

Treatment with folic acid, vitamin B12 associated with increased risk of cancer, death

17 November 2009

Patients with heart disease in Norway, a country with no fortification of foods with folic acid, had an associated increased risk of cancer and death from any cause if they had received treatment with folic acid and vitamin B12, according to a study in the November 18 issue of *JAMA*.

Most epidemiological studies have found inverse associations between folate (a [B vitamin](#)) intake and risk of colorectal cancer, although such associations have been inconsistent or absent for other cancers, according to background information in the article. "Experimental evidence suggests that folate deficiency may promote initial stages of carcinogenesis, whereas high doses of [folic acid](#) may enhance growth of cancer cells. Since 1998, many countries, including the United States, have implemented mandatory folic acid fortification of flour and grain products to reduce the risk of neural-tube birth defects," the authors write. "Recently, concerns have emerged about the safety of folic acid, in particular with respect to cancer risk."

Marta Ebbing, M.D., of Haukeland University Hospital, Bergen, Norway, and colleagues analyzed the results of two Norwegian homocysteine-lowering trials among patients with ischemic [heart disease](#), where there was a statistically nonsignificant increase in cancer incidence in the groups assigned to folic acid treatment. The researchers examined whether folic acid treatment was associated with cancer outcomes and all-cause mortality after extended follow-up. "Because there is no folic acid fortification of foods in Norway, this study population was well suited for such an investigation," they write.

The two randomized, placebo-controlled clinical trials included 6,837 patients with ischemic heart

disease who were treated with B vitamins or placebo between 1998 and 2005, and were followed up through December 31, 2007. Patients were randomized to receive oral treatment with folic acid (0.8 mg/d), plus [vitamin B12](#) (0.4 mg/d), plus vitamin B6 (40 mg/d) (n = 1,708); folic acid (0.8 mg/d) plus vitamin B12 (0.4 mg/d) (n = 1,703); vitamin B6 alone (40 mg/d) (n = 1,705); or placebo (n = 1,721). During study treatment, median (midpoint) serum folate concentration increased more than 6-fold among participants given folic acid.

The researchers found that after a median 39 months of treatment and an additional 38 months of post-trial observational follow-up, 288 participants (8.4 percent) who did not receive folic acid plus vitamin B12 vs. 341 participants (10.0 percent) who received such treatment were diagnosed with cancer, a 21 percent increased risk. A total of 100 patients (2.9 percent) who did not receive folic acid plus vitamin B12 vs. 136 (4.0 percent) who received such treatment died from cancer, a 38 percent increased risk. A total of 16.1 percent of patients who received folic acid plus vitamin B12 vs. 13.8 percent who did not receive such treatment died from any cause.

"Results were mainly driven by increased lung [cancer](#) incidence in participants who received folic acid plus vitamin B12. Vitamin B6 treatment was not associated with any significant effects," the authors write.

"Our results need confirmation in other populations and underline the call for safety monitoring following the widespread consumption of folic acid from dietary supplements and fortified foods."

[More information:](#) *JAMA*. 2009;302[19]:2119-2126.

Source: JAMA and Archives Journals ([news](#) : [web](#))

APA citation: Treatment with folic acid, vitamin B12 associated with increased risk of cancer, death (2009, November 17) retrieved 9 July 2022 from <https://medicalxpress.com/news/2009-11-treatment-folic-acid-vitamin-b12.html>

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