Folic acid fortification: The safe and effective action towards spina bifida prevention

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Global Alliance for Prevention of Spina Bifida F
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Main messages

Fortifying food with folic acid is

**Safe**

- Fortifying with folic acid does not
  - Mask vitamin B12 deficiency
  - Increase adenoma risk
  - Cause cancer or increase deaths from cancer

**Cost-effective**

- Fortifying with folic acid
  - Reduces neural tube defects
  - Costs less than treating neural tube defects

Adenomas are benign tumors that can develop into cancer.
Folic acid is better absorbed than food folate
What is food fortification (enrichment)?

The addition of vitamins and minerals to foods during their processing.
Foods fortified with folic acid

Folic acid in fortification standards

- Wheat flour: 80 countries
- Maize flour: 18 countries
- Rice: 11 countries

Research

Global Fortification Data Exchange 2022, Tsang unpublished
Fortifying food with folic acid does not mask vitamin B12 deficiency
Folate and vitamin B12 deficiencies cause megaloblastic anemia

Folate deficiency

Causes

Vitamin B12 deficiency

Causes

Megaloblastic Anemia

IOM 2008
Folic acid masking of vitamin B12 deficiency

Megaloblastic anemia due to vitamin B12 deficiency only

If folic acid is provided: Anemia is corrected

If vitamin B12 is not provided: Vitamin B12 deficiency persists

“Folic acid masking of vitamin B12 deficiency”
Studies to assess if fortification with folic acid causes masking of vitamin B12 deficiency

People with vitamin B12 deficiency and no anemia who consume food fortified with folic acid

- Folic acid is provided
- Vitamin B12 is not provided

- Anemia does not develop
- Vitamin B12 deficiency persists

Mills 2003, Qi 2014
Fortification with folic acid does not mask vitamin B12 deficiency

People with low vitamin B12 status and no anemia who consume food fortified with folic acid

Folic acid is provided

Vitamin B12 is not provided

Anemia does not develop

Vitamin B12 deficiency persists

If fortification with folic acid masks vitamin B12 deficiency, the percentage of individuals with both of these conditions should increase after fortification with folic acid

<table>
<thead>
<tr>
<th>Study</th>
<th>Pre-fortification</th>
<th>Post-fortification</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mills 2003</td>
<td>39.2%</td>
<td>37.6%</td>
<td>No masking of vitamin B12 deficiency</td>
</tr>
<tr>
<td>Qi 2014</td>
<td>4.0%</td>
<td>3.9%</td>
<td>No masking of vitamin B12 deficiency</td>
</tr>
</tbody>
</table>

Mills 2003, Qi 2014
Free folic acid in the blood does not increase adenoma risk

Adenomas are benign tumors that can develop into cancer
“Free folic acid” is also referred to as “unmetabolized folic acid”
After folic acid consumption, free folic acid appears in the blood

“Free folic acid” is also referred to as “unmetabolized folic acid”
Free folic acid does not increase the risk of adenomas

<table>
<thead>
<tr>
<th>Free folic acid (nmol/L)</th>
<th>Interval 1: Relative Risk (95% CI)</th>
<th>Interval 2: Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>&gt; 0 - &lt; 3</td>
<td>1.04 (0.81-1.33)</td>
<td>0.88 (0.62-1.25)</td>
</tr>
<tr>
<td>3 - &lt; 20</td>
<td>1.00 (0.74-1.35)</td>
<td>1.31 (0.95-1.82)</td>
</tr>
<tr>
<td>≥ 20</td>
<td>0.83 (0.58-1.18)</td>
<td>0.96 (0.64-1.43)</td>
</tr>
</tbody>
</table>

Interval 1: three years
Interval 2: an additional three years

Adenomas are benign tumors that can develop into cancer
“Free folic acid” is also referred to as “unmetabolized folic acid”
Fortifying food with folic acid does not cause cancer or increase deaths from cancer.
Fortification with folic acid does not cause cancer

Colorectal Cancer Rate per 100,000 Population, USA

- 1973: voluntary fortification of breakfast cereals with folic acid
- 1998: mandatory grain fortification with folic acid

Siegel 2019
Fortification with folic acid does not increase deaths from cancer
Fortifying food with folic acid reduces the risk of neural tube defects and is cost-effective.
Fortification with folic acid reduces the risk of neural tube defects: Costa Rica

1997: wheat flour fortification with folic acid  
1999: maize flour fortification with folic acid

Pre-fortification (1996-1998):
• 9.7 NTDs / 1000 live births

Post-fortification (1999-2000):
• 6.3 NTDs / 1000 live births

Figure 2. Costa Rica. Neural tube defects cases at National Children's Hospital.
Fortification with folic acid reduces the risk of neural tube defects: Canada

1998: wheat flour fortification with folic acid

46% reduction

Pre-fortification (1993-1997):
- 1.58 NTDs / 1000 live births

- 0.86 NTDs / 1000 live births

Figure 1. Prevalence of Neural-Tube Defects, According to Diagnostic Category, in Seven Canadian Provinces from 1993 through 2002.
NOS denotes not otherwise specified.
Fortification with folic acid reduces the risk of neural tube defects: Jordan

2002: wheat flour fortification with folic acid

<table>
<thead>
<tr>
<th>Period</th>
<th>Years</th>
<th>Livebirths</th>
<th>NTDs</th>
<th>Rate per 1000</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before fortification</td>
<td>2000–01</td>
<td>18392</td>
<td>34</td>
<td>1.85</td>
<td>[1.2, 2.4]</td>
</tr>
<tr>
<td>Introduction period</td>
<td>2002–04</td>
<td>26286</td>
<td>28</td>
<td>1.07</td>
<td>[0.7, 1.5]</td>
</tr>
<tr>
<td>After fortification</td>
<td>2005–06</td>
<td>16769</td>
<td>16</td>
<td>0.95</td>
<td>[0.5, 1.5]</td>
</tr>
</tbody>
</table>

49% reduction
Neural Tube Defects (per 10,000): Pre and Post Flour Fortification with Folic Acid

Prefortification NTD per 10,000  Postfortification NTD per 10,000

n=13 countries
n=35 studies

From left: Iran, Jordan, Oman, Peru(3), Saudi Arabia, and South Africa

United States of America
Fortification with folic acid reduces the risk of neural tube defects: meta-analysis

All Neural Tube Defects

Odds Ratio: 0.59 (95% CI: 0.49, 0.70)

n=19,816,008 births (reported in 8 studies)

41% reduction in the odds of neural tube defects after fortification with folic acid
Fortification with folic acid is cost-effective in reducing the risk of neural tube defects

Annual Net Savings from Adding Folic Acid to Flour

- **Chile**: 2.3 million International Dollars
- **South Africa**: 40.6 million Rand
- **USA**: 603 million US Dollars

Savings in healthcare expenses related to treating people with spina bifida, when spina bifida is prevented

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Cost-effective

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