

Routine Vitamin Supplementation To Prevent Cancer and Cardiovascular Disease: Recommendations and Rationale

U.S. Preventive Services Task Force*

This statement summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on routine vitamin supplementation to prevent cancer and cardiovascular disease and the supporting scientific evidence. Part of the information on which this statement is based, including evidence tables and references, is available in the accompanying article on vitamins to prevent cardiovascular disease in this issue. More complete information can be found in the summaries of the evidence on vitamins to prevent cancer and vitamins to prevent cardiovascular disease, available on the USPSTF Web site (www.preventiveservices.ahrq.gov) and through the National Guideline

Clearinghouse (www.guideline.gov). The summaries of the evidence on these topics and the recommendation statement are also available in print through subscription to the *Guide to Clinical Preventive Services, Third Edition: Periodic Updates*. A subscription costs \$60 U.S. and can be ordered through the Agency for Healthcare Research and Quality Publications Clearinghouse (call 800-358-9295 or e-mail ahrqpubs@ahrq.gov).

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See related article on pp 56-70.

* For a list of the members of the U.S. Preventive Services Task Force, see the Appendix.

SUMMARY OF THE RECOMMENDATIONS

The U.S. Preventive Services Task Force (USPSTF) concludes that the evidence is insufficient to recommend for or against the use of supplements of vitamins A, C, or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer or cardiovascular disease. This is a **grade I recommendation**. (See Appendix Table 1 for a description of the USPSTF classification of recommendations.)

The USPSTF found poor evidence to determine whether supplementation with these vitamins reduces the risk for cardiovascular disease or cancer. (See Appendix Table 2 for a description of the USPSTF classification of levels of evidence.) The available evidence from randomized trials is either inadequate or conflicting, and the influence of confounding variables on observed outcomes in observational studies cannot be determined. As a result, the USPSTF could not determine the balance of benefits and harms of routine use of supplements of vitamins A, C, or E; multivitamins with folic acid; or antioxidant combinations for the prevention of cancer or cardiovascular disease.

The USPSTF recommends against the use of β -carotene supplements, either alone or in combination, for the prevention of cancer or cardiovascular disease. This is a **grade D recommendation**.

The USPSTF found good evidence that β -carotene supplementation provides no benefit in the prevention of cancer or cardiovascular disease in middle-aged and older adults. In two trials restricted to heavy smokers, β -carotene supplementation was associated with higher incidence of lung cancer and higher all-cause mortality. The USPSTF concludes that β -carotene supplements are unlikely to provide important benefits and might cause harm in some groups.

CLINICAL CONSIDERATIONS

The USPSTF did not review evidence regarding vitamin supplementation for patients with known or potential

nutritional deficiencies, including pregnant and lactating women, children, elderly persons, and people with chronic illnesses. Dietary supplements may be appropriate for people whose diet does not provide the recommended dietary intake of specific vitamins. Individuals may wish to consult a health care provider to discuss whether dietary supplements are appropriate.

With the exception of vitamins for which there is compelling evidence of net harm (for example, β -carotene supplementation in smokers), there is little reason to discourage people from taking vitamin supplements. Patients should be reminded that taking vitamins does not replace the need to eat a healthy diet. All patients should receive information about the benefits of a diet high in fruits and vegetables, as well as information on other foods and nutrients that should be emphasized or avoided in their diet (see the 2002 USPSTF recommendations on counseling to promote a healthy diet [1]).

Patients who choose to take vitamins should be encouraged to adhere to the dosages recommended in the Dietary Reference Intakes of the Institute of Medicine. Some vitamins, such as A and D, may be harmful in higher doses; therefore, doses greatly exceeding the Recommended Dietary Allowance or Adequate Intake should be taken with care while considering whether potential harms outweigh potential benefits. Vitamins and minerals sold in the United States are classified as "dietary supplements," and there is a degree of quality control over content if they have a U.S. Pharmacopeia seal (2). Nevertheless, imprecision in the content and concentration of ingredients could pose a theoretical risk not reflected in clinical trials using calibrated compounds.

The adverse effects of β -carotene on smokers have been observed primarily in those taking large supplemental

doses. There is no evidence to suggest that β -carotene is harmful to smokers at levels occurring naturally in foods.

The USPSTF did not review evidence supporting folic acid supplementation among pregnant women to reduce neural tube defects. In 1996, the USPSTF recommended folic acid for all women who are planning, or capable of, pregnancy (see the 1996 USPSTF chapter on screening for neural tube defects [3]).

Clinicians and patients should discuss the possible need for vitamin supplementation when taking certain medications (for example, folic acid supplementation for patients taking methotrexate).

SCIENTIFIC EVIDENCE

The USPSTF reviews (4–6) focused on the quality of the evidence regarding the effect of routine supplementation with certain vitamins on primary prevention of cancer and cardiovascular disease. These reviews were undertaken because of the growing epidemiologic evidence that dietary factors may play a role in the etiology of these diseases (7–9). The reviews focused on prospective trials of vitamin supplementation and observational studies of associations between the use of specific supplements and the risk for cancer or cardiovascular disease. The value of vitamins naturally occurring in food, the use of vitamin supplements for the prevention of other conditions (for example, neural tube defects), and the use of vitamin supplements for the secondary prevention of complications in patients with existing disease were outside the scope of these reviews.

Vitamin A

No prospective trials have examined the effect of vitamin A supplements alone on the risk for cancer. Observational studies provide no evidence that such supplements prevent cancer in men. In women, observational studies have reported a statistically significant inverse association between use of vitamin A supplements and risk for colon and breast cancer (10, 11). Despite efforts to adjust for confounding variables, the observational, nonrandom design of these studies makes it difficult to assess the extent to which the reduced cancer risk is attributable to vitamin A or to other characteristics of women who take vitamin A supplements. No evidence from prospective trials is available regarding the benefits of vitamin A alone in preventing cardiovascular disease. One good-quality cohort study found no effect of vitamin A supplementation in reducing cardiovascular disease mortality (12).

Vitamin C

No primary prevention trial of the effect of vitamin C supplementation alone on cancer or cardiovascular disease has been reported. Observational studies have generally shown no statistically significant associations between use of vitamin C supplements and risk for cancer of the breast, prostate, colon, or lung (12–14). The observational cohort

studies examining the effects of vitamin C on cardiovascular disease have produced inconsistent results (12, 15, 16).

Vitamin E

Only a few trials have examined the effects of vitamin E on the primary prevention of cancer or cardiovascular disease. A randomized, controlled trial (RCT) involving Finnish male smokers found that vitamin E supplementation is not protective against lung cancer but may have a beneficial impact on prostate cancer (14). Because prostate cancer was not a primary end point of the trial and the trial had other limitations, further evidence is needed to confirm this finding. Observational studies have shown no statistically significant association between use of vitamin E supplements and risk for prostate, lung, or breast cancer (5). One study suggested that vitamin E protects against colon cancer, but the influence of confounding variables cannot be fully excluded (17). Among primary prevention trials, two good-quality trials (14, 18) and one fair-quality trial (19) found no statistically significant benefit of vitamin E supplementation in preventing cardiovascular disease (20). Only one of seven trials of vitamin E supplementation for secondary prevention demonstrated a statistically significant reduction in cardiac events (4). Some prospective cohort studies have suggested a significant benefit, but the results are mixed and the influence of confounding variables cannot be excluded (4).

β -Carotene

A consistent body of evidence from clinical trials suggests that β -carotene supplementation does not decrease the risk for lung, prostate, colon, breast, or nonmelanoma skin cancer (14, 21–25). β -Carotene supplements were associated with an increased risk for lung cancer among smokers, especially heavy smokers, in two RCTs (14, 25). Results from four RCTs demonstrated no reduced risk for cardiovascular events or death after β -carotene supplementation (14, 21, 22, 26–28).

Antioxidant Vitamin Combinations

Studies of the effects of antioxidant vitamin combinations to prevent cancer have yielded mixed results. A recent RCT reported no statistically significant effect of daily supplementation with a combination of antioxidants: vitamin E, vitamin C, and β -carotene (29). Some studies have suggested an adverse effect of antioxidant combinations on cancer, but the results may have been confounded by the inclusion of β -carotene (5). Some observational studies of antioxidant vitamin combinations have suggested a benefit in preventing cardiovascular disease (13, 30, 31), but other studies, including well-designed RCTs, have shown no benefit (29, 32, 33). One secondary prevention trial showed an increase in all-cause mortality among women taking antioxidant supplements (34).

Multiple Vitamin Combinations

The incremental benefit of taking supplemental doses of folic acid and B vitamins has been examined by com-

paring the outcomes of observational studies while controlling for the total intake of antioxidant vitamin supplements (35). In these analyses, folic acid supplementation was associated with significantly decreased risk for colon cancer, but the protective effect requires confirmation in prospective trials. There is conflicting evidence regarding the use of multivitamins and the risk for cardiovascular disease. Among cohort studies, one good-quality study reported a statistically significant reduction in coronary events (36), two good-quality studies reported no statistically significant effect on mortality (16, 37), and one fair-quality study reported an increase in all-cause mortality in men (31). No trial has examined the effect of folate or multivitamins on the primary prevention of cardiovascular disease, but such studies are currently under way.

POTENTIAL HARMS OF VITAMIN SUPPLEMENTATION

Several known adverse effects are caused by excessive doses of vitamins. For example, moderate doses of vitamin A supplements may reduce bone mineral density and high doses may be hepatotoxic or teratogenic. A small but statistically significant increase in lung cancer mortality observed in trials of smokers has been ascribed to β -carotene supplementation; adverse effects of β -carotene supplementation have not been observed in other trials. The adverse effects of vitamin supplementation were not reported in most studies reviewed by the USPSTF. More studies are needed to better understand the harms of vitamin supplementation.

DISCUSSION

The findings of these USPSTF reviews must be placed in context because they focused only on vitamin supplements and their role in preventing cancer and cardiovascular disease. The value of taking vitamin supplements for other purposes, such as folic acid supplementation by women capable of pregnancy to prevent the birth of babies with neural tube defects, has stronger scientific support. Although the health benefits of vitamin supplementation remain uncertain, there is more consistent evidence that a diet high in fruit, vegetables, and legumes has important benefits; other constituents besides vitamins may account for the benefits of such diets.

Dietary supplementation with folic acid, vitamin B₆ (pyridoxine), and vitamin B₁₂ (alone or in combination) appears to lower plasma homocysteine levels, and higher levels of homocysteine may be an independent risk factor for cardiovascular disease (38). However, definitive evidence of the role of vitamin supplementation on altering cardiovascular outcomes is lacking. The results of a secondary prevention trial will be available within the next few years.

RECOMMENDATIONS OF OTHERS

The American Academy of Family Physicians states, "The decision to provide special dietary intervention or

nutrient supplementation must be on an individual basis using the family physician's best judgment based on evidence of benefit as well as lack of harmful effects. Megadoses of certain vitamins and minerals have been proven to be harmful" (39). The Canadian Task Force on Preventive Health Care is reviewing the role of vitamin E supplementation in the prevention of cardiovascular disease and cancer (40). The American Cancer Society recommends a well-balanced diet and does not recommend the use of vitamin and mineral supplements as a preventive or therapeutic intervention (41). The American Heart Association Dietary Guidelines: Revision 2000 recommends that vitamin and mineral supplements not be considered a substitute for a balanced and nutritious diet designed to emphasize intake of fruits, vegetables, and grains (42).

Appendix Table 1. U.S. Preventive Services Task Force Grades and Recommendations*

Grade	Recommendation
A	The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. <i>The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.</i>
B	The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. <i>The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.</i>
C	The USPSTF makes no recommendation for or against routine provision of [the service]. <i>The USPSTF found at least fair evidence that [the service] can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.</i>
D	The USPSTF recommends against routinely providing [the service] to asymptomatic patients. <i>The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.</i>
I	The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. <i>Evidence that the [service] is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.</i>

* The U.S. Preventive Services Task Force (USPSTF) grades its recommendations according to one of five classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

Appendix Table 2. U.S. Preventive Services Task Force Grades for Strength of Overall Evidence*

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes
Poor	Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes

* The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a three-point scale (good, fair, poor).

APPENDIX

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* Members of the Task Force at the time these recommendations were finalized.

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