Invited Commentary

Invited Commentary: Preventing Neural Tube Defects and More via Food Fortification?

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Many neural tube defects can be prevented if women take folic acid around the time of conception. However, the majority of women do not take folic acid at the critical time, so the US government required that food be fortified with folic acid effective January 1, 1998. Whether the amount being added was sufficient to prevent all folate-related neural tube defects has been hotly debated. Mosley et al. (Am J Epidemiol. 2008;169(1):9–17) found no evidence that folic acid supplement use or dietary folate intake was related to neural tube defects, indicating that fortified food is probably providing sufficient folic acid to prevent folate-related defects. Because data on the effectiveness of fortification in the United States are scarce, this is an important contribution. There is great interest in the other effects of fortification. Folic acid reduces homocysteine levels, and homocysteine has been linked to cardiovascular disease and cancer. On the basis of current evidence, however, it seems unlikely that fortification will reduce cardiovascular disease rates. Its effect on cancer remains unclear. Folic acid may be useful in primary prevention but may also stimulate the growth of existing malignancies or premalignant lesions. Although these issues remain unresolved, Mosley et al. have provided important data to address the primary question: Does fortification prevent folate-related neural tube defects?

anencephaly; folic acid; food, fortified; neural tube defects; spinal dysraphism

By law, all enriched cereal grain products sold in the United States have been fortified with 140 μg of folic acid per 100 g of grain since January 1, 1998 (1). This regulation was enacted to provide women who became pregnant with sufficient folic acid to prevent their babies from having neural tube defects. Determining the effectiveness of this public health strategy has been a challenge for 2 reasons. First, it is not clear exactly what percentage of neural tube defects is folic acid preventable. Second, it is difficult to detect changes in neural tube defect rates in the US system.

It is often stated that 70% of neural tube defects are folic acid preventable on the basis of a clinical trial conducted by the Medical Research Council (2) that showed a relative risk of 0.28 for recurrence of neural tube defects in the group that received folic acid compared with the group that did not. However, several points about that study are often overlooked. Their subjects had previously had affected children, so their results may not be applicable to the general population. Many of their subjects came from higher-risk areas than the United States. Perhaps most importantly, the confidence interval around their point estimate was very wide, ranging from an 88% to a 29% protective effect. Thus, it is not obvious what the maximum benefit of food fortification would be in the United States, and weaker evidence from case-control studies suggests that it might be in the range of 50%–60% (3–6).

The US health-care system does not make it easy to determine neural tube defect rates. Many defects are identified by ultrasound or prenatal screening (7) and often are not tallied in vital statistics reports. Thus, using birth and fetal death certificates provides only partial information. US studies on changes in rates after fortification that had to rely on birth and death data with some prenatal diagnosis data found a disappointing drop in neural tube defect rates of 19%–27% (8–10). Fortunately, Canada instituted a very similar fortification program, adding 150 μg of folic acid per 100 g of grain (11). They were able to capture many of the cases that the US system could not, including...
ultrasound-diagnosed cases in some studies (12–16). Their findings were quite different, showing almost a 50% reduction. In addition, there was a positive correlation between the quality of ascertainment and the percentage drop in neural tube defect rates following fortification (17).

In fact, it is not easy to estimate the expected fall in rates or the minimal effective dose to prevent folate-related neural tube defects. The US Food and Drug Administration estimated that women of childbearing age would, on the average, receive 100 μg of folic acid per day from fortified food (18). Because industry added more than the required amount (19), it was later estimated that women were actually receiving approximately 200 μg per day. Because it would have been unethical to give women different doses of folic acid to determine what the minimal effect dose was, my colleagues and I conducted a clinical trial to determine how much folic acid it would take to reach a red-cell folate level in the blood that was known to be protective. On the basis of data from a large Irish study (20), it was possible to show that neural tube defect risk was related to red blood cell folate levels and to construct a curve showing the risk at each level. A red blood cell folate level of 400 ng/mL was associated with a low risk of neural tube defects. We gave women who were not at risk for pregnancy doses of folic acid ranging from 0 to 400 μg per day to see how much their red-cell folate levels would rise and to calculate the protective effect of each dose. We demonstrated that 200 μg of folic acid per day would produce a drop in risk of 41% (21). This was considered the minimal benefit because women did not take the tablets 100% of the time, and food fortification does not depend on compliance. Interestingly, the Canadian data showed a fall between 32% and 54% that was very close to the fall predicted in our trial. These data did not, however, answer a critical question: Were more neural tube defects folic acid preventable? Thus, the data presented here by Mosley et al. (22) add an important piece to the puzzle.

They show that neither periconceptional folic acid supplement use nor dietary folate intake was associated with neural tube defect risk in the National Birth Defects Prevention Study. The authors offer the possible explanation that most folate-related neural tube defects had been prevented because of mandatory fortification. They show that median daily intake of folic acid from fortified foods among case women and control women was in the range of 100–140 μg, an intake that was estimated to reduce the risk of neural tube defects by between 22% and 41% in our Irish study (21). It is noteworthy that the distributions of dietary folic acid intake were similar for cases and controls, indicating that there was no association between dietary folic acid intake and neural tube defects regardless of supplement use or nonuse. The fact that there was no increased risk of neural tube defects among nonusers of supplements who had less than the median daily intake of folic acid from fortified foods suggests that the level of folic acid needed to prevent neural tube defects may be lower than previously appreciated.

There are, however, some limitations to these data. Supplement use and dietary intake data were based solely on maternal report and were subject to recall error because of the long interval between neural tube defect closure and conduct of the interviews (up to 2 years after the expected delivery date). In addition, the results may have been affected by incomplete case ascertainment because some study centers did not consistently include neural tube defects that resulted in elective terminations or stillbirths, although the results were unchanged when only centers with routine collection of prenatally diagnosed cases were analyzed.

Despite these shortcomings, the National Birth Defects Prevention Study has provided us with useful, population-based data on the association between folic acid and neural tube defects after the institution of mandatory fortification in the United States. It is the largest, ongoing study of risk factors for birth defects in the United States, and case medical records are reviewed by experts to ensure that those included in the study meet well-defined clinical criteria. Mothers were queried regarding a large number of risk factors, including obstetric and medical history, environmental exposures, and demographic characteristics, enabling the investigators to adjust for potential confounders and to assess effect modification. The authors were able to gather an impressive amount of data on folate, making it possible to estimate folate bioavailability and to distinguish folic acid in fortified foods from other dietary folate sources.

In short, this study provides the best evidence to date that the US food fortification program has been a success and that the current level of fortification is preventing the folate-related neural tube defects. From the public health perspective, this program has made a major impact on the risk of having a baby with a neural tube defect and has greatly reduced the burden of folate-deficiency anemia in the US population.

However, many issues remain unresolved regarding the benefits and the risks of fortification. Because homocysteine has been shown to be a risk factor for cardiovascular disease and homocysteine can be reduced by taking folic acid, there was great hope that food fortification would reduce cardiovascular disease rates. Over the last decade, many randomized trials of folic acid for secondary prevention of cardiovascular disease have been performed (23). The results have been disappointing. A meta-analysis (23) showed that even a 10% benefit in reducing cardiovascular disease could be ruled out with 84% power. Although some hold out hopes that longer term exposure might be beneficial or that there might be a beneficial effect on stroke (24), these seem unlikely. If folic acid did reduce stroke rates, it would be difficult to explain why it produced no beneficial effect on cardiovascular mortality overall. Could it be producing a counterbalancing increase in coronary artery disease? Moreover, a recent study that treated participants for 7 years found no beneficial effect on stroke (25). The interpretation of US trials is complicated by the fact that controls were exposed to folic acid through fortified foods. Fortunately, there are a sufficient number of trials from areas where fortification is not done that, when all are completed, we will know if there is a very small (<10%) beneficial effect, although it is less certain that we will know whether stroke risk is reduced (26).

The other major unresolved issue regarding fortification is its effect on cancer. It has been recognized for over half a century that folate is an important factor for cancer
growth. Antifolate drugs such as methotrexate are a cornerstone of chemotherapy. Yet there are also studies suggesting that a high-folate diet can protect against cancer (27–31). This is biologically plausible given that folate plays an important role in DNA regulation via methylation and provides 1-carbon atoms for purine and pyrimidine production (32). A recent clinical trial of folic acid to prevent recurrence of colon adenomas (33) illustrates the problem. Subjects who received folic acid were no less likely to develop recurrent adenomas and were significantly more likely to have 3 or more adenomas at longer-term follow-up. Do these results tell us that folic acid increases the growth of premalignant lesions? From a public health perspective, would it be worth a short-term increase in malignant and premalignant lesions if there were a long-term reduction in both? These questions cannot be answered at this point. After reviewing the data from this study, the Food Standards Agency of the United Kingdom elected to go ahead with a recommendation to fortify food and to limit folic acid in other dietary sources to avoid overexposure (34). The Agency has since decided to review data from ongoing trials of folic acid and cancer before it presents a final recommendation on fortification (35).

There are other questions regarding the risks and benefits that go beyond the scope of this invited commentary. Folic acid can produce masking of vitamin B₁₂ anemia, a danger because the neurologic damage can progress irreversibly while the anemia is corrected. It is not known how common this problem is at the doses the American public receives from fortified grain, other fortified food, and supplements. In one study, there was no increase in new cases of B₁₂ deficiency presenting without anemia after fortification (36). High homocysteine levels are also linked to cognitive decline and dementia (37–41), but clinical trials using folic acid to reduce homocysteine have produced directly conflicting results (42, 43).

In summary, there are many unknowns regarding the effect of food fortification with folic acid. This report from Mosley et al. (22) goes a long way toward addressing one of the most important questions: Is fortification preventing the folate-related neural tube defects?

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