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Chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia: systematic review and network meta-analysis

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ABSTRACT

OBJECTIVE

To assess the comparative efficacy and safety of candidate agents (low and high dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs), calcium, vitamin D, folic acid, alone or in combination) for prevention of advanced metachronous neoplasia (that is, occurring at different times after resection of initial neoplasia) in individuals with previous colorectal neoplasia, through a systematic review and network meta-analysis.

DATA SOURCES

Medline, Embase, Web of Science, from inception to 15 October 2015; clinical trial registries.

STUDY SELECTION

Randomized controlled trials in adults with previous colorectal neoplasia, treated with candidate chemoprevention agents, and compared with placebo or another candidate agent. Primary efficacy outcome was risk of advanced metachronous neoplasia; safety outcome was serious adverse events.

DATA EXTRACTION

Two investigators identified studies and abstracted data. A Bayesian network meta-analysis was performed and relative ranking of agents was assessed with surface under the cumulative ranking (SUCRA) probabilities (ranging from 1, indicating that the

treatment has a high likelihood to be best, to 0, indicating the treatment has a high likelihood to be worst). Quality of evidence was appraised with GRADE criteria.

RESULTS

15 randomized controlled trials (12 234 patients) comparing 10 different strategies were included. Compared with placebo, non-aspirin NSAIDs were ranked best for preventing advanced metachronous neoplasia (odds ratio 0.37, 95% credible interval 0.24 to 0.53; SUCRA=0.98; high quality evidence), followed by low-dose aspirin (0.71, 0.41 to 1.23; SUCRA=0.67; low quality evidence). Low dose aspirin, however, was ranked the safest among chemoprevention agents (0.78, 0.43 to 1.38; SUCRA=0.84), whereas non-aspirin NSAIDs (1.23, 0.95 to 1.64; SUCRA=0.26) were ranked low for safety. High dose aspirin was comparable with low dose aspirin in efficacy (1.12, 0.59 to 2.10; SUCRA=0.58) but had an inferior safety profile (SUCRA=0.51). Efficacy of agents for reducing metachronous colorectal cancer could not be estimated.

CONCLUSIONS

Among individuals with previous colorectal neoplasia, non-aspirin NSAIDs are the most effective agents for the prevention of advanced metachronous neoplasia, whereas low dose aspirin has the most favorable risk:benefit profile.

REGISTRATION

PROSPERO (CRD42015029598).

Introduction

Colorectal cancer is the third most common cancer worldwide,¹ with annual healthcare costs in the United States alone estimated to be over \$14bn (£11bn; €13bn).² Over 85% of sporadic colorectal cancers arise from advanced adenomas.³ Colonoscopic screening with resection of adenomatous polyps has been associated with a reduction in mortality, and this is the preferred approach for preventing sporadic colorectal cancers.^{4,5} Unfortunately, suboptimal adherence, access, and expense limit population-wide adoption of preventive colonoscopy.⁶ Additionally, despite routine screening, a few individuals still develop colorectal cancer before their recommended surveillance interval, either because of missed or incompletely resected polyps or rapidly growing tumors.^{7,8} Given the limitations of screening tests and poor prognosis associated with advanced stage colorectal cancer, there is great interest in exploring chemoprevention strategies to reduce the burden of this preventable malignancy.

Many commonly available nutritional supplements and pharmacological agents have been studied as

WHAT IS ALREADY KNOWN ON THIS TOPIC

Many commonly available nutritional supplements and pharmacological agents have been studied as chemoprevention agents for colorectal cancer in individuals with previous colorectal neoplasia, with variable efficacy in randomized controlled trials

Previous meta-analyses have suggested that aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) could be effective in decreasing the risk of advanced metachronous neoplasia, but in the absence of head-to-head trials, their relative efficacy and safety are not implicit

WHAT THIS STUDY ADDS

Non-aspirin NSAIDs are superior to placebo and all other chemopreventive strategies (low and high dose aspirin, calcium, vitamin D, folic acid, alone or in combination) for the prevention of advanced metachronous neoplasia over three to five years, with moderate to high confidence in estimates

Because of the high risk of serious adverse events with non-aspirin NSAIDs, the excess benefit (of reducing advanced metachronous neoplasia) over risk (of experiencing serious adverse events) might be favorable only in individuals with previous high risk neoplasia

Though low dose aspirin was ranked second in preventing advanced metachronous adenomas with low confidence in estimates, it has the most favorable safety profile, and the excess benefit over risk might therefore be favorable for all patients with previous neoplasia (regardless of baseline neoplasia status)

chemoprevention agents for colorectal cancer in people with previous colorectal neoplasia, with variable efficacy in randomized controlled trials.⁹⁻²³ Meta-analyses have suggested that aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) could be effective in decreasing the risk of advanced metachronous neoplasia (that is, occurring at different times after resection of initial neoplasia),²⁴⁻²⁶ but in the absence of head-to-head trials, their relative efficacy and safety are not known. Pairwise meta-analyses provide only partial information in this case because they can answer questions only about pairs of treatments and do not therefore optimally inform decision making. Network meta-analyses combine direct and indirect evidence to establish comparative efficacy and safety across a network of randomized controlled trials of all agents used in a particular condition; such an analysis assumes the trials are conceptually similar with regard to design, participants, intervention (dosing, duration), co-interventions, and outcome assessment.²⁷⁻²⁸ This technique can improve the precision of the estimate (compared with direct evidence alone) and also allows estimation of the comparative efficacy of two active treatments, even if no studies directly compare them.²⁹ Such comparisons with a quantitative synthesis of risks and benefits of all candidate chemopreventive agents can inform patients, clinicians, policymakers, and other stakeholders regarding the optimal use of these agents in clinical practice.

We performed a pairwise meta-analysis and bayesian network meta-analyses, comparing the relative efficacy and safety of candidate chemoprevention strategies (low and high dose aspirin, non-aspirin NSAIDs, calcium, vitamin D, folic acid, alone or in combination) for the prevention of colorectal cancer in people with previous colorectal neoplasia. We used GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria for network meta-analysis to appraise the state of evidence for chemoprevention.³⁰

Methods

This systematic review was performed with an a priori established protocol (PROSPERO CRD42015029598), and is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) extension statement for systematic reviews incorporating network meta-analyses for healthcare interventions.³¹ We followed good research practices outlined in the International Society for Pharmacoeconomics and Outcomes Research report on interpreting indirect treatment comparisons and network meta-analysis for decision making in healthcare.³²

Data sources and searches

A medical librarian designed and conducted the search strategy with input from study investigators, using various databases from inception to 15 October 2015. Using controlled vocabulary supplemented with keywords, we searched for trials of candidate agents for chemoprevention for colorectal cancer. The databases included Medline, Embase, Scopus, Web of Science, Cochrane

Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (appendix 1). In addition, we searched clinical trial registries (www.clinicaltrials.gov, www.clinicaltrialsregister.eu), conference proceedings, and published systematic reviews for additional studies. Two study reviewers (SS, EM) independently reviewed the title and abstract of these studies to exclude any that did not examine the research question of interest. Full texts of the remaining articles were reviewed to identify studies that met all criteria (as detailed below) for inclusion in the quantitative synthesis. Figure A in appendix 2 details the study selection flowchart.

Study selection

Studies included were randomized controlled trials that met the following inclusion criteria: participants were adults (age ≥ 18) with previous colorectal neoplasia or colorectal cancer who underwent curative resection before randomization; interventions of candidate chemoprevention agents—low (≤ 160 mg/day) or high dose aspirin (≥ 300 mg/day), non-aspirin NSAIDs, calcium, vitamin D, folic acid, alone or in combination; comparators were another candidate agent or placebo; and outcome was proportion of individuals who developed metachronous neoplasia, reported as either advanced neoplasia or any neoplasia, on follow-up colonoscopy, within three to five years of the index study related colonoscopy.

We excluded observational studies, trials with short term follow-up (≤ 1 year after index colonoscopy), trials of drugs that are no longer available (such as rofecoxib), trials of non-conventional chemoprevention agents with limited clinical applicability (such as ursodeoxycholic acid), as widespread adoption of such drugs would be challenging, and trials recruiting individuals before 1990 (because of the risk of missed neoplasia at index and/or follow-up colonoscopy with older technology).³³

Data abstraction and assessment of risk of bias

Two authors independently abstracted data on study, participants, and treatment related characteristics onto a standardized form, and discrepancies were resolved by consensus, referring back to the original article, in consultation with a third reviewer. Appendix 1 provides details of data abstraction. Data on efficacy and safety were abstracted with study reported modified intention to treat analysis (that is, individuals who received at least one dose of the candidate agent and had at least one colonoscopy after randomization (for efficacy) or had one follow-up after randomization (for safety)). When trials allowed for re-randomization or extension of the follow-up interval for efficacy or safety,^{9 14 16 17 23 34-36} we abstracted data from the study interval in which the surveillance colonoscopy was planned to occur before 40 months after randomization, keeping with current societal recommendations for surveillance colonoscopy in individuals with previous colorectal neoplasia.³⁷ The risk of bias of individual studies was assessed in the context of the primary outcome, using the Cochrane risk of bias assessment tool.³⁸

Outcomes

The primary efficacy outcome was prevention of advanced metachronous neoplasia, within three to five years of the index colonoscopy. Advanced metachronous neoplasia was defined according to the study authors; if this was not clearly defined, it was classified based on presence of a villous component, high grade or severe dysplasia, and/or cancer (neoplasia size or multiplicity were not routinely reported) (table 1). Our secondary efficacy outcome was prevention of any metachronous neoplasia (advanced and non-advanced neoplasia, colorectal cancer). The rarity of metachronous colorectal cancer in the included trials precluded its assessment as an efficacy outcome in network meta-analyses. It is therefore reported narratively from individual trials. Moreover, more than 85% of all colorectal cancers are thought to arise from advanced neoplasia, and estimated annual transition probabilities from advanced neoplasia to colorectal cancer range from 2.6% to 5.2%, in an age dependent manner.³⁹ Hence, prevention of advanced neoplasia is an accepted surrogate for preventing colorectal cancer.

Our primary safety outcome was the risk of serious adverse events. There were defined as events resulting in death, admission to hospital related to an adverse event, severe gastrointestinal bleeding, vascular (cardiac or non-cardiac) complications, or discontinuation of treatment because of an adverse event or events that were graded as serious or severe by original study authors. In case of incomplete efficacy or safety data (for example, lack of safety data by exposure type in trials with factorial design), we contacted and successfully obtained unpublished data from study authors.^{10 12 17 19}

Data synthesis and statistical analysis

Direct meta-analysis was performed with DerSimonian and Laird random effects model to estimate pooled odds ratios and 95% confidence intervals incorporating heterogeneity within and between studies, with RevMan v5.2.⁴⁰ Statistical heterogeneity was assessed with I^2 statistic, with values over 50% indicating substantial heterogeneity.⁴¹ In post hoc sensitivity analyses, we also derived summary estimates with the Hartung-Knapp method to deal with possible type I error with the conventional DerSimonian and Laird approach.⁴²

To incorporate indirect with direct comparisons, we conducted random effects bayesian network meta-analyses using Markov chain Monte Carlo methods in WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).^{29 43 44} We assumed “consistency” of treatment effects across all included trials—that is, true treatment effects are on average the same from both direct and indirect analyses—and assumed that heterogeneity was common within networks. Network consistency was evaluated by comparing the direct estimates with the indirect estimates for each comparison, with a node splitting technique.³⁰ We estimated the posterior distribution of all parameters using vague priors to limit inference to data derived from the trials at hand (that is,

we made no assumptions about the efficacy of these drugs from data external to the trials included in this systematic review). We changed the precision/variance of the priors in sensitivity analyses with minimal change to the estimates suggesting robust approach. We tested three chains with different initial values and ascertained convergence. We updated our Markov chain Monte Carlo model with 100 000 simulated draws after a burn-in of 10 000 iterations. Multiple chains (that is, multiple initial values) were evaluated for each analysis. The median of the posterior distribution was reported as the point estimate odds ratio, and the corresponding 95% credible intervals were obtained with the 2.5th and 97.5th centiles of the posterior distribution, after adjustment for multiple arm trials. We tested the adequacy of burn-in and convergence (reaching a stable equilibrium distribution) using visual inspection of parameter fluctuation depicted in trace plots, monitoring the Monte Carlo error, and estimating the values of the Brooks-Gelman-Rubin statistic.⁴⁵ Model fit was evaluated with the total residual deviance, which indicated good fit, if it approximated the number of data points.

We present the relative ranking of agents on preventing metachronous neoplasia and adverse events outcomes as their surface under the cumulative ranking (SUCRA), ranging from 1, indicating that the treatment has a high likelihood of being best, to 0, which indicates the treatment has a high likelihood of being worst.⁴⁶ Higher SUCRA scores correspond to higher ranking for prevention of metachronous neoplasia and a lower risk of adverse events, compared with other interventions. We assessed small study effects with comparison adjusted funnel plot symmetry.⁴⁷

Finally, to calculate absolute risk reduction, we converted odds ratios to relative risk using the Zhang equation with network meta-analysis summary estimates (odds ratios (OR)) and baseline risks (assumed control risk) obtained from the National Cancer Institute pooling project.⁴⁸ We used the equation $RR = OR / (1 - P_0) + (P_0 \times OR)$, where P_0 refers to the risk of outcome of interest in the non-exposed group. The risk difference was calculated as $100 \times (\text{assumed control risk} - OR \times \text{assumed control risk}) / (1 - \text{assumed control risk} + OR \times \text{assumed control risk})$. The risk difference, which represents the difference between risks in the intervention and control group, was added back to the assumed control risk to generate an estimate of the absolute risk for each intervention. We generated 95% credible intervals for the estimates using the 95% credible intervals of the odds ratios in the above calculations. Proportions from single arms (placebo) were weighted for each study, and numerators and denominators were added up, to estimate the unadjusted pooled risk of serious adverse events in placebo arms. Estimates of absolute risk were generated with the GRADEpro version 3.6.1 (McMaster University, 2014). Details of the statistical analysis are reported in appendix 1.

To assess the robustness of the findings of our primary efficacy outcome we performed multiple sensitivity analyses. These were based on use of colonoscopy surveillance per protocol completer analysis (that is,

Table 1 | Characteristics of trials included in review of chemoprevention of colorectal cancer in individuals with previous colorectal neoplasia

Design	Efficacy outcomes			Safety		Definition of advanced neoplasia†
	Study group	Any neoplasia	Advanced neoplasia	Colorectal cancer	Death	
Sandler, 2003 ²²	Multi-center, double blind, placebo controlled, parallel, stratified randomization	Placebo Aspirin 325 mg	70/258 43/259	NA NA	17/318 18/317	Villous component or ≥1 cm diameter
Benamouzig, 2012 ¹³	Multi-center, double-blind, placebo-controlled, RCT, parallel, non-stratified block randomization	Placebo Aspirin 160 mg	62/116 32/68	18/116 12/68	1/132 0/73	≥1 cm diameter, ≥25% villous component, or high grade dysplasia
Ishikawa, 2014 ¹⁸	Multi-center, double blind, placebo controlled, RCT, parallel, stratified randomization	Placebo Aspirin 100mg	33/60 73/159	6/60 4/159	0/67 0/198	NR. Calculated based on No of patients with adenomas containing villous component, high grade dysplasia, or cancer
Pommergaard, 2015 ²¹	Multi-center, double blind, placebo controlled, RCT, parallel, non-stratified block randomization	Placebo Aspirin/vitamin D/calcium	58/218 52/209	7/218 5/209	0/362 0/352	≥1 cm diameter or high grade dysplasia
Baron, 2003 ¹² Cole, 2007 ¹⁷	Multi-center, double blind, placebo controlled, RCT, factorial, stratified block randomization	Placebo Aspirin 81 mg	70/162 65/166	14/162 10/166	3/202 2/203	Tubulovillous adenoma (25-75% villous), villous adenoma (≥75% villous), ≥1 cm diameter, severe dysplasia, invasive cancer
		Aspirin 325 mg	71/158	18/158	3/201	
		Folate	87/168	27/168	0/170	
		Folate+aspirin	134/333	30/333	3/346	
Logan, 2008 ¹⁹	Multi-center, double blind, placebo controlled, RCT, factorial, stratified block randomization	Placebo Aspirin 300	56/204 49/217	30/204 22/217	3/233 4/236	≥1 cm diameter, villous component, severe dysplasia, or cancer
		Folate	65/215	33/215	1/234	
		Folate+aspirin	50/217	19/217	0/236	
Wu, 2009 ²³	Multi-center, double blind, placebo controlled, RCT, parallel, non-stratified randomization	Placebo Folate	64/238 52/237	15/238 15/237	7/334 15/338	Large, tubulovillous, villous or high grade dysplasia, or colorectal cancer
Baron, 2015 ¹⁰	Multi-center, double blind, placebo controlled, RCT, factorial, stratified block randomization	Placebo Calcium	183/380 259/655	35/380 63/662	7/415 5/714	≥25% villous component, ≥1 cm diameter, high grade dysplasia, cancer
		Vitamin D	179/381	42/384	5/420	
		Vitamin D+calcium	259/643	56/648	10/710	
Baron, 1999 ¹¹	Multi-center, double blind, placebo controlled, RCT, parallel, non-stratified block randomization	Placebo Calcium	230/459 191/454	6/459 4/454	22/466 25/464	NR. Calculated based on severe atypia or cancer
Bonithon-Kopp, 2000 ¹⁵	Multi-center, double blind, placebo controlled, RCT, parallel, stratified block randomization	Placebo Calcium	36/178 28/176	8/178 10/176	9/212 8/204	NR. Calculated based on patients with adenomas ≥1cm diameter, or containing villous component, high grade dysplasia, or cancer
Chu, 2011 ¹⁶	Multi-center, double blind, placebo controlled, RCT, parallel, non-stratified randomization	Placebo Calcium	62/99 42/95	19/99 17/95	0/99 0/95	≥1 cm, containing villous component, atypical histology, or cancer
Arber, 2006 ⁹	Multi-center, double blind, placebo controlled, RCT, parallel, stratified randomization	Placebo Celecoxib	264/557 270/840	56/557 42/840	7/628 11/933	≥1 cm, containing villous component, high grade dysplasia, or cancer
Bertagnoli, 2006 ¹⁴	Multi-center, double blind, placebo controlled, RCT, parallel, stratified randomization	Placebo Celecoxib	354/608 465/1214	99/608 79/1214	6/676 4/1214	≥1 cm, containing villous component, high grade dysplasia, or cancer
Meyskens, 2008 ²⁰	Multi-center, double blind, placebo controlled, RCT, parallel, stratified block randomization	Placebo Sulindac	53/129 17/138	11/129 1/138	1/184 2/191	≥1 cm, containing villous component, high grade dysplasia, or cancer

NR=not reported; RCT=randomized controlled trial; NSAID=non-steroid anti-inflammatory drug.

*Defined as those resulting in death, admission to hospital, severe gastrointestinal bleeding, vascular complications (cerebrovascular, cardiovascular, or peripheral vascular), discontinuation of treatment, or those graded as serious or severe by study authors. Patients with Dukes' stage A or B1 colon or rectal cancer (tumor-node-metastasis (TNM) stage T1 to T2, NO, MO) who had undergone curative resection of primary tumor were immediately eligible for enrollment. Patients with Dukes' stage B2 or C (T3 to T4, NO to N1, MO) colon or rectal cancer who had undergone curative resection of primary tumor were eligible if they had been free from disease for >5 years after curative surgery.

†Risk of advanced adenoma reported by study authors to be advanced (as per study definitions) with inclusion of colorectal cancers if these were reported separately. If clear definition for advanced adenoma(s) was not presented, they were calculated and classified according to presence of villous component, high grade or severe dysplasia, or cancer.

outcomes included only those individuals who underwent colonoscopy surveillance at the prespecified time period per protocol and excluded individuals who underwent a colonoscopic surveillance assessment before, or after, the anticipated main surveillance interval; worst case scenario assumption wherein patients who did not undergo colonoscopy after randomization were assumed to have developed advanced metachronous neoplasia; exclusion of studies that did not specify for a clearing colonoscopy to occur within at least six months of study initiation; exclusion of studies that limited recruitment to individuals with previous colorectal cancer; and exclusion of studies investigating non-aspirin NSAIDs in combination with other agents (that is, difluoromethylornithine). Additionally, we tested several vague priors in sensitivity analyses to assure robustness of the analysis.

Quality of evidence

We followed the GRADE approach to rate the quality of evidence of estimates derived from network meta-analysis.^{30 44 49} In this approach, direct evidence from randomized controlled trials starts at high quality and can be rated down based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity), and/or publication bias to levels of moderate, low, and very low quality. The rating of indirect estimates starts at the lowest rating of the two pairwise estimates that contribute as first order loops to the indirect estimate but can be rated down further for imprecision or intransitivity (dissimilarity between studies in terms of clinical or methodological characteristics). If direct and indirect estimates were similar (that is, consistent) then the higher rating can be assigned to the network meta-analysis estimates.

Risk:benefit integrated analysis

To understand potential benefits of candidate chemoprevention agents at the population level, we used odds ratios derived from the placebo comparisons of each active agent in the network meta-analysis to estimate absolute risk of advanced metachronous neoplasia with different interventions and absolute anticipated excess benefit (over placebo) for every 1000 individuals who receive treatment.³⁸ We used published pooled estimates from the National Cancer Institute pooling project to estimate population level risks of advanced metachronous colorectal neoplasia: 7.4% in low risk group (individuals with 1-2 small (<1 cm), tubular adenoma(s) with low grade dysplasia) and 16.3% in high risk group (individuals with at least three adenomas, any adenomas ≥ 1 cm, with >25% villous features, or with high grade dysplasia).⁵⁰

Subsequently, to understand the potential risks of candidate chemoprevention agents, we used the pooled risk of serious adverse event in placebo groups as a measure of baseline risk (fig D in appendix 2). We then used odds ratios derived from the placebo comparisons in network meta-analysis for serious adverse events to estimate absolute risk and anticipated excess risk of serious adverse events (over placebo) per 1000 individuals who receive treatment. This was estimated for the two interventions shown to have the highest probability for preventing advanced metachronous neoplasia based on network meta-analysis. These benefits and risks were then qualitatively synthesized to analyze the relative risk and benefit of candidate agents for the chemoprevention of colorectal cancer.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design and implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results

From a total of 3566 unique citations identified using our search strategy, we included 14 randomized controlled trials comparing 10 different interventions.⁹⁻²³ These included 10 two arm trials of candidate agent compared with placebo, one three arm trial of different aspirin doses compared with placebo, and three trials with factorial design (one 2×2 and one 3×2). Figure 1 shows the available direct comparisons and network of trials (for primary outcome of advanced metachronous neoplasia), and figure B in appendix 2 shows comparisons for secondary outcomes.

Characteristics and risk of bias of included trials

Table 1 and tables A and B in appendix 3 summarize the randomized controlled trials included in the network meta-analysis.⁹⁻²³ These 14 trials dated from 1999 to 2015 and included 12234 participants (range 194-2059). All trials were multi-center, double blind, placebo

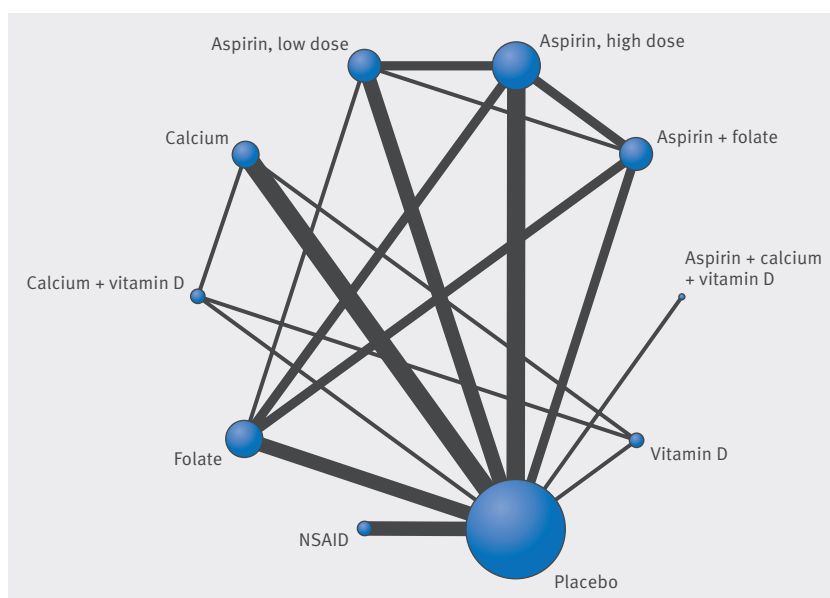


Fig 1 | Network of included studies with the available direct comparisons for primary efficacy outcome (advanced metachronous neoplasia). The size of the nodes and the thickness of the edges are weighted according to the number of studies evaluating each treatment and direct comparison, respectively.

controlled, and 11 studies used a run-in period enrichment strategy to optimize study drug adherence.⁹⁻²³ The median risk of baseline high risk neoplasia in included trials was 44% (interquartile range 23-68); two trials included only patients with previous colorectal cancer.^{16,22,36} The median initial surveillance period to assess for metachronous neoplasia was 36 months (range 24-60 months) and was before 40 months after randomization for all studies, with the exception of the studies by Sandler and colleagues²² and Benamouzig and colleagues,¹³ which allowed for surveillance to occur between 36-48 months after randomization, and the study by Baron and colleagues,¹⁰ which allowed for surveillance to occur at 36 or 60 months after randomization. The median proportion of patients with family history of colorectal cancer in first degree relatives was 21% (interquartile range 19-32%). The median of average body mass index (BMI) across trials was 27.6 (range 23.6-29.5).

Overall, median risk of advanced metachronous neoplasia and any metachronous neoplasia in the participants treated with placebo was 9.1% (range in individual studies 3.2-19.2%) and 43.4% (20.2-62.6%), respectively. On quality assessment, studies of each candidate agent were considered to be at low risk of bias. Though median attrition rate was about 15.6% (range 1.2-30.0), it was similar between intervention and placebo. Moreover, as we used modified intention to treat analysis (including only individuals with at least one colonos-

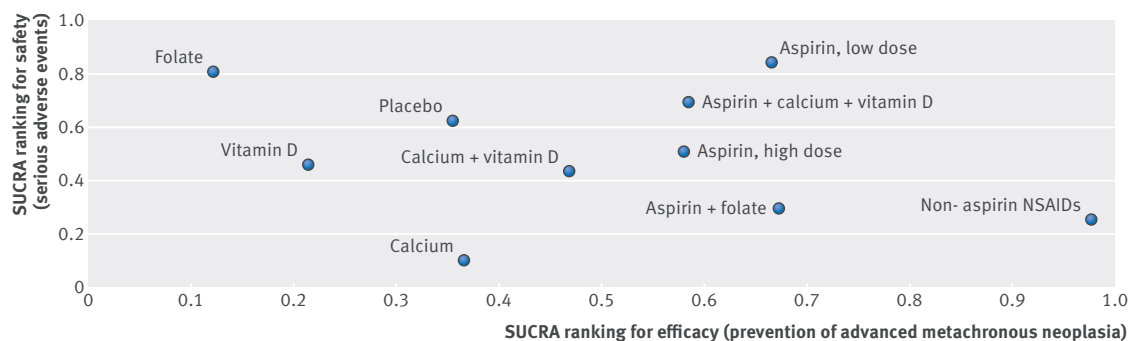
copy after randomization), there were no missing data for the primary efficacy outcome (fig C in appendix 2).

Pairwise meta-analysis

Fig D in appendix 2 summarizes results of pairwise meta-analyses. Non-aspirin NSAIDs (celecoxib and sulindac) were associated with a significant reduction in advanced metachronous neoplasia compared with placebo (odds ratio 0.38, 95% confidence interval 0.26 to 0.56). Non-aspirin NSAIDs (0.41, 0.29 to 0.58) and calcium alone (0.69, 0.59 to 0.82) or in combination with vitamin D (0.73, 0.56 to 0.94) were associated with a significant reduction in any metachronous neoplasia compared with placebo. Low dose aspirin was also associated with reduction in any metachronous neoplasia compared with placebo, though this did not reach significance (0.77, 0.58 to 1.01). When we assessed the comparative efficacy of different strategies, low and high dose aspirin alone and in combination with folic acid was superior to folic acid alone for the prevention of advanced or any metachronous neoplasia. Calcium alone and in combination with vitamin D was superior to vitamin D alone for the prevention of any metachronous neoplasia. Overall, the risk of colorectal cancer was 5, 10, and 8 per 1000 individuals treated with non-aspirin NSAIDs and low and high dose aspirin, respectively, compared with 7 per 1000 within study placebo treated individuals.

Efficacy in preventing advanced metachronous neoplasia										
Serious adverse events	Aspirin + calcium + vitamin D	0.77 (0.17 to 3.06)	0.98 (0.23 to 3.72)	0.88 (0.21 to 3.35)	1.00 (0.24 to 3.97)	1.92 (0.48 to 7.26)	0.60 (0.13 to 2.43)	0.71 (0.17 to 2.67)	0.54 (0.13 to 2.02)	0.71 (0.18 to 2.49)
	0.81 (0.41 to 1.52)	Calcium + vitamin D	1.26 (0.60 to 2.67)	1.14 (0.55 to 2.41)	1.29 (0.58 to 2.83)	2.46 (1.28 to 5.22)	0.77 (0.42 to 1.44)	0.92 (0.53 to 1.60)	0.70 (0.34 to 1.43)	0.91 (0.52 to 1.63)
	0.74 (0.39 to 1.40)	0.92 (0.54 to 1.61)	Aspirin + folate	0.90 (0.53 to 1.54)	1.02 (0.54 to 1.94)	1.96 (1.05 to 3.85)	0.61 (0.28 to 1.31)	0.73 (0.38 to 1.39)	0.56 (0.33 to 0.92)	0.73 (0.43 to 1.19)
	0.85 (0.46 to 1.58)	1.05 (0.63 to 1.81)	1.14 (0.79 to 1.66)	Aspirin, high dose	1.14 (0.61 to 2.08)	2.17 (1.20 to 4.16)	0.68 (0.32 to 1.43)	0.80 (0.43 to 1.49)	0.62 (0.37 to 1.01)	0.81 (0.50 to 1.28)
	1.15 (0.53 to 2.51)	1.43 (0.72 to 2.95)	1.55 (0.90 to 2.73)	1.35 (0.77 to 2.42)	Aspirin, low dose	1.91 (0.99 to 3.98)	0.60 (0.27 to 1.35)	0.71 (0.36 to 1.42)	0.54 (0.29 to 1.00)	0.71 (0.41 to 1.23)
	0.73 (0.40 to 1.29)	0.91 (0.57 to 1.48)	0.98 (0.62 to 1.56)	0.86 (0.55 to 1.32)	0.63 (0.33 to 1.19)	Non-aspirin NSAIDs	0.31 (0.15 to 0.62)	0.37 (0.20 to 0.63)	0.28 (0.15 to 0.49)	0.37 (0.24 to 0.53)
	0.82 (0.41 to 1.56)	1.02 (0.66 to 1.58)	1.10 (0.62 to 1.90)	0.97 (0.55 to 1.64)	0.71 (0.34 to 1.43)	1.13 (0.68 to 1.84)	Vitamin D	1.19 (0.66 to 2.12)	0.91 (0.44 to 1.89)	1.19 (0.65 to 2.15)
	0.65 (0.35 to 1.13)	0.81 (0.54 to 1.18)	0.87 (0.54 to 1.37)	0.76 (0.48 to 1.17)	0.56 (0.29 to 1.05)	0.89 (0.59 to 1.29)	0.80 (0.52 to 1.18)	Calcium	0.76 (0.42 to 1.37)	1.00 (0.66 to 1.52)
	1.05 (0.56 to 1.97)	1.31 (0.78 to 2.27)	1.42 (0.96 to 2.10)	1.24 (0.85 to 1.83)	0.92 (0.50 to 1.63)	1.45 (0.94 to 2.30)	1.29 (0.75 to 2.26)	1.62 (1.05 to 2.61)	Folate	1.32 (0.85 to 2.00)
	0.90 (0.54 to 1.51)	1.11 (0.76 to 1.70)	1.21 (0.83 to 1.77)	1.06 (0.76 to 1.49)	0.78 (0.43 to 1.38)	1.23 (0.95 to 1.64)	1.10 (0.74 to 1.70)	1.38 (1.07 to 1.89)	0.85 (0.59 to 1.22)	Placebo

Fig 2 | Comparative efficacy and safety of chemoprevention for metachronous adenomas in network meta-analysis. Comparisons should be read from left to right. Odds ratio (95% credible interval) for comparisons are in cells in common between column-defining and row-defining treatment. Bold cells are significant. For risk of metachronous advanced neoplasia, odds ratio <1 favors row-defining treatment. For risk of serious adverse events, odds ratio <1 favors column-defining treatment



Agent	Placebo	Folate	Calcium	Vitamin D	Non-aspirin NSAIDs	Aspirin, low dose	Aspirin, high dose	Aspirin + folate	Calcium + vitamin D	Aspirin + calcium + vitamin D
Efficacy rank (95% CrI)	7 (4 to 9)	9 (5 to 10)	7 (3 to 10)	9 (3 to 10)	1 (1 to 2)	3 (2 to 9)	5 (2 to 9)	4 (2 to 8)	6 (1 to 10)	3 (1 to 10)
Safety rank (95% CrI)	4 (2 to 7)	2 (1 to 7)	10 (6 to 10)	6 (1 to 10)	8 (3 to 10)	2 (1 to 9)	5 (2 to 10)	8 (3 to 10)	6 (2 to 10)	3 (1 to 10)

Fig 3 | SUCRA rankings for efficacy and safety outcomes (range 1=treatment has high likelihood of being, 0=treatment has high likelihood of being worst). For efficacy outcomes, higher score=better treatment for preventing advanced metachronous neoplasia. For serious adverse event outcome, higher scores=safest treatment with lower risk of serious adverse events. Table shows median ranks on both efficacy and safety outcomes (rank 1-10 on each scale) and 95% credible intervals

Non-aspirin NSAIDs (odds ratio 1.23, 95% confidence interval 1.04 to 1.45) and calcium (1.40, 1.06 to 1.85) were associated with a significant increased risk for serious adverse events compared with placebo. The addition of vitamin D to calcium was associated with a significant reduction in the risk of serious adverse events compared with calcium alone (0.77, 0.62 to 0.96). In post hoc sensitivity analysis, summary estimates were comparable with the Hartung-Knapp method but with wider confidence intervals (table D in appendix 3).

Network meta-analysis—efficacy outcomes

Advanced metachronous neoplasia

Network meta-analysis suggested that, compared with placebo, non-aspirin NSAIDs were ranked best for preventing advanced metachronous neoplasia (odds ratio 0.37, 95% credible interval 0.24 to 0.53; SUCRA=0.98), followed by low-dose aspirin (0.71, 0.41 to 1.23; SUCRA, 0.67), aspirin+folic acid (0.73, 0.43 to 1.19; SUCRA, 0.67), aspirin+calcium+vitamin D (0.71, 0.18 to 2.49; SUCRA, 0.59), and high dose aspirin (0.81, 0.50 to 1.28; SUCRA, 0.58) (figs 2 and 3; fig E in appendix 2). With an assumed control risk of advanced metachronous neoplasia of 16.3% in patients with baseline high risk neoplasia, the estimated risk of advanced metachronous neoplasia was 6.7% with non-aspirin NSAIDs, 12.1% with low dose aspirin, 12.4% with aspirin+folic acid, 12.1% with aspirin+calcium+vitamin D, and 13.6% with high dose aspirin (table E in appendix 3).

When we assessed comparative efficacy, non-aspirin NSAIDs were superior to all other agents for the prevention of advanced metachronous neoplasia, except low dose aspirin and aspirin+calcium+vitamin D, for which the association did not reach significance (fig B). Low and high dose aspirin were comparable with each other for preventing advanced metachronous neoplasia (low

dose aspirin v high dose aspirin: odds ratio 0.88, 95% credible interval 0.48 to 1.64).

Any metachronous neoplasia

Network meta-analysis suggested that, compared with placebo, non-aspirin NSAIDs were ranked best for preventing any metachronous neoplasia (odds ratio 0.44; 95% credible interval 0.31 to 0.55; SUCRA, 0.99), followed by calcium (0.68, 0.52 to 0.88; SUCRA, 0.70), low dose aspirin (0.69, 0.49 to 0.95; SUCRA, 0.68), calcium+vitamin D (0.71, 0.47 to 1.06; SUCRA, 0.62), and aspirin+folic acid (0.74, 0.52 to 1.03; SUCRA, 0.59). When we assessed comparative efficacy, non-aspirin NSAIDs were superior to all other candidate interventions for decreasing the risk of any metachronous neoplasia (fig E in appendix 2, table F in appendix 3), and low and high dose aspirin were comparable with each other (low v high dose aspirin 0.90, 0.61 to 1.30).

Network meta-analysis—safety outcome

Network meta-analysis suggested that, compared with placebo, calcium ranked the lowest for safety (odds ratio 1.38, 95% credible interval 1.07 to 1.89; SUCRA=0.10), followed by non-aspirin NSAIDs (1.23, 0.95 to 1.64; SUCRA=0.26). Low dose aspirin was ranked the safest among chemoprevention agents (0.78, 0.43 to 1.38; SUCRA=0.84), followed by folic acid (0.85, 0.59 to 1.22; SUCRA=0.81) and aspirin+calcium+vitamin D (0.90, 0.54 to 1.51; SUCRA=0.69), all of which ranked higher than placebo (figs 2 and 3; fig E in appendix 2). With an assumed control risk of serious adverse events of 18.7% based on pooled event risk in the placebo groups of included trials, the estimated risks of advanced metachronous neoplasia were 22.1% with non-aspirin NSAIDs, 15.2% with low dose aspirin, 21.8%

with aspirin+folic acid, 17.2% with aspirin+calcium+vitamin D, and 19.6% with high dose aspirin (table E in appendix 3).

Sensitivity analysis

Tables F-K in appendix 3 show results from multiple sensitivity analyses. Overall, the results were similar to the main analysis for the primary outcome, and non-aspirin NSAIDs remained superior to placebo when we used per protocol completer analysis (odds ratio 0.47, 95% credible interval 0.20 to 0.88); used worst case scenario assumption (0.63, 0.50 to 0.81); excluded studies that did not specify for a clearing colonoscopy to occur within at least six months of study initiation (0.37, 0.21 to 0.55); excluded studies that limited recruitment to individuals with previous colorectal cancer (0.37, 0.22 to 0.54); and excluded studies investigating non-aspirin NSAIDs in combination with other agents (0.40, 0.27 to 0.60). Results of SUCRA scores were also comparable when we used alternative priors in the network meta-analysis (table L in appendix 3).

Small study effects and network coherence

We did not find any evidence of small study effects based on funnel plot asymmetry (fig F in appendix 2), though the number of studies included in each comparison was small. There was no inconsistency in the network meta-analysis estimates when we used the node-splitting approach (table M in appendix 3) and no significant differences between direct and indirect estimates in closed loops that allowed assessment of network coherence (table N in appendix 3). The total residual deviance for the outcomes of any metachronous neoplasia (37.78, df=36), advanced metachronous neoplasia (33.96, df=33), and serious adverse events

(30.04, df=33) implied a good model fit. Convergence of chains was verified visually by looking at trace plots and inspecting the Brooks-Gelman-Rubin diagnostic statistic with values around 1.⁴⁵

Quality of evidence

Overall, there was no serious risk of bias, inconsistency, indirectness, or publication bias for any of the direct comparisons. In several comparisons, there was serious imprecision in summary estimate because the 95% credible interval crossed unity (suggesting the possibility of considerable benefit as well as serious harm in terms of the risk of developing advanced metachronous neoplasia). On applying GRADE criteria to findings from the network meta-analysis combining direct and indirect evidence, we had high confidence in estimates supporting the use of non-aspirin NSAIDs and low confidence in estimates supporting the use of low and high dose aspirin alone or in combination with folic acid compared with placebo for reducing the risk of advanced metachronous neoplasia in individuals with previous resected colorectal neoplasia. There was low confidence in estimates supporting the use of non-aspirin NSAIDs over other chemoprevention agents for preventing advanced metachronous neoplasia. Conceptually, there was no significant intransitivity, with comparable distribution of plausible effect modifiers across trials of different chemopreventive agents (previous advanced colorectal neoplasia, family history of colorectal cancer, and BMI). Tables O and P in appendix 3 summarize the GRADE quality of evidence supporting the use of each candidate chemoprevention agent, compared with placebo and against each other, in individuals with previously resected neoplasia.

Risk:benefit integrated analysis

Based on weighted pooled analyses of placebo arms from randomized controlled trial, we estimated a risk of a serious adverse event of 187 per 1000 placebo treated individuals over three to five years of follow-up. Using risk estimates of serious adverse events derived from network meta-analysis, we estimated an excess of 34 more serious adverse events per 1000 individuals treated with non-aspirin NSAIDs over placebo (compared with 45 fewer advanced neoplasia in participants with previous low risk neoplasia and 96 fewer advanced neoplasia in participants with previous high-risk neoplasia). In contrast, we estimated 35 fewer serious adverse events per 1000 participants treated with low dose aspirin over placebo (compared with 20 and 42 fewer advanced neoplasia in participants with previous low risk or high risk neoplasia, respectively; table 2). As such, participants taking aspirin had fewer serious adverse events and a trend towards a lower risk of advanced metachronous neoplasia.

Discussion

Principal findings

In this systematic review and network meta-analysis, we combined direct and indirect evidence from 14 randomized controlled trials comparing 10 different

Table 2 | Absolute anticipated benefits and risks of candidate chemoprevention interventions for colorectal cancer

Risk group*	Anticipated absolute risk difference of over 3-5 years per 1000 treated individuals	
	Advanced neoplasia	Serious adverse events†
Non-aspirin NSAIDs		
Low risk	-47 (-55 to -33)	34 (-8 to 87)
High risk	-96 (-118 to -69)	
Low dose aspirin		
Low risk	-20 (-42 to 15)	-35 (-97 to 54)
High risk	-42 (-89 to 30)	
High dose aspirin		
Low risk	-13 (-36 to 19)	9 (-38 to 68)
High risk	-27 (-74 to 37)	
Aspirin+folic acid		
Low risk	-19 (-41 to 13)	31 (-27 to 102)
High risk	-39 (-86 to 25)	
Aspirin+calcium+vitamin D		
Low risk	-20 (-60 to 92)	15 (-77 to 71)
High risk	-42 (-129 to 164)	

*Low risk group includes patients with 1-2 small (<1 cm) tubular adenoma(s) with low grade dysplasia, and estimated risk of advanced adenomas of 74 per 1000 individuals without intervention; high risk group includes patients with ≥3 adenomas, or any adenomas ≥1 cm, or with >25% villous features, or with high grade dysplasia, and estimated risk of advanced adenomas of 163 per 1000 individuals without intervention, over 3 years.

†Defined as death, admission to hospital because of adverse event, severe gastrointestinal bleeding, vascular complications, discontinuation of treatment because of adverse events, 187 per 1000 events graded as serious or severe by original study authors over same time period without any intervention.

interventions and reporting on 12234 participants with previously resected colorectal neoplasia to make several key observations regarding the potential efficacy and safety of colorectal cancer chemoprevention agents. First, non-aspirin NSAIDs (celecoxib and sulindac) are superior to placebo and all other chemopreventive strategies for the prevention of advanced metachronous neoplasia over three to five years, with moderate to high confidence in estimates. Because of the high risk of serious adverse events, however, the excess benefit (of reducing advanced metachronous neoplasia) over risk (of experiencing serious adverse events) might be favorable only in people with previous high risk neoplasia. Second, though low dose aspirin was ranked second in preventing advanced metachronous adenomas with low confidence in estimates, it has the most favorable safety profile, and hence the excess benefit over risk might be favorable for all patients with previous neoplasia (regardless of baseline neoplasia status). Third, though calcium alone or in combination with vitamin D might be effective in preventing any metachronous neoplasia, it does not decrease the risk of advanced metachronous neoplasia, and calcium alone could be associated with an increased risk of serious adverse events compared with placebo.

Comparison with other studies

Our study extends findings from primary randomized controlled trials and previous pairwise meta-analyses by systematically synthesizing the entire body of relative and absolute efficacy and safety data for candidate chemoprevention agents for colorectal cancer and by providing an integrated risk:benefit approach to their use in clinical practice. Our findings are in keeping with those from previous systematic reviews regarding the benefit of non-aspirin NSAIDs and aspirin for the prevention of metachronous neoplasia over three to five years.²⁴⁻²⁶ While there was high quality evidence supporting non-aspirin NSAIDs (over placebo) for preventing advanced metachronous adenomas, the quality of evidence supporting the use of low dose aspirin was rated as low, primarily because of imprecision in estimate (a small but not insignificant possibility of harm with increased risk of advanced metachronous neoplasia). Addition of other agents to aspirin (such as folic acid or calcium+vitamin D) does not seem to offer additional efficacy beyond low dose aspirin alone and also does not improve the safety profile of low dose aspirin. Low dose aspirin was also comparable in efficacy with high dose aspirin, while being safer.

The most recent US Preventive Services Task Force guidelines support the use of low dose aspirin for primary chemoprevention of colorectal cancer in people whose cardiovascular risk at 10 years is 10% or more and who are not at an increased risk for serious adverse events.^{51 52} These recommendations are based on observational studies, which were not able to adequately assess previous neoplasia or use of colonoscopy. Furthermore, these recommendations do not address the use of low dose aspirin for chemoprevention

of secondary colorectal cancer among patients with previous colorectal neoplasia, who might already be undergoing routine surveillance colonoscopy. Our work tackles this gap in the literature. Although we were unable to find a significant reduction in advanced metachronous neoplasia with low dose aspirin over three to five years, the highly favorable risk:benefit profile supports its use for secondary prevention of advanced metachronous neoplasia in patients with previous low or high risk neoplasia (or colorectal cancer). Given the over-use of surveillance colonoscopy currently seen in routine practice,⁵³⁻⁵⁵ and lack of confidence in recommendations for intervals between surveillance,⁵⁶ low dose aspirin as a “short term” chemoprevention for colorectal cancer over three to five years could help to extend or augment surveillance intervals, which could have a positive impact on healthcare costs and the burden of surveillance with colonoscopy. Additionally, the expansion of indications for low dose aspirin as chemoprevention for secondary colorectal cancer could also help in increasing its overall uptake for prevention of cardiovascular disease, which has historically been low.^{57 58}

Non-aspirin NSAID significantly reduced the risk of advanced metachronous neoplasia. In weighing risks and benefits, however, we found that the beneficial effects of non-aspirin NSAIDs possibly outweighed the risks of serious adverse events in individuals with baseline high risk neoplasia. Aside from the short term risk of serious adverse events we observed in our meta-analysis, concerns about long term cardiovascular safety have been raised for non-aspirin NSAIDs.⁵⁹ It is important to recognize that the risk for adverse cardiovascular events associated with non-aspirin NSAIDs is predominately seen among people with pre-existing cardiovascular risk factors or disorders,⁶⁰ and more recent literature has suggested that traditional non-aspirin NSAIDs might not be associated with an increased cardiovascular risk.⁶¹ Non-aspirin NSAIDs could therefore potentially be considered as chemoprevention agents in people with a low baseline risk for cardiovascular disease and a moderate-high baseline risk for colorectal cancer.

An important observation within our study is that, despite two decades of high quality research, we are still unable to make strong recommendations on the use of chemoprevention agents for colorectal cancer, and most candidate agents previously studied have been shown to have no efficacy or are associated with excess harm. This is probably partly because of our inability to accurately stratify patients, both for benefits of chemoprevention and risks of treatment. As we enter a new era of personalized medicine and chemoprevention research, it will be important to focus on patient stratification according to genetic factors and variations, spectral biomarkers, and end target (such as cyclooxygenase-2) mucosal expression.⁶²⁻⁶⁴ This molecular phenotyping will help to optimize early proof of study intervention trials aimed at identifying candidate chemoprevention agents for use in routine practice.

Limitations of study

There are certain limitations in our study that merit further discussion. First, the greatest threat to the validity of a meta-analysis is conceptual heterogeneity in study designs, participants, interventions, or outcome assessments. We attempted to minimize this by applying rigorous selection criteria during the design phase of our study, standardizing data abstraction, contacting study authors for missing data, and performing several sensitivity analyses to assess the robustness of our findings. Second, over-exposure or under-exposure to the study agents (relative to protocol assignment) varied across trials, and the impact of compliance on our estimates could not be accurately quantified. There was variability in timing of outcome assessment, which could not be accounted for in our analysis, and sufficient data were not available to perform time-to-event analysis and calculate hazard ratios. Third, because of the relatively short duration of analyzed trials, the risk of colorectal cancer was low, precluding quantitative assessment of efficacy for preventing colorectal cancer. Advanced neoplasia, however, is strong predictor of future colorectal cancer, and prevention of advanced metachronous neoplasia will therefore probably result in a reduced incidence of colorectal cancer. Fourth, the definition of serious adverse events was not uniform across trials and not consistent with regulatory definition, and, despite attempts to standardize this during data abstraction, we might not have completely captured serious adverse events associated with all agents. Fifth, studies were conducted over a wide time period. With improvements in colonoscopy equipment and a greater understanding of quality metrics to augment the rate of detection of neoplasia, it is possible that detection rates could have varied over time. Within these randomized controlled trials with meticulous colonoscopic exams, however, we did not observe any significant time dependent increase in detection rates in the placebo arms of trials. Finally, efficacy of chemoprevention agents for preventing serrated neoplasia could not be estimated because of a paucity of data on this endpoint.

Conclusions and policy implications

In conclusion, among people with previously resected colorectal neoplasia, non-aspirin NSAIDs are effective for the prevention of advanced metachronous neoplasia over a three to five year period, but the risk:benefit profile potentially favors use only in those with a history of high risk neoplasia. After non-aspirin NSAIDs, low dose aspirin alone has the second highest probability of being most effective for preventing advanced metachronous neoplasia and, with its favorable risk:benefit profile, could be considered as an agent for chemoprevention of secondary colorectal cancer in a select group of patients. Shared decision making with a thorough understanding of patients' values and preferences in the context of risks and benefits of each agent would be helpful. Additionally, given the low confidence in several estimates, molecular phenotyping and precision chemoprevention trials are needed to

determine how people can be optimally risk stratified according to safety of treatment and likelihood of response.

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Appendix 1: Supplementary methods and search strategy

Appendix 2: Supplementary figures A-E

Appendix 3: Supplementary tables A-P