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## Folate Supplementation Linked to Increased Cancer Incidence and Mortality



Zosia Chustecka

November 18, 2009 — Folic acid and vitamin B supplementation was associated with an increase in cancer incidence, cancer mortality, and all-cause mortality in a new analysis with long-term follow-up of data from 2 trials conducted in Norway, where there is no folic acid fortification of foods.

The results are reported in the November 18 issue of the *Journal of the American Medical Association*.

The authors, led by Marta Ebbing, MD, from Haukeland University Hospital in Bergen, Norway, say that these results, although in need of confirmation, suggest that there is a need for "safety monitoring" because there is now widespread folic acid fortification of foods and increasing use of folic acid in dietary supplements.

However, the authors of an accompanying editorial points out that data from the United States, where there has been mandatory folic acid fortification of flour and other foods since 1998, have been showing a significant decrease in cancer incidence. "These national incidence rates do not support a substantial population-wide adverse effect of the magnitude suggested in the study," write the editorialists, Bettina F. Drake, PhD, MPH, and Graham Colditz, MD, DrPH, both from the Washington University School of Medicine in St Louis, Missouri.

"The population data from the United States do not suggest that there is a problem," Dr. Drake said in an interview with *Medscape Oncology*. She pointed out that folate supplementation used in the study resulted in much higher blood levels than would be seen after eating foods fortified with folic acid. In addition, the study was conducted in individuals with heart disease and was of limited duration.

The findings from this study "do not nullify the potential long-term benefits that folic acid fortification may have on population health," Dr. Drake explained. The measure was introduced to reduce neural tube defects in newborns (which arise from folate deficiency during pregnancy). A reduction was seen within a "few years," the editorialists note.

Concerns about a link between cancer and folic acid supplementation have been raised previously, most recently with regard to colorectal cancer, as [reported](#) by *Medscape Oncology*. At that time, leading expert on nutrition and cancer Walter Willet MD, DrPH, from the Harvard School of Public Health in Boston, Massachusetts, said: "I am certain that we are not causing an epidemic of colorectal cancer with folic acid fortification of flour." He added that there was a small increase in the incidence of this cancer soon after fortification was introduced, but this coincided with an increase in colonoscopy, and he pointed out that mortality rates from this cancer have been declining steadily.

### Latest Results from Norway

The latest results come from 2 trials conducted in 6837 patients with ischemic heart disease, in which half the participants took supplements of vitamin B (including folic acid) to lower homocysteine levels to see if this would reduce cardiovascular outcomes. It did not, and these results are in line with other large trials. At the same time, both trials showed — independently — an increase in cancer in the supplementation group, compared with the placebo group, but this was not statistically significant.

In these 2 trials, participants took supplements containing folic acid (0.8 mg/d), vitamin B<sub>12</sub> (0.4 mg/d), and B<sub>6</sub> (40 mg/d), or various combinations of these. This dose of folic acid is 4 to 6 times higher than the average dose delivered by the mandatory fortification in the United States, and is twice the recommended daily allowance, the authors note, although they add that it is below the tolerable upper intake level of 1 mg/d set by the US Institute of

Medicine.

The current analysis pooled results from the 2 trials, which had a median participation of 39 months, and added data from an observational posttrial follow-up of 38 months, giving a total duration of around 5.5 years. The authors note that pooling the data from the 2 trials is "justified" because they were nearly identical.

This pooled analysis found a statistically significant increase in cancer incidence, cancer mortality, and all-cause mortality.

### Cancer Incidence, Cancer Mortality, and All-Cause Mortality Rates From the Pooled Analysis

End point	Supplement Group	Placebo Group	Hazard Ratio	95% Confidence Interval	P value
Cancer incidence	10%	8.4%	1.21	1.03–1.41	.02
Cancer mortality	4%	2.9%	1.38	1.07–1.79	.01
All-cause mortality	16.1%	13.8%	1.18	1.04–1.33	.01

These results for cancer outcomes are not supported by other studies of homocysteine-lowering vitamin B trials, the authors note.

### Increased Incidence Driven by Lung Cancer

The increase in cancer incidence and mortality was "mainly driven by an increase in lung cancer incidence," the authors write. They also pointed out that 94% of the subjects who developed lung cancer were either current or former smokers.

So the "real headline of this study should be that smoking increases the risk of lung cancer," according to the Council for Responsible Nutrition, which issued a statement about the study.

### Cancer Decreasing Significantly

In their editorial, Drs. Drake and Colditz write that these results indicate an excess of approximately 3.5 new cases of cancer per 1000 people per year, and 1 excess case of lung cancer per 1000 people per year. The excess deaths correspond to 1.7 cancer deaths per 1000 people per year.

"These numbers, if generalizable to the United States, would be substantial at the overall levels of total cancer incidence and mortality," they write. In addition, an increase in lung cancer incidence would be expected.

"However, the rates of total cancer incidence decreased significantly from 2001 to 2005, and the lung cancer incidence has also declined significantly," they point out.

Although the study suggests there is an association between folic acid supplementation and an increase in cancer, the US population data suggest that there isn't a problem with folic acid fortification of foods and cancer, Dr. Drake told *Medscape Oncology*. Folic acid fortification has been mandatory in the United States for more than 10 years and, given the results of this study, we would have expected a significant increase in the incidence of cancer by now, she suggested.

One of the issues with clinical trials is that observations are reported with a short time frame after the implementation of an intervention, the editorialists note. This can often lead to "looking for effects that fit the time frame," they add. "By analogy, when keys are missing it is common to look for them under the lamppost where the light is, rather than in the murky location where the keys were more likely to have been dropped."

*One of the coauthors on the paper, Klaus Meyer, PhD, is employed at the laboratory of Bevitel AS. The other authors and both editorialists have disclosed no relevant financial relationships.*

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## Authors and Disclosures

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Zosia Chustecka has disclosed no relevant financial relationships.

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