Review: antioxidant supplementation does not reduce gastrointestinal cancer

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

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

Q Do antioxidant supplements reduce the risk of 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 2003), 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: randomised controlled trials (RCTs) comparing antioxidant supplementation (β carotene; vitamins A, C, and E; and selenium, separately or in combination) with placebo in patients mainly with non-gastrointestinal diseases at high risk of gastrointestinal cancer. Methodological quality of individual studies was assessed based on allocation sequence, allocation concealment, blinding, and follow up.

Outcomes: gastrointestinal cancer (oesophageal, 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 had high methodological quality. 13 RCTs provided relevant data on the incidence of gastrointestinal cancer. Antioxidants, regardless of type, did not reduce overall gastrointestinal cancer (relative risk reduction [RRR] 4%, 95% CI -4 to 12). This result did not differ for high and low quality trials. In 4 RCTs (3 low quality), selenium reduced gastrointestinal cancer more than placebo (RRR 51%, CI 33 to 64). No other antioxidant or combination reduced gastrointestinal cancer. Meta-analysis of 9 RCTs (2 low quality) using a fixed effects model showed a borderline increase in mortality (relative risk increase [RRI] 5%, CI 1 to 9), whereas meta-analysis using a random effects model did not (RRI 4%, CI -3 to 11). Analysis of the 7 high quality trials using a fixed effects model showed an increase in mortality with antioxidants (RRI 6%, CI 2 to 10), whereas analysis using a random effects model did not (RRI 6%, CI -2 to 15).

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CONCLUSION

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

A modified version of this abstract appears in ACP Journal Club.

Commentary

Despite anecdotal evidence to the contrary, a growing body of scientific evidence suggests that antioxidant supplements may not be effective in disease prevention. The meta-analysis by Bjelakovic *et al* adds to that body of evidence, showing no protective effect of antioxidant supplements for the prevention of gastrointestinal cancers in high risk patients.

The most serious and unexpected finding was a higher mortality rate in the antioxidant group than the placebo group. The authors estimate that for every million people taking antioxidant supplements, 9000 premature deaths may have occurred. Possible explanations are that many studies used dosages in excess of current recommended daily intake or that some individuals are inherently more sensitive to antioxidants than others. This finding should be interpreted as preliminary, however, as many of the studies recruited high risk populations. The increased mortality rate therefore may not apply to healthy individuals who take antioxidant supplements as part of a healthy lifestyle.

The results of this review are relevant to public health nurses who work in lifestyle prevention, as well as advanced practice nurses who work in primary care or oncology. Given the increasing numbers of people who take supplements for prevention of disease, the results reinforce the importance of health teaching on the safety and efficacy of unregulated nutritional supplements. In light of these results, it may be prudent to advise high risk patients, such as people who smoke or have high alcohol intakes, of increased risks. However, further studies are needed to determine if the increased mortality rate is, in fact, related to the supplements, which supplements, and at what dosage. Thus, at this time it is difficult to infer harm for all people from supplementation. These findings remind all nurses discussing nutrition with their patients that nutritional supplements should be taken with the same care as regulated, prescribed medications.

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