Food for Thought: Implications for Public Health Practice

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Overview

- Current folic acid public health policies
- Corn masa flour-fortification efforts
- Safety issues
- Implications for public health practice
Public Health Recommendations/Policy: Folic Acid Intake- NTD Risk Reduction

US Public Health Service & Institute of Medicine:

- All women capable of becoming pregnant
- 400 μg folic acid/day

- Vitamins
- Fortified foods

- Folate from a varied diet (+RDA)
Dietary Guidelines: Folic Acid

• Dietary Guidelines Committee published preliminary report -summer 2010
  – comment period prior to publication of final guidelines

• Preliminary Guideline:
  – “women of reproductive capacity should continue to be counseled to select foods high in folate, and when necessary to take a folic acid supplement to meet their folate requirement”

• Numerous comments regarding the inappropriateness of the wording
Wording in final Dietary Guidelines 2010 changed to reflect comments:

“All women capable of becoming pregnant are advised to consume 400 mcg of synthetic folic acid daily (from fortified foods and/or supplements) in addition to food forms of folate from a varied diet.”
What is Healthy People 2020?

- Objectives: 10 year targets to guide health promotion and disease prevention efforts (US Department Health and Human Services)
- Healthy People 2020 4th of initiative
- Two folic acid-related maternal-infant-child health objectives
Objective 1

“Increase proportion of women of childbearing potential with intake of at least 400 µg of folic acid from fortified foods or dietary supplements”

- Baseline: 23.8% of non-pregnant females aged 15-44 y usual daily total intake ≥400 µg folic acid
  - fortified foods or supplements- 2003-2006
- Target 26.2%
Maternal Infant Child Health Objective

Objective 2

• “Reduce the proportion of women of childbearing potential who have low red blood cell folate concentrations”
  – Baseline: 25% <195 ng/ml (25th percentile; 2003-06)
  – Target: 22.5%
FDA Mandated Folic Acid Fortification

- FDA mandated folic acid fortification -1998
  - NTD reduction only basis

- Enriched cereal grain products
Effect of Folic Fortification on Blood Folate in US
Decrease in Number of Spina Bifida-Affected Pregnancies in the US Post-Fortification

Source: National Birth Defects Prevention Network
Could Decrease in Neural Tube Defects be Due to Increase in Folic Acid Supplement Use?
Impact of Recommendation to Take Supplements on Supplement Use - Women of Reproductive Age

All women age 18-45, March of Dimes Gallup Survey, 1995-2005
Reduction in NTDs Linked to Consumption of Fortified Foods not Supplement Use
Hispanics Higher NTD Rates than Non-Hispanics

- Hispanics: higher NTD rates/10,000 births pre and post-fortification

<table>
<thead>
<tr>
<th></th>
<th>Pre-fortification</th>
<th>Post-fortification</th>
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</thead>
<tbody>
<tr>
<td>Hispanics</td>
<td>10.34</td>
<td>7.02</td>
</tr>
<tr>
<td>Non-Hispanic whites</td>
<td>7.92</td>
<td>5.35</td>
</tr>
</tbody>
</table>

Williams et al. Ped 2005
Potential Explanations for Higher NTD Rate Hispanics

• Lower proportion Hispanic women consume $\geq 400 \, \mu g/d$ vs non-Hispanic white women
  – Williams et al. Pediatrics 2005

• Hispanics less likely to take supplements than non-Hispanic whites
Corn Masa Flour: Not Fortified

- Corn meal products manufactured in/imported from other countries
  - not fortified
- Dietary staple of Hispanics
  - may contribute to the disproportionate number of NTD cases among Hispanic women in US
Targeted Folic Acid Intervention Needed for Hispanics

- Hamner et al. (AJCN 2009)
- Estimated impact of folic acid fortification of corn masa flour for Mexican American women of reproductive age
  - NHANES 2004-06
- Predicted increased folic acid intake ~19%
FDA Petition to Fortify Corn Masa Flour Currently Being Developed

- CDC
- Spina Bifida Association
- March of Dimes
- GRUMA Manufacturer
- University Scientists
Safety Concerns

• Cancer risks
  – Are risks increased or decreased with increased folic acid intake?

• Masking diagnosis of vitamin B12 deficiency
  – Does increased folic acid interfere with diagnosis of vitamin B12 deficiency?

• “Unmetabolized” oxidized folic acid in blood
  – Are there safety issues?
Folic acid a double-edged sword
Too much gives you cancer – but too little isn’t good for you either
By DR. RICHARD BELIVEAU

Last Updated: 4th May 2009, 5:05am
Cancer

- Protective Effect - observational studies
  - Diets high in dietary folate (fruits, green leafy vegetables) associated with reduction in risk for cancer
Folic Acid Fortification Hypothesized to Increase Colorectal Cancer Risk

Hypothesis

A Temporal Association between Folic Acid Fortification and an Increase in Colorectal Cancer Rates May Be Illuminating Important Biological Principles: A Hypothesis

Joel B. Mason,1,2 Aaron Dickstein,2 Paul F. Jacques,1 Paul Haggarty,3 Jacob Selhub,1 Gerard Dallal,1 and Irwin H. Rosenberg1,2

1Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University; 2Tufts University School of Medicine, Boston, Massachusetts; and 3Rosetti Research Institute, University of Aberdeen, Aberdeen, United Kingdom

Colorectal Cancer Incidence in USA 1986-2002

From March 1996 folic acid fortification could be introduced
From January 1998 folic acid fortification was mandatory

NCI Surveillance Epidemiology and End Results (SEER) US Mortality Rates for Colon/Rectal Cancer, 1969-2004

[Graph showing trends in mortality rates per 100,000 for males, females, and both genders from 1969 to 2004.]
## Cancer

- Meta-analysis (n=37,485) intake of folic acid-containing supplements no increased risk of cancer incidence or mortality

### Meta-analysis Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment group (n=17783)</th>
<th>Control group (n=17820)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOST12</td>
<td>65 (6.3)</td>
<td>72 (7.0)</td>
<td>0.94 (0.61-1.47)</td>
</tr>
<tr>
<td>WENBIT14</td>
<td>81 (5.3)</td>
<td>63 (4.1)</td>
<td>1.32 (0.86-2.04)</td>
</tr>
<tr>
<td>VISP9</td>
<td>92 (5.0)</td>
<td>95 (5.1)</td>
<td>0.97 (0.66-1.41)</td>
</tr>
<tr>
<td>NORVIT10</td>
<td>82 (4.4)</td>
<td>67 (3.6)</td>
<td>1.17 (0.77-1.78)</td>
</tr>
<tr>
<td>WAFACS13</td>
<td>201 (7.4)</td>
<td>213 (7.8)</td>
<td>0.94 (0.73-1.21)</td>
</tr>
<tr>
<td>HOPE-211</td>
<td>342 (12.4)</td>
<td>320 (11.6)</td>
<td>1.09 (0.89-1.33)</td>
</tr>
<tr>
<td>SEARCH15</td>
<td>678 (11.2)</td>
<td>639 (10.6)</td>
<td>1.06 (0.92-1.23)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 4.68; P = .6$
Prenatal Multivitamin Supplementation: Rates of Pediatric Cancers

- Meta-analysis - effect of prenatal multivitamins on several types of pediatric cancers

- Protective effect for leukemia, pediatric brain tumors, and neuroblastoma
Prenatal Multivitamin Supplementation and Rates of Acute Lymphocytic Leukemia (ALL)

~40% Reduction in risk for ALL in children of mothers who retrospectively reported use of prenatal multi-vitamins

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (fixed)</th>
<th>OR (fixed)</th>
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<tbody>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>Ross (2005)</td>
<td>0.48 (0.29, 0.80)</td>
<td></td>
</tr>
<tr>
<td>Sarasua (1994)</td>
<td>0.50 (0.22, 1.13)</td>
<td></td>
</tr>
<tr>
<td>Wen (2002)</td>
<td>0.64 (0.52, 0.80)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0.61 (0.50, 0.74)</td>
<td></td>
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</tbody>
</table>

Total events: 1,710 (treatment), 285 (control)
Test for heterogeneity: χ² = 1.27, df = 2 (P = 0.53), I² = 0%
Test for overall effect: Z = 5.07 (P < 0.00001)

Clin Phar & Ther 81: 685, 2007
Effect of Folic Acid Fortification on Pediatric Neuroblastoma Rate: Canada

French et al. 03
Canadian Population
Masking B12 Deficiency Anemia

Base diagnosis of B12 deficiency on biochemical indicators of status.
Has Folic Acid Fortification Increased Masking?

- Studies do not provide evidence that masking occurred due to consumption of “enriched” cereal grain products
  - No increase in B12 deficiency without evidence of anemia
    - Mills et al. AJCN 77: 1474, 2003
    - Wyckoff and Ganji AJCN 86: 1187, 2007
Oxidized “Unmetabolized” Folic Acid Detected in Blood

- Folic acid in supplements and fortified foods
  - oxidized form vs reduced form naturally-occurring in food
- Small doses of folic acid reduced in body
  - reductase enzymes
- When the folic acid dose is higher than ~200 µg/dose
  - folic acid appears in blood in its oxidized “unmetabolized” form
    - new analytical methodology allows detection
Folic Acid Detected in Blood Across Lifespan

- **Cord Blood and Serum of Newborns**

- **Pregnant women**
  - Obeid et al. Am J Clin Nutr 2010

- **Older adults**
  - Troen et al. J Nutr 2006
  - Obeid et al. Metabolism 2010
  - Bailey et al. AJCN 92: 383, 2010
Is There Evidence That Oxidized Folic Acid Is a Safety Concern?

- There is no direct evidence that oxidized folic acid poses a safety concern
- Published opinions/commentaries suggest potential negative consequences

**Commentary**

Is folic acid good for everyone?^{1,2}  
*David Smith, Young-In Kim, and Helga Refsum*

- Research evidence required
Public Health Implications - NTD Risk: Women of Childbearing Potential

- It is difficult for women of childbearing potential to achieve the recommended amount of folic acid without consuming a supplement.
- More effort is required to encourage all women, and in particular, women who are obese or have diabetes, to consume supplements with folic acid.
Public Health Implications Cancer in Adults: Folic Acid Does Not Increase Risk
Public Health Implications - Pediatric Cancers:
Maternal Folic Acid Appears Protective Against Some Cancers
Public Health Implications- UL- Masking B12 Deficiency Adults

- Post-fortification
  - Consumption of enriched cereal-grain products alone or with RTE in U.S. adults is not associated with usual total daily folic acid intake > UL
  - Use of a daily supplement containing 400 μg or less in U.S. adults is not associated with intake > UL
Public Health Implications – UL Children

- Children’s intake exceeded UL when supplements & RTE cereals consumed - differed by age categories
  - Yeung et al. AJCN 2010
- No toxic effects of folic acid in children in any dosage
  - B12 deficiency non-issue in children
- IOM derived the children’s ULs from adults based on body weight differences
Public Health Implications: Children’s UL

- Since the ULs for children are not based on evidence of harm in children and no concern regarding “masking” of B12 deficiency
  - unclear what interpretations can be made when children exceed their age-specific UL
Public Health Implications Children’s UL

- If concerns about higher intakes of folic acid in children are substantiated
  - number of children consuming supplements & eating RTE cereals may need to be reduced
  - allowable levels of folic acid in ready-to-eat cereals and supplements may require further examination
Summary

• Current folic acid public health policies
  – Recommendations for supplements-NTD risk reduction
  – Dietary Guidelines for Americans 2010
  – Healthy People 2020
  – FDA mandated fortification
    • 30% reduction in NTDs
    • Hispanics higher risk

• Corn masa flour-fortification efforts

• Safety issues
  – Cancer
  – Masking B12 deficiency
  – Oxidized “unmetabolized” folic acid

• Public health implications
  – Increase folic acid intake women of reproductive age
Thank you
Public Health Implications: Children’s UL

- If fewer children consumed ready-to-eat cereals or supplements containing folic acid, or if supplements that are consumed by children contained less folic acid
  - number of children with intakes that more than double their requirements might decrease
Only 24% of Women of Reproductive Age Consume Recommended 400 μg/day Folic Acid

Enriched Cereal Grain Products

Ready to Eat Cereals

Supplements

Public Health Implications

- Increased efforts/different approaches needed to enhance daily use of folic acid supplements for women capable of becoming pregnant
Are Folic Acid Supplement Users Likely to Exceed UL?

- Use of a daily supplement containing ≤400 μg (adults) not associated with intake > UL (1000 μg/day)
Public health implications

- It is difficult for women of childbearing potential to achieve the recommended amount of folic acid without consuming a supplement; more effort is required to encourage all women, and in particular, women who are obese or have diabetes, to consume supplements with folic acid.

- Postfortification,
  - Consumption of enriched cereal-grain products alone or with RTE in U.S. adults is not associated with usual total daily folic acid intake > UL.
  - Use of a daily supplement containing 400 μg or less in U.S. adults is not associated with intake > UL.
  - Consumption of enriched cereal grain products alone in U.S. children is not associated with usual total daily folic acid intake > age-specific UL.
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Higher NTD Rates Hispanics vs Non-Hispanic Whites & Blacks

Figure 1. Three-quarter moving average of the birth prevalence (per 10,000 live births) of spina bifida according to race/ethnicity for 21 births.