Cancer risk with folic acid supplements: a systematic review and meta-analysis

Wien TN, Pike E, Wisloff T, Staff A, Smeland S, Klemp M

CRD summary
The authors concluded that there was a borderline significantly increased risk of cancer, and a moderately significantly increased risk of prostate cancer, with folic acid supplementation, compared with control groups. The limitations of the data mean that the applicability of the results is uncertain, but this was a well-conducted review and the authors’ conclusions appear to be reliable.

Authors’ objectives
To investigate whether there was an increased risk of cancer for people taking oral folic acid supplements.

Searching
The Cochrane Library, MEDLINE, EMBASE, DARE, NHS EED, HTA database, and eight other databases were searched, without language restrictions, to January 2011. Search terms were reported in an online supplement. The reference lists of review articles were handsearched, and clinical trial registries were searched to February 2011, to locate further studies.

Study selection
Eligible studies were systematic reviews, randomised controlled trials (RCTs), or controlled observational studies (case-control or cohort). Studies had to assess cancer incidence, mortality or both, in any population taking folic acid supplements orally, in daily doses of 0.4mg or more, for any indication. Supplements could be taken with or without other B vitamins, and compared with any control treatment or placebo. Studies of high doses of folic acid for cancer treatment were excluded.

Most of the included studies were conducted in the USA; others were carried out in the UK, Denmark, Canada, Norway, China, or Europe. The mean participant age ranged from 26 to 69 years; the percentage of female participants ranged from two to 100; and the percentage of smokers ranged from seven to 46, where reported. The participants had chronic renal disease, cardiovascular disease, pregnancy, atrophic gastritis, ulcerative colitis, or various cancers. Daily doses of folic acid ranged from 0.4mg to 40mg. Control groups received aspirin, placebo, or no folic acid supplement.

Two reviewers independently screened the studies for inclusion; discrepancies were resolved by discussion or by another reviewer.

Assessment of study quality
The Cochrane Risk of Bias tool was used to assess sequence generation, allocation concealment, blinding, and follow-up reported, for the RCTs. The quality of observational studies was assessed using checklists, the details of which were not reported. The quality of the evidence for each outcome was assessed using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system.

Two reviewers independently assessed study quality; discrepancies were resolved by discussion or by another reviewer.

Data extraction
Intention-to-treat data were extracted from the intervention and control groups, by three independent reviewers, to calculate the risk ratios and 95% confidence intervals. Any discrepancies were resolved by discussion or by another reviewer.

Methods of synthesis
Risk ratios and 95% confidence intervals were pooled, using the random-effects Mantel-Haenszel method. Statistical heterogeneity was assessed using I². Pre-specified sensitivity analyses were performed at the trial level, according to population characteristics (gender, age, body mass index, comorbidity, smoking habits, etc.) or intervention characteristics (dose and time of exposure, timing of follow-up, etc.).
Results of the review

Nineteen studies were included in the review, with 414,194 participants. Twelve were RCTs (40,793 participants), six were cohort studies (372,896 participants), and one was a case-control study (505 participants). Follow-up ranged from less than 12 months to 36 years. Ten RCTs had a low risk of bias; the quality of evidence from RCTs was generally high for cancer incidence, and ranged from very low to moderate for cancer mortality. The quality of evidence from the observational studies ranged from low to very low.

Cancer incidence: A borderline significant increase in the risk of cancer was observed with folic acid supplementation versus placebo or control (RR 1.07, 95% CI 1.00 to 1.14; Ι²=0; 10 RCTs). Similar results were found in the sensitivity analyses of RCTs for the following: Trials with more than 70% men; more than 30% smokers; doses of folic acid between 0.4mg and 1mg; follow-up of more than 60 months; and co-administration of aspirin with folic acid. No statistically significant differences, in the overall cancer incidence, were shown between folic acid and placebo or control groups, in the observational studies.

A weak, but significantly increased risk of prostate cancer was shown with folic acid supplementation, compared with placebo or control (RR 1.24, 95% CI 1.03 to 1.49; Ι²=17%; six RCTs). A similar result was found when an outlier trial was excluded (five RCTs).

Cancer mortality: No statistically significant difference in the risk of death from cancer was observed between folic acid and placebo or control groups (six RCTs). The sensitivity analysis of trials with more than 30% smokers demonstrated a significantly increased risk of death from cancer with folic acid supplementation, compared with placebo or control treatment (RR 1.38, 95% CI 1.10 to 1.72; three RCTs).

All other pooled results for both outcomes were not statistically significant, or the analyses could not be performed. No evidence of publication bias was found.

Authors' conclusions

Ten trials demonstrated a borderline significant increase in the overall cancer incidence, in patients taking folic acid, compared with controls, with a moderate, significant increase in prostate cancer incidence found in six trials.

CRD commentary

The review question was clear and was supported by replicable inclusion criteria. Relevant databases were searched, with no language restrictions, reducing the risk of language bias. Efforts were made to minimise reviewer error and bias throughout the review process. Suitable quality assessment criteria were used for the RCTs and most of them were of high quality. The quality assessment criteria and results were unclear for observational studies. The GRADE quality of evidence for all outcomes was variable for RCTs and low or very low for observational studies.

The study details were presented, revealing clinical heterogeneity between them. The methods of synthesis seem to have been appropriate, except that the data from two RCTs in the pooled analyses came from the same population. The inclusion of non-independent samples can increase the apparent effect size. Where reported, statistical heterogeneity was low and no evidence of publication bias was found. The authors stated that their estimated long-term risk of cancer might be conservative, given the short follow-up in most of the RCTs. They also stated that some of the trial subgroups might have had increased risks of cancer, and these results might not be applicable to the general population.

The limitations of the data mean that the applicability of the results is uncertain, but this was a well-conducted review and the authors' conclusions appear to be reliable.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that RCTs were needed with long follow-up periods to confirm the borderline significant increase in overall cancer incidence with folic acid supplementation. Prospective studies of cancer development were needed in populations where food was fortified with folic acid to confirm whether fortification moderately increased prostate cancer risk.

Funding
Supported by the Norwegian Knowledge Centre for the Health Services.

**Bibliographic details**

**PubMedID**
22240654

**DOI**
10.1136/bmjopen-2011-000653

**Original Paper URL**
http://bmjopen.bmj.com/content/2/1/e000653.abstract

**Additional Data URL**
http://bmjopen.bmj.com/content/2/1/e000653/suppl/DC1

**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Dietary Supplements; Folic Acid; Humans; Neoplasms

**AccessionNumber**
12012015016

**Date bibliographic record published**
26/04/2012

**Date abstract record published**
04/01/2013

**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.