

PART 3 Estimates of Risk

3. The evidence of an association between intake of folic acid with the development of cancer.	2
3.1 Comment on ‘Will mandatory folic acid fortification prevent or promote cancer? (Kim 2004).....	2
3.2 Review of the literature	2
Methods.....	2
<i>Table 1. Studies showing an association between circulating and dietary folate and an increased risk of cancer</i>	<i>3</i>
Colorectal cancer in men and women (Brink et al. 2005).....	3
Prostate cancer (Hultdin et al. 2005).....	4
Breast cancer and women (Charles et al. 2004).....	4
References	4

Authors:

Dr Elizabeth Milne, Telethon Institute for Child Health Research
 (Telephone: 9489 7756, email: lizm@ichr.uwa.edu.au)

Helen Bailey, Telethon Institute for Child Health Research
 (Telephone: 9489 7798 email: helenb@ichr.uwa.edu.au)

3. The evidence of an association between intake of folic acid and the development of some cancers.

3.1 Comment on 'Will mandatory folic acid fortification prevent or promote cancer? (Kim 2004)

1. We reviewed the article 'Will mandatory folic acid fortification prevent or promote cancer?' (Kim 2004). The author's main argument is that the likely beneficial effect of folate fortification on the prevention of neural tube defects needs to be balanced against possible harmful effects, particularly in relation to tumour initiation or promotion.
2. Kim acknowledges that most of the published epidemiological studies provide evidence of a protective effect (or non-significant null effect) of folate on the risk of colorectal cancer (CRC). However, he cites studies in rodents with genetically engineered CRC, in which supplementation with exceptionally high levels of folate promotes rather than suppresses carcinogenesis. Evidence from a number of other animal studies is presented, suggesting "folate possesses dual modulation effects on carcinogenesis depending on the timing and dose of folate intervention" (p1125). The main concern arising from such studies is that "folate supplementation may increase cancer risk and accelerate tumour progression if too much is given or if it is provided after neoplastic foci are established in the target organ" (p1125). The author acknowledges that caution must be used when extrapolating these results to humans. Nonetheless, the author expresses concern in relation to the high prevalence of colorectal adenomas in older human populations, and the potential increased incidence of CRC if folate accelerated the growth of these potentially precursor lesions. As yet, however, there is little evidence from studies in humans of an adverse effect of folate on the incidence of cancers (see three studies discussed in Section 3.2). The only human evidence presented in the Kim paper for a promotive effect of folate on carcinogenesis is a paper published in 1949 (Farber 1949) which reports an "acceleration phenomenon" in 11 children with acute leukaemia treated with pteroyltriglutamic acid (chemically related to folic acid).
3. Another issue raised in the Kim paper is the theoretical epigenetic effect of folate fortification in the methylation of normally unmethylated promotor CpG islands of tumour suppressor genes or mismatch repair genes, causing them to be inactivated and thus potentially promoting the development of cancer. No supporting clinical evidence is provided.
4. An analogy is also drawn to the trials of beta-carotene supplementation which found an increased risk of lung cancer, despite previous epidemiological evidence of a protective association between foods containing beta-carotene and lung cancer (BCCPSG. 1994; Omenn *et al.* 1996).
5. Overall, the author identifies the need for long-term follow-up studies in countries where mandatory fortification has been introduced. To date, insufficient time has elapsed in US and Canada to monitor the incidence of most cancers since fortification, except those occurring in infancy. As noted in the Kim article, French *et al* report that the introduction of folic acid fortification in Ontario, Canada was associated with a significant reduction in the incidence of neuroblastoma, but no change in the incidence of infant acute lymphoblastic leukaemia (French *et al.* 2003). Our literature search did not identify any other reports of disease incidence in relation to the introduction of folate fortification.

3.2 Review of the literature

Methods

6. As contracted, we identified three published human studies of the association between intake of folic acid with the development of cancer. These were identified by searching PubMed using the following MeSH terms: folic acid, folate, neoplasm. Studies were limited to those conducted on

humans and published in English from 2003 onwards. A summary of these studies is shown in Table 1.

Table 1. Studies showing an association between circulating and dietary folate and an increased risk of cancer

Study (Reference)	Study population	Age range (yrs)	Mean follow-up (yrs)	No of cases	Adjusted relative risk (95% CI)	Trends	Adjusted for
(Brink <i>et al.</i> 2005)	The Netherlands Cohort study 62,573 women 58,279 men	55-69	7.3	Rectal cancer Total n=160 51 women 99 men	Women: 1.85 (1.13-3.02) per increment of 100µg/day increase of dietary folate intake (varies slightly by K-ras mutation status of the tumor.) Men 0.58 (0.36-0.93) per increment of 100µg/day increase of dietary folate intake	NS	Age, BMI, alcohol, smoking, fresh meat, energy intake, family history of CRC, vitamin C, iron, dietary fibre.
(Hultdin <i>et al.</i> 2005)	Northern Sweden Health and Disease cohort NCC Men	40-60	Up to 15 years	Prostate cancer 254 cases 514 controls	Odds Ratio 1.3 (0.74-2.24) for highest quartile of serum folate vs lowest quartile of serum folate	p = 0.17	Smoking, BMI
(Charles <i>et al.</i> 2004) (Charles <i>et al.</i> 2005)	2928 women Randomised trial of folate supplementation in pregnancy Placebo (1977) Folic acid 0.2mg/day (466) Folic Acid 5mg/day (485)	Mean age 25.6-26	25 years	Breast Cancer Total deaths = 31 Placebo (17) Folic acid 0.2mg (6) Folic acid 5mg (8)	Hazard ratio compared to placebo 0.2mg: 1.56 (0.38-3.41) 5mg: 2.02 (0.88-4.72)	p = 0.23	Maternal age, smoking, height, weight, social class, systolic blood pressure, parity, gestational age at pregnancy booking visit.

BMI, body mass index; NS, not stated; CRC, colorectal cancer, NCC, nested case-control

Colorectal cancer in men and women (Brink *et al.* 2005)

7. In this cohort study, while there was a statistically positive association between rectal cancer and folate intake in women, there was an inverse association in men and no association with colon cancer in either sex. There were relatively few cases of women with rectal cancer (n = 51). Overall, the results were inconsistent between sexes and cancer sites, and the results may have been due to chance.

Prostate cancer (Hultdin et al. 2005)

8. The study found a non-statistically significant positive association between serum folate and prostate cancer.

Breast cancer and women (Charles et al. 2004)

9. The main aim of the study was to relate to folic acid supplementation and serum folate levels during pregnancy to various pregnancy outcomes. Information on potential confounders (eg. parity, smoking, blood pressure) was collected at the initial ante-natal clinic visit (Charles *et al.*, 2005) and appears not to have been updated. For example, the parity at data collection may not be an accurate reflection of lifetime parity. Other factors associated with breast cancer such as age at menarche and at first birth have not been adjusted for. The study found that there was a non-significant positive association between folate taken during pregnancy and breast cancer mortality. There were relatively few deaths due to breast cancer; 31 in the whole trial, and only eight in the higher folate intake group.
10. In summary, each study was of a different type of cancer, and only one adjusted for alcohol intake, which is known to be associated with folate metabolism. A statistically significant positive association between folate and cancer was only found in one of the three studies. We conclude that there is *insufficient evidence* of a causal relationship between folate supplementation and cancer.
11. It should be noted that a recently published paper (Lucock *et al.* 2005) raised the theoretical possibility that folate fortification may increase the prevalence of the MTHFR 677TT genotype in the population, and thereby introduce other potentially adverse effects such as increased risk of some cancers. However, this question requires further investigation.

Acknowledgements

We are grateful to Dr Peter O'Leary, Dr Liz Geelhoed and staff of the Genomics Directorate, WA Department of Health.

References

- BCCPSG. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *New England Journal of Medicine*. 1994, **330**(15): 1029-35.
- Brink M, Weijenberg MP, de Goeij AF, Roemen GM, Lentjes MH, de Bruine AP, van Engeland M, Goldbohm RA and van den Brandt PA. Dietary folate intake and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. *Int J Cancer*. 2005, **114**(5): 824-30.
- Charles D, Ness AR, Campbell D, Davey Smith G and Hall MH. Taking folate in pregnancy and risk of maternal breast cancer. *BMJ*. 2004, **329**(7479): 1375-6.
- Charles DH, Ness AR, Campbell D, Smith GD, Whitley E and Hall MH. Folic acid supplements in pregnancy and birth outcome: re-analysis of a large randomised controlled trial and update of Cochrane review. *Paediatric and Perinatal Epidemiology*. 2005, **19**(2): 112-24.
- Farber S. Some observations on the effect of folic acid antagonists on acute leukemia and other forms of incurable cancer. *Blood*. 1949, (4): 160-7.
- French AE, Grant R, Weitzman S, Ray JG, Vermeulen MJ, Sung L, Greenberg M and Koren G. Folic acid food fortification is associated with a decline in neuroblastoma. *Clinical Pharmacology and*

Therapeutics. 2003, 74(3): 288-94.

Hultdin J, Van Guelpen B, Bergh A, Hallmans G and Stattin P. Plasma folate, vitamin B12, and homocysteine and prostate cancer risk: a prospective study. *International Journal of Cancer*. 2005, 113(5): 819-24.

Kim YI. Will mandatory folic acid fortification prevent or promote cancer? *American Journal of Clinical Nutrition*. 2004, 80(5): 1123-8.

Lucock M and Yates Z. Folic acid - vitamin and panacea or genetic time bomb? *Nature Reviews Genetics*. 2005, 6(3): 235-40.

Omenn GS, Goodman GE, Thornquist MD, Balmes J, Cullen MR, Glass A, Keogh JP, Meyskens FL, Valanis B, Williams JH, Barnhart S and Hammar S. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *New England Journal of Medicine*. 1996, 334(18): 1150-5.

