Meta-analysis: folic acid in the chemoprevention of colorectal adenomas and colorectal cancer

Carroll C, Cooper K, Papaioannou D, Hind D, Tappenden P, Pilgrim H, Booth A

CRD summary
This well-conducted review concluded that there was no evidence that folic acid was effective in the chemoprevention of colorectal adenomas or colorectal cancer for any population. The authors’ conclusions reflected the results and are likely to be reliable, but the authors also noted that there were concerns with the small number of trials and the short duration of follow-up.

Authors’ objectives
To assess the effectiveness of folic acid in reducing the recurrence of colorectal adenomas in increased-risk populations and reducing the occurrence of colorectal cancer in the average-risk (general) population.

Searching
The Cochrane Library, MEDLINE, CINAHL, EMBASE, Web of Science, Biological Abstracts and Research Registers were searched without language restrictions to June 2008. Search strategies were not reported, but were available from the authors. Reference lists of relevant studies were searched for additional papers.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) that compared folic acid or folate (with or without other agents) with placebo (or agents other than folic acid) in adults with familial adenomatous polyposis, hereditary non-polyposis colorectal cancer, a history of colorectal adenomas, or with no increased baseline risk of colorectal cancer. Outcomes had to include the recurrence of adenomas or advanced adenomas or the occurrence of colorectal cancer.

For populations with a history of adenomas, included trials compared: folic acid (0.5mg/day) with aspirin (300mg/day); folic acid (1mg/day) with aspirin (81mg/day or 325mg/day); and folic acid (5mg/day) with placebo. The mean age of participants ranged from 57 to 62 years. The duration of treatment in all trials was three years. Trials were conducted in the UK and USA.

For average-risk or general population studies (at no increased risk of colorectal cancer), the included populations had various conditions, including cardiovascular disease, diabetes and atrophic gastritis; no patients had a history of colorectal cancer nor were they at any greater risk of colorectal cancer than the general population. All trials compared folic acid with placebo: folic acid (2.5mg/day) plus vitamin B6 (50mg/day) plus vitamin B12 (1mg/day) against placebo; folic acid (20mg/day for one year, then 20mg twice weekly for one year) plus vitamin B12 against placebo. The mean age of participants ranged from 55 to 69 years. The duration of treatment ranged from two to seven years. Trials were conducted in China and the USA.

Three reviewers selected studies for inclusion in the review; a fourth reviewer double checked a random subsample of studies. Disagreements were resolved by discussion and consensus.

Assessment of study quality
The quality of the trials was assessed against the following criteria: processes of allocation; randomisation and blinding; comparability of the treatment and control groups; and the appropriateness and quality of the analysis performed.

One reviewer assessed trial quality, which was checked by a second reviewer.

Data extraction
For discrete and numerical outcomes, relative risks (RR) and risk differences (RD) were extracted with 95% confidence intervals (CI). Authors were contacted for additional data where necessary.
One reviewer performed the data extraction which was checked by a second reviewer.

**Methods of synthesis**
Relative risks and risk difference, with 95% confidence intervals, were pooled using random-effects models. Statistical heterogeneity was assessed using the $I^2$ statistic. Sensitivity analysis was undertaken based on trial quality.

**Results of the review**
Six RCTs met the inclusion criteria. Duration of follow-up for all trials ranged from three to seven years.

**Patients with a history of adenomas** (three RCTs; n=1,970 participants): Two trials were considered to be of good quality and one of lower quality. There was no statistically significant effect of folic acid alone versus placebo on either the relative or absolute risk of adenoma, advanced adenoma recurrence, or colorectal cancer. A sensitivity analysis of the two higher quality trials yielded a non statistically significant, but increased, risk of adenoma recurrence in the folic acid group.

**Average-risk or general population** (three RCTs; n=11,180 participants): One trial was considered to be of good quality, but in the other two studies allocation concealment, generation of the randomisation sequence and methods of blinding were unclear. Folic acid plus B vitamins compared with placebo demonstrated no statistically significant effect on the relative risk of colorectal cancer.

**Authors’ conclusions**
There was no evidence that folic acid was effective in the chemo-prevention of colorectal adenomas or colorectal cancer for any population.

**CRD commentary**
Review objectives and inclusion criteria were clear. Relevant sources were searched for published and unpublished studies without language restrictions, minimising the risk of language and publication bias. It appeared that steps were taken to minimise risks of reviewer bias and error by having more than one reviewer involved in the process of selecting studies, assessing validity and extracting data.

Appropriate methods were used to assess trial quality. The chosen method of synthesis appeared to be appropriate and suitable methods were used to assess heterogeneity.

The authors’ conclusions reflected the results of this well-conducted review, and are likely to be reliable, but the authors also noted that there were concerns with the small number of trials and the short duration of follow-up.

**Implications of the review for practice and research**
**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that future trials should address the ethical issues raised by the potential for adverse effects suggested by the evidence, and whether specific groups may benefit from any potential chemo-preventive properties of folic acid.. They also recommended a greater understanding of the chemo-preventive and cancer promotion risk-benefit relationship of folate and folic acid and its dose.

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**Bibliographic details**
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.