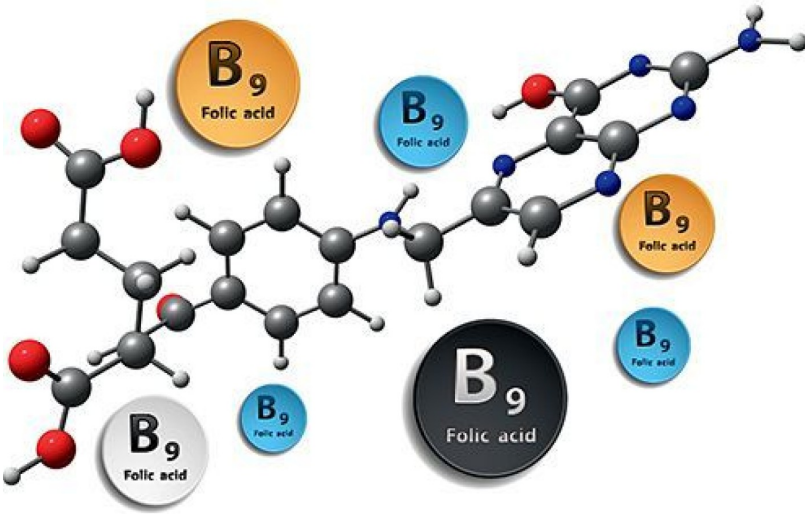
Dynamic Chiropractic



VITAMINS / SUPPLEMENTS

Fight Colorectal Cancer With Folic Acid

James P. Meschino, DC, MS

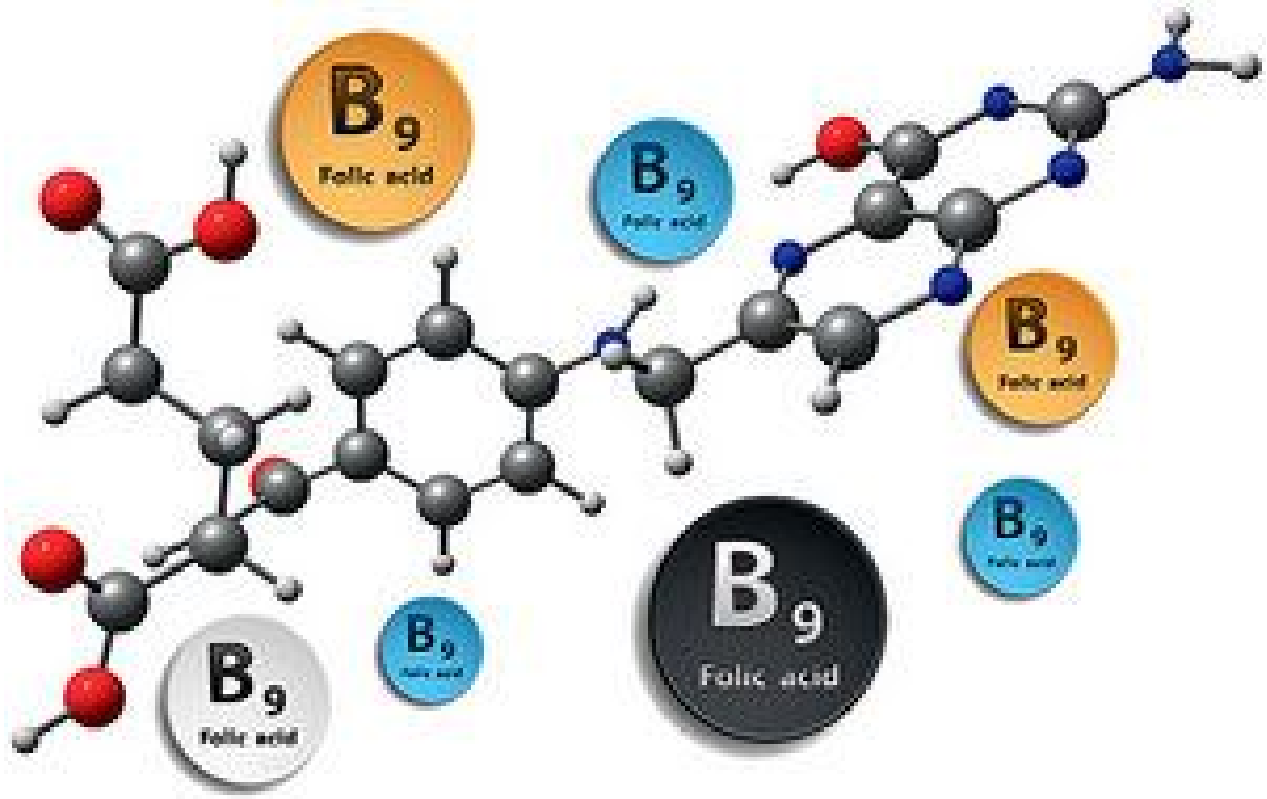
Editor's note: This is the third article in a series discussing diet / nutritional influences on colorectal cancer.

Colorectal cancer (CRC) is the second most common cause of cancer mortality in the U.S. and Canada. Although genetic susceptibility plays a role in the etiology of CRC, dietary factors, including certain vitamins, have also been shown to influence the development of the disease in various studies.

The B-vitamin folic acid is one of the vitamins that has shown promise in the chemoprevention of CRC. Studies suggest a marginal deficiency in folic acid can lead to aberrations in DNA methylation, which may contribute to abnormalities in DNA synthesis and genomic instability. In addition, a number of animal studies and several case-controlled human studies have demonstrated CRC chemoprevention effects and negligible toxicity with folic acid administration.[1]

A ground-breaking study published in the *World Journal of Gastroenterology* in 2008 demonstrated that a daily dosage of 5 mg of folic acid resulted in a significant reduction in the recurrence of colorectal adenoma. Among the 94 subjects who completed the study (49 in the folic acid group and 45 in the placebo group), there was a threefold increase in polyp recurrences in the placebo group compared to the group receiving folic acid supplementation. The mean number of recurrent polyps (adenomas) at three years was 0.36 (SD, 0.69) for the folic-acid-treated group compared to 0.82 (SD, 1.17) for the placebo-treated group. Of note, patients under 70 years of age and those with left-sided colonic adenomas, or advanced adenomas, responded the best to folic acid supplementation.[1]

Origin of Colorectal Adenoma and Colorectal Cancer



Colorectal tumors arise from unregulated cell proliferation of intestinal epithelial cells through a multistep process, with the first step usually being the formation of premalignant adenomas. As such, colorectal adenomas are classified as benign tumors, which comprise epithelial cells of glandular structures or have glandular characteristics, or both.

The colon has numerous glands within its tissues, which tend to be simple and tubular in appearance. These small glands are classified as glands because they secrete mucus into the lumen of the colon. The purpose of these glands is to absorb water from the feces back into the blood and to secrete mucus into the lumen of the colon to lubricate the dehydrated feces. Failure to lubricate the feces can result in colonic damage by the feces as it passes toward the rectum.

Although adenomas are benign, over time they can transform into malignant tumors, at which point they are called adenocarcinomas. Adenocarcinoma accounts for 98 percent of all colorectal cancers. Adenomas of the colon, also called adenomatous polyps, are quite prevalent, especially after age 60. They are found commonly at colonoscopy, upon which they are removed because of their tendency to become malignant. The different types of colorectal adenomas include:[2-5]

- Tubular adenoma
- Tubulovillous adenoma
- Villous adenoma
- Sessile serrated adenoma

How Folic Acid Prevents Adenoma Recurrence

Studies have provided various clues as to how folic acid may prevent CRC and prevent recurrence of colorectal adenoma. In the 2008 study it was suggested that the increased responsiveness of these subjects may have been due to greater tissue accumulation of folic acid. This is based on previous studies showing that mucosal folate levels may be a determining factor in the development of adenomas. Researchers have demonstrated that the levels of folate in adenoma,

carcinoma, as well as normal-appearing adjacent mucosa, are lower than in corresponding polyp-free control subjects.[6]

The mechanisms by which folic acid exerts its chemoprevention effects in colorectal carcinogenesis appear to be multifaceted. Due to folic acid's key role in DNA methylation and cellular homeostasis, folate deficiency (or marginal deficiency) may result in misincorporation of uracil for thymidine during DNA synthesis, which is shown to increase the potential for spontaneous mutation, as well as chromosomal abnormalities and errors in DNA synthesis.[1] Moreover, folic acid supplementation at supraphysiological doses (e.g., 5 mg per day) has been shown to restore DNA methylation status in patients with colorectal neoplasms.

Other studies have examined the influence of folic acid on a variety of genes involved in colon cancer development. In a one-year study in which patients took either 5 mg of folic acid or placebo, folate supplementation was shown to prevent the loss of heterozygosis (LOH) of the DCC gene in all five patients who demonstrated baseline heterozygosis, whereas two of four placebo-treated patients with baseline heterozygosis, demonstrated complete allelic loss.[7-8]

The DCC gene (deleted in colorectal cancer) is an important tumor suppressor gene in the colon cancer model. In this study, mucosal protein levels of DCC were also reduced in 70 percent of placebo-treated patients compared to only 10 percent of folate-treated patients.[7] In 70 percent of colon cancer cases, DCC allelic losses in chromosome 18q.21 is a common finding.[8]

Cell culture studies further demonstrate that supplemental folic acid and its metabolite, 5-methyltetrahydrofolate (5-MTF), inhibit epidermal growth factor-receptor (EGFR) promoter activity in colon cancer HCT-116 cells by enhancing methylation.[9] Over-expression of EGFR is known to play a critical role in the development and progression of a large number of epithelial cancers, including colorectal cancer.[1] As such, supplemental folic acid may also attenuate the downstream events of EGFR signal transduction pathways that are critically involved in modulating growth-related processes.

Clinical support of this hypothesis comes from the findings of patients who have undergone colon polyp removal (polypectomy), whereby folic acid supplementation (5 mg) for one-year led to a decreased activation of several transcription factors commonly over-expressed in cancer cells. More specifically, folic acid supplementation was shown to decrease the activation of nuclear translocation of ß-catenin, which interacts with the T-cell factor 4 (TCF-4) transcription factor to induce expression of specific target genes, including cyclin D1, VEGF (vascular endothelial growth factor) and c-Myc. Together, these transcription and growth factors are known to promote cell growth and proliferation of many forms of cancer.[1,10]

Patients at Risk for Deficiency

A low serum folic acid level (<4 ng/ml of serum) is where chromosome breaks have been seen.11 The normal range for serum folate is 7-40 nmol/L, and the normal red blood cell folate reference range is 360-1,400 nmol/L, which is a direct measure of tissue folate stores.[12]

Individuals at high risk for folic acid deficiency or marginal deficiency include women of childbearing age and non-Hispanic black women. Even when intake of folic acid from dietary supplements is included, 19 percent of female adolescents ages 14-18 years and 17 percent of women ages 19-30 years do not meet the Estimated Average Requirement (EAR) for folic acid

intake. Additionally, 23 percent of non-Hispanic black women have inadequate total intake, compared with 13 percent of non-Hispanic white women.[13]

Research has also shown that certain drugs, such as methotrexate, levopoda, niacin, phenytoin (Dilantin), carbamazepine, and theophylline, can markedly reduce folate levels in the body.[14-16] Other well-documented factors that deplete folic acid include alcohol intake (even moderate amounts) and cigarette smoking.[17-18]

Health care practitioners should be mindful of the evidence linking low folate status with increased risk of certain cancers. In patients who fall into a higher risk category for folate deficiency, folic acid blood tests should be recommended, and appropriate dietary and supplementation practices employed to help patients achieve a normal value for folate status.

Clinical Pearls: Summing Up

Researchers leading the 2008 study concluded, "Our data, for the first time, show that the daily consumption of a high dose of folic acid over a period of 3 years prevents the recurrence of colorectal adenomas," adding that "none of the patients in the folate treatment group [was] found to have histologically aggressive adenomas or carcinoma at final endoscopy." They further indicated that the marked reduction in adenoma recurrence seen in this study could not be attributed to differences in other dietary or lifestyle factors, as all patients completed a detailed lifestyle questionnaire and nutritional assessment, with both study groups demonstrating statistically similar caloric, fiber, fat and protein intake, as well as similar baseline BMI, folate, B12 and calcium status. Additionally, the groups were similar with regard to aspirin use, and the number and type of adenoma at baseline.

Since colorectal cancer is an age-related disease typically diagnosed after the age of 50, any delay in the onset and subsequent progression of this disease through the use of dietary agents, such as folic acid, is likely to have significant health benefits.[1]

The recent evidence that supraphysiological doses of folic acid (3-5 mg per day) have been shown to reduce recurrence of colorectal adenoma and improve outcomes for patients with cervical dysplasia and other health problems (e.g., high homocysteine) has opened up an new application for the therapeutic administration of folic acid. In patients who have had previous colorectal adenoma, the groundbreaking 2008 study suggests supplementation with 5 mg per day of folic acid can help prevent colorectal adenoma recurrence by threefold compared to placebo. This research should be brought to the attention of all patients with a history of colorectal adenoma (those who have had colon polyps removed), as well as their attending physician / oncologist.

Finally, it is worth noting that prior to the folic acid food fortification program that commenced in January 1998, 15 percent of the U.S. adult population ingested less than the EAR for folic acid on a daily basis. The folate food fortification program has improved folate status significantly in recent years, but various groups remain at risk for suboptimal folate status, which may affect their risk of colorectal cancer.[11,19]

It is also worth mentioning that a 19 percent reduction in neural-tube-defect birth prevalence occurred following folic acid fortification of the U.S. food supply. While some researchers have noted that factors other than fortification may have contributed to this decline, folic acid fortification is likely a main factor.[19]

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