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[Intervention Review]

Antioxidant supplements for preventing gastrointestinal cancers

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ABSTRACT

Background

Oxidative stress may cause gastrointestinal cancers. The evidence on whether antioxidant supplements are effective in preventing gastrointestinal cancers is contradictory.

Objectives

To assess the beneficial and harmful effects of antioxidant supplements in preventing gastrointestinal cancers.

Search methods

We identified trials through the trials registers of the four Cochrane Review Groups on gastrointestinal diseases, *The Cochrane Central Register of Controlled Trials* in *The Cochrane Library* (Issue 2, 2007), *MEDLINE*, *EMBASE*, *LILACS*, *SCI-EXPANDED*, and *The Chinese Biomedical Database* from inception to October 2007. We scanned reference lists and contacted pharmaceutical companies.

Selection criteria

Randomised trials comparing antioxidant supplements to placebo/no intervention examining occurrence of gastrointestinal cancers.

Data collection and analysis

Two authors (GB and DN) independently selected trials for inclusion and extracted data. Outcome measures were gastrointestinal cancers, overall mortality, and adverse effects. Outcomes were reported as relative risks (RR) with 95% confidence interval (CI) based on random-effects and fixed-effect model meta-analysis. Meta-regression assessed the effect of covariates across the trials.

Main results

We identified 20 randomised trials (211,818 participants), assessing beta-carotene (12 trials), vitamin A (4 trials), vitamin C (8 trials), vitamin E (10 trials), and selenium (9 trials). Trials quality was generally high. Heterogeneity was low to moderate. Antioxidant supplements were without significant effects on gastrointestinal cancers (RR 0.94, 95% CI 0.83 to 1.06). However, there was significant heterogeneity ($I^2 = 54.0\%$, $P = 0.003$). The heterogeneity may have been explained by bias risk (low-bias risk trials RR 1.04, 95% CI 0.96 to 1.13 compared to high-bias risk trials RR 0.59, 95% CI 0.43 to 0.80; test of interaction $P < 0.0005$), and type of antioxidant supplement (beta-carotene potentially increasing and selenium potentially decreasing cancer risk). The antioxidant supplements had no significant effects on mortality in a random-effects model meta-analysis (RR 1.02, 95% CI 0.97 to 1.07, $I^2 = 53.5\%$), but significantly increased mortality in a fixed-effect model meta-analysis (RR 1.04, 95% CI 1.02 to 1.07). Beta-carotene in combination with vitamin A (RR 1.16, 95% CI 1.09 to 1.23) and vitamin E (RR 1.06, 95% CI 1.02 to 1.11) significantly increased mortality. Increased yellowing of the skin and belching were non-serious adverse effects

of beta-carotene. In five trials (four with high risk of bias), selenium seemed to show significant beneficial effect on gastrointestinal cancer occurrence (RR 0.59, 95% CI 0.46 to 0.75, $I^2 = 0\%$).

Authors' conclusions

We could not find convincing evidence that antioxidant supplements prevent gastrointestinal cancers. On the contrary, antioxidant supplements seem to increase overall mortality. The potential cancer preventive effect of selenium should be tested in adequately conducted randomised trials.

PLAIN LANGUAGE SUMMARY

Antioxidant supplements cannot be recommended for gastrointestinal cancer prevention

Our body cannot synthesize all compounds that are essential for health. Therefore such compounds must be taken through diet. Oxidative stress may cause cell damage that is implicated in chronic diseases like cancer. Gastrointestinal cancers are among the most common cancers worldwide. The poor prognosis of patients diagnosed with gastrointestinal cancers made primary prevention a potentially attractive approach. The evidence on whether antioxidant supplements are effective in decreasing gastrointestinal cancers is contradictory.

In this review prevention with antioxidant supplements of oesophageal, gastric, small intestinal, colorectal, pancreatic, liver, and biliary tract cancers is assessed. The review includes 20 randomised clinical trials. In total, 211,818 participants were randomised to antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) versus placebo. Trial quality was exceptionally good.

Based on properly designed and conducted randomised clinical trials, convincing evidence that beta-carotene, vitamin A, vitamin C, and vitamin E or their combinations may prevent gastrointestinal cancers is not found. A total of 2057 of 95084 participants (2.2%) randomised to antioxidant supplements and 1548 of 78935 participants (2.0%) randomised to placebo developed gastrointestinal cancers. These antioxidant supplements even seem to increase mortality. A total of 17114 of 122,501 participants (14.0%) randomised to antioxidant supplements and 8799 of 78693 participants (11.2%) randomised to placebo died. Selenium alone may have preventive effects on gastrointestinal cancers. This finding, however, is based on trials with flaws in their design and needs confirmation in properly conducted randomised clinical trials.