations of study

Our study has several important limitations. First, most data on long-term CRC incidence and mortality were collected post hoc as a part of follow-up trials that included other outcomes as predefined endpoints, rather than CRC incidence or mortality. The completeness in capturing those events may be questionable. Second, differences in patient population, trial conducts, and trial methodology across studies may

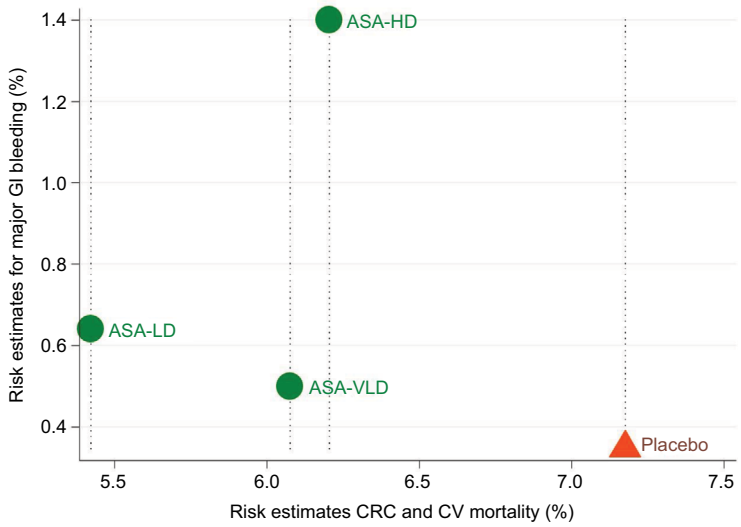

Figure 4 Scatter plot of combined risk estimates of CRC and CV mortality vs pooled risk estimates for major GI bleeding.
Note: Treatments lying in the left lower corner are more effective and acceptable than the other treatments.
Abbreviations: CRC, colorectal cancer; CV, cardiovascular; GI, gastrointestinal; ASA, aspirin; HD, high-dose; LD, low-dose; VLD, very-low-dose.

create an inherent heterogeneity especially the difference in treatment duration and follow-up period. Third, our analysis on the effects of aspirin doses can be perceived as hypothesis generation since data are still too limited to make a definitive conclusion on the dose-specific effects of aspirin. However, we still believe that aspirin at the dose of 75–325 mg/day is best supported by not only our study but also previous reports. Until new large RCTs comparing different doses of aspirin are available, we believe that our findings offer a range of aspirin dose for clinician and patient to discuss and make a shared decision to choose what dose of aspirin may suit the differential risk-benefit profile of each patient. While recognizing the impact of age on the risk-benefit of aspirin, we were unable to perform detailed analysis based on age due to the lack of individual patient data. Based on this limitation along with the definite incremental risk of aspirin with advanced age and lack of robust data to support efficacy for long-term CRC prevention in the elderly, we caution the readers to avoid extrapolating these results toward elderly patients.

Conclusions and policy implications

Our analysis suggests that aspirin was the only intervention that showed protective effects with potential dose-dependent effects while none of the other CPAs was found to be effective. Aspirin at the dose range of 75–325 mg/day is a safe and effective primary prevention for long-term CRC among people at average risk. For patients with low risk of bleeding, low-dose aspirin (>100–325 mg/day) may slightly be more attractive due to a larger reduction in CRC mortality and the best net clinical benefit. For patients at high risk of bleeding, very-low-dose aspirin (<100 mg/day) might be appropriate due to its best safety profile especially GI bleeding. There may potentially be differential effects among various doses of aspirin that needs further investigation.

Data sharing

Technical appendix and dataset available from the corresponding authors.

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Author contributions

SKV, NC, SN, KGL, SS and PJ designed and organized research. NC supervised the study. SKV, KGL and SMC acquired, analyzed and interpreted data. SKV, PJ and NT performed the statistical analysis. SKV and SN wrote the manuscript. NC, SN, CR and PP revised the review. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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