

Abstract

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Cancer incidence and mortality after treatment with folic acid and vitamin B12.

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CONTEXT: Recently, concern has been raised about the safety of folic acid, particularly in relation to cancer risk.

OBJECTIVE: To evaluate effects of treatment with B vitamins on cancer outcomes and all-cause mortality in 2 randomized controlled trials.

DESIGN, SETTING, AND PARTICIPANTS: Combined analysis and extended follow-up of participants from 2 randomized, double-blind, placebo-controlled clinical trials (Norwegian Vitamin Trial and Western Norway B Vitamin Intervention Trial). A total of 6837 patients with ischemic heart disease were treated with B vitamins or placebo between 1998 and 2005, and were followed up through December 31, 2007.

INTERVENTIONS: Oral treatment with folic acid (0.8 mg/d) plus vitamin B(12) (0.4 mg/d) and vitamin B(6) (40 mg/d) (n = 1708); folic acid (0.8 mg/d) plus vitamin B(12) (0.4 mg/d) (n = 1703); vitamin B(6) alone (40 mg/d) (n = 1705); or placebo (n = 1721).

MAIN OUTCOME MEASURES: Cancer incidence, cancer mortality, and all-cause mortality.

RESULTS: During study treatment, median serum folate concentration increased more than 6-fold among participants given folic acid. After a median 39 months of treatment and an additional 38 months of posttrial observational follow-up, 341 participants (10.0%) who received folic acid plus vitamin B(12) vs 288 participants (8.4%) who did not receive such treatment were diagnosed with cancer (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.03-1.41; P = .02). A total of 136 (4.0%) who received folic acid plus vitamin B(12) vs 100 (2.9%) who did not receive such treatment died from cancer (HR, 1.38; 95% CI, 1.07-1.79; P = .01). A total of 548 patients (16.1%) who received folic acid plus vitamin B(12) vs 473 (13.8%) who did not receive such treatment died from any cause (HR, 1.18; 95% CI, 1.04-1.33; P = .01). Results were mainly driven by increased lung cancer incidence in participants who received folic acid plus vitamin B(12). Vitamin B(6) treatment was not associated with any significant effects.

CONCLUSION: Treatment with folic acid plus vitamin B(12) was associated with increased cancer outcomes and all-cause mortality in patients with ischemic heart disease in Norway, where there is no folic acid fortification of foods. TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00671346.

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