Review: Antioxidant supplements for primary and secondary prevention do not decrease mortality


Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Cardiology ★★★★★☆ Endocrinology ★★★★★☆ Gastroenterology ★★★★★☆☆ Geriatrics ★★★★☆☆☆☆ Nephrology ★★★★★☆☆☆ Neurology ★★★★★☆☆☆☆ Oncology ★★★★★☆☆☆☆ Rheumatology ★★★★★☆☆ Dermatology ★★★★★☆☆☆☆

Question
In healthy people or patients with chronic diseases, do antioxidant supplements (ASs) decrease mortality?

Methods
Data sources: MEDLINE (1966 to October 2005), EMBASE/Excerpta Medica (1985 to October 2005), Cochrane Central Register of Controlled Trials (Issue 3, 2005), Science Citation Index Expanded (1945 to October 2005), and bibliographies of relevant studies.

Study selection and assessment: Randomized controlled trials (RCTs) that compared ASs (β-carotene; vitamin A, C, or E; or selenium, separately or in combination) with placebo or no intervention in healthy adults or patients with chronic diseases. Trials on acute, infectious, or malignant diseases except for nonmelanoma skin cancer were excluded. Of the remaining ASs, only those with high-quality RCTs (excluding selenium trials) showed that β-carotene (RR 1.07, CI 1.02 to 1.11), vitamin A (RR 1.16, CI 1.10 to 1.24), or vitamin E (RR 1.04, CI 1.01 to 1.07), alone or combined, increased mortality. Subgroup analysis also showed that vitamin C or selenium had no significant effect on mortality.

Main results
Meta-analysis of 68 RCTs showed that groups did not differ for mortality (Table). Meta-analysis of 47 high-quality RCTs showed that ASs increased mortality, while meta-analysis of 21 low-quality RCTs showed that ASs decreased mortality (borderline significance) (Table). Subgroup analysis of high-quality RCTs (excluding selenium trials) showed that β-carotene (RR 1.07, CI 1.02 to 1.11), vitamin A (RR 1.16, CI 1.10 to 1.24), or vitamin E (RR 1.04, CI 1.01 to 1.07), alone or combined, increased mortality. Subgroup analysis also showed that vitamin C or selenium had no significant effect on mortality.

Conclusion
In healthy people or patients with chronic diseases, antioxidant supplements do not decrease mortality.

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Commentary
ASs are used by a large segment of the population. Hence, the review by Bjelakovic and colleagues has major implications for public health. More relevant than the overall analysis that combined chemically diverse antioxidants (including combinations) in diverse settings, the agent-specific analyses suggest that β-carotene, vitamin A, or vitamin E, alone or combined, increase mortality, whereas vitamin C or selenium has no effect. The results are believable because of the careful, pre-specified protocol, comprehensive sensitivity analyses, and precise confidence limits.

2 other features of the review lend further support to the findings. First, signals of increased mortality were even more prominent in methodologically strong trials characterized as being at low risk for bias. Second, causality was strengthened by significant dose-response gradients for several of the antioxidants. Given the number of persons exposed to these agents, this review suggests that several thousand deaths each year may result from use of ASs, which have hitherto been considered by many physicians to be benign or even beneficial compounds. The public perception that vitamins and other antioxidants have favorable health effects because they are “natural” rather than pharmacologic is clearly wrong and in light of this review must be corrected by clinicians and other health advocates.

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