Routine Vitamin Supplementation to Prevent Cancer: Update of the Evidence from Randomized Controlled Trials 1999–2002*

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In 2001, the U.S. Preventive Services Task Force developed draft recommendations on the use of vitamin supplements to prevent cancer and cardiovascular disease, drawing on systematic reviews of the evidence available from randomized trials and well-conducted observational studies. The evidence pertaining to vitamin supplementation and cancer was originally summarized for the USPSTF in a manuscript covering publications through the end of 1999. To help the USPSTF finalize their draft recommendations, we updated the literature review through the end of 2002, focusing on the randomized trial evidence that was the basis of the draft recommendations.

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Methods

An electronic search completed on December 23, 2002, identified relevant studies from the MEDLINE database of publications from 1999 through December 2002. The search was limited to publications in English and studies involving human subjects. The MEDLINE search terms included precancerous conditions, neoplasms, antioxidants, vitamins/administration and dosage, and vitamins/therapeutic use, as well as "randomized" or "controlled" or "clinical" trial. (See Evidence Table 1.)

The search identified 197 studies; abstracts were reviewed by two independent reviewers. Studies included were original trials or supplemental analyses of primary prevention trials using vitamin or antioxidant supplements that reported cancer incidence or mortality outcomes. Studies were excluded if focus was on treatment or control of existing disease or if endpoints consisted of

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Reprints of this update, the chapter it updates (Routine Vitamin Supplementation to Prevent Cancer: A Summary of the Evidence from Randomized Controlled Trials for the U.S. Preventive Services Task Force), a related chapter (Routine Vitamin Supplementation to Prevent Cardiovascular Disease: A Summary of Evidence for the U.S. Preventive Services Task Force), and the USPSTF recommendations based on these two chapters (Routine Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease: Recommendations and Rationale) are available from the AHRQ Web site (www.preventiveservices.ahrq.gov) and through the National Guideline Clearinghouse™ (www.guideline.gov). The recommendation statement and summaries of the evidence are also available from the AHRQ Publications Clearinghouse in print 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 <mailto:ahrqpubs@ahrq.gov>.

intermediate cancer outcomes, such as dysplasia. Of the 197 studies found in the search, 10 studies met the inclusion criteria for this review. Two studies were new randomized controlled trials not included in an earlier review, and the remaining 8 were follow-up studies of two large clinical trials. The excluded trials included secondary prevention trials, trials involving chemotherapy for patients with cancer, and reviews. Descriptive data was abstracted from the included trials and summarized in an evidence table. (See Evidence Table 1.)

Results

New Trials

Two recent clinical trials reported no beneficial effect of vitamin E, vitamin C, or beta-carotene supplementation on incidence of cancer. In the MRC/BHF Heart Protection Study,[1] 20,536 United Kingdom hospital clinic patients at risk for heart disease were randomized to receive a combination of antioxidant nutrients (vitamin E, vitamin C, and beta-carotene) or placebo. The participants were followed for an average of five years and assessed for incidence of major coronary events as the primary endpoint. Incidence of new primary cancers excluding nonmelanoma skin cancers was recorded as a pre-planned secondary endpoint. The authors reported 800 new primary cancers in the nutrient group and 817 cases in the placebo group. There was no association between use of antioxidant supplementation and the incidence of cancer when compared with placebo (RR, 0.98; 95% CI, 0.89–1.08; *P*=.7) and no effect of supplementation on mortality caused by cancer (RR, 1.04; 95% CI, 0.90–1.21). In addition, no significant difference was found between treatment groups and controls in the incidence of any site-specific cancers.

In the second study, Green and colleagues[2] investigated the association between beta-carotene supplementation and the incidence of new basal cell and squamous cell cancers in 1,621 Australian subjects recruited from the community. Subjects were randomized to one of four interventions as a part of a 2x2 factorial design: daily sunscreen application and beta-carotene supplementation, sunscreen and placebo, beta-carotene only, or placebo only. During the four to five years of follow-up, no evidence was found of a protective effect of beta-carotene on basal cell or squamous cell carcinoma of the skin (RR, 1.04; 95% CI, 0.73–1.27 and RR,1.35; 95% CI, 0.84–2.19, respectively). Similar results were reported after subjects assigned to sunscreen were excluded from the analysis.

Follow-up Trials

Physicians' Health Study

The current search identified three supplemental analyses of the Physician's Health Study (PHS),[3] a 12-year follow-up study of 22,071 apparently healthy U.S. male physicians who were randomized into one of four intervention groups as part of a 2x2 factorial design: aspirin and placebo, beta-carotene and placebo, aspirin and beta-carotene, or both placebos. The aspirin component of the randomization design was discontinued six years into the study due to significant benefits on the risk for myocardial infarctions. As part of its primary analysis, the PHS concluded that there was no evidence that beta-carotene supplementation was associated with the overall incidence of malignant neoplasms, cardiovascular disease, or mortality after an average of 12 years of treatment.

Two of the three additional analyses reviewed were consistent with the PHS in finding no association of beta-carotene supplementation with cancer incidence. Frieling and colleagues[4] performed a subgroup analysis on the PHS data to assess the association of beta-carotene supplementation and the incidence of nonmelanoma skin cancer (basal cell and squamous cell carcinoma), an endpoint that was excluded from the original study. The study identified 1,786 cases of basal cell and squamous cell carcinoma in the beta-carotene group versus 1,821 cases in the placebo group. No protective or harmful effect of beta-carotene supplementation on non-melanoma skin cancer was found (RR, 0.98; 95% CI, 0.92–1.05).

In an update of the PHS analysis based on inclusion of data from additional cancer cases presenting during the trial period that were identified after publication, the authors reported no association

of beta-carotene with total incidence of cancer (RR, 1.0; 95% CI, 0.9–1.0; *P*=.41) or site-specific cancers, including prostate, colon, or lung cancers.[5] A positive association was noted between beta-carotene supplementation and cancers of the bladder (103 cases; RR, 1.5; 95% CI, 1.0–2.2; *P*=.04) and thyroid (21 cases; RR, 9.5; 95% CI, 2.2–40.7; *P*=.003); however, these findings are based on a small number of cases and could be due to chance because of examination of multiple endpoints. Additionally, the authors evaluated the effect of beta-carotene within subgroups defined by certain baseline characteristics. There was no significant association of beta-carotene supplementation with cancer incidence among subjects defined by several baseline factors, including age, alcohol use, smoking status, BMI, exercise, multivitamin use, or dietary beta-carotene.

A nested case-control study based on data from the 14,916 subjects of the PHS who submitted baseline blood specimens prior to randomization suggests that beta-carotene supplementation may reduce the risk for prostate cancer in those with low baseline serum beta-carotene levels.[6] A total of 1,439 cases of cancer and 631 cases of prostate cancer were identified during the 12-year follow-up period in this subgroup. Consistent with other studies, no significant association was reported between beta-carotene supplementation and total cancer or prostate cancer incidence. When baseline plasma levels of beta-carotene were taken into account, a marginally significant protective effect of beta-carotene on prostate cancer incidence was found among participants in the lowest quartile for baseline plasma beta-carotene (RR, 0.68; 95% CI, 0.46–0.99; *P*=.04 and *P*=.01 for trend).

The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC)

The ATBC study was a large clinical trial investigating the effect of alpha-tocopherol (vitamin E) and beta-carotene on lung cancer incidence and mortality among male Finnish smokers over an average six years of follow-up.[7] Subjects were randomized into one of four intervention groups in a 2x2 factorial design: alpha-tocopherol only, beta-carotene only, both nutrients, and placebo only. The ATBC study group reported no preventive effect of vitamin E or beta-carotene supplementation on cumulative incidence of lung cancer (RR,1.02; 95% CI, .86–1.12; *P*=.8 and RR, 1.18; 95% CI, 1.03–1.36; *P*=.01, respectively). Follow-up studies of the ATBC trial have continued to support this finding for various subgroups and cancer endpoints.

Rautalahti and colleagues[8] analyzed the ATBC data for effects of alpha-tocopherol and beta-carotene supplementation on pancreatic cancer incidence and mortality over the same follow-up period. No statistically significant effect on pancreatic cancer risk was found in the intervention groups that received alpha-tocopherol (RR, 1.34; 95% CI, 0.88–2.05) or in the groups receiving beta-carotene (RR, 0.75; 95% CI, 0.49–1.14).

Two recent supplementary analyses of the ATBC study investigated two cancer endpoints, colorectal and urinary tract cancer incidence and mortality. Albanes and colleagues[9] reported no significant preventive or harmful effects of beta-carotene or alpha-tocopherol on colorectal cancer risk. Based on the cumulative incidence of colorectal cancer over the study period, the relative risk among the patients in the groups receiving alpha-tocopherol supplementation was 0.78 (95% CI, 0.55–1.09; *P*=.15) and in groups receiving beta-carotene, 1.05 (95% CI, 0.75–1.47; *P*=.78). Virtamo and colleagues[10] reported similar findings with respect to urothelial (bladder, renal pelvis, and ureter) and renal cell carcinoma. In the groups receiving alpha-tocopherol supplements there was no significant effect on incidence of urothelial or renal cell cancer (RR, 1.10; 95% CI, 0.8–1.5; *P*=.48 and RR,1.10; 95% CI, 0.7–1.6; *P*=.55, respectively). Among groups randomized to beta-carotene supplementation, there was no significant change in risk for urothelial cancers (RR, 1.0; 95% CI, 0.7–1.3; *P*=.92) and renal cell cancers (RR, 0.8; 95% CI, 0.6–1.30; *P*=.57) when compared with groups not receiving beta-carotene.

Two recent prospective cohort studies based on ATBC data have presented mixed results regarding the association of cancer risk and baseline serum levels of nutrient oxidants and dietary antioxidants. These studies did not examine the independent

effect of supplementation on cancer risks. Malila and colleagues[11] analyzed data from a cohort of 26,951 participants of the ATBC trial who had completed dietary surveys and provided serum samples prior to randomization to assess the effect on colorectal cancer risk. One hundred eighty-four cases of colorectal cancer cases were diagnosed in this cohort over an average eight-year follow-up period. No association was found between dietary intake of various antioxidants, including vitamin C, vitamin E, alpha-tocopherol, gamma-tocopherol, beta-carotene, and retinol, and colorectal cancer risk. After adjusting for age, BMI, smoking, supplementation assignment, and other factors, similar results were obtained when comparing the highest to the lowest quartiles of baseline serum levels of alpha-tocopherol (RR, 0.94; 95% CI, 0.57–1.57; *P*=.72 for trend), beta-carotene (RR, 0.86; 95% CI, 0.54–1.36; *P*=.82 for trend), and retinol (RR, 1.02; 95% CI, 0.65–1.58; *P*=.75 for trend). No interaction was noted between supplementation assignment and dietary or serum alpha-tocopherol and beta-carotene levels.

The second study[12] examined lung cancer incidence and mortality outcomes and reported an increased risk associated with decreasing dietary and serum alpha-tocopherol levels. Among the 29,102 participants of the ATBC trial who had had serum alpha-tocopherol levels taken prior to randomization, 1,144 cases of lung cancer were diagnosed. The relative risk for lung cancer when comparing the highest quintile of baseline serum alpha-tocopherol levels to the lowest quintile was .81 (95% CI, 0.67–0.97; *P*=.09 for trend) after controlling for age, BMI, smoking, energy, and intervention assignment. No significant interaction was found between alpha-tocopherol supplementation assignment and baseline serum alpha-tocopherol levels. Similar results were obtained when comparing the highest and lowest quintiles of dietary alpha-tocopherol levels (RR, 0.80; 95% CI, 0.66–0.97; *P*=.02 for trend) and dietary vitamin E intake (RR, 0.77; 95% CI, 0.64–0.93; *P*=.01 for trend).

Summary

The clinical trials reviewed here spanning 1999 to 2002 do not document any consistent association between vitamin supplementation and risk for cancer. This finding is consistent with an earlier review and with prior large, randomized controlled trials of vitamin supplementation. The possibility remains of risk reduction among certain subgroups defined by cancer type or baseline characteristics. The studies that have reported an inverse relationship between supplementation of vitamins and risk for specific cancers may be affected by small case numbers and evaluation of multiple endpoints and have yet to be replicated.

References

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Evidence Table I. Randomized controlled trials on vitamin supplementation and cancer 1999–2002

Study	Design/intervention	Endpoints
New trials		
Heart Protection Study Collaborative Group.[1]	RCT; intention-to-treat; subjects randomized to receive antioxidant nutrients (600 mg vit E, 250 mg vit C, and 20 mg beta-carotene) or placebo; follow-up visits at 4, 8, 12 months, then every 6 months for 5 years; population: men and women aged 40–80 years with non-fasting cholesterol of at least 3.5 mmol/L having substantial 5-year risk of heart disease based on past history of CHD, occipital arterial disease, DM, or HTN; recruited from clinics at 69 UK hospitals.	Primary-Incidence of major coronary events (non-fatal MI and death from coronary disease); secondary-major vascular events (major coronary events, strokes, coronary or non-coronary revascularizations; site-specific CA, cerebral hemorrhage, vascular procedures, hospitalization).
Green A, et al.[2]	RCT; intention-to-treat; subjects from Queensland, Australia, community randomized to one of four groups: daily sunscreen and 30 mg beta-carotene, daily sunscreen and placebo, beta-carotene only, or placebo only, aged 20–69 years.	Incidence of basal cell carcinoma and squamous cell carcinoma and number of tumors among subjects with newly diagnosed skin CA. CAs diagnosed within first year of study were excluded.
Physicians' Health Study		
PRIMARY RESULTS **Hennekens CH, et al.**[3]	RCT, double-blinded, 2x2 factorial design; intervention—4 groups: 1) aspirin + beta-carotene placebo; 2) beta-carotene + aspirin placebo; 3) both active agents; 4) both placebos; aspirin component terminated in 1988.	Cases of malignant neoplasms excluding nonmelanoma skin CA; lung CA; malignant CA mortality; cardiovascular events—MI, strokes, cardiovascular mortality, all-cause mortality; all important cardiovascular events.
Frieling UM, et al.[4]	Subgroup analysis of PHS; excluded data from 187 subjects with diagnosis of NMSC at time of randomization.	Incidence of first NMSC (basal cell carcinoma and squamous cell carcinoma); new endpoint.

Note: AT indicates alpha-tocopherol; ATBC, Alpha-Tocopherol Beta-Carotene study; BC, beta-carotene; CA indicates cancer; CHD, coronary heart disease; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; NMSC, nonmelanoma skin cancer; P, probability; PHS, Physicians Health Study; RCT, randomized controlled trial; RR, relative risk; UK, United Kingdon; vit, vitamin.

Number of subjects/ follow-up period	Results (95% CI)	Conclusions
63,603 screened; 32,145 had prerandomization testing; 20,536 subjects randomized; average 5-year follow-up.	All-cause mortality (1,446 deaths in vitamin group vs 1,389 in placebo) RR 1.04 (CI .97–1.12; *P*=.3); major vascular events (2,306 in vitamin group vs 2,312 in placebo) RR 1.00 (CI 0.94–1.06; *P*=>.9); new primary cancers excluding NMSC (800 cases in vitamin group, 817 cases in placebo) RR 0.98 (CI 0.89–1.08; *P*=.7); no significant difference between treatment groups in incidence of any site-specific CA.	Supplementation of vit E, vit C, and beta-carotene found to be safe but showed no benefit among individuals at high risk or low risk for vascular events or CA.
1,621 subjects randomized; follow-up 4-5 years.	Basal cell CA (102 cases in beta-carotene groups vs 93 cases in placebo)—RR 1.04 (CI 0.73–1.27); squamous cell CA (40 cases in beta-carotene groups vs 28 cases in placebo)—RR 1.35 (CI 0.84–2.19; not significant); number similar with subjects receiving sunscreen excluded from analysis.	Beta-carotene supplementation found to have no protective or harmful effect on incidence of basal cell or squamous cell carcinoma.
22,071 U.S. male physicians aged 40–84 in 1982 with no history of CA, MI, stroke, or transient cerebral ischemia; beta-carotene (11,036) and placebo (11,035); follow-up average 12 years.	All CA (1,273 cases in beta-carotene group vs 1293 in placebo)—RR .98 (95% CI 0.91–1.06); no statistically significant effect of beta-carotene on incidence of lung, colorectal, prostate, stomach, pancreas, or brain CA or melanoma, leukemia, or lymphoma; no effect of beta-carotene on CA mortality (386 in beta-carotene group vs 380 in placebo)—RR 1.02 (0.89–1.18).	No statistically significant benefit or harm of 12 years of supplementation of beta-carotene on incidence of malignant neoplasms, cardiovascular disease, or death among current smokers or nonsmokers.
See above.	NMSC (1,786 cases in beta-carotene group vs 1,821 in placebo)—RR 0.98 (CI 0.92–1.05); BCC (1,574 cases vs 1,598 cases)—RR 0.99 (CI 0.92–1.06); SCC (340 cases vs 352 cases)—RR 0.97 (CI 0.84–1.13).	No effect of beta-carotene supplementation on incidence of NMSC (basal cell carcinoma or squamous cell carcinoma).

Evidence Table I. Randomized controlled trials on vitamin supplementation and cancer 1999–2002 (cont.)

Study	Design/intervention	Endpoints
Physicians' Health Study, cont.		
Cook, NR, et al.[6]	Nested case-control study among the 14,916 subjects of the Physicians' Health Study who submitted baseline blood specimens prior to randomization; 1,439 total CA cases were compared to 2,204 controls matched on smoking status and age.	Incidence of total and prostate CA among subjects differing by baseline blood levels of beta-carotene.
Cook, NR, et al.[5]	Update of PHS analysis including primary CAs occuring during trial period but not identified until after publication. Also, subgroup analysis of PHS defined by baseline characteristics of subjects.	Any malignant neoplasm except non-melanoma skin CA, primary-lung CA.

Note: AT indicates alpha-tocopherol; ATBC, Alpha-Tocopherol Beta-Carotene study; BC, beta-carotene; CA indicates cancer; CHD, coronary heart disease; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; NMSC, nonmelanoma skin cancer; P, probability; PHS, Physicians Health Study; RCT, randomized controlled trial; RR, relative risk; UK, United Kingdon; vit, vitamin.

Number of subjects/ follow-up period	Results (95% CI)	Conclusions
See above.	1,439 CA cases: 631 prostate, 169 colon, 93 melanoma, 85 lung, 94 lymphoma, and fewer than 50 other; total CA in beta-carotene supplementation group—RR 0.96 (CI 0.83–1.10) and prostate CA—RR 0.91 (CI 0.75–1.11); total CA in beta-carotene group in lowest baseline plasma beta-carotene quartile—RR 0.83 (CI 0.63–1.09) and in highest quartile—RR 1.14 (CI 0.86–1.52) [nonsignificant]; prostate cancer in beta-carotene group in lowest baseline plasma beta-carotene quartile—RR 0.68 (CI 0.46–0.99; *P*=.04) and in highest quartile—RR 1.33 (CI 0.91–1.96; *P*=.14).	Beta-carotene supplementation may reduce risk of prostate CA in those with low baseline levels.
See above.	2,667 confirmed cases of CA with 1,314 in beta-carotene group and 1,353 in placebo; total CA: RR 1.0 (CI 0.9–1.0; *P*=.41); no association with prostate (1,117 cases): RR 1.0 (CI 0.9–1.1), colon (267 cases): RR 0.9 (CI 0.7–1.2); positive association of supplementation with bladder CA (103 cases): RR 1.5 (CI 1.0–2.2; *P*=.04) and thyroid (21 cases): RR 9.5 (CI 2.2–40.7; *P*=.003); no significant association of beta-carotene assignment with baseline cancer risk factors (including age, smoking status, body mass index, exercise, multivitamin use, or dietary beta-carotene) with CA incidence; colon CA among those who drink alcohol daily (86 cases): RR 0.5 (CI 0.3–0.8).	No effect of beta-carotene on total CA or prostate, colon, or lung CA specifically; positive association with bladder and thyroid CA, but may be due to methodology and not consistent with previous findings.

Evidence Table I. Randomized controlled trials on vitamin supplementation and cancer 1999-2002 (cont.)

Study	Design/intervention	Endpoints
ATBC Trial		
PRIMARY RESULTS **The ATBC Cancer Prevention Study Group.**[7]	RCT; male smokers from southwestern Finland aged 50 through 69; subjects with history of CA or serious illness, taking anticoagulents, or taking vit E, A, or beta-carotene supplements in excess were excluded; subjects were randomized into 1 of 4 groups: 50 mg alpha-tocopherol daily, 50 mg alpha-tocopherol and 20 mg beta-carotene daily, 20 mg beta-carotene daily, or placebo.	Primary lung CA incidence and mortality; secondary CAs other than lung CA.
Rautalahti MT, et al.[8]	Supplemental analysis of ATBC data on effect of alpha-tocopherol and beta-carotene supplementation on pancreatic CA incidence.	Pancreatic CA incidence and mortality.
Albanes D, et al.[9]	Supplemental analysis of ATBC data on effect of alpha-tocopherol and beta-carotene supplementation on colorectal CA incidence.	Colorectal CA incidence and mortality.

Note: AT indicates alpha-tocopherol; ATBC, Alpha-Tocopherol Beta-Carotene study; BC, beta-carotene; CA indicates cancer; CHD, coronary heart disease; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; NMSC, nonmelanoma skin cancer; P, probability; PHS, Physicians Health Study; RCT, randomized controlled trial; RR, relative risk; UK, United Kingdon; vit, vitamin.

Number of subjects/ follow-up period	Results (95% CI)	Conclusions
29,133 subjects randomized; follow-up, 5–8 years (median 6.1 years).	Lung CA incidence in alpha-tocopherol groups (433 cases vs. 443 in non-tocopherol)—RR 0.98 (CI 0.86–1.12; *P*=.8); lung cancer incidence in beta-carotene groups (474 cases vs. 402 in non-beta-carotene)—RR 1.18 (CI 1.03–1.36; *P*=.01); overall mortality in alpha-tocopherol groups—RR 1.02 (CI 0.95–1.09; *P*=.6); in beta-carotene groups—RR 1.08 (CI 1.01–1.16; *P*=.02).	No effect of vitamin E or beta-carotene supplementation in the prevention of lung cancer incidence or mortality.
See above	Pancreatic carcinoma: 25 cases in AT group, 12 cases in BC, 26 cases in ATBC, and 26 cases in placebo; incidence in BC and ATBC groups—RR 0.75 (CI 0.49–1.14); incidence in AT and ATBC groups—RR 1.34 (CI 0.88–2.05); pancreatic CA mortality in BC and ATBC groups—RR 0.81 (0.53–1.26); pancreatic CA mortality in AT and ATBC groups—RR 1.10 (CI 0.72–1.72).	Neither supplement had a statistically significant effect on pancreatic CA incidence; suggests benefit of BC.
See above	Colorectal carcinoma: 29 cases in AT group, 39 cases in BC group, 30 in ATBC, and 37 in placebo; cumulative incidence in BC and ATBC groups—RR 1.05 (CI 0.75–1.47, *P*=.78); cumulative incidence in AT and ATBC groups—RR 0.78 (CI 0.55–1.09; *P*=.15); colorectal CA mortality in BC and ATBC groups: RR 1.01 (CI 0.56–1.79); colorectal CA mortality in AT and ATBC groups: RR 0.92 (CI 0.51–1.64).	No beneficial or harmful effect of beta-carotene but found a nonsignificant preventive effect of alpha-tocopherol on colorectal CA.

Evidence Table I. Randomized controlled trials on vitamin supplementation and cancer 1999-2002 (cont.)

Study	Design/intervention	Endpoints
ATBC Trial, cont.		
Virtamo J, et al.[10]	Supplemental analysis of ATBC data on effect of alpha-tocopherol and beta-carotene supplementation on urinary tract CA.	Urothelial CA (bladder, renal pelvis, ureter) and renal cell CA incidence.
Malila N, et al.[11]	Nested prospective cohort study using data from ATBC trial to study association between dietary and serum levels of antioxidants at baseline.	Colorectal CA incidence.
Woodson K, et al.[12]	Nested prospective cohort study using data from ATBC trial to study association between baseline serum alpha-tocopherol levels and incidence of lung CA.	Lung CA incidence and mortality.

Note: AT indicates alpha-tocopherol; ATBC, Alpha-Tocopherol Beta-Carotene study; BC, beta-carotene; CA indicates cancer; CHD, coronary heart disease; CI, confidence interval; DM, diabetes mellitus; HTN, hypertension; MI, myocardial infarction; NMSC, nonmelanoma skin cancer; P, probability; PHS, Physicians Health Study; RCT, randomized controlled trial; RR, relative risk; UK, United Kingdon; vit, vitamin.

Number of subjects/ follow-up period	Results (95% CI)	Conclusions
See above.	Urothelial carcinoma: 47 cases in AT group, 43 in BC; 42 cases in ATBC; 37 in placebo. Cumulative incidence of urothelial CAs in BC and ATBC groups: RR 1.0 (CI 0.7–1.3; *P*=.92); urothelial CAs in AT and ATBC groups: RR 1.1 (CI 0.8–1.5; *P*=.48); renal cell CA—27 cases in AT group, 21 in BC, 27 in ATBC, and 27 in placebo; cumulative incidence of renal cell CA in AT and ATBC: RR 1.1 (CI 0.7–1.6; *P*=.55); cumulative incidence of renal cell CA in BC and ATBC: RR 0.8 (CI 0.6–1.3; *P*=.57).	No effect of alpha-tocopherol or beta-carotene supplementation on the incidence of urothelial or renal cell CA.
26,951 participants of ATBC study with all baseline data including baseline serum samples and complete baseline dietary history available; median follow-up, 8 years.	184 colorectal CA cases were diagnosed by end of follow-up; no association described between dietary anitoxidant nutrients (vit C, vit E, alpha-tocopherol, beta-carotene, retinol, lycopene, or lutein + zeaxanthin) and colorectal CA incidence; no association between highest and lowest quartiles of serum alpha-tocopherol (RR 0.94; CI 0.57–1.57; *P*=.72 for trend), beta-carotene (RR 0.86; CI 0.54–1.36; *P*=.82 for trend) or retinol (RR 1.02; CI 0.65–1.58; *P*=.75 for trend) and colorectal CA incidence; adjusted for supplementation assignment.	No effect of dietary alpha-tocopherol or beta-carotene on colorectal CA risk; no association between serum levels of antioxidants and colorectal CA risk.
29,102 participants of ATBC study with baseline serum alpha-tocopherol levels taken prior to randomization; median follow-up, 7.7 years.	1,144 cases of lung CA diagnosed in cohort; nonsignificant inverse association (*P*=.09 for trend) with baseline alpha-tocopherol and lung CA risk, RR 0.81 (CI 0.67–0.97) highest quintile compared to lowest quintile; dietary alpha-tocopherol showed inverse association (*P*=.02 for trend) for lung CA risk, RR 0.80 (CI 0.66–0.97) highest quintile compared to lowest quintile; adjusted for supplementation assignment.	Baseline serum alpha-tocopherol and dietary serum alpha-tocopherol found to be inversely associated with lung CA risk.

Table 1. Search strategy and yield	
#18	Search #17 AND #14 Limits: Publication Date from 1999 to 2002, English, Human
#17	Search #16 AND #15 Limits: Publication Date from 1999 to 2002, English, Human
#16	Search randomized or controlled or clinical Limits: Publication Date from 1999 to 2002, English, Human
#15	Search trial Limits: Publication Date from 1999 to 2002, English, Human
#14	Search #8 AND #9 Field: All Fields, Limits: Publication Date from 1999 to 2002, English, Human
#13	Search #8 AND #9 Field: All Fields, Limits: Publication Date from 1999 to 2002, English, Randomized Controlled Trial, Human
#12	Search #8 AND #9 Field: All Fields, Limits: English, Randomized Controlled Trial, Human
#11	Search #8 AND #9 Field: All Fields, Limits: English, Human
#10	Search #8 AND #9
#9	Search #6 OR #7
#8	Search #4 OR #5
#7	Search “precancerous conditions” [MESH]
#6	Search “neoplasms” [MESH]
#5	Search “antioxidants” [MESH]
#4	Search “Vitamins/administration and dosage” [MESH] OR “Vitamins/therapeutic use” [MESH]

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