The Vitamin Folate & Folic acid – Health & Risk

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Bottom Line At The Top: A diet containing an abundance of the vitamin folate confers protection against anemia, dementia, birth defects, nerve dysfunction, colon cancer, infection and elevated homocysteine. Since 1998 food cereal grain products have been fortified with folic acid to prevent neural tube birth defects and huge numbers of people take high dose folic acid supplements to lower homocysteine levels. High folic acid intake, particularly in the elderly, may not be perfectly safe. It may mask dementia due to vitamin B12 deficiency and may accelerate growth of pre-existing cancer cells. These adverse effects may be related to the interaction of folate and B12 or the difference between folic acid supplements and natural dietary folates. To be safe, get your daily 400 micrograms (mcg) of folate from food. If you must take folic acid supplements, prevent B12 deficiency with food or supplements and be on the look-out for cancer.

Folate is one of the B vitamins essential for life. Deficiency may cause:

- Anemia
- Severe neural tube defects in babies (birth defects of the brain and spinal cord, the most common of which are spina bifida and anencephaly (no brain))
- Cognitive dysfunction (not thinking straight), dementia (not thinking at all) and neuropathy (nerves don't work), because of its crucial role in DNA and protein metabolism.
- Diarrhea, since folate promotes a functional intestinal lining.
- High homocysteine levels (an amino acid by-product of protein metabolism that is associated with heart attack risk)
- Colon and rectal cancer
- Infection: Natural killer lymphocytes need folate to be able to fight off infection.

Scientists have identified these deficiency states, but there must be even more, since every cell in the body requires folate for metabolic processes absolutely crucial for cell function, repair and replacement.

Green vegetables, nuts, beans and whole grains supply the bulk of *natural* dietary folate. Nutritional supplements and food fortification uses a different form of the vitamin, folic acid. The Recommended Daily Allowance for folate is 400 micrograms (mcg), easy to achieve without supplements or food fortification. For example, a day's diet including 1 cup oatmeal, ½ cup cooked spinach, 1 ounce peanuts, 1 cup baked beans, 1 cup broccoli and ½ cup avocado meets the requirement. For most people 400 mcg suffices, but many don't consume even this much.

Two major impetuses launched a push for adequate and even higher folate intake. In 1998, in order to prevent neural tube birth defects, **the US Food and Drug Administration mandated folic acid fortification of grain products,** including enriched breads, flour, corn meal, pasta, rice and cereals. Since 1998 neural tube defects have decreased by 25-50%. Initial over-fortification, subsequent correction and the advent of extremely popular low carb-there-goes-the-folic-acid diets threw a few blips in the curve of folate intake, but the program continues to work to keep neural tube defect incidence low.

The second impetus relates to homocysteine. High blood levels are associated with heart attacks and other blood vessel occlusions. Normal metabolism utilizing folate and vitamin B12 keeps homocysteine levels low by converting it into methionine (an amino acid crucial for normal brain function) or using vitamin B6 to turn it into another amino acid, cysteine. Levels go up with a deficiency of any of the three vitamins. Homocysteine also accumulates in the face of alcohol consumption or renal failure.

Numerous factors and vitamins influence homocysteine levels, but, rather than address all of them**, many doctors treat high homocysteine levels only by prescribing high doses of folic acid.** Not only does this ignore the infinite complexity of human metabolic processes, but it doesn't solve the problem if folate deficiency wasn't the cause in the first place. When folic acid food fortification started, the prevailing view held that extra folic acid would not only prevent neural tube defects, but would also lower

homocysteine levels and prevent heart attacks. In actuality fortification has had only a measly effect on cardiovascular disease, but patients continue to fill folic acid prescriptions for 1000 mcg or more.

So what? Since folate is a water-soluble B vitamin, one would predict no adverse effects of high doses. Turns out there are a few, with only theories about their causes.

The first adverse effect relates to vitamin B12 deficiency dementia: Folic acid makes it harder to diagnose B12 deficiency dementia and in some people actually makes it worse. In people whose vitamin B12 status is good, folate supplementation poses little danger. However, superimposing high dose folic acid supplements and fortification on vitamin B12 deficient people is not safe.

What happens is this: A B12 deficient person becomes anemic and cognitively deficient or outright demented. If that person takes high dose folic acid, the anemia corrects, but the mental problems do not. Elderly people risk low vitamin B12 levels more than any other age-group, but we **expect** them to be demented. If they are demented without an anemia typical of B12 deficiency, we don't suspect it or do the test. Thus **folic acid is said to "mask" B12 dementia and neuropathy, which are often irreversible if not caught early.**

Two extra-ominous studies found that, rather than just masking a B12 dementia, folic acid supplements in excess of 400 mcg per day make things worse. **Low B12 along with high folate levels nearly doubles the risk of cognitive impairment, compared to people with low B12 and normal folate**.

Possible cause: We know that B12 deficiency dementia results from not being able to convert homocysteine to methionine, a deficiency of which leads to deficient S-adenosyl methionine (SAM). SAM is necessary for normal brain function.

Folate's job in the body is to facilitate the transfer of single carbons (methyl groups) from one molecule to another. Once done, the active forms of folate need to be regenerated by completing a cycle. That cycle includes the B12-mediated conversion of homocysteine to methionine. Without B12, the blocked cycle builds-up 5-MTHF, a folate that can't correct for the lack of B12.

In a B12 deficient person, folic acid supplements pour in a supply of active folate, enabling on-going DNA and protein synthesis for cell growth. But it siphons off methionine (it is, after all, an amino acid needed to make protein), depleting it and SAM even further and worsening dementia. Perhaps the balance between B12 and folate is as important as maintaining adequate levels of each.

As an aside, 5-MTHF does not convert into the form that transfers inside cells, so in B12 deficiency cell folate content declines, even as inactive blood levels rise. **For this reason, the best measure of functional folate adequacy is red cell folate, not serum level.**

The second potential problem with supplementation is cancer. A huge amount of scientific data links **dietary** folate intake with protection against colon cancer growth in both humans and animals. Folate also seems to protect against lung, pancreas, mouth, throat, esophagus, cervix and ovarian cancers, neuroblastoma and leukemia. A few dissenting studies exist, but over 30 case-control and prospective cohort studies found that people consuming diets high in folate and with high blood folate levels, have a 40–60% reduction in the risk of developing colon or rectal cancer or their precursor lesion, the adenomatous polyp. Moderate-to-heavy alcohol drinkers benefit more from folate, probably because alcohol blocks folate function. A benefit for breast cancer is more iffy and probably confined to those women who are moderate-to-high imbibers of alcohol.

However, inklings that high dose supplemental **folic acid might paradoxically accelerate cancer growth**, date back to studies in the 1940's. Two groups of investigators gave large doses of folic acid to patients with acute leukemia and observed what was politely termed "the acceleration phenomenon", whereby the leukemia went out of control.

More recently, of 25,000 postmenopausal women, those taking folic acid supplements (average 853 mcg/day) had a significantly higher risk of developing breast cancer. In people who have had colonic polyps removed, folic acid supplements don't affect polyp recurrence within the first three years, but more than double the number of polyps, including dangerous ones at 6-8 years. These results argue that, given enough time in a high risk group of people who tend to grow new pre-cancerous cells, high dose folic acid might help those cells to turn into cancer.

Short term studies don't generate as ominous results, but would only apply to you if you plan to live short term. In the first year after mandatory folic acid food fortification in 1998, an extra 5 colon cancers per 100,000 individuals were diagnosed nationwide.

Studies using folic acid supplementation (to lower homocysteine) have yielded variable results concerning cancer incidence, but none included adequate numbers of subjects to come to meaningful conclusions. Plus there is

the confounding probability that supplementation might correct a deficiency state and prevent cancer.

To summarize the effects on cancer, **under most circumstances adequate availability of dietary folate protects against cancer, presumably by enhancing genetic stability. However, in select circumstances in which an individual who harbors a neoplasm or group of abnormal pre-neoplastic cells consumes excess folate, it may instead facilitate cancer promotion.**

Theory: Cancer cells proliferate at a rapid rate, requiring large quantities of folate to maintain DNA synthesis. **Folate's central role in the synthesis of genetic material means that it might help cancer cells to reproduce even faster.** This might propel pre-cancerous and small malignant neoplasms to full-blown dangerous growth.

Alternate theory: There may be some adverse effect of free folic acid. Folic acid, used for fortification and supplements, is not a naturally occurring form of the vitamin folate. The intestine converts both dietary folate and folic acid supplements to 5-MTHF in the process of digestion and absorption. Folic acid supplements in doses as light-weight as 200 mcg, can overwhelm the conversion mechanism, resulting in detectable levels of free folic acid in the blood. Daily 400 mcg doses lead to sustained circulating folic acid levels, which isn't normal. Eighty one percent of supplement users have unmetabolized folic acid circulating chronically in the bloodstream.

Cancers afflict the elderly more than the young. Forty percent of US adults over 60 years of age regularly consume at least 400 mcg folic acid as a supplement. When fortification started, adding an estimated ~100-200 mcg /day from fortified food, supplement users' already high folate levels rose 62%. That puts them most at risk for folic acid induced cancer growth, should they have nascent cancer cells lying in wait.

Another alternate theory: Preliminary data suggests that folic acid supplements improve immune function up to a point, but if total intake surpasses 633 mcg per day, one of the body's crucial immune defenses, **natural killer cells, lose their lethal effect. These cells not only fight infection, but also kill isolated cancer cells** before they can become full-blown cancers. High dose folic acid might block this function.

Yet another alternate theory: Folate doesn't work alone. It is both myopic and misleading to attribute all of folate's effects to it alone. Folate's active form has to continually be regenerated, requiring vitamins B6 (pyridoxine), B12 and B2 (riboflavin), critical cofactors for pivotal enzymes in the regeneration process. Marginal vitamin status is far more common than we would hope, and low levels of vitamin B6, B2 and B12 occur in as many as 20% of the population. **These vitamins are essential to known functions involving folate, so why should we think that folate acts alone in preventing or promoting cancer?**

Dilemma: Countries now dealing with folic acid fortification issues must balance 1) the clear benefit of adequate folate levels for all with respect to anemia, cognitive function, gut and immune function and homocysteine levels, and 2) the extra benefit for child-bearing women and their offspring at risk for neural tube defects, against 3) incomplete knowledge about the potential for harm in older individuals at risk for cancer or B12 deficiency cognitive dysfunction.

The benefit of fortification in relation to neural tube defects would be negated if just 1 in 100,000 subjects eating folic acid-fortified food experiences a serious adverse effect. Mandatory fortification exposes the entire population to extra folic acid, including those who might be susceptible to harm.

In addition, malaria parasites seem to like folate. People who are folate deficient tend not to become infected with malaria. Universal food fortification could put millions of Third World people at greater risk for malaria.

Thus, ***under select circumstances*** folate supplementation contributes to disease. In the face of B12 deficiency, an overly abundant folic acid intake worsens cognitive function. In someone with pre-cancerous cells lurking in the background, folic acid supplements promotes cancer cell proliferation. Have we set people up for these problems by the fortification effort to prevent neural tube defects and the prescription of high dose folic acid to lower homocysteine levels? Since **adequate** folate levels prevent cancer, anemia, dementia and high homocysteine levels, the problem is not simple. **We all need *adequate* levels, not high, not low.** More is not better: Such an un-American concept.

Solution: The ideal solution requires all people, especially women of child-bearing age, to consume a folate-rich diet of vegetables, legumes, nuts and whole grains and stop drinking alcohol, so they don't need folic acid supplements or fortified food.

Fat chance that all people will suddenly eschew their crappy diets and alcohol and eat their vegetables and beans. To prevent neural tube defects we at least need grain fortification. But do we really need high dose folic acid supplements? If we do, we need to be more vigilant in our suspicion for and diagnosis of B12 deficiency, dementia and cancer. ⚕