

Food Fortification with Folic Acid: Has the Other Shoe Dropped?

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Folic acid (FA) supplementation effectively reduces the rates of children born with neural tube defects (NTDs). Currently, 42 nations practice mandatory FA fortification to combat NTD. In addition to NTD, FA fortification may also have salutary effects on the incidence of orofacial cleft birth defects and have secondary benefits in reducing serum homocysteine concentrations and stroke mortality. However, a recent note of caution has been raised concerning a possible negative effect of mandatory FA fortification on the incidence of colorectal cancer.

Key words: food fortification, folic acid, colorectal cancer rates, North America

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FOLIC ACID FORTIFICATION

Neural tube defects (NTDs), ranging from treatable and relatively benign bulging (myelomeningocele), to debilitating defects in spinal tissue (spina bifida), to lethal brain atresia (anencephaly), occur in rates from <1.0 to >100 per 10,000 live births across different societies.¹ It was determined in the 1980s that supplementation with folic acid (FA) reduced the recurrence rate of NTD pregnancies among women with a prior history.² Additional randomized supplementation trials, this time in non-selected fertile women, established an efficacy of FA for the primary prevention of NTDs.^{3,4}

Public health policy makers in two North American nations took note of the success of FA prophylaxis of

NTD. In March 1996, the US Food and Drug Administration instituted a mandate for fortification of flour and uncooked grains to a level of 140 $\mu\text{g}/100\text{ g}$, to be fully instituted by January 1998⁵; voluntary compliance among millers and purveyors began immediately in 1996. Canada followed with a similar FA fortification requirement for flour, to a level of 150 $\mu\text{g}/100\text{ g}$, to commence no earlier than the end of 1996 and be in place by November 1998.⁶ Currently, according to a global map published by Scott,⁷ 42 nations across the world have mandatory FA fortification. Meanwhile, in 1998, the United States and Canada revised their recommended daily adult intakes for folate to 400 μg daily in their *Dietary Reference Intakes*⁸ and this was emulated by the United Nations system in 2004.⁹ The implementation of the derivative FA recommendation, namely, a daily intake of 400 μg of FA in supplemental form, was poorly adhered to in practice.

Reductions in NTD incidence have been estimated to range from 19% to 49% using serial monitoring after FA fortification.^{10–13} The implementation of food fortification with FA also appears to have had a positive, ripple effect on other aspects of the public's health in the two index nations. Conclusive evidence of a nutritional impact on folate status of the FA fortification interventions in both the United States^{14,15} and Canada¹⁶ has also emerged over the years. For example, a comparison of blood chemistry in a cohort of adults in Massachusetts obtained both before FA fortification and after fortification's full implementation showed a 50% reduction in elevated concentrations of plasma homocysteine, a putative mediator or marker of vascular injury.¹⁷ A marked acceleration in the reduction in stroke mortality by 5- and 7-fold in Canada and the United States, respectively, occurred between the pre-fortification period (1990–1997) and the advent of FA fortification of grains (1998–2002).¹⁸ Finally, orofacial cleft birth defect rates declined by 6% between the intervals of 1990–1996 (pre-fortification) and 1998–2002 (post-fortification).¹⁹ Of course, any attribution of these secondary benefits of homocysteine lowering, stroke mortality reduction, and

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orofacial cleft attenuation to FA fortification of the national food supplies of the two North American countries is based on two pillars: 1) a time-dependent association with the initiation of the fortification programs; and 2) a plausible mechanism of action related to known effects of FA. Definitive cause-effect relationships cannot be confirmed by time associations alone.

DEVELOPMENT OF THE FOLIC ACID FORTIFICATION-COLORECTAL CANCER HYPOTHESIS

Biology is complex and populations are heterogeneous. A group of investigators from Tufts University in Boston and the Rowett Institute in Aberdeen underscores these points, while putting forth a hypothesis concerning the effects of national FA fortification;²⁰ their report should raise a loud note of caution for an important sub-segment of the American (and probably most non-tropical) populations—the 35–50% of persons over 50 years of age who harbor one or more colonic adenomas.²¹ The central concern of Mason et al.²⁰ is the effect of mandatory FA fortification in the food supply on a specific tumor site—colorectal cancer (CRC).

Whereas evidence of a protective effect of folate intake on a number of cancer sites has been suggested,²² experimental findings for the large bowel were intriguing. In laboratory research conducted in Toronto and reported by Kim,^{23,24} the possibility of FA exposure producing a pro-carcinogenic result was raised. Normal rodents given high exposures to dietary FA in the laboratory developed colonic neoplasms. Lower FA intakes induced rapid tumor development after exposure to carcinogenic induction of microscopic foci of intestinal cell dysplasia. From this perspective, a suggestion emerged that “FA supplementation may enhance the development and progression of already existing, undiagnosed, premalignant and malignant lesions”.²⁴

Mason et al.,²⁰ moreover, join in a concern advanced by other colleagues in the field^{16,25,26} related to the chemical nature of FA (pteroylglutamic acid). Unlike any of the “natural” folate forms in foods, all of which are found in reduced oxidation states, FA is fully oxidized. Human exposure to this form was virtually nonexistent until the chemical synthesis of the pteroylglutamic acid vitamer in the 1940s; FA is now, however, the exclusive species used for food fortification and dietary supplements. Moreover, ingestion of as little as 200 μg of FA fortificant has been shown to overwhelm the intestinal metabolic capacity and result in detectable levels of “free folic acid” arising in the systemic circulation, an overtly non-evolutionary situation for *Homo sapiens*.²⁶

For the presentation of their hypothesis, Mason et al.²⁰ obtained nationally representative data on CRC

incidence for the years 1986–2002 for the United States and Canada from two freely available online databases—the Surveillance, Epidemiology and End Result Registry (www.seer.cancer.gov) and the Canadian Cancer Statistics (www.cancer.ca), respectively. This interval represents approximately the decade of run up to the FA fortification and includes 4 years after it was in full implementation. They applied a curve-smoothing software program to define the time-dependent trends. This yielded symmetrical findings in both nations. The national CRC incidence rate had shown an almost linear decline from 64 diagnoses per 100,000 in 1986 to a rate of 54 in 1996 in the United States. This downward trend abruptly reversed itself in that year and rose again, reaching a re-incidence peak of 56 in 1998. However, with trend modeling, based on the expected continuation of the established decline, a calculation of a net excess of CRC incidence of 5 cases per 100,000 was maintained over the 1998–2002 interval. In Canada, the trajectory of the decline in CRC rates, over the decade beginning in 1986 was from 57 to 51 per 100,000. The reversal in this nation was not detected until 1997, when the trend line of CRC incidence deflected in a positive direction. From 2000 through 2002, the excess CRC incidence was also about 5 cases per 100,000.

What factor or factors detained and reversed the downward march of CRC incidence rates in these two nations? The authors first address the possibility of an artifact due to an abruptly enhanced diagnostic surveillance. Indeed, endoscopic screening procedures increased in the United States, but this could not explain the observed reversal in trend. The concordance across two nations with different healthcare systems, moreover, adds a robust element to the notion that the trends represent true changes in the incidence of large bowel tumors. The dysphasic nature of the upward inflections, with a 1-year head start in the United States, where voluntary fortification of the grain supply began a year earlier than in Canada, is offered to provide further validation of the common-factor(s) proposition for both nations. An obvious common factor was the implementation of a FA-fortification mandate. So, the authors projected the hypothesis that the institution of FA fortification may have been wholly or partly responsible for the observed increase in CRC rates in the mid-1990s.²⁰ They included the caveat that “these observations alone do not prove causality”,²⁰ such would apply equally, however, to the heralded declines in homocysteine concentrations,¹⁷ cerebrovascular deaths,¹⁸ and lip and palate birth defects,¹⁹ which have also been attributed to the public health fortification measures on the basis of a time-sequence argument. All must be cast at the level of hypotheses.

Mason et al.²⁰ comment that “by presenting these

data, we wish to highlight the complexity of the response to this nutrient and emphasize prior observations that have been made in both the preclinical and clinical studies that indicate that administering high doses of folic acid to susceptible individuals or in an inappropriate time frame may accelerate the growth of existing neoplasms".²⁰ Scott⁷ has framed an argument for a greater lethality of CRC when its rate of development from a dysplastic growth to a neoplasm is accelerated; he comments: "It is estimated from various strands of evidence that such polyps may be there for perhaps a decade prior to their conversion to an adenoma, but a conservative estimate is that in most instances they are present for in excess of 3 years. Clearly if this conversion to full cancer took place more rapidly, as is suggested could be brought about by folic acid, particularly high levels of folic acid, this diagnostic window of opportunity is decreased".⁷

Mason et al.²⁰ conclude their hypothesis paper with a restatement of the justification for their inquiry: "By bringing attention to these CRC trend data in relation to fortification, and pointing out their consistency with research on folic acid and cancer development, our aim is to encourage better monitoring and further research in the field". The incidence trend data presented, along with the supporting mechanistic data, should lead us at least to the conclusion that one size of dietary FA exposure does not fit all. It can be beneficial to some and detrimental to others at the same time. Moreover, for an older person with a dual risk of stroke and colonic neoplasia, the enhanced FA intake may simultaneously abort a potential cerebral accident while accelerating the progression of a colonic adenoma—a catch-22. In fact, however, unless one is willing to derive all carbohydrates from legumes, tubers, and unrefined grains, mandatory fortification presents them with a Hobson's choice—in other words, no free choice at all.

TOWARDS RESOLUTION OF THE DILEMMAS POSED

A series of considerations come to mind to address the cautions raised within the hypothesis of Mason et al.²⁰

Re-Evaluate the Risk-Benefit Profile of Voluntary FA Fortification of Ready-To-Eat Cereal

Although flour and pasta fortification is mandated, that for ready-to-eat cereals is optional and voluntary on the part of industry.²⁷ Cereal manufacturers could take an independent look at the risk-benefit profile of continuing their contribution to the FA pool in the US and Canadian food supply. Such action, however, would only

dilute some of the intended impact for reducing NTDs, while not completely eliminating the collateral damage to older persons whose susceptibility to the reproductive health benefits of FA has passed.

Revisit Focused Promotion and Social Marketing of FA Supplementation to Women of Reproductive Age

The prophylactic measure initially conceived to prevent NTDs was supplementation targeted to fertile women of reproductive age.^{2,3} The fact that half of all pregnancies in the United States are unplanned and that the experience with adherence to supplement regimens was poor,²⁸ led to activating the fall-back option of universal fortification in lieu of supplementation. Perhaps another attempt at focused promotion of daily consumption of 400 μg , this time, using more creative vehicles (e.g. snack products, chewing gum, candies) and more effective social marketing, could achieve the desired goals of a targeted approach. It may be worth reopening this avenue, while recognizing that gestational screening for excess circulating maternal alpha-fetoprotein, with or without ultrasonography, allows for detection of pregnancies at risk for NTDs in time for their voluntary termination.

Evaluate the Bioequivalency of Reduced and Oxidized Species of Folate

We would finally need to clarify further whether the chemistry of reduced and oxidized species of folates reflects a continuum from more benign to more problematic formats of the vitamin. Reduced folates are currently less stable as fortificants,²⁰ but food technology might improve their conservation in foodstuffs. Even if the instability obstacle of reduced folates could be overcome, a lingering question of their "comparable bioequivalency" for the primary outcome, i.e. the prevention of NTDs, would have to be addressed. This derives from the fact that all of the background evidential experience that substantiates efficacy is based on the administration of FA itself.²⁻⁴

Find the Right Balance of Risk and Benefits of Fortification to Optimize Health and Prevent Disease

Indeed, the hypothesis on FA fortification, so skillfully generated and cautiously prudently presented by Mason et al.,²⁰ gives the expression that "one person's meat is another person's poison" a new corollary in the domain of dietary grains and cereals. All of us concerned with folate biology or public policy must pick up their

gauntlet²⁰ and move toward NTD-prevention measures that will reassure skeptics while assuring an equitable sharing of risks and benefits across generations in our societies.

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