Food Policy and Public Health: Fact and Fantasy

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The Folic Acid Story

- **Learning Goals**

- Discuss the history of US food fortification policy including the rationale behind folic acid fortification
- Describe current research findings on the effects of folic acid in different age groups and physiologic states
- Consider use of an evidence-based framework for folic acid recommendations for individuals
- Apply lessons from folic acid fortification to future food policy

Background Information

- Folate - two dietary forms:
  - Food folate
    - Folate is pteroylpolyglutamate - reduced form with multiple glutamic acid groups
    - Spinach (132 mcg), broccoli (84 mcg), lentils (180 mcg), orange juice (74 mcg), peanuts (62 mcg)
    - Available in most foods (approximately 10 mcg)
  - Supplemental folic acid
    - Folic acid is pteroylmonoglutamic acid – more stable oxidized form with 1 glutamic acid group
    - Cereal (200 mcg – 400 mcg), bread (80 mcg)
    - Multivitamin supplements (400 mcg)

Recommended Intake

- Dietary Reference Intake:
  - As "dietary folate equivalents" (DFE)
    - Bioavailability
      - Food folate: 50%
      - Folic acid: 85-100%
    - Infants 65-80 mcg
    - Children 1-3 150 mcg
    - Children 4-8 200 mcg
    - Males and Females 9-13 years 300 mcg
    - Males and Females 14+ years 400 mcg *
    - Pregnancy 600 mcg *
    - Lactating 500 mcg *
- *Women of child-bearing age women should consume 400 mcg from supplements or fortified foods in addition to food folate

Tolerable Upper Intake Level

- Tolerable Upper Intake Level (UL)* – includes intake from fortified foods or dietary supplements or both, and does NOT include naturally occurring food folate.
  - Infants – ND
  - Children 1-3 years – 300 mcg
  - Children 4-8 years – 400 mcg
  - Males, Females 9-13 years – 600 mcg
  - Males, females 14-18 years – 800 mcg (including pregnant and lactating females)
  - Males, females 19+ years – 1,000 mcg (including pregnant and lactating females)

*Historically, the UL is based on the theoretical potential that excessive folic acid intake may mask Vitamin B12 deficiency resulting in neurologic effects.

Folate Metabolism

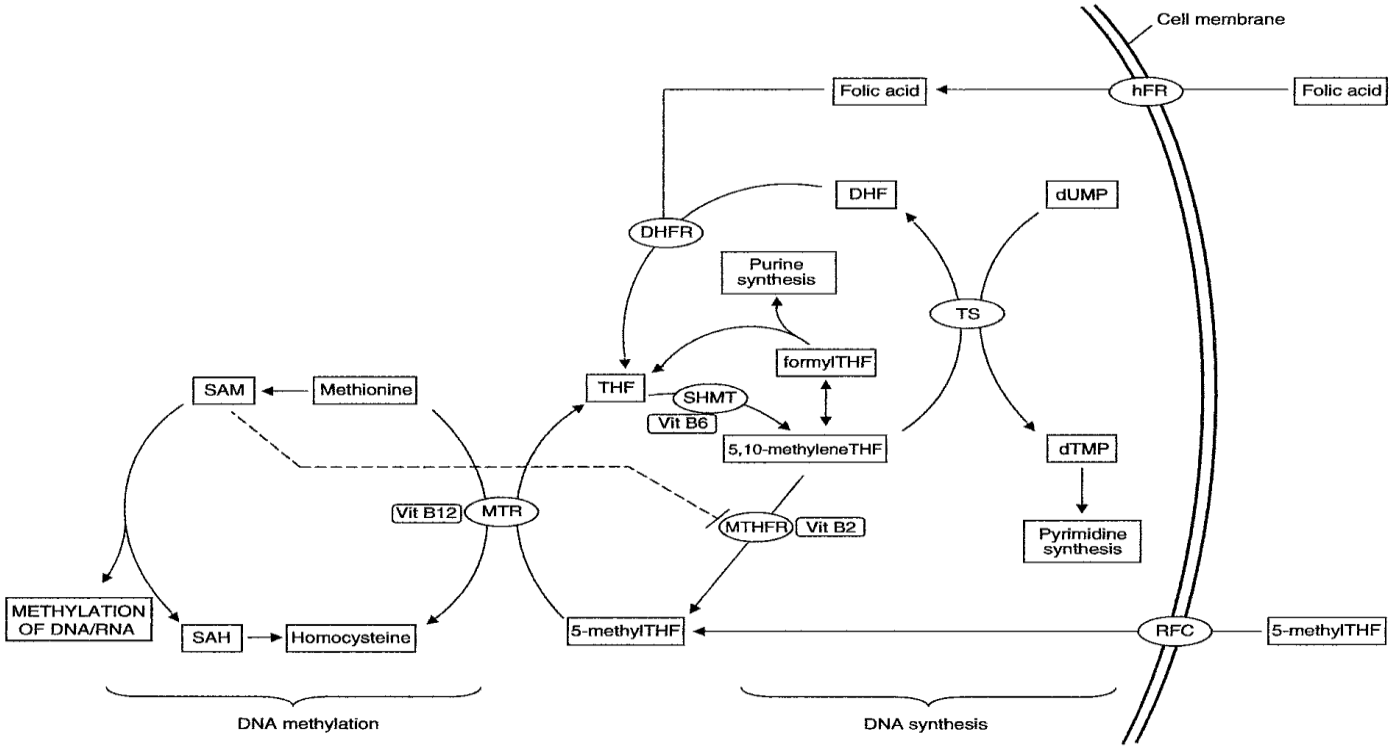
- Food folate
  - Food folate is absorbed in the upper small intestine via active carrier
  - The active carrier is saturated at about 200 mcg folate, the amount typically found in food
  - Within the intestinal cell it is converted into 5-methyl THF and transported to body cells.
- Supplemental folic acid
  - Folic acid is absorbed in the upper small intestine by the same active carrier but is typically in 400 mcg or more quantities
  - Anything above 200 mcg will be absorbed by passive diffusion
  - Within the intestinal cell it is transformed into 5-methyl THF and transported to body cells
  - Intake over 400 mcg will saturate the enzyme that converts it into 5-methyl THF, resulting in free folic acid transport to body cells

Folate Metabolism

- Folate and folic acid enter body cells in the same way as they enter intestinal calls (active carrier or passive diffusion)
- Both are converted to THF for cellular function but through different pathways
- Normal biochemical role:
  - DNA synthesis
  - Amino acid metabolism
  - DNA methylation (“epigenetics”)

Choi, Sang-Woon and Friso, Simonetta. Epigenetics: A New Bridge between Nutrition and Health. Adv. Nutr 2010; 1:8-16.

Folate Metabolism



From: Hubner, R. A. & Houlston, R. S. (2009). Folate and Colorectal Cancer Prevention. *British Journal of Cancer, 100,* 233 – 239.

Folate Deficiency

- Historical Summary of Folate Research (1980s and 1990s)
  - Widespread folate deficiency (20%) in US population noted in NHANES data in the 1980s and 90s
  - Positive effect on risk of neural tube defects shown in clinical trials of supplemental folic acid (early 1990s)
  - Epidemiologic (population) data showed that low folate intake was associated with increased cancer risk (research focused on colon cancer)
  - It was hypothesized that folate deficiency might also be associated with increased risk of CVD through its interaction with homocysteine metabolism.

Folic Acid Fortification

- US Food Policy: mandatory fortification of grains with 140ug folic acid/100g grain began in 1998.
  - Grains, instead of vegetables, became the largest source of folate in the US diet.
  - Folate deficiency significantly decreased in the US population
  - NTD births significantly decreased in the US population

Junod, S.W. Folic Acid Fortification: Fact and Folly. Food and Drug Law Institute, 2001.

The Folic Acid Story

Happy Ending

Fact or Fantasy?

The Folic Acid Story - Part II

Fantasy

Monitoring of any fortification policy is required to assess if continued research indicates that the intended policy is effective and whether there are any negative outcomes.

Registered Dietitians as the food and nutrition experts need to be aware of current research and be involved in the conversation about the role of specific nutrients for chronic disease prevention.

This is an important emerging area of dietetic practice that RDs are uniquely qualified for in regard to the wider healthcare arena.

Folic Acid Story Part II

Current Research Questions:

1. What is intake after folic acid fortification?
2. Is there potential for harm from too much folic acid?
3. Do we know any more about the optimal level of folic acid intake for individuals and populations?

Folate Intake

- NHANES Population Data
  - The mean dietary total folate intake of the population increased by 76 µg/d (28%), from 275 µg/d before fortification to 351 µg/d after fortification.
  - High folic acid intake is generally related to dietary supplements, not food fortification *except…*
  - Food fortification in children may cause high intakes folic acid in some children.

http://www.cdc.gov/nchs/ppt/nchs2010/25_Pfeiffer.ppt from *Dietrich M et al. J Am Coll Nutr 2005 and*
Bailey, R.L. et al. Dietary Supplement Use in the United States 2003-2006. J. Nutr 2011; 141:261-266

Folic Acid Intake

- At-risk for inadequate intake:
  - Women of child-bearding age have not reached optimal folic acid intake levels.
  - Health disparities also exist: 29% of non-Hispanic black women have been shown to have inadequate intake.

*"To reduce the risk of NTDs for women capable of becoming pregnant, the recommendation is to take **400 µg folic acid daily** from fortified foods, supplements, or both in addition to consuming food folate from a varied diet".*

http://www.cdc.gov/nchs/ppt/nchs2010/25_Pfeiffer.ppt and

Bailey, R. et al. Total dietary folic acid intake from foods and dietary supplements in the United States: 2003-2006. Am. J. Clin Nutr 2010; 91:231.

Folic Acid Intake

- At risk for excessive intake:
  - Older adults
    - > 50 years, 5% exceed UL for folic acid intake
    - > 60 years - 40% have circulating **unmetabolized** folic acid levels
  - Children -
    - 1-13 years
      - 5 % 1-8 year olds exceed UL for folic acid from fortified foods
      - 30-66% who use supplements exceeded UL

- Bailey, R.L. et al. Unmetabolized serum folic acid and its relation to folic acid intake from diet and supplements in a nationally-representative sample of adults aged greater-than or equal to sixty years in the United States. Am J. Clin Nutr 2010; 92:383
- Bailey, R.L. et al. Total folate and folic acid intakes from foods and dietary supplements of US children aged 1-13 years. Am J. Clin Nutr 2010; 353-8.

Folic Acid Effects

- Why is excessive intake a potential problem?
  - Physiologic effects
    - Doses above 200-400 mcg (normally found in supplements or fortified cereal) by-pass of normal physiologic control mechanisms
    - Result is circulating unmetabolized folic acid
  - Biochemical effects
    - Effects of chronically high blood and cellular folic acid levels are unknown
  - Potential issues:
    - Effect on enzymes that influence folate metabolism
    - Increased DNA synthesis from increased
    - Epigenetic influences
      - Hypermethylation of DNA or other DNA-effector molecules (histones)

Folic Acid Effects

- Animal Studies – colorectal cancer in rats
  - Folate deficiency increases cancer development
  - Folate in physiologic levels inhibits cancer formation
  - High doses folic acid increases cancer – especially in the presence of pre-cancerous cells
    - Mechanism – theoretical
      - Support of DNA synthesis in cancer calls
      - Epigenetic – hypermethylation of DNA may turn off tumor suppressor genes
  - Application to humans questioned – previous rat studies had induced cancer; newer studies are looking for rats that develop spontaneous colon cancer in order to better study cellular mechanisms that are affected by high folic acid levels

- Sanderson, P., Stone, E., Kim, Y-I, Mathers, J. C., et al. (2007). Folate and Colo-rectal Cancer Risk. *British Journal of Nutrition, 98,* 1299 – 1304.

Folic Acid Effects

- Ecological Studies
  - Some researchers have hypothesized that an uptick in CRC incidence in 1996-1998 in the US is due to folic acid fortification.
    - Biologically plausible from animals studies
    - Mortality continued to decline throughout the same period so this may indicate increased screening rather than incidence.
    - An often-cited study from Chile showed increased rates of colorectal cancer diagnosis in hospital patients in a 10 year period after mandatory fortification
  - A closer look at changing patterns of cancer incidence, mortality and survival rates may be indicated in response to increased folic acid levels.

Folic Acid Effects

- Epidemiological (observational) studies
  - Generally, food folate alone or combined with supplemental folic acid has not shown an association with increased cancer incidence in data from the US National Health and Nutrition Examination Survey through early 2000 – **before food fortification**
  - Studies since fortification have looked at various cancer rates in populations and outcomes have been inconsistent in the US and internationally
    - Cancer of breast, gastric, colorectal, lung, pancreas, cervix, and prostate
    - Positive, neutral, and negative associations of cancer incidence with folic acid intake have been observed
    - Folic acid is protective when folate deficiency exists
    - Unknown effects of high unmetabolized folic acid levels

Folic Acid Effects

- Clinical Studies
  - *Cole, B. F., Baron, J. A., Sandler, R. S., Haile, R. W., et al. (2007). Folic Acid for the Prevention of Colorectal Adenomas: A Randomized Clinical Trial. JAMA, 297:21, 2351.*
  - Double-blind placebo-controlled trial that used 1000 micrograms folic acid/day to test the effect of folic acid or aspirin on adenoma recurrence
  - 1, 021 healthy subjects between 21 and 80 years
  - At least one histologically confirmed adenoma within 16 months before recruitment and a complete colonoscopy with all polyps removed within 3 months of enrollment
  - Results: Significantly increased rate of multiple adenomas in the folic-acid supplemented group at after 6 years

Folic Acid Effects

- Clinical Studies
- *Wu, K., et al. A randomized trial on folic acid supplementation and risk of recurrent colorectal adenoma. Am J Clin Nutr 2009; 90: 1623.*
- Double-blind placebo-controlled trial that used 1000 micrograms folic acid/day to test the effect of folic acid on adenoma recurrence
- 672 participants between 50 and 78 years
- Part of two large prospective cohorts – the Health Professionals Follow-Up Study and the Nurses Health Study
- Had a history of colorectal adenoma confirmed by medical record review and planned on having another endoscopy < 4 years after initiation of the trial (1996-2004)
- Results: Supplemental folic acid had no significant affect on adenoma recurrence

Folic Acid Effects

- The role of folic acid in the periconceptional period, during pregnancy, and early childhood has also been questioned in regard to health outcomes per its role in NTD prevention
  - Childhood health outcomes – little research, most is speculation (?)

- Smith, A. David. Folic Acid Nutrition: What about the little children? (Letter to the Editor). Am J Clin Nutr 2010; 91:1408.

  - Childhood cancer
    - One case-control study - decreased central nervous system tumors
    - One case-control study – no effect on childhood acute lymphoblastic leukemia
    - increased cancer incidence ?

- Ross, J. and Davies, S. Recent report in the etiology of childhood cancer: “Greatest Hits”. Pediatr Blood Cancer 2004; 42: 3-7.

Folic Acid Effects

- Autism and other developmental conditions ?
  - Ecological association between folic-acid fortification and increased incidence of autism spectrum disorders
  - No studies ?
  - Increased screening and diagnosis as a cause for increased rates of autism is a debated in the field of autism
  - Many autism studies have shown other associated factors

- Leeming, R. and Lucock, M. Autism: Is there a folate connection? J Inherit Metab Dis 2009; 32:400-402

- Allergic Disease and Asthma ?
  - Ecological Association between folic acid fortification and increased incidence of food allergies in children
  - One prospective observational study – greater likelihood of asthma by 3.5 years of age in children of mothers who took folic acid in supplements in the third trimester of pregnancy

- Whitrow, MJ et. al. Effect of supplemental folic acid in pregnancy on childhood asthma: a prospective birth cohort study. Am J. Epidemiology 2009; 170: 1486-93.

Folic Acid Risks ?

- Further studies need to examine the specific effects of high circulating folic acid on cancer and other health and developmental outcomes, in light of possible epigenetic effects
- A particular emphasis should be placed on individuals and populations who **may** be most at risk for possible negative effects:
  - People previously diagnosed with cancer
  - People over 50 who may harbor pre-cancerous cells (colo-rectal cancer, postmenopausal women/breast cancer, men/prostate cancer, etc.)
  - Infants, children, and during the pre-natal period due to nervous system development

The Role of the RD

- Assess and evaluate folic acid intake carefully in “higher risk” individuals
  - Be aware of sources of folic acid in fortified foods, supplements, and drugs
  - Evaluate intake for the “right amount” per age and physiologic status
  - Educate high-risk groups about avoiding supplemental folic acid in supplements and/or foods/beverages so that the UL is not exceeded
  - Consider:
    - Multivitamin supplement – 200 mcg(child), 400 mcg (adult), 800 mcg (pre-natal)
    - Cereal – 200 - 400 mcg
    - Grain servings - 80 mcg
    - Oral contraceptive – Beyaz 400 mcg

- Mason, J. Revisiting the Goldilocks Phenomenon: Folate and Colon Cancer Risk. Am J Gastroenterology 2010; 105:1914-1916

The Role of the RD

- Emphasize a total diet approach with patients and clients for best health outcomes in the general population
  - Dietary Guidelines/MyPyramid
  - DASH Diet
  - Example: Lean Beef
    - 27 g protein
    - 2.2 mg iron
    - 4.8 mg zinc
    - 230 mg potassium
    - 9 mcg folate
    - Riboflavin, Vitamin B6, B12, selenium, pantothenic acid

Position of the American Dietetic Association: Total Diet Approach to Communicating Food and Nutrition Information. JADA 2007; 107:1224

The Role of the RD

- Future Practice
  - The Science of Epigenetics
  - American Dietetic Association Evidence Analysis Process
    - The needs and effects of folic acid in individuals and populations will continue to be evaluated through increased research on epigenetic mechanisms and evidence-based analysis of human studies
    - Other nutrients currently in the same category include Vitamin D and omega-3 fatty acids

Choi, Sang-Woon and Friso, Simonetta. Epigenetics: A New Bridge between Nutrition and Health. Adv. Nutr 2010; 1:8-16.

http://www.adaevidencelibrary.com/default.cfm?auth=1

The Role of the RD

Fact:

Practice guidelines and public health decisions about folic acid and other nutrients and their role in health and disease processes will continue to be updated based on further research.

Stay informed and stay tuned!