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Effect of food fortification on folic acid intake in the United States[1–3]

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ABSTRACT

Background: The addition of folic acid to all enriched cereal-grain foods, mandated by the Food and Drug Administration (FDA), was initiated in January 1998. Although this program was designed such that typical folate intakes would be increased by ≈100 μg/d and that the risk of intakes > 1000 μg/d (the FDA's safe upper limit of daily intake) would be minimal, its actual effect on folate intake has yet to be determined.

Objective: The objective was to estimate the effect of folic acid fortification on the amount of folate consumed by persons in the United States.

Design: Linear regression analysis of data from published studies was used to determine the relation between a chronic folic acid dose and the resulting increase in steady state concentrations of folate in plasma or serum. Using this regression equation and reverse prediction, we quantified the increase in folic acid intake from fortification required to achieve the increase in plasma or serum folate observed in published studies.

Results: The increase in circulating folate concentration was linearly related to folic acid intake over the range of 100–1000 μg/d ($r = 0.984$, $P < 0.0001$). Predicted increases in folic acid intake from fortified food ranged from 215 to 240 μg/d.

Conclusions: Typical intakes of folic acid from fortified foods are more than twice the level originally predicted. The effect of this much higher level of fortification must be carefully assessed, especially before calls for higher levels of fortification are considered. *Am J Clin Nutr* 2003;77:221–5.

KEY WORDS Food fortification, folic acid, folate, neural tube defects, nutrition

INTRODUCTION

January 1998 was the mandatory deadline for the fortification of enriched grain products with folic acid (pteroylglutamic acid, the synthetic, oxidized form of folate) in the United States. However, the process of implementation was essentially complete by mid-1997 (1). The main motivation behind fortification (2) was to abate the occurrence of neural tube defects (NTDs), a birth defect shown to be responsive to folic acid administration (3). Similarly, it was felt that a secondary benefit of fortification might be a reduction in the incidence of cardiovascular disease (4) and certain cancers (5), the occurrences of which are associated with low folate status.

The success of fortification was quickly seen (1) with the declining incidence of folate deficiency (plasma concentration < 3 ng/mL, or 6.8 nmol/L) and a concurrent decrease in the incidence of elevated (> 13 μmol/L) plasma total homocysteine, a biochemical marker of folate deficiency. Of possibly greater import was the 19% decrease in the incidence of NTD since the onset of fortification (6).

Initial estimates by the Food and Drug Administration (FDA) anticipated an increase in folate intake by adults of between 70 and 130 μg/d (2) depending on age and consumption patterns. Nonetheless, much evidence suggests that the nutritional and health benefits of current fortification practices may be due to an increase in folate consumption greater than that predicted by the FDA model (7–9). Yet, despite the ubiquitous nature of fortified foods and foods containing ingredients with added folic acid (eg, enriched flour) in the United States, no determination of the effect of fortification on actual folate consumption has been made.

In light of this lack of information on the true nature of the increase in folic acid consumption, we propose that it is possible to estimate the intake indirectly from existing data. Specifically, by comparing the change in folate status achieved through fortification with that achieved by controlled oral folic acid administration, novel information can be derived on how typical daily folate consumption increased with the introduction of fortification.

METHODS

Intervention studies: relation between controlled folic acid intake and the resulting increase in serum or plasma folate concentration

A literature review was conducted to identify intervention studies in which folic acid was administered orally daily. It was previously shown that an intervention period of 6 wk is required to achieve a plateau in serum or plasma folate concentration when ≤ 200 μg folic acid/d is consumed (10), whereas a 12–14-wk intervention is required when ≥ 400 μg folic acid/d is consumed (10, 11). Thus, intervention studies of shorter duration than these periods were excluded on the basis that serum or plasma folate concentrations may not have reached a plateau (10–12). We plotted the change in serum or plasma folate concentration against daily folic acid consumption

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TABLE 1
Change in serum or plasma folate concentrations observed in intervention studies that examined the effect of oral folic acid consumption

Study group	Males in study	Duration of intervention	Type of intervention[1]	Level of intervention[2]	Assay type[3]	No. of subjects	Increase in folate concentration[4]
	%			μg/d			μg/L
Ward et al (10)	100	6 wk	Supplement	100	MB	30	2.0[5]
Ward et al (10)	100	6 wk	Supplement	200	MB	30	4.5[5]
Schorah et al (13)	52	24 wk	Fortification	200	RA	33	5.1
Schorah et al (13)	58	24 wk	Fortification	200	RA	31	6.0
Wald et al (15)	83	3 mo	Supplement	200	MB	25	4.5
Riddell et al (12)	62	12 wk	Fortification	298	CL	16	4.9
Ward et al (10)	100	14 wk	Supplement	400	MB	30	10.9[5]
Wald et al (15)	83	3 mo	Supplement	400	MB	25	11.5
Riddell et al (12)	62	12 wk	Supplement	437	CL	16	11.9
Wald et al (15)	83	3 mo	Supplement	600	MB	25	13.9
Wald et al (15)	83	3 mo	Supplement	800	MB	25	20.3
Wald et al (15)	83	3 mo	Supplement	1[6]	MB	25	24.4

[1] Folic acid was administered either in tablet form (supplement) or through consumption of fortified breakfast cereal (fortification).
[2] Amount of additional folic acid consumed daily by subjects.
[3] Assay method used to measure serum or plasma folate: MB, microbiological (16); RA, radioassay (Diagnostic Products Corp, Los Angeles); CL, chemiluminescence (ACS 180; Ciba-Corning, East Walpole MA).
[4] Change in median or adjusted mean serum or plasma folate concentrations due to intervention.
[5] Original data were reported as nonadjusted mean values; median values were provided by the author (M Ward, personal communication, 2001).
[6] mg/d.

and fitted a linear regression line to the plot. Geometric mean or median concentrations were used because folate and total homocysteine concentrations are not normally distributed (1, 13).

Observational studies: determining the effect of folic acid fortification on serum and plasma folate concentrations

A literature review was conducted to identify studies in which serum or plasma folate concentrations were measured within the same population group before folic acid fortification and again after fortification. With the use of reverse prediction, comparing the postfortification changes in serum or plasma folate concentrations to the linear regression equation derived from the intervention studies, the apparent increase in daily folate consumption due to fortification was calculated.

Statistics

The disparity in the way the data were presented among the published studies precluded the calculation of CIs or further statistical analysis and resulted in the need to use both median and geometric mean values. However, variations between median or geometric mean values were considered sufficiently minor so as to not bias our conclusions. For example, the differences between the median and geometric mean serum folate concentrations in 2 studies conducted by our laboratory (n = 179 and 358) was <2.5% (SR Davis, EP Quinlivan, LB Bailey, JF Gregory, unpublished observations, 2002). The analyses were conducted by using DATA DESK 5.0.1 software (Data Description Inc, Ithaca, NY).

RESULTS

Intervention studies

Seven published studies meet the criteria for study design and duration. However, 2 studies examining the effect of supplementation during lactation were rejected on the basis that lactation represented a drain on folate stores that could alter the relation between folic acid intake and blood folate concentration. A further study (14) was omitted because neither median nor adjusted mean values were available for the data. From the remaining 4 studies (10, 12, 13, 15; **Table 1**), a positive linear correlation (n = 12 data points; r = 0.984, P < 0.0001) was observed between the median or adjusted mean change in serum or plasma folate concentrations and daily folic acid consumption (**Figure 1**). In all 4 studies, subjects had fasted before blood collection.

Observational studies

The regression equation we derived from the intervention studies (Figure 1) suggests that an increase in folic acid intake of

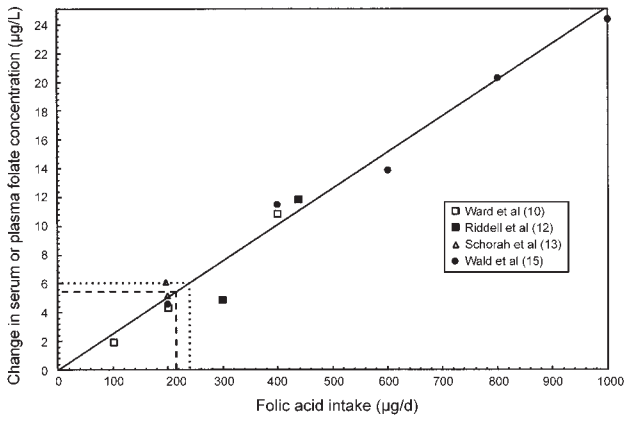

FIGURE 1. Relation between controlled folic acid intake and the resulting change in median or adjusted mean serum or plasma folate concentration. Data were derived from intervention studies looking at the effect of longitudinal folic acid supplementation or fortification with known daily amounts of folic acid on median or adjusted mean serum or plasma folate concentrations. The broken and dotted lines represent the change in plasma or serum folate concentration observed by Jacques et al (1) and by Lawrence et al (17), respectively, in 2 studies examining the effect of the current US folic acid fortification regimen on folate status. $y = 0.0254x + 0.0514$ (r = 0.984, P < 0.0001).

70–130 μg/d, the increase the FDA predicted would result from fortification (2), would induce an increase in serum or plasma folate concentration of between 1.9 and 3.5 μg/L. However, all 3 observational studies found far larger increases in serum or plasma folate concentrations after the introduction of fortification (1, 17, 18). Results from the Framingham Offspring study (1) show that the geometric mean increase in fasting plasma folate concentration was 5.4 μg/L for nonsupplemented subjects (n = 248) sampled between January 1991 and December 1994 and again between September 1997 and March 1998. Similarly, the median serum folate concentration of routine samples measured by a laboratory in California (17) increased by 6.0 μg/L between 1994–1995 (n = 29 243) and 1998 (n = 26 662). Reverse prediction using the regression equation derived in Figure 1 suggests that folate consumption increased in these study groups by 215–240 μg/d, respectively—values approximately twice that predicted by the FDA.

Similarly, the 7.9-μg/L increase in serum folate concentration observed (18) in nonsupplemented women between the third National Health and Nutrition Examination Survey (NHANES III, 1988 to1994) and the 1999 NHANES suggests that folate consumption increased by > 200 μg/d. However, a more precise estimate of the increase was not possible because the results were not adjusted to reflect the fact that serum folate concentrations are not normally distributed.

No information was provided on whether subjects in either the Southern California (17) or the NHANES (18) studies were fasted; subjects in the Framingham Offspring study (1) had fasted for ≥ 10 h before blood was drawn. Data concerning supplement use in the Southern California study were unavailable (17). Data from both the Framingham Offspring (1) and NHANES (18) studies were for subgroups within the studies who did not use supplements.

DISCUSSION

The results of this analysis are internally consistent, suggesting that the fortification of cereal-grain food products in the United States has increased typical folic acid consumption by > 200 μg/d, approximately twice the 70–130-μg/d increment predicted by the FDA (2). In our analysis of the Framingham Offspring (1) and NHANES (18) studies, we used data only from nonsupplemented subjects to avoid the effects of concomitant changes in supplement use. No data regarding supplement use in the Southern California study were available (17), but the change in serum folate concentration, at least for 1998, was consistent with and of similar magnitude to the change observed for plasma in the Framingham Offspring study. The larger increase in serum folate concentration observed in the Southern California study in 1999 (19) is not readily explicable, but may be due to factors other than fortification, such as the growing use of folic acid supplements as a result of ongoing national folic acid health campaigns. The effect of such supplement use is evident in both the Framingham Offspring (1) and NHANES (18) studies.

Factors affecting predicted and actual intake of fortified foods

The increase in folic acid consumption due to fortification (> 200 μg/d) reported here greatly exceeds the 70–130-μg/d range predicted by the FDA (2). However, our observations are consistent with a growing body of both anecdotal and empirical evidence (7–9, 20) that suggests that the effect of folic acid fortification on folic acid intake has exceeded original predictions. This discrepancy may be due in part to wide-scale overfortification. Initial studies suggest that fortified foods typically contain 160% (9) to 175% (7) of their predicted folate content. Similarly, although the FDA made allowances (2) for the fact that most food surveys underreport food intake (21), such bias still represents an inestimable margin of error. Disparities in reportage between food surveys may thus account for the variation in predicted folate intakes observed between studies (2, 8, 20).

What is the significance of the current folic acid intake

Because the main motivation behind fortification was to prevent NTDs (2), this program has been at least partially successful, as indicated by the reported 19% reduction in NTD incidence (6). It is too early to determine what other health benefits mandatory fortification may have, such as possible reductions in the rates of vascular disease (4) and certain cancers (5). The conclusion of our study is that the benefits that accrue from fortification are a result of a far larger increase in folate consumption than that envisioned—twice the amount originally deemed safe by the FDA (2).

The FDA-mandated fortification level was chosen (2) to maximize folate consumption by women of childbearing age while minimizing the risk of high-folate consumers consuming > 1 mg/d folate, ie, the safe upper limit of intake set by the FDA. However, at least one estimate (8) suggests that between 0.5% and 5% of adults, depending on age and sex, consume > 1 mg folic acid/d based on the FDA's fortification protocol. Had actual food analysis values (7, 9) been used to calculate total folate consumption (natural folate + folic acid), the percentage of people consuming > 1 mg total folate/d (2) would have been higher. This situation is further complicated by the finding that many breakfast cereals are significantly overfortified with folic acid (7, 9) and are typically consumed in amounts twice the labeled serving size (7). Thus, an individual could easily exceed the FDA's safe upper limit of intake (1 mg folic acid/d) by eating just one typical serving of superfortified cereal (labeled as 400 μg/30 g). Because breakfast cereals were commonly fortified before mandatory fortification, their use would not contribute to the increase in folate consumption accruing to fortification but would contribute to one's daily folate consumption, predominantly as folic acid.

Although small doses of oral folic acid are efficiently metabolized to 5-methyltetrahydrofolate before entering the portal blood, intakes > 200 μg appear to overload this metabolic capacity, leading to the appearance of unmetabolized folic acid in plasma (22). In view of this phenomenon, the current net folic acid intake (≥ 200 μg/d) is likely to lead to a chronic presence of unmetabolized folic acid in the blood, as was observed previously (23). Delivery of folic acid to tissue could, theoretically, be detrimental because of possible circumvention of normal homeostatic regulation of the cellular retention and metabolic function of folate. 5-Methyltetrahydrofolate, the major form of folate found in serum (24), must be metabolized to tetrahydrofolate before it can be retained by the cell as a polyglutamate (25) or before it can be converted to other folate coenzymes (26). Methionine synthase (EC 2.1.1.13) is the only enzyme to utilize 5-methyltetrahydrofolate as substrate; thus, modulation of that enzyme's activity may be one mechanism by which folate homeostasis is regulated (25, 27). Because cobalamin (vitamin B-12) is a coenzyme for methionine synthase (28), cobalamin deficiency can retard methionine synthase activity, causing a concomitant folate deficiency in cells

TABLE 2
Effect of the consumption of ≈200 μg folic acid/d on serum or plasma folate concentrations and on total plasma homocysteine concentrations

Study group	Males in study	Study type	Level of intervention[1]	No. of subjects	Increase in folate concentration[2]	Decrease in homocysteine concentration[3]
	%		μg/d		μg/L	μmol/L
Ward et al (10)	100	Supplement	200	30	4.5[4]	1.7[4]
Schorah et al (13)	52	Fortification	200	33	5.1	1.1
Wald et al (15)	83	Supplement	200	25	4.5	1.2
Jacques et al (1)	55	Fortification	≈215[5]	248	5.4	0.7

[1] Amount of additional folic acid consumed daily by subjects.
[2] Change in median or adjusted mean serum or plasma folate concentrations due to intervention.
[3] Change in median or adjusted mean total plasma homocysteine concentrations due to intervention.
[4] Original data were reported as a nonadjusted mean value; median value was provided by the author (M Ward, personal communication, 2001).
[5] Calculated from the change in plasma folate concentration with the equation for the line in Figure 1.

(29) and disruption of the biosynthetic pathways that utilize folate as substrate (26), ie, purine and thymidine synthesis. In contrast, on entering the cell, folic acid can be retained and subsequently metabolized independently of methionine synthase and cobalamin. The first indicator of cobalamin deficiency is often the resulting folate deficiency, ie, megaloblastic anemia. However, because folic acid is retained and metabolized independently of cobalamin, a high intake of folic acid may prevent the accompanying folate deficiency (30), possibly delaying diagnosis of the underlying cobalamin deficiency, even to a point where irreversible neurologic damage has occurred.

The FDA's conclusion that folic acid fortification was unlikely to perturb antifolate drug therapies (2) was based on the limited data then available. This conclusion should be reassessed in view of recent studies that suggest that folic acid decreases the antiinflammatory efficacy of methotrexate (31) and that newer antifolate drugs appear more sensitive to perturbation (32).

Use of total plasma homocysteine as a biomarker of folate intake and status

The total plasma homocysteine concentration, nominally a good biomarker of folate intake and status, typically reaches a plateau when dietary folate is supplemented with ≥200 μg folic acid/d (10, 15). This threshold may explain why the decrease in plasma homocysteine due to fortification was not commensurate with the change in plasma folate concentration (**Table 2**), because the relative change in homocysteine concentration would differ between those consuming >200 μg folic acid/d and those consuming less. The further decrease in homocysteine concentrations in subjects taking B vitamin supplements (1) may reflect the distinct homocysteine-lowering effect of other components of the multivitamin, ie, cobalamin (33–35), vitamin B-6 (34, 35), or riboflavin (35, 36).

Conclusions

The aim of mandatory fortification as a prophylactic against NTDs (2) has proven to be partially successful (6); however, this success has been a result of a higher than intended intake of folic acid. Although no evidence exists to suggest that this higher intake of folic acid may harm the US public, the detection of circulating unmetabolized folic acid (23) may be of concern. Moreover, calls for increasing the current levels of folic acid fortification, in an attempt to further lower serum homocysteine concentrations (37, 38), appear futile (10, 15) because cobalamin, not folate, appears to be the major determinant of homocysteine concentration (33, 39). It would be prudent to first assess thoroughly the consequences of the current fortification regimen (eg, its metabolic effects and health benefits and risks) before any changes to the current fortification program are made.

Shortly after the acceptance of this article, Choumenkovitch et al (40) reported estimates of folic acid intake due to fortification. Their study involved the use of a database containing > 105 fortified foods (9) and food-frequency questionnaires form the Framingham Offspring study. Choumenkovitch et al estimated that folic acid consumption increased by 190 μg/d in the Framingham group as a result of fortification. This increase is similar to that which we estimated (215 μg folic acid/d) for the Framingham cohort. Their slightly lower value may be due to disparities in sample groups between the 2 studies or because the use of food-frequency questionnaires may have slightly underestimated food consumption (21).

We thank M Ward for graciously providing median values for her published data. EQ conceived the original concept and conducted the statistical analysis, JFG III was the principal investigator and provided input toward the execution of the concept, and both authors wrote the report. Neither author has personal or financial interests in any organization sponsoring the research.

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