

## RESEARCH POINTERS

## Taking folate in pregnancy and risk of maternal breast cancer

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Taking folate before conception and then for the first three months of pregnancy reduces the risk of recurrence of neural tube defects,<sup>1</sup> and fortification of food has been proposed. The effects of long term exposure to high concentrations of supplemental folate are unknown, and antimetabolite effects are theoretically possible.<sup>2</sup> Data on the long term effects of increased folate intake in pregnancy are limited. We followed up a large trial of folate supplementation in pregnancy from the 1960s.<sup>3-4</sup> We examined the association between folate status and death, and we also analysed the effects of folate supplementation.

## Participants, methods, and results

From June 1966 to June 1967, 3187 women were identified as potentially eligible for a trial of folate supplementation.<sup>3-4</sup> At her booking visit, the mother's age, gestation, parity, weight, and blood pressure were recorded, and blood was taken to measure serum folate concentrations. Tablets were supplied in six colours, two of which contained folate in 0.2 mg and 5 mg daily doses. The tablets were kept in numbered drawers and distributed in sequence. The trial was double blind. The husband or partner's occupation at the time of delivery was used to determine social class. Linking the trial data

to the Aberdeen maternity and neonatal databank added information on maternal smoking and maternal height. No women withdrew from the trial. Compliance was assessed by self report and by measurement of folate status.

The records were linked with those held by the National Health Service Central Registry in Edinburgh and the cause of death ascertained. In all, 3037 women were recruited to the study, and 2928 were randomised. In the placebo group, 1.9% reported that they had not taken their tablets regularly compared with 1.7% in the group taking 0.2 mg folate and 3.2% in the group taking 5 mg. Initial folate concentrations were similar in the three groups. For later folate measurements there was a dose-response relation between dose of folate and folate status. Baseline characteristics of the women in the three treatment groups were comparable.

By the end of September 2002, 210 women had died; 40 deaths were attributable to cardiovascular disease, 112 to cancer, and 31 to breast cancer (table).

## Comment

In women randomised to high doses of supplemental folate, all cause mortality was about a fifth greater, and

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BMJ 2004;329:1375-6

Unadjusted and fully adjusted\* hazard ratios for mortality from all causes, deaths attributed to cardiovascular disease, cancer, and breast cancer in the groups given folate supplements in the Aberdeen Folate Supplementation Trial, 1966-7 (n=2928)

	No	%	Unadjusted hazard ratio (95% CI; P value)	P for trend	Fully adjusted hazard ratio (95% CI; P value)	P for trend
Mortality risk in the two separate supplement groups						
All cause mortality:						
Placebo	134	6.8	1.00	0.48	1.00	0.13
0.2 mg folate	37	7.9	1.18 (0.82 to 1.70; 0.38)		1.21 (0.83 to 1.77; 0.30)	
5 mg folate	39	8.0	1.20 (0.84 to 1.71; 0.33)		1.42 (1.00 to 2.04; 0.06)	
Cardiovascular mortality:						
Placebo	28	1.4	1.00	0.95	1.00	1.00
0.2 mg folate	6	1.3	0.91 (0.38 to 2.21; 0.84)		1.02 (0.42 to 2.48; 0.97)	
5 mg folate	6	1.2	0.88 (0.36 to 2.12; 0.77)		1.02 (0.42 to 2.48; 0.97)	
All cancer deaths:						
Placebo	69	3.5	1.00	0.31	1.00	0.09
0.2 mg folate	19	4.1	1.18 (0.71 to 1.95; 0.53)		1.20 (0.71 to 2.02; 0.51)	
5 mg folate	24	4.9	1.43 (0.90 to 2.27; 0.13)		1.70 (1.06 to 2.72; 0.02)	
Breast cancer mortality:						
Placebo	17	0.9	1.00	0.28	1.00	0.23
0.2 mg folate	6	1.3	1.51 (0.59 to 3.81; 0.39)		1.56 (0.38 to 3.41; 0.35)	
5 mg folate	8	1.6	1.92 (0.83 to 4.47; 0.13)		2.02 (0.88 to 4.72; 0.10)	
Mortality risk in the two supplement groups combined						
All cause mortality:						
Placebo	134	6.8	1.00		1.00	
Supplemented	76	8.0	1.18 (0.90 to 1.58; 0.23)		1.32 (0.99 to 1.76; 0.06)	
Cardiovascular mortality:						
Placebo	28	1.4	1.00		1.00	
Supplemented	12	1.3	0.90 (0.46 to 1.76; 0.76)		1.01 (0.51 to 2.02; 0.96)	
All cancer deaths:						
Placebo	69	3.5	1.00		1.00	
Supplemented	43	4.5	1.31 (0.89 to 1.91; 0.17)		1.44 (0.97 to 2.13; 0.07)	
Breast cancer mortality:						
Placebo	17	0.9	1.00		1.00	
Supplemented	14	1.5	1.72 (0.85 to 3.49; 0.13)		1.79 (0.88 to 3.64; 0.10)	

\*Adjusted for maternal age, smoking, height, weight, social class, and systolic blood pressure; parity; and gestational age.

### What this paper suggests

Women taking high doses of folate throughout pregnancy may be more likely to die from breast cancer in later life than women taking no folate

### What research is needed now

This may be a chance finding, so further studies should examine the association between folate supplementation in pregnancy and risk of breast cancer

the risk of deaths attributable to breast cancer was twice as great. This increased risk in deaths attributable to breast cancer is unlikely to be due to competing causes as the number of deaths was small and all cause mortality appeared to be greater. The increase in mortality and in death from breast cancer with high doses of folate could be a chance finding. The number of deaths was small, the confidence intervals were wide, and we had no prespecified hypothesis that taking folate supplements in pregnancy would increase the risk of cancer. As this randomised trial was of high quality, bias and confounding are unlikely explanations for our findings. A recent study indicated that rats fed diets deficient in folate had increased mammary tumorigenesis compared with

rats fed diets with sufficient folate,<sup>5</sup> whereas rats fed a high dose folate diet had similar levels of tumorigenesis to deficient rats.<sup>5</sup> Our data are preliminary and these findings require confirmation.

**Contributors:** DC did the fieldwork and the analysis. AN wrote the first draft. All the authors commented on this and subsequent drafts. AN is guarantor.

**Funding:** The original study had a project grant from the board of management for the Aberdeen Special Hospitals. Glaxo supplied the tablets. A project grant from the British Heart Foundation supported the reanalysis and follow up.

**Competing interests:** None declared.

**Ethical approval:** Multi-Centre Research Ethics Committee and the local Grampian Research Ethics Committee.

- 1 MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council vitamin study. *Lancet* 1991;338:131-7.
- 2 Lucock M. Is folic acid the ultimate functional food component for disease prevention? *BMJ* 2004;328:211-4.
- 3 Hall MH. Folic acid deficiency and congenital malformation. *J Obstet Gynaecol Br Commonw* 1972;79:159-61.
- 4 Charles DHM, Ness AR, Campbell D, Davey Smith G, Whitley E, Hall MH. Folate and birth outcome: reanalysis of a large randomised controlled trial. *Paediatr Perinat Epidemiol* 2005;19. (In press.)
- 5 Kotsopoulos J, Kyoung-Jin S, Martin R, Choi M, Renlund R, McKelvie C, et al. Dietary folate deficiency suppresses N-methyl-N-nitrosourea-induced mammary tumorigenesis in rats. *Carcinogenesis* 2003;24:937-44.

(Accepted 7 October 2004)

## Commentary: Folic acid fortification remains an urgent health priority

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Charles and colleagues report a non-statistically significant association between short term prenatal consumption of folic acid and breast cancer.<sup>1</sup> As the authors note, even though these data are from a randomised controlled trial, they had no prespecified hypothesis. The randomised controlled trial sought to evaluate the effect of antenatal folate consumption and pregnancy outcomes, not breast cancer. Only 31 breast cancer deaths were found, and the confidence intervals were wide and include one. We believe that the most likely explanation for the reported association is chance.

In contrast to the results reported by Charles and colleagues, the existing literature indicates that increased chronic consumption of folate and higher blood folate concentrations lower the risk of breast cancer, especially among women who consume one or more drinks of alcohol a day. Shrubsole and colleagues found, in a population based study of 1321 cases and 1382 controls, that dietary folate is inversely associated with breast cancer (odds ratio 0.71; 95% confidence interval 0.56 to 0.92).<sup>2</sup> In a prospective follow up cohort, Zhang and colleagues did a nested case-control study, which included 712 breast cancer cases and 712 controls. Comparing women in the upper quintile for blood folate with those in the lowest quintile, they reported a protective relative risk of 0.73 (95% confidence interval 0.50 to 1.07). Among women consuming more than 15 g of alcohol a day, they found a highly protective relative risk of 0.11 (0.02 to 0.59).<sup>3</sup>

Mutagenic mechanisms by which folate deficiency might induce cancer have also been sought. The current search is focused on DNA that is damaged by imbalanced base excision repair of DNA that had uracil incorporated because there was not enough folate to provide sufficient thymine.<sup>4</sup> Fenech and colleagues have looked at in vitro human cell systems and found an inverse dose-response

effect between mutagenic end points and concentrations of folic acid in the culture.<sup>5</sup> Thus, there are biologically plausible mechanisms by which increasing folic acid consumption would lower the risk for breast cancer.

Our argument that Charles' and colleagues' finding is a chance one is buttressed by these epidemiological and mutation studies, which indicate that more folic acid is likely to prevent breast cancer rather than to cause it. Charles' report should not deter mandatory folic acid fortification of wheat and corn flour around the world. Mandatory fortification should be immediately implemented for the known benefits of preventing birth defects and anemia. Folic acid fortification in the United States was followed each year with a reduction in deaths from strokes and heart attacks that is greater than the annual deaths from vehicular crashes, indicating another important public health improvement from fortification. Inertia on mandatory folic acid fortification continues to be bad policy.

**Competing interests:** GPO is coinventor (while at CDC, compensation will be under the regulations of CDC) of a patent that covers adding folic acid to contraceptive pills and JSM is a paid consultant to Ortho McNeil on this issue.

- 1 Charles D, Ness AR, Campbell D, Smith GD, Hall MH. Taking folate in pregnancy and risk of maternal breast cancer *BMJ* 2004;329:1375-6.
- 2 Shrubsole MJ, Jin F, Dai Q, Shu XO, Potter JD, Hebert JR, et al. Dietary folate intake and breast cancer risk: results from the Shanghai Breast Cancer Study. *Cancer Res* 2001;61:7136-41.
- 3 Zhang SM, Willett WC, Selhub J, Hunter DJ, Giovannucci EL, Holmes MD, et al. Plasma folate, vitamin B6, vitamin B12, homocysteine, and risk of breast cancer. *J Natl Cancer Inst* 2003;95:373-80.
- 4 Cabelof C, Raffoul J, Nakamura J, Kapoor D, Abdalla H, Heydari A. Imbalanced base excision repair in response to folate deficiency is accelerated by polymerase beta haploinsufficiency. *J Biol Chem* 2004;279:36504-13.
- 5 Wang X, Fenech M. A comparison of folic acid and 5-methyltetrahydrofolate for prevention of DNA damage and cell death in human lymphocytes in vitro. *Mutagenesis* 2003;18:81-6.