

# Folate for therapy

## Serena Parker

Consultant rheumatologist  
Hobart

## Patrick Hanrahan

Consultant rheumatologist  
South Perth

## Claire Barrett

Consultant rheumatologist  
Redcliffe  
Queensland

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## SUMMARY

Folate is a B vitamin which is needed for DNA synthesis, replication and repair. It is found in leafy green vegetables.

Folic acid supplementation in pregnancy reduces the risks of neural tube defects. In the general population, supplements have no clear benefit in reducing the risk of cardiovascular disease or dementia.

There is conflicting evidence about cancer prevention. Some studies suggest folic acid supplements increase the risk of malignancy.

Routine folic acid supplementation in patients receiving low-dose methotrexate for rheumatic diseases reduces the risk of some adverse effects.

## Introduction

Folate is vitamin B<sub>9</sub>. It was named after the Latin word folium (leaf) and it was first isolated from spinach in 1941. Folate-rich foods include green leafy vegetables (broccoli, spinach, salad greens), chickpeas, nuts, orange juice and some fruits. Many foods are fortified with folic acid including some breakfast cereals, bread and products containing wheat flour.

The active form of folate is tetrahydrofolate. This has a role in the synthesis, replication and repair of DNA. A deficiency of folate can lead to megaloblastic anaemia.

## Supplements

Synthetic folate used as a supplement differs from the main naturally occurring folate. In its oxidised state folic acid has a significantly higher bioavailability. A dose of more than 200 microgram saturates normal intestinal absorptive mechanisms. Raised total folate and unmetabolised folate in the serum may interfere with the regulatory functions of natural folates by competing for binding with enzymes, carrier proteins and binding proteins.<sup>1</sup>

Taking supplements around the time of conception reduces the risks of neural tube defects. As the neural tube is closed by embryonic day 26, folic acid supplementation needs to begin one month before conception and be maintained for at least three months after. The Australian Government recommendation is that all pregnant women

take a folic acid supplement of at least 400 microgram/day and aim for a dietary intake of 600 microgram. Australian wheat flour is fortified to 120 microgram/100 g of bread (about three slices).<sup>2</sup> Supplementation has also been purported to prevent some types of cancer, cardiovascular disease and dementia. More recently there has been concern that folic acid supplements may increase the risk of some cancers.

## Cardiovascular disease

In 1969 a connection between homocysteine and cardiovascular disease was proposed. Patients with homocystinuria, an inherited enzyme deficiency, leading to elevated plasma concentrations of homocysteine, were noted to develop severe cardiovascular disease in their early twenties. It was speculated that high homocysteine concentrations could contribute to atherosclerosis.

Homocysteine elevation also occurs in people with diets deficient in folate, vitamin B<sub>6</sub> or B<sub>12</sub>. Regardless of the cause, supplementation with folate, vitamin B<sub>6</sub> or B<sub>12</sub> can lower plasma homocysteine. In patients with homocystinuria, lowering homocysteine reduced the risk of cardiovascular events.<sup>3</sup>

Folic acid supplementation reduces homocysteine concentrations typically by 25% in those with hyperhomocysteinaemia. Maximum responses are seen with 800 microgram/day over six weeks. Higher doses do not result in further significant lowering.<sup>4</sup>

Randomised controlled trials in people without homocystinuria are inconclusive regarding the benefit of folic acid supplementation. There was no significant evidence of change in the risk of cardiovascular events, stroke or all-cause mortality in those with a history of cardiovascular disease.<sup>3</sup> Lowering homocysteine does not confer a secondary prevention benefit, but some studies show a primary prevention benefit for stroke.<sup>5</sup> The benefit of folic acid supplementation in cardiovascular disease in patients with rheumatoid arthritis is unknown.<sup>6</sup>

## Dementia

The effect of folic acid supplements on cognitive impairment is uncertain. Higher concentrations of homocysteine have been associated with worse function across a number of cognitive domains<sup>7</sup> and a study of 818 patients aged 50 to 70 years with hyperhomocysteinaemia found improvement in cognitive tests in those taking supplements.<sup>8</sup> However,

the role of folic acid in lowering homocysteine for the primary prevention of dementia is not established.

A study in the USA after the introduction of fortification found an association between increased cognitive decline and increased folic acid intakes (greater than 400 microgram/day).<sup>9</sup> In a Cochrane review of eight trials there was no evidence that folic acid improved the cognitive function of unselected elderly people with or without dementia.<sup>10</sup>

## Cancer

Although folic acid supplementation had been considered safe, there has been increasing concern that it may raise the risk of cancer. In Norway, where food is not fortified with folic acid, two randomised controlled trials found an increased incidence of cancer among patients taking supplements for secondary prevention of cardiovascular events. The Norwegian Vitamin Trial (NORVIT) and Western Norway B Vitamin Intervention Trial (WENBIT) included 6837 Norwegians taking supplementary folic acid 800 microgram/day, vitamin B<sub>12</sub> and vitamin B<sub>6</sub> in various combinations. In those taking folic acid for a median of 39 months, with a further 38 months of post-trial follow-up, there was an increase in cancer incidence (hazard ratio 1.2) and mortality (hazard ratio 1.38). The predominant cancer was lung cancer.<sup>11</sup>

Other observational studies have shown source-specific effects, with dietary folate being protective while folic acid supplements were harmful or without effect in relation to cancer risk.<sup>12</sup> A Swedish study found the risk of pancreatic cancer was reduced by diets rich in folate, but not by supplements.<sup>13</sup>

The dose and timing of folic acid supplementation relative to the development of premalignant lesions may be important, but the mechanism by which supplementation may promote cancer development is unknown.<sup>14</sup> After a review of the risk, the UK Scientific Advisory Committee on Nutrition considered that, despite uncertainties, the mandatory fortification of flour was supported, with controls to limit excessive folic acid intake.<sup>15</sup>

There is no evidence that folic acid supplementation reduces the risk of colorectal, breast or prostate cancer. Some reported studies suggest an increased risk of breast, prostate, colorectal and endometrial cancer with folic acid supplementation.

## Breast cancer

An observational study found that folic acid supplementation of at least 400 microgram/day led to a 20% increased risk of breast cancer.<sup>16</sup> However, the Women's Antioxidant and Folic Acid Cardiovascular study found no association with breast cancer.<sup>17</sup> Similarly, another study found no association

with breast cancer when folic acid supplementation was 200 microgram/day or less.<sup>18</sup>

## Colorectal cancer

A randomised controlled trial for the prevention of colorectal cancer in genetically predisposed patients found folic acid 1 mg/day for six years did not prevent recurrence of colorectal adenoma. However it reported a 67% increased risk of advanced lesions with malignant potential and a twofold increased risk of having three adenomas.<sup>19</sup>

An intake below 200 microgram daily is recommended in those with a history of colorectal adenomas and those more than 50 years old, due to the increased risk of developing colorectal cancer after this age.<sup>15</sup>

## Prostate cancer

There has been a meta-analysis of 10 randomised controlled trials of oral folic acid supplementation of at least 400 microgram/day. This showed a small but significant increase in prostate cancer compared with controls.<sup>12</sup>

## Methotrexate and folic acid

Methotrexate is a cornerstone of disease-modifying antirheumatic drug therapy for rheumatoid arthritis. It is an analogue of folic acid and thus classed as an antimetabolite. Methotrexate inhibits dihydrofolate reductase (which converts dihydrofolate to tetrahydrofolate), but the mechanism of action in rheumatoid arthritis is unclear.

On average, 30% of patients cease methotrexate within one year due to adverse effects and 60% experience mild adverse effects.<sup>20</sup> Gastrointestinal intolerance and transaminase elevation are the main reasons for dose reduction or cessation. The risk factors for methotrexate toxicity include alcohol use, obesity ( $\geq 8\%$  hepatotoxicity with body mass index 20–25;  $\geq 20\%$  hepatotoxicity with body mass index 30–35), older age and folate deficient status.

Concurrent folic acid supplementation reduces elevations of hepatic transaminases, gastrointestinal intolerance and stomatitis, and may increase the maximum tolerated dose of methotrexate.<sup>21</sup> Supplementation does not appear to have a protective effect on the development of cytopenia or liver disease, such as cirrhosis.

Folinic acid is a metabolically active reduced form of folate that bypasses dihydrofolate reductase.<sup>20</sup> It is a stronger methotrexate antagonist than folic acid, as folic acid must be enzymatically converted to a fully reduced form. However it seems to have no greater effect than folic acid in the prevention of methotrexate-related adverse effects. As folinic acid

may reduce the effectiveness of methotrexate and is more expensive, its routine use is not recommended.<sup>22</sup> It has an important role in the treatment of methotrexate overdose and acute bone marrow toxicity, due to its faster action and independence of dihydrofolate reductase.

Studies have shown no reduced efficacy of methotrexate with a folate:methotrexate dose ratio of 3:1, that is, the dose of folate can be at least three times that of methotrexate before there is any effect on efficacy. For a once-weekly dose of 15 mg methotrexate, up to 45 mg of folic acid could be prescribed concurrently if required. There is no difference in benefit between folic acid 1 mg/day or 5 mg/week during methotrexate therapy.<sup>23</sup>

Recommendations for the use of folic acid with methotrexate are varied. Patients with a normal mean corpuscular volume and no adverse effects from methotrexate may not require prophylactic folic acid.<sup>24</sup> If the red blood cell folate is low, 1 mg/day folic acid is recommended (except on the day of the methotrexate dose to avoid competing for absorption). When the red blood cell folate is persistently low the folic acid dose should be gradually escalated up to a maximum folate:methotrexate ratio of 3:1. The British Society for Rheumatology<sup>25</sup> recommends a single weekly dose of folic acid 5 mg the morning following the day of the methotrexate dose. A consensus statement from 751 rheumatologists from 17 countries in 2008 recommended at least 5 mg/week of folic acid during methotrexate therapy.<sup>22</sup>

It is unknown if patients with rheumatoid arthritis who take folic acid supplements have increased rates of cancer. Theoretically, they may incur a higher risk of cancer because of the doses of folic acid prescribed concurrently with methotrexate.

The role of folic acid supplementation when methotrexate is used in juvenile idiopathic arthritis and psoriatic arthritis is uncertain. Folic acid supplementation in patients with psoriasis possibly reduces the efficacy of methotrexate.<sup>26</sup>

## Conclusion

Supplementation with folic acid has a clear role to correct folate deficiency and in the prevention of neural tube defects. Prophylactic folic acid is recommended with low-dose methotrexate for rheumatic diseases, to reduce the risk of some adverse effects.

The routine use of more than 5 mg/week folic acid exceeds many formal recommendations. The harm versus benefit of higher doses is unclear. There is a limited benefit in vascular disease and a possible increase in malignancy. ◀

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### SELF-TEST QUESTIONS

*True or false?*

3. Folic acid supplements increase the efficacy of methotrexate.

4. To reduce fetal neural tube defects, folic acid supplements should be started before conception.

*Answers on page 67*

## REFERENCES

- Mullin GE. Folate: is too much of a good thing harmful? *Nutr Clin Pract* 2011;26:84-7.
- Food Standards Australia New Zealand. New territory for bread: mandatory fortification of bread with folic acid and iodine. [www.foodstandards.gov.au/\\_srcfiles/Mandatory%20Fortification%20Brochure%20for%20Health%20Professionals.pdf](http://www.foodstandards.gov.au/_srcfiles/Mandatory%20Fortification%20Brochure%20for%20Health%20Professionals.pdf) [cited 2013 Jan 14]
- Loscalzo J. Homocysteine trials – clear outcomes for complex reasons. *N Engl J Med* 2006;354:1629-32.
- Anderson CA, Jee SH, Charleston J, Narrett M, Appel LJ. Effects of folic acid supplementation on serum folate and plasma homocysteine concentrations in older adults: a dose-response trial. *Am J Epidemiol* 2010;172:932-41.
- Wang X, Qin X, Demirtas H, Li J, Mao G, Huo Y, et al. Efficacy of folic acid supplementation in stroke prevention: a meta-analysis. *Lancet* 2007;369:1876-82.
- Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325-31.
- Schafer JH, Glass TA, Bolla KI, Mintz M, Jedlicka AE, Schwartz BS. Homocysteine and cognitive function in a population-based study of older adults. *J Am Geriatr Soc* 2005;53:381-8.
- Durga J, van Boxtel MP, Schouten EG, Kok FJ, Jolles J, Katan MB, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. *Lancet* 2007;369:208-16.
- Morris MC, Evans DA, Bienias JL, Tangney CC, Hebert LE, Scherr PA, et al. Dietary folate and vitamin B12 intake and cognitive decline among community-dwelling older persons. *Arch Neurol* 2005;62:641-5.
- Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. *Cochrane Database Syst Rev* 2008;4:CD004514.
- Ebbing M, Bønaa KH, Nygård O, Arnesen E, Ueland PM, Nordrehaug JE, et al. Cancer incidence and mortality after treatment with folic acid and vitamin B12. *JAMA* 2009;302:2119-26.
- Wien TN, Pike E, Wisløff T, Staff A, Smeland S, Klemp M. Cancer risk with folic acid supplements: a systematic review and meta-analysis. *BMJ Open* 2012;2:e000653.
- Larsson SC, Håkansson N, Giovannucci E, Wolk A. Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men. *J Natl Cancer Inst* 2006;98:407-13.
- Lee JE, Willett WC, Fuchs CS, Smith-Warner SA, Wu K, Ma J, et al. Folate intake and risk of colorectal cancer and adenoma: modification by time. *Am J Clin Nutr* 2011;93:817-25.
- Scientific Advisory Committee on Nutrition. Folic acid and colorectal cancer risk: review of recommendation for mandatory folic acid fortification. London: Department of Health; 2009. [www.sacn.gov.uk/pdfs/summary\\_of\\_sacn\\_report\\_to\\_cmo\\_19\\_october\\_2009.pdf](http://www.sacn.gov.uk/pdfs/summary_of_sacn_report_to_cmo_19_october_2009.pdf) [cited 2013 Jan 14]
- Kim YI. Does a high folate intake increase the risk of breast cancer? *Nutr Rev* 2006;64:468-75.

17. Zhang SM, Cook NR, Albert CM, Gaziano JM, Buring JE, Manson JE. Effect of combined folic acid, vitamin B6, and vitamin B12 on cancer risk in women: a randomized trial. *JAMA* 2008;300:2012-21.
18. Larsson SC, Giovannucci E, Wolk A. Folate and risk of breast cancer: a meta-analysis. *J Natl Cancer Inst* 2007;99:64-76.
19. Cole BF, Baron JA, Sandler RS, Haile RW, Ahnen DJ, Bresalier RS, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. *JAMA* 2007;297:2351-9.
20. Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. *Rheumatology (Oxford)* 2004;43:267-71.
21. Hoekstra M, van Ede AE, Haagsma CJ, van de Laar MA, Huizinga TW, Kruijsen MW, et al. Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. *Ann Rheum Dis* 2003;62:423-6.
22. Visser K, Katchamart W, Loza E, Martinez-Lopez JA, Salliot C, Trudeau J, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E Initiative. *Ann Rheum Dis* 2009;68:1086-93.
23. Morgan SL, Baggott JE. Folate supplementation during methotrexate therapy for rheumatoid arthritis. *Clin Exp Rheumatol* 2010;28:S102-9.
24. Endresen GK, Husby G. Folate supplementation during methotrexate treatment of patients with rheumatoid arthritis. An update and proposals for guidelines. *Scand J Rheumatol* 2001;30:129-34.
25. Chakravarty K, McDonald H, Pullar T, Taggart A, Chalmers R, Oliver S, et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology (Oxford)* 2008;47:924-5.
26. Salim A, Tan E, Ilchyshyn A, Berth-Jones J. Folic acid supplementation during treatment of psoriasis with methotrexate: a randomized, double-blind, placebo-controlled trial. *Br J Dermatol* 2006;154:1169-74.

## Book review

### Bad Pharma: How drug companies mislead doctors and harm patients

Ben Goldacre

London: Fourth Estate; 2012.

364 pages

The stated aims of this openly polemic book are to explain how the relationship between the pharmaceutical industry and the field of medicine has distorted the practice of medicine.

The author strongly emphasises the important issue of missing data. He describes how negative clinical trial data, that are not published due to strong industry bias and some academic journal bias, distort the evidence regarding the benefits and adverse effects of drugs.

This book has chapters covering the flaws in the drug development process, in the design and reporting of drug trials, and in the ability of regulators to carry out their roles. There is also an extensive discussion of drug marketing practices. He goes on to describe the role prescribing doctors and key opinion leaders

play in the practice of medicine, which is now strongly influenced by pharmaceutical companies. The author, Dr Ben Goldacre, who has also published a book called *Bad Science*, has referenced his points well and illustrated them using examples.

The author accurately introduces this book as pop science. I found the writing style colloquial and repetitive. The examples and explanations are too simplistic for healthcare practitioners. This is a shame because the book provides important evidence of the ongoing problems in the relationship between medical practitioners, healthcare systems and the pharmaceutical industry, and offers concrete actions that could be taken. However, given the redundancy, digressions and patronising exposition, it is likely that this book will mainly be of interest to a motivated lay audience.

*Dr Ahmad is a member of the Editorial Executive Committee of Australian Prescriber.*

**Laura Ahmad**

Geriatrician

Royal North Shore Hospital  
Sydney

