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. Explanations of the ratings and of the strength of overall evidence are given in Appendix A and in Appendix B, respectively. The complete information on which this statement is based, including evidence tables and references, is available in the articles, "Routine Vitamin Supplementation to Prevent Cardiovascular Disease: A Summary of the Evidence for the U.S. Preventive Services Task Force,"[1] "Routine Vitamin Supplementation to Prevent Cancer: A Summary of the Evidence from Randomized Controlled Trials for the U.S. Preventive Services Task Force,"[2] and "Routine Vitamin Supplementation to Prevent Cancer: Update of the Evidence from Randomized Controlled Trials, 1999–2002,"[3] which can be obtained on the USPSTF Web site (http://www.preventiveservices.ahrq.gov) and through the National Guideline Clearinghouse™ (http://www.guideline.gov).

The recommendation statement and summaries of the evidence on these topics are also available from the AHRQ Publications Clearinghouse in print or through subscription to the *Guide to Clinical Preventive Services, Third Edition, Periodic Updates*. To order, contact the Clearinghouse at 1-800-358-9295 or e-mail ahrqpubs@ahrq.gov.

The USPSTF recommendations are independent of the U.S. government. They do not represent the views of the Agency for Healthcare Research and Quality (AHRQ), the U.S. Department of Health and Human Services, or the U.S. Public Health Service.

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Summary of 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. **I recommendation**.

The USPSTF found poor evidence to determine whether supplementation with these vitamins reduces the risk for cardiovascular disease or cancer. 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 beta-carotene supplements, either alone or in combination, for the prevention of cancer or cardiovascular disease. **D recommendation**.

The USPSTF found good evidence that beta-carotene supplementation provides no benefit in the prevention of cancer or cardiovascular disease in middle-aged and older adults. In 2 trials restricted to heavy smokers, beta-carotene supplementation was associated with higher incidence of lung cancer and higher all-cause mortality. The USPSTF concludes that beta-carotene supplements are unlikely to provide important benefits and might cause harm in some groups.

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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, the elderly, 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 (eg, beta-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 2002 USPSTF evidence summary on counseling to promote a healthy diet).[4]
- Patients who choose to take vitamins should be encouraged to adhere to the dosages recommended in the Dietary Reference Intakes (DRI) 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 (RDA) or Adequate Intake (AI) 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 (USP) seal.[5] 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 beta-carotene on smokers have been observed primarily in those taking large supplemental doses. There is no evidence to suggest that beta-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 1996 USPSTF chapter on screening for neural tube defects).[6]
- Clinicians and patients should discuss the possible need for vitamin supplementation when taking certain medications (eg, folic acid supplementation for those patients taking methotrexate).

Scientific Evidence

The USPSTF reviews[1–3] focused on the quality of the evidence regarding the effect of routine supplementation with certain vitamins on the 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 (eg, 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 the risk for colon and breast cancer.[10,11] Despite efforts to adjust for confounding variables, the observational, non-random 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 on 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 significant associations between use of vitamin C supplements and the risk for cancers 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 was not protective against lung cancer but may have a beneficial impact on prostate cancer.[14] Because prostate cancer was not a primary endpoint of the trial, and the trial suffered from other limitations, further evidence is needed to confirm this finding. Observational studies have shown no significant association between vitamin E supplement use and the risk for prostate, lung, or breast cancer.[2] 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, 2 good-quality[14,18] and 1 fair-quality trial[19] found no significant benefit of vitamin E supplementation on preventing cardiovascular disease.[20] Only 1 of 7 trials of vitamin E supplementation for secondary prevention demonstrated a significant reduction in cardiac events.[1] Some prospective cohort studies have suggested a significant benefit, but the results are mixed and the influence of confounding variables cannot be excluded.[1]

Beta-carotene

A consistent body of evidence from clinical trials suggests that beta-carotene supplementation does not decrease the risk for lung, prostate, colon, breast, or non-melanoma skin cancer.[14,21–25] Beta-carotene supplements were associated with an increased risk for lung cancer among smokers, especially heavy smokers, in 2 RCTs.[14,25] Results from 4 RCTs demonstrate no reduced risk for cardiovascular events or mortality after beta-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 significant effect of daily supplementation of a combination of antioxidants: vitamin E, vitamin C, and beta-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 beta-carotene.[2] 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 the B vitamins has been examined by comparing 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, 1 good-quality study reported a significant reduction in coronary events,[36] 2 good-quality studies reported no significant effect on mortality,[16,37] and 1 fair-quality study reported an increase in all-cause mortality in men.[31] No trial has examined the effect of either folate or multivitamins on the primary

prevention of cardiovascular disease, but such studies are currently underway.

Potential Harms of Vitamin Supplementation

There are several known adverse effects 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 significant increase in lung cancer mortality observed in trials of smokers has been ascribed to beta-carotene supplementation; adverse effects of beta-carotene supplementation on non-smokers 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 this review must be placed in context because it 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. Furthermore, dietary supplementation with folic acid, vitamin B-6 (pyridoxine), and vitamin B-12 (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 that "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 on 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 are not a substitute for a balanced and nutritious diet designed to emphasize the intake of fruits, vegetables, and grains.[42]

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Appendix A
U.S. Preventive Services Task Force – Recommendations and Ratings

The Task Force grades its recommendations according to one of 5 classifications (A, B, C, D, I) reflecting the strength of evidence and magnitude of net benefit (benefits minus harms):

A. The USPSTF strongly recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B. The USPSTF recommends that clinicians routinely provide [the service] to eligible patients. *The USPSTF found at least fair evidence that [the service] improves important health outcomes and concludes that benefits outweigh harms.*

C. The USPSTF makes no recommendation for or against routine provision of [the service]. *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.*

D. The USPSTF recommends against routinely providing [the service] to asymptomatic patients. *The USPSTF found at least fair evidence that [the service] is ineffective or that harms outweigh benefits.*

I. The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing [the service]. *Evidence that the [service] is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.*

Appendix B
U.S. Preventive Services Task Force – Strength of Overall Evidence

The USPSTF grades the quality of the overall evidence for a service on a 3-point scale (good, fair, poor):

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.

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