Clinical Update

New *folic acid* data raises concerns about this synthetic vitamin's use and cancer risk

Too little folate may cause the formation of cancer cells to develop and other problems like neural tube defects in a fetus. Too much folate can cause pre-cancerous cells (from various causes) to multiply too fast and may exceed the immune system's capability to recognize and eradicate them.

After reviewing hundreds of papers on folic acid, it has been decided by some of the more progressive supplement companies that *synthetic folic acid* is not an ideal choice for a nutritional supplement because it is an unnatural molecule that now can be replaced by naturally occurring folates. One's genetic history, genetic "make up" and exposure to a lifetime of the unnatural molecule *folic acid* could possibly increase a person's risk of some cancers.

There is also the issue of who will suffer and who will benefit from the fortification of foods with the unnatural molecule *folic acid*. Those with most to gain are pregnant women. Those with most to lose maybe those with certain cancer predispositions.

About when mandatory fortification of foods with *folic acid* started in 1998, it has been estimated that an additional 15,000 per year of colon cancer have occurred per year[1] whereas neural tube defects decreased by about 19 %.

Choose to ingest only natural folates as found in natural foods and select vitamin supplements and not the unnatural synthetic compound *folic acid*, which is found in the majority of vitamins and in fortified-foods.

BACKGROUND on FOLIC ACID

Folate and *folic acid* derive their names from the Latin word *folium*, which means "leaf", since there is a fair amount of folates in green vegetables, although they are also found in significant quantities in some animal foods, especially liver, eggs etc. *Folic acid* is a synthetic oxidized molecule that does not occur in nature, but can be utilized by the human body as a precursor to form natural folates that are biologically active. *Folic acid* and the natural folates are also known as Vitamin B9 and are water-soluble.

Many vitamins, such as other B-Vitamins, vitamin C, vitamin K, vitamin E or amino acids can also be produced as *synthetic compounds* in the laboratory and many of them are identical molecules to the ones that occur naturally in plants, animals or inorganic matter. The *folic acid* molecule does not occur in nature and it is very different than the natural forms of folates.

Folic acid is not biologically active on its own but is converted to biologically active forms after it enters the body. The liver and gut transform *folic acid* into the active forms such as: tetrahydrofolate, 5-methyl-tetrahydrofolate, folinic acid (5-formyl-tetrahydrofolate) and a few other natural folate forms. The capacity of the human liver to perform these conversions is rather slow. Oral ingestion of *folic acid* over about 200 micrograms leads to appearance of *unmetabolized folic acid* in the serum as well as natural folate metabolites (5-methyltetrahydrofolate etc.) The result is an accumulation of the *unnatural molecule folic acid*, which has a greater capacity to enter cells and stimulate cell growth, potentially 100 times more than natural folates. Which can set the stage for cancer cell growth.

Most have heard that women who are about to become pregnant or are pregnant or lactating have been advised to have a daily intake of 400 to 800 micrograms of *folic acid* in order to prevent neural tube defects in the fetus. The US Reference Daily Intake (Daily Value) for adults is 400 micrograms, (mcg).

However, supplementation with 400 to 800 micrograms of natural folates would be much better, however very few have heard about the availability of natural folates in vitamins.

Pregnant or lactating women could achieve adequate folate vitamin status if they took in about 800 mcg of natural folates from a natural balanced diet high in fruits and vegetables and with an adequate amount of animal derived foods. Natural folates are found in leafy greens, spinach, lentils, romaine lettuce, liver, eggs, beans, orange juice, broccoli, and vegetable juices, Brewer's yeast etc.

US public health policy (1998) instituted the cheap and readily available *synthetic folic acid* fortification of many common foods, such as refined flour products (pasta, cereal, breads, crackers, cakes, cookies and many pre-packaged foods), because the majority of the population consumes these in large enough quantities. One serving of ready-to-eat cereals can have up to 800 mcg of *folic acid* per standard serving. The April, 2010 issue of *Prevention Magazine* article on *folic acid* states: “Is your breakfast giving you cancer? Research links too much folic acid - a staple in multivitamins, as well as cereal and bread - to colon, lung and prostate cancer." (article by Laura Beil).

Some European countries such as Norway are not fortifying foods at all with *folic acid*. Last summer New Zealand abruptly delayed its mandatory plans for fortification of bread products.

Food fortification with *folic acid* has created a complicated scenario depending on what foods are consumed and the fact that some people may ingest significant amounts or maybe excess amounts of the *unnatural molecule folic acid* from their diet adding to what they may also be taking in from most vitamin formulations. The populations that are at risk for excess folic acid intake over a lifetime are all men and those women who can not or will not get pregnant. The long-term consequences of excess consumption of the *unnatural molecule folic acid* and even *natural folates* are not yet well known. The Institute of Medicine Food and Nutrition Board recommends the upper limit for *folic acid* is 1 mg, which includes a combination of synthetic and natural sources of folate. Marion Neuhauser of the Fred Hutchinson Cancer Center, in Seattle states: "Folic acid is important to take, but not to over do it. A tailored approach works best as individuals have different needs." (from Emily Sohn, *Los Angeles Times* "How much folic acid you should get? Does it matter where you get it from?” March 11, 2009).

FOLATE PHYSIOLOGY AND RISK OF CANCER

Vitamin B9 represents a family of compounds called natural folates, which convert to various folate types in the body. The plant and animal derived folates occur more than 90% as an equal mix of 5-MethylTetraHydroFolate (5-MTHF) and folinic acid. Other minor occurring folate forms are tetrahydrofolate and 5,10-methenyl-tetrahydrofolate. Technically *folic acid* is considered a pro-vitamin because the body can convert it partially into natural folates. However, *synthetic folic acid* is a compound that does not occur in nature as such and this should be of concern.

Natural folates and *folic acid* influences many important functions in human physiology such as:

- Act as a coenzyme necessary for the synthesis of thymine and also purine bases, which are needed for DNA synthesis.
- Participate in the process of DNA repair and DNA methylation, which dictates which genes are expressed.
- Support cell division whether it is beneficial for new fetal cells, tissue repair and renewal or detrimental when it may support pre-cancerous or cancerous cells to divide and multiply.
- Control homocysteine levels, a vascular and cell toxin.
- Influence NK (Natural Killer) cells of the immune system, which are in charge of fighting infections and malignant cells
- Support immune cell replication and red blood cell replication

Clinical Update

Important research findings about *folic acid* which are causing many scientists to raise concerns about *folic acid:*

1. Laboratory studies have shown that that *folic acid* can stimulate cells to proliferate much more rapidly, potentially 100 times more so than natural folates.

2. When the *unnatural folic acid molecule* is ingested in amounts greater than 200 micrograms at one time from *folic acid* fortified-food and/or vitamin supplements, the liver and gut cannot convert all the *unnatural folic acid molecule* to the natural biologically active forms such as 5-Methyl TetraHydroFolate (5-MTHF). This allows for a significant amount of the unnatural molecule *folic acid* to accumulate. Consequentially an unnatural compound can enter many cells. One study estimated that as many as 80% of Americans have detectable levels of *unmetabolized folic acid* in their bloodstream. This can be hazardous due to its ability to promote excessive cell proliferation when it is not desirable such as in pre-malignant cells.

3. *Unmetabolized folic acid* is associated with a reduction of natural killer cytotoxicity, which reduces the immune systems to capacity to kill off malignant or pre-malignant cells.

4. The long-term consequences of having our cells exposed to the *unnatural folic acid molecule* in the bloodstream and in the gut are not completely known today, but this abnormal physiology should be of concern. Pre-cancerous cells normally occur in our bodies all the time but they are typically identified and killed-off by a competent immune system. When there is an excessive amount of the *unnatural folic acid molecule* around, pre-cancerous cells can multiply faster, and there is a greater chance they may escape our natural immune surveillance system and become malignant.

People who have cancer or are predisposed or are under treatment such as chemotherapy or have overcome cancer and wish to reduce their risk of cancer re-occurrence should be advised to avoid the *unnatural folic acid molecule* in fortified-foods and supplements. The recommended minimum Daily Value by the FDA is 400 micrograms per day for adults. Many vitamins and most fortified foods contain that much or more per a standard serving. In general it may be best to keep a daily intake from all sources at no more than about 400 to 500 micrograms. Natural foods have a much lower concentration of the folates than fortified-foods. Also natural folates or natural folate supplements are slower absorbed than *folic acid*. You would have to eat a greater volume of natural folate foods than taking a natural folate supplement or eating *folic acid* fortified-foods to get equivalent folate levels.

CANCER DATA AND THE *FOLIC ACID* CONNECTION

A Norwegian study published in the Journal of the American Medical Association[2] tracked over 6,800 people who received 800 micrograms of the *unnatural folic acid molecule* and vitamin *B12* after a heart attack. These people later were found to be 21% more likely to develop lung cancer and 38% greater chance of dying from it. Norway does not fortify its foods with *folic acid* as the U.S. does.

Daily intake of the *unnatural molecule folic acid* may double the risk of prostate cancer[3] Daily supplements of *folic acid* of 1 milligram was associated with increased risk of prostate cancer. The authors state "These findings highlight the potential complex role of folate in prostate cancer and the possibly different effects of *folic acid-containing* vs natural sources of folate". Dietary natural - folate intake has shown a trend toward reduced risk of prostate cancer.

A Swedish study in 2004 showed that a high dietary natural folate intake may play a role in reducing ovarian cancer especially among those women who consumed alcohol more than 20 gm per week.[4]

Another Swedish study just published by Susanna C. Larrson, Ph.D. at the Karolinska Institute in Stockholm studied 35,000 Swedish women (ages 49 to 83) who took multivitamins[5]. Those taking multivitamins were 19 % more likely to develop breast cancer than the controls. One of the reasons for the increased breast cancer risk was *folic acid*, which may increase breast density and potentially stimulate development of cancer. Vitamin C, E and B6 did not increase risk. Calcium appeared to be protective.

It makes sense that ingesting an adequate, but not excessive amount of natural folates may be able to reduce cancer occurrence because folate deficiency predisposes the body to the risk of DNA errors during cell replication. This is due to improper or irregular formation of new DNA in new cells. This is similar to the situation when copier toner runs low and then the copies do not look exactly like the original. They are faded and may contain errors. This is how DNA mutations may occur and dangerous pre-cancerous cells may be created. This especially may be a problem in those over age 60 or those with immune system impairment.

If the *unnatural folic acid molecule* is so inferior to natural folates and may potentially cause problems, why is the *unnatural folic acid molecule* still used in food and other fortification and is found in most widely used supplements? The answer is simple, natural folates have not been available in a stable form until recently and their prices are much higher than *folic acid* (about more than 400 times more expensive). Very few supplement companies have decided to replace *folic acid* with natural folates in their formulations.

WHAT ARE THE BEST OPTIONS FOR GETTING THE NATURAL FOLATES?

Have a diet rich in leafy greens, spinach, beans, Brewer's yeast, chickpeas, lentils, eggs, liver and some fruit like oranges, melons and others. Minimize the consumption of foods fortified with the *unnatural molecule folic acid.* These foods are typically made with refined flours, such as white breads, pasta, bagels, cereals, cakes, cookies, crackers, and packaged-processed foods, even in many "nutritional" shakes and bars.

These foods are also problematic due to their high carbohydrate load (glycemic load), and are absorbed in the bloodstream very fast, and can rapidly produce elevated blood glucose and insulin levels. Excessively elevated blood levels of glucose and insulin can be stimulants for cell proliferation and may increase the risk of cancer. Also there is increased risk of obesity, diabetes, elevated blood cholesterol, (triglycerides) and the metabolic syndrome, which support cancer cell proliferation in synergistic ways.

Since most people do not have an adequate intake of vegetables and other nutritious foods, supplementing with high quality multivitamins can support optimal health and performance but make sure your vitamins contain the natural form of folates such as 5-MTHF (5-MethylTetraHydroFolate) and/or folinic acid (or calcium folinate).

People beyond childbearing years and those with "weakened" immune systems and history of precancerous lesions should be monitored to avoid excessively high levels of all folates. It is estimated that as many as half of adults over age 60 could have in their tissues some pre-cancerous cells such as in colon polyps or in the prostate gland.

ARE WE GETTING TOO MUCH OR NOT ENOUGH FOLATES FROM OUR DIET AND SUPPLEMENTS?

Keep in mind that some people have trouble absorbing natural folates from greens and other natural folate foods and those may be the people that need natural folate supplementation the most. It is a good idea to test everybody because health is not optimal at both ends of the spectrum, too high or too low red blood cell folate status may be problematic. Measuring folate status is imperative for women trying to

conceive (who need higher folate levels) or any male or female with pre-cancerous colon, polyps, or other suspicious cells and have strong family histories of cancer. They need to have lower folate levels.

SUMMARY

Obtain natural folate from non-fortified foods and or vitamins containing natural forms of folates such as 5-MTHF (5-Methyl-tetradydrofolate), folinic acid (5-formyl-tetrahydrofolate) (or calcium folinate), with the proprietary formulation. Avoid the extremes of folate deficiency or folate excess status.

Other relevant lab tests to evaluate your cancer risk and overall health status may include:

1. The urinary marker (8-OHDG), which is an indicator of DNA damage of various cells in the body.
2. The red blood cell AA/EPA (arachidonic acid/ omega 3 fatty acid) ratio which influences cell proliferation, immune response, inflammation, clotting, vasoconstriction etc.
3. Homocysteine blood levels. High homocysteine or too low are not optimal and is an indicator of methylation status, which influences many aspects of health including the risk for cardiovascular disease. It also affects the methylation of DNA which dictate how genes are expressed or silenced and may influence the risk of cancer .
4. Immune system status indicators such as NK (natural killer) cell numbers and NK cell activity (as a marker for immune status), WBC (white blood cells) and others.
5. HS-CRP (high sensitive C-Reactive protein), an inflammation and/or infection marker.
6. Lipid peroxides, marker for oxidative stress, which may induce DNA damage.
7. Vitamin D levels, which influence cell proliferation and DNA repair.
8. Insulin levels. High insulin levels stimulate cell proliferation and can lead to weight gain.
9. HBA1C, marker of average 90 day glucose levels. High glucose levels can stimulate cell proliferation.

The tests mentioned above are some important general markers of cancer risk and overall health. These markers, along with medical history-exam and a genetic evaluation can help with designing a rational program and specific interventions for each individual's long term well-being.

REFERENCES

[1] Mason JB et al. A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis*, Cancer Epidemiol Biomarkers Prev.* 2007 Jul;16(7):1325-9.

[2] Ebbing M et al. Cancer incidence and mortality after treatment with folic acid and vitamin B12, *JAMA*. 2009 Nov 18;302(19):2119-2126.

[3] Figueiredo, JC et al. Folic acid and the risk of prostate cancer: results from a randomized clinical trial*, J Natl Cancer Inst* 2009;101:432-435.

[4] Larsson SC et al. Dietary folate intake and incidence of ovarian cancer: the Swedish Mammography Cohort. *J Natl Cancer Inst.* 2004 Mar 3;96(5):396-402.

[5] Larsson SC et al. Multivitamin use and breast cancer incidence in a prospective cohort of Swedish women.*Am J Clin Nutr*. 2010 May;91(5):1268-72.

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