Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force


CRD summary
This review concluded that non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 inhibitors reduce the incidence of colonic adenomas; NSAIDs also reduce colorectal cancer risk. The authors also stated that the harms outweigh the benefits in average-risk individuals. The review was well-conducted and is likely to be reliable. However, the harms were evaluated in a review of reviews, which was not assessed here.

Authors' objectives
To evaluate the effects of non-acetylsalicylic acid (non-ASA) non-steroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase (COX-2) inhibitors for the prevention of colorectal cancer and adenoma.

Searching
MEDLINE (1966 to December 2006), EMBASE (1980 to week 14, 2005), the Cochrane CENTRAL Register and the Cochrane Library (Issue 4, 2004) were searched using the reported search terms. In addition, the PubMed Cancer subset was searched for any material not published on MEDLINE. The search was restricted to studies reported in English.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), controlled clinical trials, cohort and case-control studies were eligible for inclusion.

In order to evaluate the possible gastrointestinal, cardiovascular and renal harms, previous systematic reviews were eligible for inclusion. The methods and results of this review of reviews will not be reported in this abstract.

Specific interventions included in the review
Studies that evaluated the effects of non-ASA NSAIDs and COX-2 inhibitors were eligible for inclusion. The interventions in the included studies were ASA and non-ASA NSAIDs, ibuprofen, celecoxib and rofecoxib. All of these were given at regular doses for between 1 and 9 years.

Participants included in the review
Studies that included participants who were at average risk for colorectal cancer (i.e. no known risk factors other than age) or participants with higher risks (such as a personal or family history of colorectal adenoma or a family history of sporadic colorectal cancer) were eligible for inclusion. Studies with high-risk patients with familial adenomatous polyposis or hereditary nonpolyposis colon cancer syndromes were excluded, as were studies of participants with a personal history of colorectal cancer. Both men and women were enrolled in the included studies.

Outcomes assessed in the review
Studies that assessed the incidence of colorectal adenomas and/or colorectal cancer, colorectal cancer-related death and all-cause mortality were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers screened the studies and any conflicts were resolved by consensus.
Assessment of study quality
The authors did not state how many reviewers performed the validity assessment, although it was possible it was performed as part of the data extraction process. Predefined criteria from the U.S. Preventive Screening Task Force were used to rate studies as good, fair or poor. The scale comprised of 6, 7 or 7 criteria (for case-control studies, cohort studies and RCTs, respectively). A good rating was awarded if all criteria were met, and a fair rating awarded for studies achieving at least 80% of the criteria.

Data extraction
Several reviewers independently extracted the data using a web-based system (TrialStat). Relative risks (RRs) with 95% confidence intervals (CIs) were directly extracted from studies and their standard errors were computed. For the case-control studies, the odds ratio used was considered a close approximation to the RR.

Methods of synthesis
How were the studies combined?
The studies were grouped according to disease (i.e. colorectal cancer or colorectal adenomas), study design, study population and medication. The combined RR was calculated using an inverse variance-weighted random-effects model.

How were differences between studies investigated?
Differences between the studies were formally assessed using the I-squared statistic. Studies were only combined if the I-squared statistic was less than 50%. Studies were also subcategorised based on dose effect, treatment duration and secondary outcomes (where reported).

Results of the review
A total of 29 studies were included in the effectiveness synthesis (n at least 562,094): 4 RCTs (n at least 5,972), 5 cohort studies (n=486,264) and 20 case-control studies (n at least 69,858).

Three of the 4 RCTs were rated as good quality, while all 5 cohort studies were rated good to fair. Of the case-control studies, five were rated as good quality, eleven as fair and four as poor.

One cohort study found that ibuprofen had no significant effects on mortality.

Three cohort and 4 case-control studies assessed the effect of non-ASA NSAIDs on colorectal cancer incidence. The pooled RRs suggested statistically significant reductions in colorectal cancer incidence: the RRs were 0.61 (95% CI: 0.48, 0.77) and 0.70 (95% CI: 0.63, 0.78), respectively.

Three RCTs in high-risk patients found that COX-2 inhibitors significantly reduced the incidence of all adenomas and advanced adenomas: the pooled RRs were 0.72 (95% CI: 0.68, 0.77) and 0.56 (95% CI: 0.42, 0.75), respectively. A reduction was also suggested by a cohort study and 4 case-control studies evaluating non-ASA NSAID use: the RRs were 0.64 (95% CI: 0.48, 0.85) and 0.54 (95% CI: 0.4, 0.74), respectively.

Cost information
The authors stated that 3 cost-effectiveness analyses on COX-2 inhibitors were identified. One simplified cost-benefit analysis stated that, assuming that COX-2 inhibitors reduce colorectal cancer incidence by 50%, significantly more cardiovascular events would occur than colorectal cancer cases prevented.

Authors' conclusions
NSAIDs reduce the incidence of colorectal cancer and colorectal adenomas, as do COX-2 inhibitors which also reduce the incidence of colorectal adenomas. However, the associated cardiovascular and gastrointestinal harms (as assessed in a review of reviews) outweigh any benefits in average-risk individuals.
CRD commentary
This review addressed a clear question with defined inclusion criteria for the participants, interventions, outcomes and study designs. In restricting the search to English language articles, it is possible that some language bias might have been introduced. Furthermore, it is possible that some unpublished studies were missed. Multiple reviewers were involved in screening, data extraction and validity assessment, which minimises the risk of reviewer bias or error. The validity of the included studies was appropriately assessed and discussed in the context of the results. A meta-analysis appears to have been conducted when appropriate, with studies categorised according to several factors. The conclusions regarding the effects of NSAIDs and COX-2 inhibitors appear appropriate, although the overall conclusions also considered evidence from a review of reviews, the reliability of which has not been assessed in this abstract.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice. Research: The authors stated that further research is required to ascertain if there is a reduction in colorectal cancer mortality with non-ASA NSAIDs and COX-2 inhibitors. In addition, the cost-effectiveness of any chemoprevention needs to be compared with other strategies, such as colorectal cancer screening alone.

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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.