Chemoprevention of colorectal cancer: systematic review and economic evaluation
Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, Maquire C, Hind D, Tappenden P

CRD summary
This review concluded that aspirin and celecoxib (non-steroidal anti-inflammatory drug) might reduce adenomas and incidence of advanced adenomas in individuals with an increased risk of colorectal cancer; calcium might also reduce recurrence of adenomas in this population. Aspirin and non-steroidal anti-inflammatory drugs were associated with adverse effects. The authors’ conclusions reflect the evidence presented and are likely to be reliable.

Authors’ objectives
To evaluate the effectiveness of drug and micronutrient interventions for the prevention of colorectal cancer and/or adenomatous polyps. The separate analyses of cost-effectiveness and patient views on chemoprevention are not included in this abstract.

Searching
MEDLINE, EMBASE, CINAHL, the Cochrane Library, Science Citation Index, BIOSIS Previews, and the Current Controlled Trials research register were searched up to June 2008. Search terms were reported.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) of any dose or combination of the following: aspirin; non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 inhibitors; folic acid; calcium and/or vitamin D; and/or antioxidants (vitamins A, C, E, selenium, and beta-carotene). Eligible participants were members of the general population or those at no increased risk of colorectal cancer (low risk), those with increased risk due to history of colorectal cancer, adenomatous polyps or inflammatory bowel disease (intermediate risk), and people with genetic predisposition due to familial adenomatous polyposis or hereditary non-polyposis colorectal cancer (high risk). Studies of low and intermediate risk participants had to have at least one year of treatment and follow-up. Comparators could be placebo, no intervention, or any other single or combination of intervention(s).

The outcomes of interest were incidence/recurrence of any adenoma, change in polyp burden, incidence of colorectal cancer, compliance and discontinuation rates, and adverse events.

The included trials were comprised of men and women with a wide age range. Treatment and dosing regimens varied within each intervention category. Full details are reported in the paper.

Two reviewers selected studies for inclusion; disagreements were resolved by discussion.

Assessment of study quality
The CRD critical appraisal checklist was used to assess trial quality including randomisation, allocation concealment, blinding, baseline comparability of study groups, and confounding.

The authors did not state how many reviewers carried out the quality assessment.

Data extraction
For dichotomous outcomes, data were extracted to enable the calculation of relative risks (RR), along with 95% confidence intervals (CIs). For continuous outcomes, mean differences (MD) were calculated with 95% confidence intervals.

Data were extracted by one reviewer and checked by a second reviewer. Disagreements were resolved by discussion.

Methods of synthesis
Relative risks and weighted mean differences (using the inverse variance method) and 95% confidence intervals were pooled in a random-effects meta-analysis. Statistical heterogeneity was assessed using $I^2$. The procedure for analysing the different combinations of interventions and comparators was reported in the paper.

Results of the review
Forty-four RCTs and six on-going RCTs were included in the review. There were 10 RCTs of aspirin, nine RCTs of non-aspirin NSAIDs, six RCTs of calcium and/or vitamin D, six RCTs of folic acid, and 19 RCTs of antioxidants. Six RCTs assessed more than one intervention type.

Aspirin: Aspirin compared with no-aspirin (with or without the addition of folic acid) was associated with a statistically significant reduction in the risk of adenoma recurrence in intermediate-risk individuals at three years of follow-up (RR 0.79, 95% CI 0.68 to 0.92; four good quality RCTs; n=2,692 patients; $I^2=34%$); a similar result was found when compared with placebo alone. Aspirin was also associated with a statistically significant reduction in the risk of colorectal cancer incidence in low-risk individuals at 23 years of follow-up (RR 0.74, 95% CI 0.57 to 0.97; two lower quality RCTs; n=7,588 patients; $I^2=0$).

Non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs): The non-aspirin NSAID celecoxib was associated with statistically significant reductions in the risks of adenoma recurrence (RR 0.66, 95% CI 0.60 to 0.72) and advanced adenoma incidence (RR 0.45, 95% CI 0.35 to 0.58) in intermediate-risk individuals at three years of follow-up (two good quality RCTs; n= 2,618 patients; $I^2=0$).

Calcium: Calcium was associated with a statistically significant reduction in the risk of adenoma recurrence in intermediate-risk individuals at three to four years of follow-up (RR 0.82, 95% CI 0.69 to 0.98; two good quality RCTs; n=1,186 patients; $I^2=0$).

Folic acid and antioxidants: There were no statistically significant differences between groups in the available RCTs for folic acid or antioxidant use.

Adverse effects: Adverse effects were noted for aspirin (upper gastrointestinal toxicity) and NSAIDs (serious cardiovascular events). One trial found that calcium had a greater risk of side effects compared with placebo, but there was no difference between the groups for major adverse events.

Cost information
Compared with screening alone, aspirin in addition to screening within the general population could result in a discounted cost-per life-year gained of approximately £10,000 and a discounted cost per quality-adjusted life-year (QALY) gained of approximately £23,000. For intermediate-risk individuals, the optimum economically viable age-range policy was to provide chemoprevention to those aged 61 to 70 years following polypectomy.

Calcium could have a discounted cost per QALY of approximately £8,000 compared with screening alone.

Authors' conclusions
Aspirin and non-steroidal anti-inflammatory drugs (celecoxib) might reduce adenomas and incidence of advanced adenomas in individuals who have an increased risk of colorectal cancer. Calcium might also reduce recurrence of adenomas in this population group. Aspirin and NSAIDs were associated with adverse effects.

CRD commentary
The review question was clear. Inclusion criteria were sufficiently detailed to enable replication. Relevant data sources were included in the search strategy and some attempt was made to locate unpublished material. It was not clear how many reviewers carried out the quality assessment, but the remainder of the review process included efforts to minimise error and bias.

An appropriate quality assessment checklist was applied to the included trials; the results of this assessment were taken into account in the interpretation of results. Trial details were presented. The chosen method of synthesis seemed appropriate and took account of statistical heterogeneity.
The authors’ conclusions reflect the evidence presented and are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that health professionals should attempt to clarify the balance of benefits and risks associated with aspirin and NSAIDs when recommending these treatments to patients.

**Research:** The authors stated that larger studies with longer follow-up periods (20 years) are needed to establish the balance of risks and benefits of chemoprevention, with specific focus on colorectal cancer incidence as an outcome. Research is also recommended: newer agents should be tested, as well as combinations of chemopreventive agents for which individual effectiveness has been proposed; studies in higher-risk patients; and comparisons of chemoprevention with action to improve screening programme compliance.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.