

Surviving Antioxidant Supplements

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An association between healthy diet and good health has been noted since Hippocrates (460–377 BC)—and in fact long before (1). Our diet provides numerous vitamins and trace elements that are essential to good health. Observational studies have shown that there is a positive association between a healthy diet, especially high intake of fruits and vegetables, and delayed aging, reduced risk of cancer, and reduced risk of cardiovascular diseases (2,3). Fruits and vegetables contain numerous micronutrients, including β -carotene (a precursor of vitamin A), vitamin C, vitamin E, and selenium. These organic components have antioxidant potential and are defined as essential micronutrients (4). Because our body cannot synthesize them, they must be consumed.

In spite of intensive research, it is still not clear exactly which specific dietary constituents of fruits and vegetables might be beneficial. Antioxidant vitamins and elements have attracted most attention in this regard. It is assumed that antioxidants may prevent oxidative damage to cellular components, a potentially important function given that oxidative stress might play a role in aging and the pathogenesis of number of diseases, including cardiovascular diseases and cancer, the leading causes of death in high-income countries (5).

Hypotheses as to the role played by oxidative stress in human disease have stimulated interest in the preventive potential of antioxidant supplements. Worldwide, institutions have been created to study antioxidants, and many resources have been allocated to this area. Consumption of antioxidant supplements in high-income countries has become widespread—it is estimated that about one-third of adults in high-income countries consume antioxidant supplements (6). A large number of primary or secondary prevention randomized trials have been conducted to assess the benefits and harms of antioxidant supplements versus placebo or no intervention. Systematic reviews and meta-analyses of these randomized trials have not demonstrated that β -carotene, vitamin A, and vitamin E in the administered dosages lead to decreased mortality, and some analyses have suggested the possibility of increased mortality (7–11). As to vitamin C and selenium, the verdict is still out (11).

There are several possible explanations for the potential negative effect of antioxidant supplements. Reactive oxygen species in moderate concentrations are essential mediators of reactions by which the body gets rid of unwanted cells. Thus, if administration of antioxidant supplements decreases free radicals, it may interfere with essential defensive mechanisms for ridding the organism of damaged cells, including those that are precancerous and cancerous (12). Thus, antioxidant supplements may actually cause some harm (7–11,13). Our diets typically contain safe levels of vitamins, but high-level antioxidant supplements could potentially upset an important physiologic balance (7–11,13).

The amounts of antioxidants that may afford protection are not known and may differ among individuals. People exposed to

increased oxidative stress may have elevated antioxidant requirements. Furthermore, antioxidants could be beneficial in people with innate or acquired high baseline levels of reactive oxygen species but be harmful in people with lower innate levels (12). It is important to keep in mind that antioxidant supplements are synthetic and possess prooxidant properties as well (14). These factors could explain a possible increase in the risk of cancer (8,9,13) and cardiovascular diseases (7). Meta-analyses of randomized clinical trials have not shown that antioxidant supplements reduce cancer incidence (8,9,13,15).

In this issue of the journal, Lawson et al. (16) report the results of a prospective observational study. They investigated the association between multivitamin use and prostate cancer risk in 295 344 men enrolled in the National Institutes of Health (NIH)–AARP Diet and Health Study (16). The men were clinically cancer free at enrollment. The authors found that use of multivitamins more than seven times per week, when compared with never use, was associated with a doubling in the risk of fatal prostate cancer (relative risk = 1.98, 95% confidence interval = 1.07 to 3.66). The study of Lawson et al. (16) is observational, and therefore confounding by indication and other confounding cannot be excluded. But the sample studied is very large, which reduces random errors, and the study seems well conducted. The results are in accord with the results of systematic reviews and meta-analyses of randomized clinical trials (7–11,13). The findings lend further credence to the possibility of harm associated with increased use of supplements, including increased rates of cancer (8,9,13,15) and cardiovascular mortality (7).

Lawson et al. (16) add to the growing evidence that questions the beneficial value of antioxidant vitamin pills in generally well-nourished populations (16) and underscore the possibility that antioxidant supplements could have unintended consequences for our health. There are still many gaps in our knowledge of the mechanisms of bioavailability, biotransformation, and action of antioxidant supplements. How much fruit and vegetables do we

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DOI: 10.1093/jnci/djk211

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have to eat to obtain an optimal amount of these nutrients? Why is it not possible to take a vitamin pill to obtain the same effect as a balanced diet? Antioxidant supplements in pills are synthetic, factory processed, and may not be safe compared with their naturally occurring counterparts (17–21). A possible explanation for the negative effects of antioxidant supplementation observed in trials is that the studies were conducted in middle- and high-income countries among populations already well saturated with vitamins and trace elements (11). The American diet provides 120% of the recommended dietary allowances for β -carotene, vitamin A, and vitamin C, and dietary vitamin E deficiency has never been reported in the United States (17–21). Whether oxidative stress is a primary cause of chronic diseases and the aging process itself or merely a secondary phenomenon is another question that deserves debate and scrutiny (22).

Results of ongoing clinical trials and further studies will be required to extend our knowledge of the impact of antioxidant supplements on health. Is oxidative stress the cause of disease or rather a consequence? Is it wise to artificially modulate the delicate balance between oxidative stress and antioxidants in our cells? Ideally, we should have more data to address these questions.

One way to extend our knowledge about the effects of supplemental vitamins on health would be to test for benefits and harms of supplements before they come to the market. This would entail fair testing of all commercial ingested products with claimed health benefits, as we intend to do with pharmaceutical drugs (23,24). What happens in a petri dish or in preclinical assays may not happen in people (<http://www.jameslindlibrary.org>; <http://www.cochrane.org>). Public investment in independent clinical research will be needed to adequately test hypotheses generated in the laboratory.

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