

LETTERS TO THE EDITOR

Folic acid and neuroblastoma: Too soon to tell

To the Editor:

French et al¹ present data showing that the incidence of neuroblastoma in Ontario, Canada, seems to have declined dramatically since the start of folic acid fortification of grains in Canada. Neuroblastoma is a cancer of early childhood: 33% of neuroblastomas are diagnosed before age 1 year and 55% before age 2 years. For most study children conceived before folic acid supplementation began, the greatest period of risk for neuroblastoma was captured during follow-up. However, this is not true for the children conceived during fortification, and the observed decline may be a result of short follow-up for these children.

The incidence of neuroblastoma was ascertained between January 1985 and October 2000. The critical period of exposure was considered to be around the time of conception. Children exposed to folic acid supplementation were conceived in a 25-month period from January 1998 through January 2000. At the end of the study period, October 2000, children conceived during fortification were aged between 0 and 25 months. We know the cumulative percent of cases by age from a population-based registry.* For example, 21% of all neuroblastomas are diagnosed at age 5 months or younger. Assuming that the incidence of neuroblastoma is stable over time, we can estimate that 21% of all neuroblastomas that would eventually occur in study children born in May 2000 were diagnosed by the time the children were aged 5 months in October 2000. We made the simplifying assumptions that birth and death rates were the same and were constant for all age groups and, therefore, that each 3-month age group (0-25 months) had an equal number of children at the end of follow-up. We calculated the total percentage of neuroblastomas observable for the exposed study population in October 2000 by summing the cumulative percentages for each age group (sum of the first 8 percentages in Table I + 0.67 × Oldest age group [which was a 2-month range rather than a 3-month range]) and dividing by the sum of the total cumulative percentages of neuroblastomas that would be observed with complete follow-up (100% × 8 age groups + 67% for the oldest age group). By this calculation, we estimated that 37% of neuroblastomas that would eventually occur in children conceived during the fortification period could be ob-

*Data provided by the Bureau of Health Statistics and Research, Pennsylvania Department of Health. The Department specifically disclaims responsibility for any analysis, interpretations, or conclusions.

Table I. Cumulative percentage of neuroblastoma by age; Pennsylvania Cancer Registry, 1991-2000

Age (mo)	Cumulative percentage of neuroblastoma
0-2	13
3-5	21
6-8	27
9-11	33
12-14	41
15-17	46
18-20	49
21-23	55
24-25	56

served by October 2000. This value is very similar to the reported 0.40 incidence rate ratio comparing children conceived during fortification versus before fortification. Thus the observed reduction in neuroblastoma incidence likely resulted from the short follow-up for children conceived after fortification began. Short follow-up would also result in the lower mean age at diagnosis in the postfortification children reported by the authors.

The interest in folate is warranted, and the incidence of various childhood cancers including neuroblastoma should continue to be monitored after fortification.

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Reference

1. French AE, Grant R, Weitzman S, Ray JG, Vermeulen MJ, Sun L, et al. Folic acid fortification is associated with a decline in neuroblastoma. *Clin Pharmacol Ther* 2003;74:288-94. doi:10.1016/j.cpt.2004.01.005