Comparative effectiveness of chemopreventive interventions for colorectal cancer: protocol for a systematic review and network meta-analysis of randomised controlled trials

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Background: Colorectal cancer (CRC) is the third most common cancer worldwide and is associated with substantial socioeconomic burden. Despite considerable research, including numerous randomised controlled trials (RCTs) and systematic reviews assessed the effect of various chemopreventive interventions for CRC, there remains uncertainty regarding the comparative effectiveness of these agents. No network meta-analytic study has been published to evaluate the efficacies of these agents for CRC. Therefore, the aim of this study is to summarise the direct and indirect evidence for these interventions to prevent CRC in average-high risk individuals, and to rank these agents for practical consideration.

Methods: We will acquire eligible studies through a systematic search of MEDLINE, EMBASE, the Cochrane Central Registry of Controlled Trials, CINAHL plus, IPA and clinicaltrials.gov website. The Cochrane Risk of Bias Tool will be used to assess the quality of included studies. The primary outcomes are the incidence of CRC, the incidence/recurrence of any adenoma or change in polyp burden (number or size). Quantitative synthesis or meta-analysis will be considered. We will also construct a network meta-analysis (NMA) to improve precision of the comparisons among chemo-preventive interventions by combining direct and indirect evidence. The probability of each treatment being the best and/or safest, the number-needed-to-treat [NNT; 95% credible interval (CrIs)], and the number-needed-to-harm (NNH; 95% CrIs) will be calculated to provide measures of treatment efficacy. The GRADE approach will be used to rate the quality of evidence of estimates derived from NMA.

Results: This protocol has been registered (registration number: CRD42015025849) with the PROSPERO (International Prospective Register of Systematic Reviews). The procedures of this systematic review and NMA will be conducted in accordance with the PRISMA-compliant guideline. The results of this systematic review and NMA will be submitted to a peer-reviewed journal for publication.

Conclusions: To the best of our knowledge, this study will be the first NMA to identify the comparative effectiveness of interventions for the prevention of CRC. The results of our study will update evidence for chemoprevention of CRC, identify key areas for future research, and provide a framework for conducting

large systematic reviews involving indirect comparisons.

Introduction

Colorectal cancer (CRC) is the third most common cancer in the world, with approximately 1.36 million new cases in 2012 (1); it is the fourth leading cause of cancer death worldwide (1). The lifetime probability of a CRC diagnosis in the average-risk individual, defined as without personal history or family history of CRC and above the age of 50, is 5–6% (2,3). This increases up to 20% when there is an association of family history, and reaches a lifetime risk of 80–100% in hereditary CRC syndromes, such as in hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP), respectively (2). Mortality due to CRC is increasing owing to the late stage at which many cases present (3). Attention is therefore focusing on preventative strategies. Early detection and removal of pre-cancerous colorectal adenomas by screening, followed by appropriate therapy and continued surveillance, can decrease mortality (4). Despite evidence of the effectiveness of several screening methods (4), uptake of screening by any method continues to be low (5). Moreover, adoption of screening recommendations requires a large amount of health care resources; its success will also depend on a high compliance rate and regular follow-up. Therefore, there is increased focus on the potential use of chemoprevention as a complement to, or instead of, screening in the prevention of CRC.

Chemoprevention comprises the use of drugs or natural compounds to prevent the development of benign or malignant tumours (6). It is believed that the majority of CRCs develop from benign precursor lesions, the so-called adenomatous polyps or adenomas, through a series of genetic changes (adenoma-carcinoma sequence) during a time interval of at least 5 to 10 years (7,8). Mechanisms underlying chemoprevention include modulation of signalling cascades, and/or of the expression of genes involved in the regulation of cell proliferation, differentiation, and apoptosis, as well as the suppression of chronic inflammation, metastasis, and angiogenesis in adenoma-carcinoma sequence (9,10). Systematic reviews have shown that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) [cyclo-oxygenase-2 (COX-2) inhibitors] reduce the risk of developing colorectal adenomas and cancer (11-14). Similarly calcium and/or vitamin D (15,16), folic acid (17-19) and some anti-oxidants such as selenium (20-22) have also been linked to a possible decreased incidence of CRC. This has led to the concept of using such agents for the chemoprevention of CRC.

Despite evidence of the effectiveness of NSAIDs in preventing CRC, it was concluded that their benefits are outweighed by harms in average risk individuals, including those with a family history of CRC (23,24). However, their use continues to be recommended for high risk individuals with FAP, hereditary nonpolyposis colon cancer syndromes (Lynch I or II), or a history of CRC or adenomas (23,24). The use of other agents such as calcium, vitamin D and folic acid in preventing CRC is not clearly acknowledged in any clinical guidelines. Therefore, evidence of the comparative advantages of various agents for different risk individuals is required to guide clinical decision-making for the chemoprevention of CRC. There have been at least 22 systematic reviews addressing chemoprevention for CRC (11-14,20,25-42); however, no reviews have compared the effectiveness of different chemopreventive agents.

Considerable data are available for clinical outcomes for each chemopreventive agent; moreover, there are validated methodologies to indirectly compare their effectiveness (43-45). Therefore, we will use network meta-analysis (NMA) to perform a comprehensive comparative appraisal of the effects of agents used in the chemoprevention of CRC.

The objective of this study is to conduct a systematic review and NMA to identify the comparative effectiveness of agents for the prevention of CRC in average-high risk individuals.

Methods and analysis

Design

A systematic review of the clinical effectiveness of drug or natural product interventions for the prevention of CRC and/or adenomatous polyps will be undertaken according to the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA-P) statements (46).

Data sources

We will identify relevant randomised controlled trials (RCTs), by a systematic search of MEDLINE 1946 to Present (Via Ovid), MEDLINE In-Process & Other Non-Indexed Citations (Via Ovid), Embase 1974 to present (Via Ovid) Cochrane CENTRAL Register of Controlled Trials 1991 to present (Via Ovid), CINAHL plus, International Pharmaceutical Abstracts and clinicaltrials.gov website. To identify comprehensive studies not captured by database searches, we will manually check the reference lists of published systematic reviews and articles retrieved after title and abstract exclusion.

Search strategies

A search of human studies in these databases from inception through to August/September, 2015 will be performed by using subject headings and free text terms. Three sets of search terms will be combined: terms for CRC or adenomatous polyps and terms for the relevant interventions and a search filter to identify RCTs. For all interventions, search will restrict to studies published from 2008 onwards because studies published up to 2007 could be identified from the published systematic reviews (12-14,20,28-30). The MEDLINE search strategy is shown in Supplementary 1; the same search strategy will be used for EMBASE and Cochrane CENTRAL Register of Controlled Trials (via OVID). We will use the appropriate keywords from MEDLINE search strategy to identify studies from CINAHL plus, International Pharmaceutical Abstracts and clinicaltrials.gov website.

Eligibility criteria

The retrieved reports will be screened according to the checklist of eligibility (see online Supplementary 2) and the eligibility criteria shown below including participants, interventions, controls, outcomes, types of study and other criteria.

Participants

Inclusion—the use of chemopreventive interventions will be assessed in the following three defined populations (4,47): individuals with no increased risk for CRC (described in this assessment as 'average risk individuals'); individuals at increased risk of CRC (described in this assessment as 'increased risk individuals') because of history of adenomatous polyps, personal history of CRC, family history of CRC, or inflammatory bowel disease; individuals at high risk of CRC (described in this assessment as 'high risk individuals') because of FAP or Lynch syndrome/hereditary nonpolyposis colorectal cancer (HNPCC). Exclusion—individuals diagnosed with CRC.

Interventions

Inclusion—any RCT that evaluates the efficacy of following interventions at any dose and frequency, alone or in combination: aspirin, non-aspirin NSAIDs (including COX-2 inhibitors), folic acid, calcium and/or vitamin D, antioxidants: vitamin A, vitamin C, vitamin E, selenium and beta-carotene. Exclusion—this study will exclude whole-food interventions (such as fruits, fibre, green tea, vegetables). Other agents such as curcumin, omega-3 fatty acids, and resveratrol will not be included, because there are only preliminary data relating to these substances. Rofecoxib and valdecoxib were withdrawn from the market (48); and will therefore be excluded.

Controls

Inclusion—any RCT that evaluates the efficacy of intervention of interest, placebo, no intervention or another intervention not included in this assessment. Exclusion—any RCT that evaluates the efficacy of whole-food interventions.

Outcomes

Inclusion—any RCT that includes outcome measures of incidence of CRC, incidence/recurrence of any adenoma or change in polyp burden (number or size). The secondary outcomes include the incidence of adverse events and compliance to the treatment or discontinuation rates. Exclusion—any RCT with outcome measures other than outcome of interest.

Types of study

Inclusion—only RCTs will be included. Exclusion—observational cohort and case-control studies, case reports, experimental studies and reviews will be excluded.
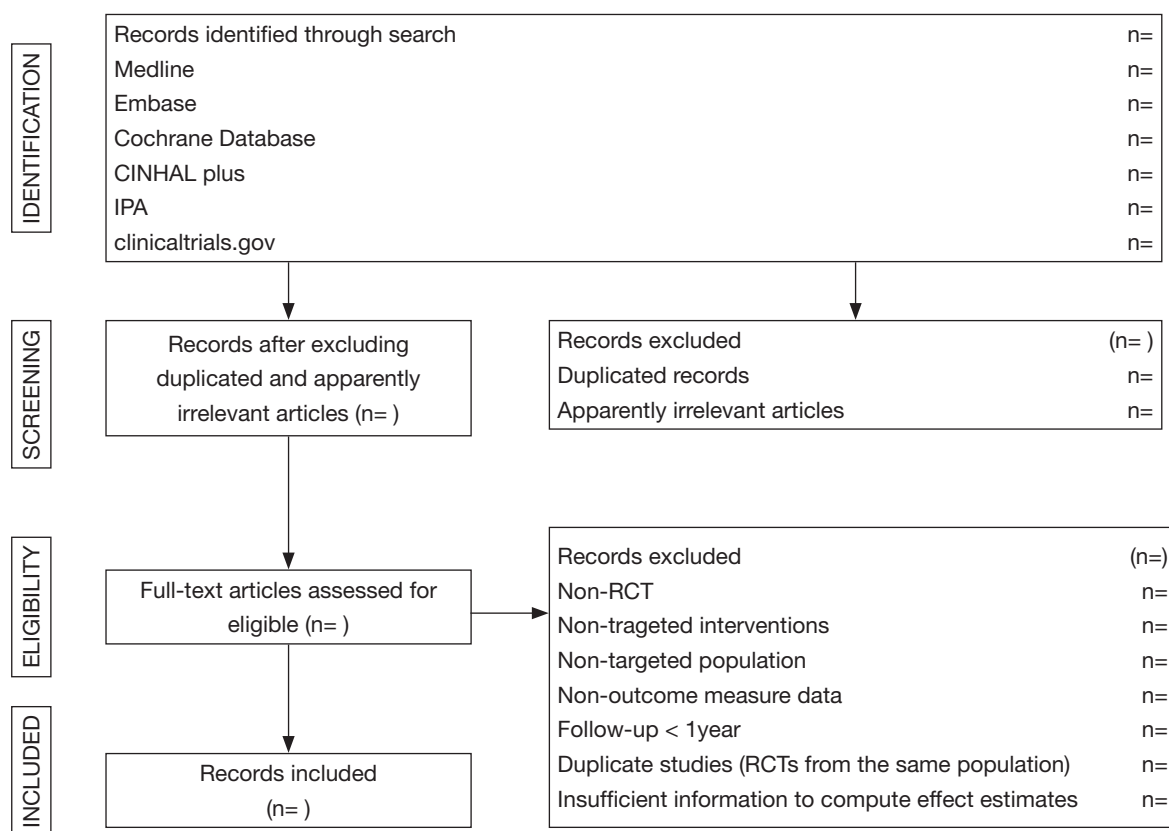
Figure 1 The primary selection process.

Other criteria

Other inclusion criteria—follow-up period or duration in RCTs are at least 1 year for incidence of CRC. There will be no restrictions by type of setting of studies. Other exclusion criteria—we will exclude RCTs from the same population (duplicate studies) and not reporting effect estimates or with insufficient information to compute effect estimates.

Study section

The titles and abstracts of literature search will be screened by one reviewer for potentially relevant studies according to the eligibility criteria (Supplementary 2) and double-checked by a second reviewer. After excluding the duplicated and apparently irrelevant studies, the remaining studies will be read in full text by two reviewers. We will document reasons for the exclusion of records during full-text screening. Disagreements between reviewers will be resolved by consensus. The primary selection process is presented in *Figure 1*.

Data extraction and quality assessment

The following data will be extracted independently and in duplicate by two reviewers into a data extraction form (Supplementary 3)*:* the name of the first author, year of publication, country in which the study was conducted, study setting, follow-up duration, patient's characteristics (study population, number of participants in each group, age (mean/range), gender, and ethnicity), characteristics of interventions (interventions evaluated, dosage form, dose, frequency, length of treatment) and outcome measures (number of participants in whom a new adenoma occurred in the intervention and control groups, number of participants in whom CRC occurred in both groups, number of participants who developed adverse events related to interventions, compliance rate to interventions, drop-outs before the end of study and reasons for dropping out). Disagreement will be documented and resolved by discussion with the third reviewer; where there is still doubt, we will contact the authors for clarification.

Two reviewers will independently assess the risk of bias

Table 1 Quality assessment with the Cochrane Collaboration's risk of bias tool

Criteria for RCT quality assessment	RCT 1	RCT 2	RCT 3	RCT 4	--------
Random sequence generation					
Allocation concealment					
Blinding of participants and personnel					
Blinding of outcome assessment					
Incomplete outcome data					
Selective reporting					
Other sources of bias					

Each item of included RCT is evaluated at low risk and high risk of bias based on the Cochrane Collaboration's risk of bias tool (49,50).

within each study by using a modified Cochrane risk of bias instrument (49,50). We will evaluate sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias (*Table 1*) (49,50). Reviewers will resolve disagreements by discussion, and one of two arbitrators will adjudicate unsolved disagreements.

Data synthesis

Quantitative synthesis or meta-analysis will be considered. If unsuitable due to the heterogeneity and/or small number of studies, a narrative overview of the findings of included studies will be presented with tabular summaries of extracted data. As an initial examination of the data, we will undertake traditional meta-analyses by combining evidence from direct, within-study comparisons between chemopreventive interventions. Heterogeneity between trials will be assessed by considering the I^2 inconsistency statistic alongside the Chi^2 (P>0.1). An I^2 estimate greater than or equal to 50% accompanied by statistical significant Chi statistic, will be interpreted as evidence of substantial levels of heterogeneity (50). When substantial levels of heterogeneity are present, we will explore the underlying reasons. Publication bias will be assessed by using funnel plot asymmetry testing and Egger's regression test. Direct meta-analysis will be performed using a random effects model to estimate effect size such as pooled relative risk (RR) and 95% confidence intervals (CI) incorporating within- and between-study heterogeneity (51). For continuous outcomes, weighted mean differences or standardized mean difference will be calculated, as appropriate, using the random-effects model and reported with 95% confidence intervals.

We will construct NMA to improve precision of the comparisons among chemopreventive interventions by combining direct and indirect evidence (43). Model with either consistency or inconsistency will be assessed in STATA (StataCorp LP, College Station, TX, USA) by contrasting direct and indirect estimates in each triangular loop by the methods described by Veroniki and colleagues (52).

The probability of each treatment being the best (lowest rate of CRC/adenomas) and/or safest (lowest rate of adverse events), the number-needed-to-treat [NNT; 95% credible interval (CrIs)], and the number-needed-to-harm (NNH; 95% CrIs) will be also calculated to provide measures of treatment efficacy. We will construct rankograms of cumulative rank probabilities of how each treatment ranks against each other in terms of being the 1st, 2nd, 3rd, and so forth, best treatment option. In addition, we will present a hierarchy of the efficacy and safety of the various chemopreventive interventions based on their cumulative rank probabilities and the Surface Area Under the Cumulative Rankograms (SUCRA, %) as proposed by Salanti and colleagues (45).

Quality of evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach will be used to rate the quality of evidence of estimates derived from NMA (53). Reviewers will, independently, assess the confidence in effect estimates for all outcomes using the following categories: risk of bias, inconsistency, indirectness, imprecision and publication bias (54). The confidence in estimates for each outcome will be categorized as follows: 'high' quality of evidence (we are very confident that the

true effect lies close to that of the estimate of the effect); 'moderate' quality of evidence (we are moderately confident in the effect estimate and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different); 'low' quality of evidence (our confidence in the effect estimate is limited and the true effect may be substantially different from the estimate of the effect); and 'very low' quality of evidence (we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect) (53).

Subgroup analysis

Several subgroup analyses will be performed based on the follow-up period, characteristics of interventions (dosage form, dose and frequency), types of treatment (alone or in combination) and patients' characteristics (age, sex).

Sensitivity analysis

We will assess the robustness of our results through sensitivity analysis by excluding trials at high risk of bias and using both fixed and random effects models.

Ethics and dissemination

Ethical issues

No ethical approval is required because this study includes no confidential personal data or interventions with the patients.

Publication plan

This protocol has been registered (registration number: CRD42015025849) with the PROSPERO (International Prospective Register of Systematic Reviews) (55). The procedures of this systematic review and NMA will be conducted in accordance with the PRISMA-compliant guideline. The results of this systematic review and NMA will be submitted to a peer-reviewed journal for publication.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary 1 Search strategy for RCTs [Medline (via Ovid)]

The following search strategy will be used to identify RCTs of relevant interventions.

(I)   Terms for colorectal cancer or adenomas

(exp Colorectal Neoplasms/ OR exp Colonic Neoplasms/ OR exp Rectal Neoplasms/ OR exp Adenomatous Polyps/ OR exp Adenocarcinoma/ OR exp Intestinal Polyps/ OR exp Colonic Polyps/) OR ((colorectal cancer$. tw OR colorectal tumo$.tw OR colorectal neoplas$.tw OR colon cancer$.tw OR colon tumo$.tw OR colon neoplas$.tw OR colonic cancer$.tw OR colonic tumo$.tw OR colonic neoplas$.tw OR rectal cancer$.tw OR rectal tumo$.tw OR rectal neoplas$.tw OR rectum cancer$.tw OR rectum tumo$.tw OR rectum neoplas$.tw OR polyp$.tw OR adenoma$.tw OR adenomatous$.tw) OR (exp Adenoma/))

(II)   Terms for NSAIDs and aspirin

(exp Anti-Inflammatory Agents, Non-Steroidal/ OR exp cyclooxygenase inhibitors/ OR exp cyclooxygenase 2 inhibitors/ OR exp Aspirin/) OR (NSAID$.tw. OR Non-steroidal anti-inflammatory$.tw. OR Nonsteroidal anti-inflammatory$.tw. OR Non-steroidal antiinflammatory$.tw. OR Nonsteroidal antiinflammatory$.tw. OR Cyclo-oxygenase inhibitor$.tw. OR Cyclooxygenase inhibitor$.tw. OR Cyclooxygenase 1 inhibitor$.tw. OR Cyclooxygenase 2 inhibitor$.tw. OR COX-2 inhibitor$.tw. OR COX-2 selective inhibitor$.tw. OR COX-1 inhibitor$.tw. OR Coxib$.tw. OR Aspirin.af. OR Acetylsalicylic acid.tw.)

(III)   Terms for folic acid

(exp Folic Acid/ OR folate$.tw. OR folic$.tw. OR folic Acid.af.)

(IV)   Terms for calcium

(exp Calcium, Dietary/ OR exp Calcium/ OR calcium.tw.)

(V)   Terms for vitamin D

(exp Cholecalciferol/ OR exp Ergocalciferols/ OR vitamin d.tw. OR Cholecalciferol$.tw. OR Ergocalciferol$.tw.)

(VI)   Terms for antioxidants

(exp Antioxidants/ OR anti-oxidant$.tw. OR antioxidant$.tw. OR Selenium/ OR exp Vitamin A/ OR exp Carotenoids/ OR carotenoid$.tw. OR beta-carotene.tw. OR exp Ascorbic Acid/ OR vitamin c.tw. OR exp Vitamin E/ OR exp Tocopherols/ OR Tocotrienols/ OR alpha-tocopherol$.tw. OR tocopherol$.tw. OR tocotrienol$.tw.)

(VII)   Terms for randomized controlled trial

(randomized controlled trial.pt. OR controlled clinical trial.pt. OR exp Clinical Trial/ OR Randomized controlled trials/ OR random allocation/ OR double blind method/ OR single blind method/ OR clinical trial.pt. OR placebos/ OR placebo$.ti,ab. OR random$.tw OR blind$.ti,ab.)

(VIII)   (1 AND (2 OR 3 OR 4 OR 5 OR 6) AND 7)

(IX)   Limit 8 to (humans and yr="2008 - 2015")

Supplementary 2 Checklist of eligibility

The study will be excluded when there is a negative ("No") answer to any of following questions:

1. Is the study a randomized controlled trial?

   Yes _____

   No _____

   Unclear _____

2. Are the participants comes under the following risk group?

   a) Average risk individuals: Individuals with no increased risk for colorectal cancer

   b) Increased risk individuals: Individuals at increased risk of colorectal cancer because of history of adenomatous polyps, personal history of colorectal cancer, family history of colorectal cancer, inflammatory bowel diseases

   c) High risk individuals: Individuals at high risk of colorectal cancer because of familial adenomatous polyposis (FAP), Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC)

   Yes _____

   No _____

   Unclear _____

3. Is the intervention under treatment with any one of selected chemopreventive agents listed below?

   Aspirin, non-aspirin NSAIDs (including COX-2 inhibitors), folic acid, calcium and/or vitamin D, antioxidants: vitamin A, vitamin C, vitamin E, selenium and beta-carotene.

   Yes _____

   No _____

   Unclear _____

4. Do the outcome measures include at least one of Incidence of colorectal cancer or Incidence/recurrence of any adenoma or change in polyp burden, number and size?

   Yes _____

   No _____

   Unclear _____

5. Is the follow-up period at least 1 year?

   Yes _____

   No _____

   Unclear _____

6. Is the study a non-duplicated and non-redundant publication?

   Yes _____

   No _____

   Unclear _____

Supplementary 3 Data extraction form

Trial ID (Number; First author; Year of publication):			
Action			
Methods			
Country:	Study setting:	Duration:	Funding:
Allocation:		Blindness:	
Participants			
Study population (average/increased risk/high risk individuals):			
Number of participants (N):	Number of participants in each group:		Age:
Sex:	Ethnicity	Included:	Excluded:
Interventions Evaluated			
Comparators:			
Outcomes:			
Incidence/recurrence of new adenoma:		Incidence of colorectal cancer:	
Incidence of adverse events:		Compliance rate:	
Drop-outs (reason):			
Outcomes – unable to use –and WHY			
Results:			
Notes:			