Research letters

Association of neural tube defects and folic acid food fortification in Canada

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Many women do not receive folic acid supplements before conception. In response, most of Canada's cereal grain products were being fortified with folic acid by January, 1998, thereby providing an additional 0·1–0·2 mg per day of dietary folate to the Canadian population. We assessed the effect of supplementation on prevalence of open neural tube defects in the province of Ontario. Among 336 963 women who underwent maternal serum screening over 77 months, the prevalence of open neural tube defects declined from 1·13 per 1000 pregnancies before fortification to 0·58 per 1000 pregnancies thereafter (prevalence ratio 0·52, 95% CI 0·40–0·67, p<0·0001). At a population level, folic acid food fortification is associated with a pronounced reduction in open neural tube defects.

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Periconceptional supplementation with folic acid tablets reduces the risk of neural tube defects by more than 50%,[1] yet many women do not receive folic acid supplements before conception.[2,3] In response, most of Canada's cereal grain products were being fortified with folic acid by January, 1998, providing an additional 0·2 mg per day of dietary folate to most of the population. Our aim was to assess whether or not this mandatory programme was associated with a decline in the prevalence of antenatally and postnatally detected open neural tube defects in Ontario.

Under the universal Ontario health insurance plan, antenatal maternal serum screening (MSS) at 15–20 weeks' gestation, amniocentesis, level 2 fetal ultrasonography, and genetic counselling are offered to all women residents of Ontario. Those with a positive MSS are referred for counselling at one of 17 genetics centres across the province. Each of these centres contributes follow-up data to the Ontario MSS database, from which we obtained our data. Because follow-up information from one of the genetics centres was only 87% complete, we excluded it from our data set; however, the prevalence of open neural tube defects at this centre was similar to that seen across the other 16 centres.

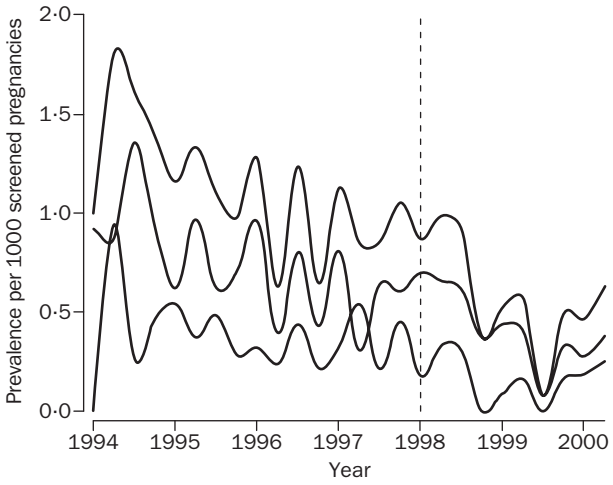
Both the month of screening and diagnosis of open neural tube defects were defined by the date of conception, typically estimated by an early dating ultrasonograph. Hence, analysis began in January, 1994, and ended in May, 2000. We based an antenatal diagnosis of open neural tube defect on ultrasonography, or fetal autopsy after therapeutic termination. A postnatally diagnosed event comprised all liveborn and stillborn affected infants after 20 weeks' gestation, identified by data linkage of the mother's Ontario health insurance number with that of her infant, through the Canadian Institute for Health Information Discharge Abstract Database.

We compared the prevalence of open neural tube defects before (January, 1994, to December, 1997) and after (January, 1998, to May, 2000) folic acid fortification by estimation of a prevalence ratio and 95% CI. We used Poisson regression to adjust the prevalence ratio for

	Period of observation		Crude prevalence ratio (95% CI)	Age-adjusted prevalence ratio (95% CI)	p*
	Before fortification	After fortification			
Anencephaly or spina bifida					
Length of observation (months)	48	29	..	..	
Maternal age (mean, SD) (years)	30·1 (0·16)	30·3 (0·081)	..	..	
Number of women screened	218 977	117 986	..	..	
Number of women with an affected fetus	248	69	..	..	
Prevalence (per 1000 pregnancies)	1·13	0·58	0·52 (0·40–0·67)	0·62 (0·46–0·83)	<0·0001
Anencephaly					
Number of women with an affected fetus	84	19	..	..	
Prevalence (per 1000 pregnancies)	0·38	0·16	0·42 (0·26–0·69)	0·49 (0·29–0·84)	<0·0002
Spina bifida					
Number of women with an affected fetus	164	50	..	..	
Prevalence (per 1000 pregnancies)	0·75	0·42	0·57 (0·41–0·78)	0·69 (0·49–0·97)	<0·0001

*After adjustment for age.

Maternal characteristics and risk of open neural tube defects detected before and after mandatory folic acid food fortification



Quarterly prevalence of open neural tube defects (upper), spina bifida (middle), and anencephaly (lower) before and after (vertical dashed line) folic acid food fortification

maternal age, a possible influence on the uptake of MSS. We also used an autoregressive integrated moving average (ARIMA) time series model to assess the effect of fortification on the subsequent monthly rate of all open neural tube defects. The preintervention series met the assumption of stationarity—ie, constant mean, variance, and autocovariance over time—and we identified the final ARIMA model variables (6, 0, 0) by examination of the partial autocorrelation and autocorrelation functions. The effect of folic acid fortification was represented by a ramp function, beginning in January, 1998, and declining linearly from that point. Maternal age was again included as a covariate in the model. The research ethics board of the North York General Hospital approved the study.

218 977 and 117 986 women were screened for open neural tube defects before and after fortification, respectively. The number of documented defects was significantly higher before fortification than after (table). 65% (160) of open neural tube defects were diagnosed antenatally before fortification and 61% (42) after fortification. We also noted a significant decline after fortification in the prevalence of anencephaly and spina bifida (table). In the time series analysis, folic acid food fortification was associated with a significant decline in the monthly prevalence of open neural tube defects ($p<0·0001$ figure).

In the figure, the observed fall in open neural tube defects before folic acid fortification might be explained by the increased use of periconceptional folic acid tablet supplements since the mid-1990s.[1] However, in addition to naturally occurring folates, the consumption of 0·2 mg of synthetic folic acid every day, through fortified cereal grain products, has likely provided most Canadian women with a daily dose of at least 0·3–0·4 mg of folic acid. This statement is supported by the observed 41% associated increase in mean red cell folate concentrations in Ontarian women of reproductive age.[4] Researchers in the USA noted only a 19% relative decline in the prevalence of neural tube defects after US folic acid fortification, as might be expected, since antenatally identified cases were not included in their assessment.[2] However, in a large prospective cohort study,[5] periconceptional supplementation with 0·4 mg per day of folic acid was associated with significantly lower risk of all neural tube defects in both high-prevalence (risk ratio 0·21) and low-prevalence (0·59) regions of China. Together, our data and those of others indicate that a daily intake of 0·3–0·4 mg of folate-containing foods over several months should be sufficient to reduce the relative risk of neural tube defects by at least 30–40%. Whether food fortification with higher quantities of folic acid is even more effective remains to be tested, especially within high-risk populations.[5]

Even under quite suitable conditions, neural tube defect prevention programmes based solely on periconceptional folic acid tablet supplementation seem to fall far short of achieving their potential effectiveness.[2,3] On the basis of our results, and those of others,[2] we recommend that other countries consider adopting a programme of folic acid food fortification, in addition to encouraging increased use of periconceptional folic acid tablets. Epidemiological surveillance of the general population might also be initiated to monitor for any untoward effects related to folic acid fortification and to allow for modification of the programme as necessary.

Contributors

J G Ray and M J Vermeulen designed the study, and obtained and analysed data. P R Wyatt and C Meier helped with study design and data collection. D E C Cole was involved with study design and data analysis, and S Boss with data collection. All authors were involved in the writing of the report.

Conflict of interest statement

None declared.

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