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Recent Research on Folate Intake, Rice Products, Fiber Intake, and Enzyme Degradation of Gluten

Impact of Too Little Folate During Pregnancy

The incidence of autism is increasing in the United States and in other countries. The reason for this increase and the causes of autism are not understood, including any potential relationships with the environment, diet, or nutrients. A recent study looked at the role of folic acid in subjects in the Childhood Autism Risks from Genetics and Environment Study (14). In this study children were categorized by developmental category using strict diagnostic criteria. The folate intake of the mothers of three groups of children were compared: 1) mothers whose children had a diagnosis of autism spectrum disorder (ASD) (n = 429); 2) mothers whose children were classified as developmentally delayed (DD) (n = 130); and 3) mothers whose children were developing typically (n = 278). Folate intake was quantified based on the frequency of intake of vitamins, supplements, and breakfast cereals.

Children developing normally had mothers whose mean folic acid intake in the first month of pregnancy was higher than that of mothers of children with ASD. A mean daily folic acid intake of ≥600 µg during the first month of pregnancy versus lower intakes was associated with a 38% reduction in risk of ASD. Further, there was a seeming dose response. The association between folic acid and reduced ASD risk was strongest for mothers and children with methylenetetrahydrofolate reductase (MTHFR) 677C→T variant genotypes. (The MTHFR 677C→T polymorphism is a genetic alteration in an enzyme involved in folate metabolism that causes elevated homocysteine concentrations. This genetic variant has also been associated with increased risk of congenital heart defects [19].) There was also a trend toward an association between lower maternal folic acid intake during the three months before pregnancy and DD children. However, after adjustment for confounders, the association failed to be significant. The data strongly suggest that folic acid intake prior to conception and during very early gestation may reduce ASD risk in those with inefficient folate metabolism. Studies are needed to verify this and identify a mechanism. The data add to our knowledge about folate's important role in neural development.

A major source of folate in the U.S. diet, as well as diets in many other countries, is enriched cereal grain products. U.S. regulations currently mandate the fortification of cereal grain flours with folic acid at 140 µg/100 g. Many ready-to-eat cereals add as much as 400 µg of folic acid per serving, which is the amount found in many dietary supplements.

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Since 1988, when mandatory fortification of flour-based products was implemented, neural tube defects have decreased by more than 30% in the United States, and there have been even greater reductions in many other regions of the world. The U.S. National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, assessed the effect of fortification efforts and folate supplementation in U.S. adults (N = 14,353) 19 years of age or older (15). This sample included the target population of nonpregnant women of childbearing age (n = 4,272) (15).

Median intake of folate was most influenced by the intake of enriched cereal grain products, according to analysis of the data from the National Health and Nutrition Examination Survey. Folic acid intake above the tolerable upper intake level of 1,000 µg/day was associated with dietary supplement usage.

Columnist's Note. Data such as these should give women of childbearing age pause before eliminating enriched and fortified grain foods and the folate they deliver from their diet.

Rice Products, Arsenic, and Chronic Disease

Brown rice is the grain with the lowest dietary fiber content. Nonetheless, it does show hypocholesterolemic activity, the mechanism of which is not well understood. One possible mechanism for the cholesterol lowering effect of rice bran is the action of some of the phytochemicals found in brown rice, especially γ-oryzanol—a unique mixture of triterpene alcohol and sterol ferulates. A cell-culture model was used to test the effect of γ-oryzanol on the uptake of cholesterol into Caco-2 intestinal cells and cholesterol metabolism (10). In the cell-culture model an excess of γ-oryzanol reduced the uptake of cholesterol and inhibited a key enzyme in cholesterol synthesis—3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. Thus, the cholesterol lowering observed with brown rice may be due to impaired uptake of cholesterol by enterocytes and inhibition of HMG-CoA reductase activity.

Rice and brown rice syrup have been highlighted in numerous recent news reports because of concerns about arsenic. All cereal grains, regardless of whether they are cultivated organically or conventionally, take up inorganic arsenic from the soil in which they are grown. Rice is particularly efficient at taking up arsenic from the soil. Inorganic arsenic is a cause for concern in many countries, including Argentina, Bangladesh, Chile, China, India, Mexico, Thailand and the United States. In countries such as Bangladesh in which there are high levels of arsenic in the soil as well as in rice, other plants, and water, the population is at risk for arsenicosis. Arsenicosis occurs with chronic arsenic

exposure, usually from drinking water, over long periods of time (often from 5 to more than 20 years).

In contrast to most other metals, the inorganic form of arsenic is the most toxic. For many toxic and heavy metals, the organic form, such as methyl mercury, is the more toxic form. As a result, the arsenic found in fish, which is mostly organic, lacks toxicity.

Like all toxic metals and most minerals, the highest concentrations of arsenic are found in the bran. Hence, brown rice has higher levels of arsenic than refined forms. However, a recent study emphasized the fact that just because a particular compound is present, it does not mean that is absorbed in the body. The arsenic levels of 31 rice samples (60% domestic and 40% foreign) purchased in markets in New York City were tested (6). Total arsenic ranged from 0.090 ± 0.004 to 0.85 ± 0.03 mg/kg, with a mean value of 0.275 ± 0.161 mg/kg. Rice samples with relatively high total arsenic levels (>0.20 mg/kg; $n = 18$) were put through a system simulating digestion in the human gastrointestinal tract. The amount of bioaccessible arsenic ranged from 53 to 102%. The bioaccessibility of different types of rice, from most to least, was ranked as follows: extra long grain, long grain, long grain parboiled, and brown. Like many trace minerals, such as iron, the presence of arsenic in the bran layer does not necessarily mean that the metal will be absorbed (16).

Organic brown rice syrup is a sweetener used by consumers and organic processors as an alternative to sucrose and high-fructose corn syrup. Recent studies showing it to be a source of arsenic in toddler formula and some cereal/energy bars has created fear and prompted calls for reduction of arsenic to levels found in drinking water (8). The authors of the paper noted that an organic toddler milk formula containing organic brown rice syrup had total arsenic concentrations up to six times higher than the U.S. Environmental Protection Agency's (EPA) safe drinking water limit. While this is a accurate statement, it is not a useful comparison because standards for drinking water are set to reflect the widespread use of water as an ingredient in everything from soups to breads to beverages, as well as its role in the boiling and steaming of foods and the cleaning of food contact materials. Further, arsenic in water is more bioaccessible than arsenic in food (1). Consumers should also be aware that the brown rice syrup was found in toddler formulas not infant formulas, as was erroneously reported by some media. Formula is not commonly given to toddlers since most toddlers move to drinking milk. Finally, the authors note that they could only find two formulas containing organic brown rice syrup (7).

Following reports during the past year of arsenic found in rice and apple juice, the U.S. Food and Drug Administration has expanded its surveillance of rice to ensure that consumers are protected against this naturally occurring metal. The EPA has classified inorganic arsenic as a Group A, human carcinogen (18). Despite this, some studies suggest that inorganic arsenic is an essential dietary nutrient for goats, chicks, and rats. In 1988 the EPA convened a Technical Panel on Arsenic that concluded that "if arsenic is a required nutrient for humans, current environmental arsenic exposures are not known to produce human arsenic deficiency." The EPA has concluded that the essentiality of arsenic, although not rigorously established, is plausible (17).

The effect of any food toxicant depends on the individual person and their nutritional and health status. In countries where arsenic is naturally high in soil and water, the adverse effects of arsenic are more pronounced when diets are marginal or inadequate (11,12). Higher intakes of protein, methionine, and cysteine and other sulfur compounds, such as those found in alliums and brassica, increase arsenic excretion. Diets high in selenium (which is obtained from flours and foods from areas where selenium is high, such as the northern Great Plains of North America) can counteract the absorption and effects of arsenic. Zinc, calcium, potassium, and other metals can also help reduce arsenic toxicity.

Methyl transfers are also impaired with high levels of arsenic. Since methyl transfers can be adversely affected, diets adequate in B_{12} and folate have been shown to be important in countering arsenic toxicity. Antioxidants in the diet, such as vitamins E and C and lipoic acid, can lower reactive oxygen species and other adverse products of arsenic in the body (4,9). Diets high in fiber and low in animal fat have also been shown to protect against arsenic toxicity (2,13).

Columnist's Note. Every attempt should be made to reduce exposure to arsenic and other toxic metals. Measures should be taken agronomically to reduce its uptake by plants. For consumers, the most important strategy to avoid arsenic toxicity is to follow dietary recommendations regarding consumption of optimal amounts ofother minerals, fats, and good quality proteins (either through complementarity or by including meat, fish, and eggs in the diet) with adequate amounts of sulfur amino acids and the regular ingestion of a source of B_{12} and folate. Consumers should make an effort to eat the suggested amounts of grains, whole grains, fruits, legumes, and vegetables replete with vitamins, minerals, and dietary fiber and strive to include a variety of foods from diverse regions to ensure ingestion of a wide array of nutrients and phytochemicals and a minimum of toxicants. Consumers should focus on including a variety of the many grains and whole grains that are available in order to ingest a mixture of fiber types and obtain adequate folic acid by making "half of your grains whole."

Fiber Intake Associated with Lower Total and Heart Disease Mortality

Two reports from the European Prospective Investigation into Cancer and Nutrition show that higher dietary fiber intakes were associated with lower overall and specific disease mortality (3,5). The relationship between fiber intake, mortality, and cause-specific mortality was assessed in 452,717 men and women. Food intakes in the cohort were documented both by country-specific food frequency questionnaires (FFQs) and 24 hr diet recalls, which were used to verify the data from the FFQs. Each 10 g/day increase in dietary fiber intake decreased the risk of total mortality by 10%. There was also a 10–20% drop in mortality from circulatory and inflammatory diseases. The largest drops in death rates were seen with digestive and respiratory diseases, for which the risk dropped between 20 and 40%. There was also a 10% or greater drop in risk from smoking-related cancers; however, no effect was seen with non–smoking-related cancers. The associations were stronger for fiber from cereals and vegetables than from fruits. Neither body mass index nor physical activity affected the relationships, but the associations were more robust in smokers and participants who consumed one-half ounce (≈18 g) or more of alcohol per day. The authors (5) concluded that the results support the recommendations for high dietary fiber intake for health maintenance.

The second study (3), which used a portion of the cohort (306,331 men and women from eight European countries), focused on death from ischemic heart disease (IHD). Each 10 g/

day increase in dietary fiber intake was associated with a 15% lower risk of IHD. The reduction in risk based on food fiber type was not significantly different. For each 5 g/day increase in cereal fiber intake, the risk was reduced by 9%; for each 2.5 g/day increase in fruit fiber intake, the risk was reduced by 6%; and for each 2.5 g/day increase in vegetable fiber intake, the risk was reduced by 10%. The authors (3) concluded that the reduction in IHD mortality across all fiber types (fruit, vegetable, and cereal) was not different.

Potential of Enzymes to Make Wheat Less Problematic for Those with Gluten Intolerance

The digestion of gluten results in some peptides that do not readily break down in the human gut. These peptides can interact and cause problems in people who are predisposed to celiac disease. Recent studies show that gluten and its resulting peptides can be degraded by prolyl endopeptidases (20). Microbial sources of transglutaminase could be used to selectively modify glutamine residues of intact gluten through transamidation. In beverages, gluten peptides could be polymerized and removed by filtration. Thus, gluten-containing materials could potentially be rendered less problematic for most celiac patients through the use of these enzymes in the production of foods intended for this population or through ingestion of these enzymes with or immediately prior to the ingestion of a gluten-containing food.

References

1. Akter, K. F., Owens, G., Davey, D. E., and Naidu, R. Arsenic speciation and toxicity in biological systems. Rev. Environ. Contam. Toxicol. 184:97, 2005.
2. Basu, A., Mitra, S., Chung, J., Mazumder, D. N. G., Ghosh, N., Kalman, D., von Ehrenstein, O. S., Steinmaus, C., Liaw, J., and Smith, A. H. Creatinine, diet, micronutrients, and arsenic methylation in West Bengal, India. Environ. Health Perspect. 119:1308, 2011.
3. Chuang, S. C., Norat, T., Murphy, N., Olsen, A., Tjønneland, A., et al. Fiber intake and total and cause-specific mortality in the European Prospective Investigation into Cancer and Nutrition cohort. Am. J. Clin. Nutr. 96:3, 2012.
4. Chung, C. J., Pu, Y. S., Chen, Y. T., Su, C. T., Wu, C. C., Shiue, H. S., Huang, C. Y., and Hsueh, Y. M. Protective effects of plasma alpha-tocopherols on the risk of inorganic arsenic-related urothelial carcinoma. Sci. Total Environ. 409:1039, 2011.
5. Crowe, F. L., Key, T. J., Appleby, P. N., Overvad, K., Schmidt, E. B., et al. Dietary fibre intake and ischaemic heart disease mortality: The European Prospective Investigation into Cancer and Nutrition—Heart study. Eur. J. Clin. Nutr. DOI: 10.1038/ejcn.2012.51, 2012. (Electronic publication prior to print)
6. He, Y., Pedigo, C. E., Lam, B., Cheng, Z., and Zheng, Y. Bioaccessibility of arsenic in various types of rice in an in vitro gastrointestinal fluid system. J. Environ. Sci. Health B 47:74, 2012.
7. Holtcamp, W. Suspect sweetener: Arsenic detected in organic brown rice syrup. Environ. Health Perspect. 120:A204, 2012.
8. Jackson, B. P., Taylor, V. F., Karagas, M. R., Punshon, T., and Cottingham, K. L. Arsenic, organic foods, and brown rice syrup. Environ. Health Perspect. 120:623, 2012.
9. Liu, C. B., Feng, Y. H., Ye, G. H., and Xiao, M. Effects of α-lipoic acid and vitamin C on oxidative stress in rats exposed to chronic arsenic toxicity. (In Chinese) Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi 28:891, 2010.
10. Mäkynen, K., Chitchumroonchokchai, C., Adisakwattana, S., Failla, M., and Ariyapitipun, T. Effect of gamma-oryzanol on the bioaccessibility and synthesis of cholesterol. Eur. Rev. Med. Pharmacol. Sci. 16:49, 2012.

11. Milton, A. H., Hasan, Z., Shahidullah, S. M., Sharmin, S., Jakariya, M. D., Rahman, M., Dear, K., and Smith, W. Association between nutritional status and arsenicosis due to chronic arsenic exposure in Bangladesh. Int. J. Environ. Health Res. 14:99, 2004.
12. Milton, A. H., Shahidullah, S. M., Smith, W., Hossain, K. S., Hasan, Z., and Ahmed, K. T. Association between chronic arsenic exposure and nutritional status among the women of child bearing age: A case-control study in Bangladesh. Int. J. Environ. Res. Public Health 7:2811, 2010.
13. Mitra, S. R., Mazumder, D. N., Basu, A., Block, G., Haque, R., Samanta, S., Ghosh, N., Smith, M. M., von Ehrenstein, O. S., and Smith, A. H. Nutritional factors and susceptibility to arsenic-caused skin lesions in West Bengal, India. Environ. Health Perspect. 112:1104, 2004.
14. Schmidt, R. J., Tancredi, D. J., Ozonoff, S., Hansen, R. L., Hartiala, J., Allayee, H., Schmidt, L. C., Tassone, F., and Hertz-Picciotto, I. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am. J. Clin. Nutr. 96:80, 2012.
15. Tinker, S. C., Cogswell, M. E., Hamner, H. C., and Berry, R. J. Usual folic acid intakes: A modelling exercise assessing changes in the amount of folic acid in foods and supplements, National Health and Nutrition Examination Survey, 2003–2008. Public Health Nutr. 15:1216, 2012.
16. Trinidad, T. P., Mallillin, A. C., Sagum, R. S., Briones, D. P., Encabo, R. R., and Juliano, B. O. Iron absorption from brown rice/brown rice-based meal and milled rice/milled rice-based meal. Int. J. Food Sci. Nutr. 60:688, 2009.
17. U.S. Environmental Protection Agency. Special report on ingested inorganic arsenic. Skin cancer; nutritional essentiality. Rep. No. EPA-625/3-87/013. Risk Assessment Forum, EPA, Washington, DC, 1988.
18. U.S. Environmental Protection Agency. Arsenic compounds, rev. 2000. Published online at www.epa.gov/ttn/atw/hlthef/arsenic.html. EPA, Washington, DC, 2007.
19. van Beynum, I. M., den Heijer, M., Blom, H. J., and Kapusta, L. The MTHFR 677C→T polymorphism and the risk of congenital heart defects: A literature review and meta-analysis. Q. J. Med. 100:743, 2007.
20. Wieser, H., and Koehler, P. Detoxification of gluten by means of enzymatic treatment. J. AOAC Int. 95:356, 2012.