Folic Acid Fortification and the Controversy

Folic acid fortification and its impact on public health remain controversial more than 10 years after many countries instituted either mandatory or voluntary flour fortification. In countries with mandatory fortification, the reduction in neural tube defects (NTDs) and some other birth defects has been remarkable. However, excitement over these decreases and immediate enactment of folate fortification in many countries has been tempered with concerns of potential adverse effects on nontarget populations. These issues will be discussed in this and an upcoming column.

Folate and Pregnancy

Folate is a B vitamin required for tissue growth. It is critical during pregnancy because of the one-carbon transfer reactions necessary for the synthesis of DNA and RNA bases, including the purines, adenosine and guanosine, and the pyrimidine, thymidine. The formation of these components and DNA methylation are some of folate’s functions. Folate inadequacy results in DNA changes through the incorporation of uracil (in place of thymidine) into DNA and aberrant patterns of DNA methylation. Thus, folate deficiency during embryogenesis is an established risk factor for NTDs and other birth defects.

The 1998 fortification policy for North America and Chile mandating that grain products be fortified with 140 µg of synthetic, bioavailable folic acid per 100 g of flour has reduced NTDs—most commonly spina bifida and anencephaly—in infants by as much as 50% (3,4,8,10,28). In addition, severe congenital heart disease in Quebec was documented as being decreased by 6% in the period following folate fortification (11). Other positive effects on pregnancy outcomes are attributed to folate fortification. For example, folate supplementation for one year or longer has been shown to reduce the risk of preterm birth (2). A similar trend, albeit of smaller magnitude, was documented by the California Birth Defects Monitoring Program in Berkeley, CA, U.S.A., where folate fortification was associated with reduced incidence of low birth weight and preterm births (25). Other benefits of fortification on brain development and behavior have been indicated. For example, a study in Australia showed that folate inadequacy during early pregnancy was associated with a higher risk of behavioral problems in the offspring (21). In another study of 100 mother-child pairs, low total folic acid intake in early pregnancy, with its resultant lower maternal red blood cell folate concentrations, was associated with higher childhood hyperactivity and peer problem scores in the offspring (23). More data are needed to see if fortification programs address these concerns.

Folate Fortification—Its Effect on Actual Intakes in the United States

Despite the very promising data on birth defect reduction and improved pregnancy and offspring outcomes, there is concern that other nontarget segments of the population may be put at risk by current folate fortification levels. Furthermore, there is fear that the levels chosen for the fortification program fail to adequately raise serum levels of folic acid in the target population. These precise questions were evaluated recently by the U.S. Office of Dietary Supplements and the National Cancer Institute using National Health and Nutrition Examinations Survey (NHANES) data from the period 2003–2006 (1). This analysis confirmed that fortification levels chosen by the U.S. FDA in the 1990s, which were based on consumption models of likely intakes, both addressed needs of the target population and did not put other population segments at risk. Specifically, only 2.7% of the population had daily intakes above the U.S. Institute of Medicine’s upper level of 1,000 µg per day. Furthermore, they found it unlikely that U.S. adults, who consume fortified food and supplements averaging up to 400 µg of folic acid per day, would exceed upper levels for folic acid (30). This analysis also showed that consumption of folate-fortified cereals and/or supplements was associated with higher serum folate and vitamin B-12 and lower homocysteine concentrations. (And consumption of vitamin B-12 supplements was associated with lower methylmalonic acid concentrations.) In a study by the U.S. National Center for Health Statistics, folate blood levels in the United States increased between 1988–1994 and 1999–2000. In subsequent years, the median red blood cell (RBC) folate level of the U.S. population increased from 311 ng/mL in 1999–2000 to 351 ng/mL in 2005–2006 (1). These data show that the folic fortification levels seem to be in the right ball park. Yet, there are benefits and concerns that will be discussed in the remainder of this column and in the subsequent one.

Folic Acid—Its Intake from Food, Benefits, and Concerns

Folic acid has been listed as a nutrient of concern by the 2005 U.S. Dietary Guidelines Advisory Committee (DGAC) (27). Supporting material from DGAC recommends that folate-containing foods should be encouraged particularly by women of childbearing age. Furthermore, it notes that intakes are often below required levels in many sectors of the population, primarily because of a failure to eat folate sources, such as green, leafy vegetables, legumes, and fruits, including avocados and oranges. The NHANES intake data document shows that for 42% of Americans, enriched grains are the only major source of folic acid.
acid in their diets. If fortified cereal is added to the mix, 60% of Americans get their folate from grains and fortified cereals (1). This is good news for the cereal industry (but not good news with respect to intake data on fruit and vegetable consumption). The low folate intake is of concern for all segments of the population because too little folate is related to an increased risk for cancer and coronary disease (22). However, there have been a number of studies and reports that have also expressed concerns about the amount of folate, particularly synthetic folate, in the food supply because of indications that it could potentially increase the risk for some cancers and other chronic diseases and could mask B-12 deficiency in the elderly, thus contributing to senile dementia. In this column, I will review the findings with respect to folate and various cancers. In my next column, I will address folate, cardiovascular disease, dementia, and the elderly.

Folate and Colon Cancer

While epidemiological evidence and plausible mechanisms strongly suggest that folate adequacy lowers the risk of colorectal cancer (CRC) (18), there are no clearcut conclusions regarding high levels of folate being either a cancer inhibitor or promoter. For example, in a study feeding large doses (500–5,000 mug/day) of a synthetic form of folate, there was no measurable impact on adenoma recurrence in the colon. One proposed explanation is that the use of unphysiologically large doses of synthetic folic acid found in supplements fails to offer protection observed with smaller intakes of natural food folates. Further, there is a significant concern that excess folate, especially synthetic folate, may actually favor the growth of certain cancers. One study showed that with intakes of folic acid greater than 400 mug/day, unmetabolized folic acid appears in peripheral blood. Some postulate that this “free” folic acid may actually change physiological response, such as reducing cytotoxicity of natural killer cells (18). Although, one randomized trial failed to show that folate supplementation increased adenoma risk (29). In fact, participants with low plasma folate concentrations at baseline (≤7.5 ng/mL), who received folic acid showed a significant decrease in adenoma recurrence. If folate concentrations were high at baseline (>7.5 ng/mL), supplemental folic acid had no significant effect. This study’s authors concluded that folic acid supplementation may be beneficial among those with lower folate concentrations at baseline. A metaanalysis (7) assessing the effect of folic acid supplementation on colorectal cancer risk shows that the overall risk of an adenomatous lesion was not increased among patients who received folate supplementation for up to three years; it did show increased risk for those who received folate supplementation for longer than three years. The results of the metaanalysis suggest that the risk of an adenomatous lesion with long-term folate supplementation was increased especially for advanced lesions. Rat data also suggest that folic acid supplementation at up to 8 mg folic acid/kg diet may promote the progression of aberrant crypt foci to colorectal tumors (12). A rather nonspecific human study in Chile looked at the rates of hospital discharge due to certain diagnosis before and after the start of their mandatory flour fortification. The authors showed increased colon cancer in patients in the period after fortification and suggest that a folate fortification program could be associated with an additional risk of colon cancer (9). A Norwegian trial of patients with coronary heart disease (5) showed slightly increased cancer risk, especially for lung cancer, and overall mortality, with supplements of folic acid (0.8 mg/day) (a high level), plus vitamin B-12 (0.4 mg/d). Thus, folate’s role in preventing or promoting cancer appears to depend on the folate status of the subject, the dose, and perhaps the form of folic acid.

Folate and Other Cancers

Folate has been shown to reduce the risk of other cancer types. Several epidemiologic studies suggest that higher folate intake is associated with decreased pancreatic cancer risk. Folate from dietary sources was associated with lower prostate cancer risk in a case-control study (24). In the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial cohort, with 51,988 male and 57,187 female participants, folate intake was associated with the reduced risk of pancreatic cancer in women, but not in men (19).

In terms of breast cancer, folate intake did not affect breast cancer risk in case-control studies in Japan, Sweden, and Brazil (6,15,16). However, Brazilian and Swedish women with a certain polymorphism of a folate enzyme had an increase in breast cancer risk with increased folate. One animal study looked at the effects of intrauterine exposure to folic acid. The offspring of rats, where the dams have ingested folate amounts comparable to what North American women might ingest during pregnancy and lactation with fortified foods and prenatal supplements (26), had a significantly lower number of terminal end buds than the pups from the dams fed the control diet. These data suggest that folic acid supplementation provided in utero and during lactation may lower mammary tumor risk in the offspring.

Folate was shown to reduce cervical cancer risk in those women with high plasma folate (>19.8 ng/mL) who also had sufficient plasma vitamin B12 (>200.6 pg/mL). In fact, there was a 70% lower chance of being diagnosed with an aberrant pap smear when compared with women with plasma folate of ≤19.8 ng/mL and plasma vitamin B12 of ≤200.6 pg/mL (20). Thus, higher folate is associated with significantly lower risk of abnormal cervical cells especially when vitamin B12 is sufficient, demonstrating the importance of vitamin B12 in the high-folate environment created by the folic acid fortification program.

Looking at the cancer data in totality, the following emerges: a) diets too low in folate increase cancer risk for many cancer types; b) diets with excessive supplementation have been shown in some studies to have an adverse effect especially on subjects with a certain genetic polymorphism; c) greater understanding is needed of the physiological roles of free, synthetic versus bound folic acid as found in food (17); d) more precise endpoints than those gleaned by comparing hospital discharge rates are needed to accurately assess the effects of folate fortification on cancer risk; and e) levels of folate that are problematic are more likely to be the result of a high use of supplements rather than food fortification.

My next column will look at folate fortification and its relationship to a variety of other endpoints. It will try to address the charge in the title of a recent review “Folic acid fortification: A double-edged sword” (14).

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