kunnskapssenteret
Nasjonalt kunnskapssenter for helsetjenesten

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

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Abstract

Folic acid is a synthetic form of the B vitamine folate, and is widely used for prophylaxis and treatment of various conditions, such as:

1) Prophylaxis of neural tube defects
2) Treatment of folate deficiency and prophylaxis of folate deficiency in groups at risk
3) Prophylaxis of adverse events associated with antifolates

Folic acid supplementation has been considered safe. A combined analysis from 2009 (1) of two Norwegian randomized controlled clinical trials (2,3) with extended follow-up, however, demonstrated an increased incidence of cancer among patients taking folic acid for homocystein reduction in secondary prevention of cardiovascular events.

The purpose of the present project is to conduct a systematic review to explore if there excist an increased cancer risk with respect to folic acid supplementation.

Background

Folic acid is a synthetic form of the B vitamin folate, which is an essential vitamin, i.e. the vitamin has to be obtained from a dietary source. Folic acid and folate are in the human body converted to the active form tetrahydrofolate, which, among other things, is an important coenzyme for DNA synthesis. Folate deficiency may lead to disturbances in growth and development such as neural tube defects in developing embryos and megaloblastic anaemia.

Folate occurs naturally in deep green vegetables and whole-grain products. In Norway folic acid supplements are administered in various forms, such as tablets or mixtures, as pure folic acid supplements or in combination with other vitamins. In addition several other countries, including US, add folic acid as fortification to flour and grain products. The rationale behind folic acid fortification is prevention of neural tube defects in developing embryos (4).

In Norway folic acid is used by several different groups. Folic acid has the approved indications for established folate deficiency caused by malnutrition or in conditions where there are increased need as for example before and during pregnancy, decreased utilization or increased

metabolism of folate, and as prevention of folate deficiency for the same conditions (www.noma.no). An important cause of folate deficiency is malabsorption, as with celiac disease. Another group exposed to folate deficiency is premature/dysmature infants, which are routinely given folic acid supplements for their first year of living. The largest group that use folic acid supplements is probably fertile women. A Norwegian guideline (5) has since 1998 recommended folic acid supplement of 0.4 mg per day to women from the last month before planned pregnancy and during the first trimester in order to prevent neural tube defects. Higher doses (4 mg daily) is recommended to women with increased risk to give birth to children with of neural tube defects. In addition, folic acid supplements in a dose of 1 mg is used to reduce antifolate-adverse events as nausea in patients treated with methotrexate. Methotrexate is used in low dose for inflamatory diseases such as rheumatoid arthritis (6) and in higher doses for several types of cancer.

Folic acid supplementation has been considered safe, and folic acid has even been suggested as chemoprophylaxis against cancer based upon data from epidemiological studies that showed a negative correlation between folate intake and the occurrence of colon cancer (7). Other studies have, however, shown that folic acid supplementation may promote the progression on precancerous colorectal lesions (8,9).
A study from Ebbing et al. from 2009 (1) which is a follow-up study and a combined analysis of the data on individual level from two earlier randomized, controlled clinical trials (NORVIT (2) and WENBIT (3)), has shown increased incidence of cancer among patients taking folic acid supplements. Folic acid supplements was given in order to reduce homocysteine as secondary prevention of cardiovascular events. In the analysis (1) the aim was to evaluate the effect of treatment with B-vitamins for the outcomes cancer and death (total death). The analysis showed that the groups receiving folic acid and vitamin B12 had no lower incidence of cardiovascular events, but however increased cancer incidence compared to the groups not receiving folic acid/B12 (HR 1.21; 95% CI 1.03-1.41). A total of 6837 patients were included in the analysis. The increased cancer incidence was not statistically significant in each of the primary studies.

Methods

We plan to perform a a systematic review of randomized controlled trials and controlled observational studies of folic acid supplementation.

Aim: To examine whether folic acid supplements are associated with increased risk of cancer. The outcomes are cancer incidence and cancer mortality.

Inclusion/exclusion criteria

	Inclusion criteria	*Exclusion criteria*
Population	All that receive folic acid supplements	
Intervention	Folic acid supplements ≥0. 4 mg/day (tablet or mixture), possible in combination with other B- vitamins	Folic acid given as a part of a high-dose cytostatic regimen (to protect against advere events) Folic acid supplements in the form of diet fortificated with folic acid (for example flour)
Control	All other comparisons	
Outcome	Cancer incidence, Cancer mortality	
Study design	In order of priority: Systematic Reviews (SR's) of high quality, Randomized Controlled Trials (RCT's), Controlled observational studies (case-control and cohort studies)	
Language	Scandinavian, english and german. Other language if a relevant english abstract is present	

Literature search

The search strategy will be based upon the described inclusion/exclusion criteria.
Actual databases to search in will be Embase, Ovid Medline, Cohrane Library, Centre for Reviews and Dissemination, INAHTA, Clinical Evidence, ISI Web of Knowledge, NHS Evidence, AHRQ, SBU, Dacehta og Finohta.

Selection of literature

Two persons will independently review the results from the search. The first selection is based on titles and abstracts to determine if they meet the eligibility criteria. The second selection is based upon full text of the articles. If disagreements between the independent reviewers a third person will be consulted.

Data extraction and data handling

Data will be extracted from the articles in accordance with our predefined outcomes. This will be done by one person, and controlled by another.
For the types of cancer where increased cancer incidence is suspected we will do meta-analyses including all studies (ie studies with increased, reduced or no differences from the control group). If possible sensitivity analyses will be done with respect to demographic factors as sex, age, cancer status (persons assumed not to have cancer er precancers, patients with documented cancer or precancer), other co-morbidity, other risk factors for cancer as smoking, alcohol and characteristics of intervention such as dose and time of exposure.

Quality assessment

The selected full text articles will be assessed for quality of two independent persons. The systematic reviews will be assessed using Check list for systematic reviews, the controlled studies will be assessed using the tool for Risk of Bias (10). In cases of doubt or disagreement a third person will be consulted.

We will use Grading of Recommendations Assessment, Development and Evaluation" (GRADE) to evaluate the overall quality for the specific outcome data (11). This tool evaluate the level of confidence we have to the results.

Publication

This systematic review is planned to be published in a recognized international research journal by the end of 2011.

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