The use of aspirin for primary prevention of colorectal cancer: a systematic review prepared for the U.S. Preventive Services Task Force


CRD summary
This review concluded that aspirin reduces the incidence of colonic adenoma and colorectal cancer (CRC), particularly if used in high doses for more than 10 years. The conclusions were primarily based on lower evidence level studies: randomised controlled trials failed to support the findings regarding CRC incidence and mortality, or for adenoma in average-risk populations.

Authors' objectives
To evaluate the benefits and harms of aspirin chemoprevention. Harm was assessed in a review of systematic reviews and was not extracted for this abstract.

Searching
MEDLINE (to December 2006), PREMEDLINE (to April 2005), PubMed (Cancer subset), EMBASE (to week 14, 2005), the Cochrane CENTRAL Register and the Cochrane Library (Issue 4, 2004) were searched from inception. The PubMed Cancer subset was searched for non-MEDLINE material.

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

Specific interventions included in the review
Studies of aspirin were eligible for inclusion. The participants used 81 to 325 mg or more aspirin per day, where reported, and the duration of regular use observed in the studies ranged from 1 to 21 years. Aspirin exposure was assessed by means of a questionnaire or interview, or was one of the interventions given in the randomised controlled trials (RCTs).

Participants included in the review
Studies with participants at average risk for colorectal cancer (CRC) (no risk factors other than age) were eligible for inclusion; participants with a personal or family history of colorectal adenoma, or a family history of sporadic CRC, were also eligible. Participants with familial adenomatous polyposis or hereditary nonpolyposis colon cancer syndrome (Lynch I or II) were excluded, as were secondary prevention studies of patients with a history of CRC. The participants in the included studies belonged to various populations (e.g. patients with histologically confirmed adenoma, patients with positive results on faecal occult blood tests, health care professionals) or stemmed from a general practice database.

Outcomes assessed in the review
Studies addressing the incidence of colorectal adenoma or CRC and reductions in CRC mortality or overall mortality were eligible for inclusion.

How were decisions on the relevance of primary studies made?
Two reviewers independently screened the search results, and any conflicts were resolved by consensus.

Assessment of study quality
Predefined published criteria from the U.S. Preventive Services Task Force were used to assess the quality of the included studies. The studies were classified as good, fair or poor quality; studies rated as good met all criteria, whilst
those rated as fair met at least 80% of criteria and had no fatal flaw. It is possible (i.e. as part of the data extraction) that one reviewer assessed the validity and one reviewer checked the assessment.

**Data extraction**

One reviewer extracted the data and another one checked them. Data to determine the relative risk (RR) (odds ratios for case-control studies) and 95% confidence interval (CI) were either extracted or derived from the data presented. The standard error was computed from the CI.

**Methods of synthesis**

*How were the studies combined?*

Pooled RRs and their 95% CIs were calculated using a random-effects model; odds ratios were treated as RRs as the event rates were low. Pooling was only undertaken if clinically and statistically appropriate.

*How were differences between studies investigated?*

The studies were grouped by disorder, study design, study sample and medication exposure. Subgroup analyses investigated dose effect, duration of exposure and secondary outcomes. Statistical heterogeneity was assessed using the I-squared statistic; studies were combined when I-squared was 50% or less.

**Results of the review**

Twenty-seven studies (n=2,515,822) were included in the review. Of these, four were RCTs (n=63,340).

Most observational studies were graded as fair quality. One of the RCTs was rated as fair quality and the other three as good quality.

Incidence of colorectal adenomas (3 RCTs, 4 cohort studies, 7 case-control studies).

One RCT in average-risk men found no effect of aspirin on colorectal adenomas. Two RCTs in patients with a history of colorectal adenomas found that aspirin at dosages of 81 to 325 mg/day for one year reduced adenoma: the pooled RR was 0.82 (95% CI: 0.7, 0.95). Two good-quality cohort studies in average-risk Americans showed a pooled RR of 0.72 (95% CI: 0.61, 0.85) with doses of at least six 325-mg tablets per week. Two small cohort studies assessed the effects of aspirin on iodoamino in patients with a history of adenoma; both reported a statistically significant beneficial effect. Five mainly fair-quality case-control studies in average-risk populations showed a pooled RR of 0.87 (95% CI: 0.77, 0.98). Two case-control studies in high-risk populations found no beneficial effects of aspirin.

CRC incidence (2 RCTs, 7 cohort studies, 7 case-control studies).

Two RCTs found no significant effect of aspirin use on CRC incidence. One poor-quality cohort study was excluded from the meta-analysis because of incomplete data presentation; the 6 remaining cohort studies found that regular (at least 2 to 3 times weekly for more than 1 year) use of aspirin was associated with a 22% RR reduction in CRC incidence (RR 0.78, 95% CI: 0.63, 0.97). The case-control studies reported trends or statistically significant improvements in the aspirin group, but were too heterogeneous to allow pooling.

CRC mortality.

A large good-quality RCT conducted among women aged over 45 found no benefit of 100-mg aspirin every second day on CRC mortality compared with placebo; this study included 10 years’ follow-up. A large, fair-quality cohort study found that regular use of aspirin for longer than 15 years was associated with a reduction in CRC mortality in both men and women; shorter durations of exposure also showed a protective effect in men.

**Authors’ conclusions**

Aspirin reduces the incidence of colonic adenoma and CRC, particularly if used in high doses for more than 10 years.
CRD commentary
This review stated a clear question and well-defined inclusion criteria. The search was comprehensive and aimed to avoid language and publication bias. The study details were presented in detail; more information is available in the full report (see Other Publications of Related Interest). Study quality was assessed and taken into account when presenting the results, and the analyses were clear. The reviewers undertook measures to avoid errors and bias throughout the review process. The conclusions were primarily based on the lower evidence level studies: few RCTs found statistically significant effects of aspirin on CRC.

Implications of the review for practice and research
Practice: The authors stated that aspirin chemoprevention must be weighed against the relatively large costs associated with its adverse effects, as well as the relative inefficacy of aspirin compared with colonoscopy screening in average-risk populations and in the context of regular endoscopic screening for CRC.

Research: The authors stated that more research to clarify the optimal dose, starting age, and duration of aspirin use is required. Furthermore, the effect on CRC incidence and mortality, as well as the cost-effectiveness of chemoprevention compared with and in combination with a screening strategy, should be assessed.

Funding
Centers for Disease Control and Prevention, for the Agency for Healthcare Research and Quality and the U.S. Preventive Services Task Force.

Bibliographic details

PubMedID
17339622

Original Paper URL
http://www.annals.org/cgi/content/full/146/5/365

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adenoma /prevention & control; Adult; Anti-Inflammatory Agents, Non-Steroidal /adverse effects /therapeutic use; Aspirin /adverse effects /therapeutic use; Cardiovascular Diseases /chemically induced; Colonic Polyps /prevention & control; Colorectal Neoplasms /epidemiology /mortality /prevention & control; Female; Gastrointestinal Diseases /chemically induced; Humans; Incidence; Male; Primary Prevention; United States /epidemiology

AccessionNumber
12007008089

Date bibliographic record published
30/09/2007
Date abstract record published
30/09/2007

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.