Review: Antioxidant supplementation does not reduce gastrointestinal cancer

Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. **Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis.** Lancet. 2004; 364:1219-28.

Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. **Antioxidant supplements for preventing gastrointestinal cancers.** Cochrane Database Syst Rev. 2004;(4):CD004183.

QUESTION

Do antioxidant supplements reduce the risk for gastrointestinal cancer?

METHODS

Data sources: Cochrane controlled trial registers for 4 gastrointestinal disease groups, Cochrane Central Register of Controlled Trials (2003, Issue 1), MEDLINE (1966 to February 1991), EMBASE/Excerpta Medica (1985 to February 2003), LILACS (1982 to February 2003), Science Citation Index Expanded (1945 to February 2003), Chinese Biomedical Database (1978 to March 2003), reference lists of retrieved studies, and manufacturers of antioxidant supplements.

Study selection and assessment: Studies were selected if they were randomized controlled trials (RCTs) comparing antioxidant supplementation (β-carotene; vitamins A, C, and E; and selenium, separately or in combination) with placebo in patients who primarily had nongastrointestinal diseases and were at high risk for gastrointestinal cancer. Method-

ological quality was assessed using Cochrane Collaboration software and considered allocation sequence, allocation concealment, blinding, and follow-up.

Outcomes: Gastrointestinal cancer (esophageal, gastric, colorectal, pancreatic, or liver) and all-cause mortality.

MAIN RESULTS

14 RCTs (*n* = 170 525, mean age 55 y) met the selection criteria; 7 were of high methodological quality. 13 RCTs provided relevant data for the incidence of gastrointestinal cancer. Antioxidants, irrespective of type, did not reduce overall gastrointestinal cancer (relative risk reduction [RRR] 4%, 95% CI −4 to 12). This result did not differ between high- or low-quality trials. In 4 RCTs (3 low-quality), selenium reduced gastrointestinal cancer more than placebo (RRR 51%, CI 33 to 64). No reduction was seen with any other antioxidant or combination. In 9 RCTs (2 low-quality) that assessed mortality, a

borderline increase in mortality was seen using a fixed-effects model (relative risk increase [RRI] 5%, CI 1 to 9) but not using a random-effects model (RRI 4%, CI −3 to 11). When the 7 high-quality trials were analyzed, an increase in mortality was seen with antioxidants with the fixed-effects model (RRI 6%, CI 2 to 10) but not the random-effects model (RRI 6%, CI −2 to 15).

CONCLUSION

Antioxidant supplements, with the possible exception of selenium, do not reduce the risk for gastrointestinal cancer and may increase all-cause mortality.

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COMMENTARY

Systematic reviews with meta-analyses often provide definitive answers to important questions, but not this time. Bjelakovic and colleagues have done a valuable service by identifying all the RCTs of antioxidants and vitamins and showing that the quality of many of the 14 trials was high. But the antioxidant vitamins, individually and in various combinations, and gastrointestinal cancers, are just too different from each other for pooling to give a sensible answer. Even inveterate "lumpers" should have misgivings about this particular meta-analysis.

Specifically, is it appropriate to consider vitamin C (ascorbic acid), members of the vitamin A family (retinol, β-carotene, and others), and the several forms of vitamin E (e.g., α-, γ-, δ-tocopherol), as well as the trace metal selenium, all just "antioxidants"? Empiric evidence suggests that each is biologically active in its own way and effects differ according to dose. Similarly, is it appropriate to assume that all types of gastrointestinal cancer have the same pathogenesis and the same opportunities for chemoprevention? The authors use state-of-the-art methods. A statistical test for heterogeneity was negative, and effects were compared in high- and low-quality studies. But when it comes to combining studies, methodological rigor is not a sufficient substitute for a well-informed view of the difference in study questions, based on all that is known about these antioxidants and these types of cancer.

Selenium seemed to be effective, but the number of trials was too small and the trials themselves too weak for strong inference. The trend

toward increased total mortality in the β-carotene trials is not surprising, since other trials have shown that pharmacologic doses of β-carotene increase cardiovascular and cancer mortality (1). In a recent meta-analysis, all-cause mortality was increased in patients taking high-dose vitamin E (> 400 IU/d) (2).

There is plenty of biological support for the hypothesis that antioxidants might prevent cancer. Also, people like to believe that food supplements are remarkably effective and safe. But so far there is not enough clinical trial evidence to decide whether antioxidants prevent gastrointestinal cancer or not. Considering the weight of existing evidence, we should act as if antioxidants are not effective for this purpose.

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Reference
1. **Goodman GE, Thornquist MD, Balmes J, et al.** The Beta-Carotene and Retinol Efficacy Trial: incidence of lung cancer and cardiovascular disease mortality during 6-year follow-up after stopping beta-carotene and retinol supplements. J Natl Cancer Inst. 2004 Dec 1;96:1743-50.
2. **Miller ER 3rd, Pastor-Barriuso R, Dalal D, et al.** Meta-analysis: High-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med. 2004 Nov 10; [Epub ahead of print].