Routine Vitamin Supplementation to Prevent Cancer: A Summary of the Evidence From Randomized Controlled Trials for the U.S. Preventive Services Task Force

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Cancer is the second leading cause of death in the United States, accounting for 1 of every 4 deaths.[1] Nutritional status has long been speculated to play a significant role in certain cancers. One theory holds that oxidative damage to cells contributes to carcinogenesis. In laboratory experiments, the antioxidant vitamins, vitamin C, vitamin E (alpha-tocopherol), and beta-carotene, counteract damage to biomolecules due to oxidants,[2] raising the possibility that increased intake of these vitamins might prevent cancer. Vitamin A (retinol), which acts within the cell to control gene expression, and folic acid,[3] which is involved in DNA methylation and purine and pyrimidine synthesis, may also have a role in preventing cancer.[4]

In epidemiological studies, low dietary intake and blood levels of certain antioxidant vitamins have been associated with a higher incidence of certain cancers and higher cancer mortality.[5] Several randomized controlled trials designed to test the efficacy of vitamin supplements in the primary prevention of cancer have also been undertaken. These randomized trials have examined the effect of vitamin supplements on cancer biomarkers, on the incidence and progression of precancerous lesions, on the incidence of invasive cancer, and on cancer-specific and all-cause mortality.

Most of the trials that examined cancer incidence and mortality have been published in the last decade. In light of the large body of new evidence, the U.S. Preventive Services Task Force decided that it was timely to review the benefits of vitamin supplementation. This summary reviews randomized trials that addressed this question, posed by the Task Force: *Do antioxidant vitamin supplements reduce all-cause mortality, cancer mortality, or the incidence of cancer or certain precancerous lesions in the general adult population of the United States?*

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Reprints are available from the AHRQ Web site (www.preventiveservices.ahrq.gov) and through the National Guideline Clearinghouse (www.guideline.gov). The 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. This chapter first appeared on the AHRQ Web site on July 1, 2003.

The USPSTF recommendations based on this evidence review and another review, Routine Vitamin Supplementation to Prevent Cardiovascular Disease, can be found in Routine Vitamin Supplementation to Prevent Cancer and Cardiovascular Disease: Recommendations and Rationale, available on the AHRQ Web site and in the *Guide to Clinical Preventive Services, Third Edition: Periodic Updates.*

Methods

Literature Search and Study Selection

The criteria for inclusion in the review were developed in consultation with members of the USPSTF. English-language randomized controlled trials and prospective cohort studies concerning adults in developed countries were eligible for inclusion. Case-control studies were excluded unless they were performed in the context of a prospective cohort study (ie, a nested case-control study). Studies of supplementation with vitamin A, vitamin C, vitamin E, beta-carotene, folic acid, combinations of these vitamins, or a multiple vitamin were eligible if they reported a) the incidence of or mortality from any invasive cancer other than nonmelanoma skin cancer or b) the incidence of colonic polyps. Studies of other precancerous lesions, carcinoma *in situ*, and regression of cancer or of precancerous lesions were excluded.

This summary reports the results of our review of randomized trials that address this question. The results of the cohort studies were presented to the USPSTF, but they are excluded from this report because they did not contribute to the Task Force's recommendations. Appendix I summarizes the results of the included cohort studies.

We searched the Cochrane Controlled Trials Registry (December, 2001) and the MEDLINE database from 1966 to December 2001 using terms for the 5 nutrients (A, C, E, beta-carotene, and folate) as well as multivitamin and antioxidant supplements and terms for cancer and precancerous lesions. We also searched the reference lists of review articles and, in several rounds of review of earlier manuscripts, asked experts for additional references. Finally, we searched MEDLINE again (December 2001) using the acronyms or full titles of the major trials and cohort studies to identify additional publications. Two reviewers applied the eligibility criteria listed above after reviewing the titles and abstracts of retrieved citations and again after selecting full-text articles for closer review.

The searches identified 932 citations, of which 102 were reports from 36 randomized controlled trials. Ten of these trials were included in this review. The excluded trials either had no eligible cancer endpoints, combined included with excluded nutrients, or had not yet reported results (Appendix II).

Analysis/Synthesis

Two reviewers independently abstracted descriptive data from the included trials, using one form for abstraction of information about the study design and another form for results. To assess study quality, we used the system developed by the USPSTF, which includes a set of 6 criteria to rate the internal validity of each study as "good," "fair," or "poor."[6] For clinical trials we also assessed study quality using the Jadad score.[7] We summarized the results of studies in evidence tables organized by type of study, nutrient, and outcome. For supplement/outcome combinations with sufficient evidence, we assessed heterogeneity among studies and conducted meta-analyses using a pairwise, sequential procedure based on maximum likelihood methods (M. Aickin, PhD, and M. Helfand, MD, MPH, unpublished data, 2000).

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Results

Table 1 summarizes the characteristics of the 9 randomized controlled trials that met the criteria for inclusion. Beta-carotene supplementation has been studied in 5 controlled trials. Only 1 trial examined the effect of vitamin E supplementation on cancer incidence and mortality. For these outcomes, no studies of vitamin A or vitamin C alone versus placebo have been completed. Vitamin C has been studied only in combination with other vitamins. None of the included trials addressed supplementation with folic acid. Six studies examined vitamin combinations; 4 did so as part of a factorial design and 2 did not.

Beta-Carotene

Evidence from 5 randomized controlled trials[8–12] indicates that beta-carotene supplementation increases lung cancer incidence in smokers and has no effect on cancer incidence in nonsmokers. These trials were designed to test beta-carotene at levels above those that could be achieved through food, approximately 10 times the average U.S. intake.[13] They achieved substantially higher blood levels of beta-carotene than those associated with benefit in epidemiological studies.

Lung Cancer

Lung cancer was the primary endpoint in the Alpha-Tocopherol Beta-Carotene (ATBC) trial.[9] In ATBC, 29,133 male smokers were randomized in geographically defined blocks to vitamin E, beta-carotene, both, or neither.[9] Baseline characteristics were similar in the 4 groups. There were only 113 exclusions after randomization, 97 of whom were excluded because Finnish cancer registry records or a chest x-ray showed that cancer was present prior to randomization. Analysis was by intention-to-treat. The study was terminated early for a significant adverse effect of beta-carotene on lung cancer incidence among heavy smokers (relative risk [RR], 1.19; 95% confidence interval [CI], 1.03–1.35). Total mortality was 8% higher (RR, 1.08; 95% CI, 1.01–1.16) among the participants who received beta-carotene than among those who did not, primarily because there were more deaths from lung cancer and ischemic heart disease.

The Beta-Carotene and Retinol Efficacy Trial (CARET)[14] was designed to test the combination of beta-carotene (30 mg/d) and vitamin A (retinyl palmitate 25,000 IU/d) to prevent lung cancer in 18,000 high-risk participants—asbestos workers and heavy smokers. After 4 years, there were statistically significant increases in the incidence of lung cancer (RR, 1.28; 95% CI, 1.04–1.57; P=0.02), mortality from lung cancer (RR, 1.46; 95% CI, 1.07–2.00), and all-cause mortality (RR, 1.17; 95% CI, 1.03–1.33).

A randomized controlled trial among 1,024 asbestos workers in Australia[15] compared a group receiving beta-carotene (30 mg) with a group receiving vitamin A (25,000 IU/d retinol) without a placebo group. The vitamin A group had lower total mortality than the beta-carotene group, largely due to a significantly lower risk for developing mesothelioma (RR, 0.24; 95% CI, 0.07–0.86; 3 vs 12 cases). Incidence of lung cancer, however, was not significantly lower in the subjects randomized to vitamin A (RR, 0.66; 95% CI, 0.19–2.32). Without untreated controls, it is uncertain whether these findings indicate a harmful effect of beta-carotene or a beneficial effect of vitamin A, but they confirm the findings of other trials of a lack of benefit of beta-carotene.

The Physicians' Health Study found no impact of beta-carotene on lung cancer incidence in an average-risk population with a low prevalence of smokers (RR, 0.93; 95% CI, 0.69–1.25).[8] There was also no significant increase in lung cancer incidence in the beta-carotene arm of the Women's Health Study (RR, 1.43; 95% CI, 0.82–2.48).[10] However, this arm was terminated early after a median duration of treatment of only 2.1 years due to the lack of benefits of beta-carotene (and suggestion of possible adverse effects) observed in the other trials discussed above.[10]

Prostate Cancer

For prostate cancer, there was no significant effect of beta-carotene on the incidence of prostate cancer in ATBC (RR, 1.23; 95% CI, 0.95–1.60).[16] In the Physicians' Health Study, there was no effect on lung cancer incidence among all men randomized to beta-carotene (RR, 0.99; 95% CI, 0.88–1.11).[8] However, among subjects in the lower quartile of serum beta-carotene at baseline, the incidence of prostate cancer was significantly reduced among subjects who received beta-carotene compared with those receiving placebo.[17, 18]

Colon Cancer

Beta-carotene supplementation had no effect on the incidence of colon cancer in ATBC[21], (RR, 1.05; 95% CI, 0.75–1.47), in the Physicians' Health Study[8] (RR, 0.96; 95% CI, 0.78–1.18), or in the Women's Health Study (RR, 0.99; 95% CI, 0.62–1.60).[10]

Two studies tested the impact of beta-carotene on the recurrence of adenomatous polyps. A US trial[11]

Table 1. Randomized controlled trials of vitamin supplementation to prevent cancer (beta-carotene)*

Study, publication	Setting/population	Treatment	Duration of follow-up; follow-up rate
Hennekens 1996[8] **Physicians' Health Study**	22,071 US male physicians aged 40–84 years; no history of: • cancer • myocardial infarction • stroke • cerebral ischemia • noncompliance in run-in phase	50 mg beta-carotene on alternate days; cointervention with 325 mg aspirin on alternate days in 2 x 2 factorial design	Mean 12 years; 99.99%
Alpha-Tocopherol Beta-Carotene (ATBC) Study Group 1994[9]	SW Finland; 29,133 male smokers aged 50–69 years	20 mg/day beta-carotene; 50 mg/day alpha- tocopherol in 2 x 2 factorial design	5–8 years; median 6.1 years
Greenberg 1994[11] **Polyp Prevention Study**	6 US gastroenterology clinics; 864 subjects; 79% male < 80 years; at least 1 polyp	25 mg/day beta-carotene vs placebo; cointervention with combination of 1 g/day vitamin C and 400 mg/day vitamin E or placebo in 2 x 2 factorial design	3 years between year 1 and year 4 colonoscopies (mean 36.6 months; no difference between groups)
MacLennan 1995[12] **Australian Polyp Prevention Study**	Australian gastrointestinal clinics; 424 subjects; 67% male; aged 30–74 years; at least 1 polyp	20 mg/day beta-carotene; fat reduction (25% of total energy target); wheat bran fiber (25 g/day of finely milled raw wheat bran) in 2 x 2 x 2 factorial design	2–4 years
I-M Lee 1999[10] **Women's Health Study**	39,876 US female health professionals > 45 years	50 mg beta-carotene on alternate days vs placebo; cointervention with 100 mg aspirin or placebo on alternate days and 600 IU vitamin E or placebo on alternate days in 2 x 2 x 2 factorial design. Beta-carotene study terminated early.	4 years
DeKlerk 1998[15] **Mesothelioma Prevention Study**	1,024 Australian male (92%) and female (8%) asbestos mine workers; mean age 57; 21% current smokers, 52% ex-smokers, 27% never smokers	30 mg/day beta-carotene (n=512) or 25,000 IU/day retinol (n=512); No placebo group	Through 5/95; mean FU 4.5 years

*See Appendix III for additional information on these trials.

Note: ATBC indicates Alpha-Tocopherol Beta-Carotene; g**,** gram; mg, milligram; n, number; FU, followup; NR, not reported; CARET, Beta-Carotene and Retinol Efficacy Trial.

Outcomes (95% confidence interval)						
Lung cancer	**Prostate cancer**	**Breast cancer**	**Colon cancer**	**Other cancer**		**All-cause mortality**
Incidence: 0.93 (0.69–1.25; NS)	*Incidence:* 0.99 (0.88–1.11)	NR	*Colon/ Rectum Incidence:* 0.96 (0.78–1.18)	*Incidence:*		1.01 (0.93–1.10)
				Stomach:	0.90 (0.49–1.67)	
				Pancreas:	1.38 (0.79–2.40)	
				Brain:	0.81 (0.48–1.36)	
				Melanoma:	0.88 (0.63–1.22)	
				Leukemia:	0.83 (0.53–1.30)	
				Lymphoma:	1.07 (0.79–1.45)	
				Bladder:	1.51 (1.02–2.24)	
				Thyroid:	8.00 (2.05–31.23)	
				All cancer mortality:	1.02 (0.88–1.17)	
Incidence: 1.19 (1.03–1.36)	*Incidence:* 1.23 (0.95–1.60)	NR	*Incidence:* 1.05 (0.75–1.47) *Adenomatous polyps recurrence:* 0.98 (0.71–1.35)	*Pancreatic incidence:*	0.75 (0.49–1.14)	1.08 (1.01–1.16)
				Pancreatic mortality:	0.81 (0.53–1.26)	
NR	NR	NR	*Adenomatous polyps recurrence:* 1.01 (0.85–1.20)	NR		1.03 (0.82–1.30)
NR	NR	NR	*Incidence:* 1.5 (0.9–2.5)*	NR		NR
Incidence: 1.43 (0.82–2.48)	NR	*Incidence:* 1.01 (0.81–1.24)	*Incidence:* 0.99 (0.62–1.60)	*Incidence:*		1.07 (0.74–1.56)
				Uterus:	1.15 (0.69–1.91;NS)	
				Ovary:	1.33 (0.73–2.43)	
				Thyroid:	0.75 (0.32–1.74;NS)	
				Bladder:	0.83 (0.27–2.57)	
				Brain:	0.67 (0.20–2.20)	
				Pancreas:	1.50 (0.45–4.94)	
				Cervix:	0.67 (0.13–3.33)	
				Stomach:	0.99 (0.10–9.58)	
				All cancer:	1.03 (0.89–1.18)	
				All cancer mortality:	1.11 (0.67–1.85)	
Incidence: 0.66 (0.19–2.32)	NR	NR	NR	*Malignant mesothelioma incidence:*	0.24 (0.07–0.86)	0.56 (0.33–0.95)
				Other cancer mortality:	0.97 (0.24–3.90)	

Note: ATBC indicates Alpha-Tocopherol Beta-Carotene; g, gram; mg, milligram; n, number; FU, followup; NR, not reported; CARET, Beta-Carotene and Retinol Efficacy Trial.

*Unadjusted odds ratio

Table 1. Randomized controlled trials of vitamin supplementation to prevent cancer (vitamin E and multivitamin and antioxidant combinations) (continued)

Study, publication	Setting/population	Treatment	Duration of follow-up; Follow-up rate
Vitamin E			
ATBC Study Group 1994[9]	SW Finland; 29,133 aged 50–69 years male smokers	20 mg/day beta-carotene; 50 mg/day alpha-tocopherol in 2 x 2 factorial design	5–8 years; median 6.1 years
Multivitamin and antioxidant combinations			
Greenberg 1994[11] **Polyp Prevention Study**	6 US gastroenterology clinics; 864 subjects; 79% male; < 80 years; at least 1 polyp	1 g/day vitamin C and 400 mg/day vitamin E vs placebo; cointervention 25 mg/day beta-carotene or placebo in 2 x 2 factorial design	3 years between year 1 and year 4; colonoscopies (mean=36.6 months, no difference between groups)
Omenn 1996[14] **CARET**	4,060 West Coast male asbestos workers; 14,254 US male and female heavy smokers (66% male overall)	30 mg/day beta-carotene and 25,000 IU/day retinol or placebo	5.5 years
McKeown-Eyssen 1998[25]	Toronto hospital; 185 subjects; 60% male; at least 1 polyp	400 mg/day vitamin C and 400 mg/day vitamin E or placebo	2 years
Ponz de Leon 1997[26] **Italian Polyp Prevention Study**	Italy; 255 subjects; % male not known; at least 1 polyp	Antioxidant vitamins (30,000 IU vitamin A, 70 mg vitamin E, 1 g vitamin C per day); lactulose (crystalline powder or syrup); placebo	36 months

Note: ATBC indicates Alpha-Tocopherol Beta-Carotene; g, gram; mg, milligram; n, number; FU, followup; NR, not reported; CARET, Beta-Carotene and Retinol Efficacy Trial.

Outcomes (95% confidence interval)						
Lung cancer	**Prostate cancer**	**Breast cancer**	**Colon cancer**	**Other cancer**		**All-cause mortality**
0.98 (0.86–1.12)	*Incidence:* 0.68 (0.53–0.88) *Mortality:* 0.59 (0.35–0.99)	NR	*Incidence:* 0.78 (0.55–1.09) *Adenomatous polyps recurrence:* 1.66 (1.19–2.32)	*Cancer mortality*: *Pancreatic cancer incidence:* *Pancreatic cancer mortality:*	1.05 1.34 (0.88–2.05) 1.11 (0.72–1.72)	1.02 (0.95–1.09)
NR	NR	NR	*Adenomatous polyps recurrence:* 1.08 (0.91–1.29)	NR		NR
Incidence: 1.28 (1.04–1.57) *Mortality:* 1.46 (1.07–2.00)	*Incidence:* 1.01 (0.80–1.27)	*Incidence:* 0.78 (0.55–1.12)	*Incidence:* 1.02 (0.70–1.50)	*Incidence:* *Urinary/bladder:* *Head/neck:* *Leukemia:* *Lymphoma:* *Mesothelioma:*	0.08 (0.69–1.70) 1.26 (0.73–2.19) 2.18 (0.95–5.03) 0.91 (0.42–1.98) 1.52 (0.66–3.52)	1.17 (1.03–1.33)
NR	NR	NR	*Adenomatous polyps recurrence:* 0.86 (0.51–1.45)	NR		NR
NR	NR	NR	*Adenomatous polyps recurrence:* 0.16 0.04–0.46)	NR		NR

Note: ATBC indicates Alpha-Tocopherol Beta-Carotene; g, gram; mg, milligram; n, number; FU, followup; NR, not reported; CARET, Beta-Carotene and Retinol Efficacy Trial.

found no effect on the relative risk for recurrence in subjects randomized to beta-carotene vs placebo (adjusted RR, 1.01; 95% CI, 0.85 to 1.20), while an Australian trial[12] was terminated after 2 years because of a trend toward an increased incidence of recurrent polyps in the beta-carotene group (unadjusted odds ratio, 1.5; 95% CI, 0.9–2.5).

Breast Cancer

The Women's Health Study found no effect of beta-carotene supplementation on breast cancer (RR, 1.01; 95% CI, 0.81–1.24).[10]

All-cause Mortality

Beta-carotene supplementation had no effect on all-cause mortality in the ATBC (RR, 1.08; 95% CI, 1.01–1.16),[9] the Physicians' Health Study (RR, 1.01; 95% CI, 0.93–1.10),[8] the Women's Health Study (RR, 1.07; 95% CI, 0.74–1.56),[10] and a skin cancer prevention study (RR, 1.03; 95% CI, 0.82–1.30).[20]

Vitamin E

The only randomized controlled trial data on vitamin E supplementation and cancer risk come from the ATBC trial, which included only male smokers. No studies in women have been completed.

Lung Cancer

In ATBC, vitamin E had no effect on the primary endpoint, lung cancer incidence (RR, 0.98; 95% CI, 0.86–1.12).

Prostate Cancer

In ATBC, the effect of vitamin E supplementation on incidence and mortality from several cancers was examined as part of a planned secondary endpoint analysis.[21] Patients who took supplemental vitamin E had a lower incidence of prostate cancer than those who did not (RR, 0.66; 95% CI, 0.44–0.94; number of cases 99/14,564 compared with 151/14,569) and also had lower mortality from prostate cancer (RR, 0.59; 95% CI, 0.35–0.99).[16, 22] Protection against prostate cancer was greater among men with more pack-years of smoking, differing from the lung cancer result.

How valid is this result likely to be? The examination of multiple individual cancers as secondary endpoints raises the possibility that this is a chance finding. Comparability between groups in the baseline risk for prostate cancer was only partially ascertainable; this is a concern because baseline differences in risk cannot be ruled out in a trial that used geographically defined blocks as the unit of randomization. Geographic differences in rates of prostate procedures, such as transurethral resection of the prostate, could also result in spurious differences in incidence. This ascertainment bias could also affect the likelihood that a death was attributed to prostate cancer. These biases cannot be ruled out, but, if they are present, one would expect them to affect the results of beta-carotene as well as vitamin E. As noted earlier, beta-carotene had no protective effect on prostate cancer incidence or mortality in ATBC; in fact, there was a trend toward harm.

Colon Cancer and Polyps

In 2 reports from the ATBC trial, vitamin E supplementation did not reduce colon cancer incidence significantly (RR, 0.78; 95% CI, 0.55–1.09).[19] Vitamin E supplementation increased the risk for adenomatous polyps (RR, 1.66; 95% CI, 1.19–2.32).[23] This finding might have been due to differences in rates of detection because the patients diagnosed to have polyps who received vitamin E supplement were more likely to have pre-diagnosis rectal bleeding and intestinal pain, symptoms which may have led to higher rates of colonoscopy.

Other Cancers

In ATBC, vitamin E supplementation was not associated with a significant difference in the incidence of stomach cancer (70/14,564 in those receiving vitamin E compared with 56/14,569; P=0.21).[21] It had no effect on pancreatic cancer incidence (RR, 1.34; 95% CI, 0.88–2.05) or mortality.[24]

All-cause Mortality

The relative risk for all-cause mortality in the vitamin E supplemented arm in ATBC was 1.02 (95% CI, 0.95–1.09).

Vitamin Combinations

Three of the studies described above, CARET, ATBC, and the Polyp Prevention Study,[11] and 2 additional trials of polyp prevention, randomized at least 1 arm to a vitamin combination. The results from CARET (beta-carotene plus vitamin A) were discussed above. In ATBC, there was no benefit in the combined antioxidant (beta-carotene plus vitamin E) arm for any cancer, and there were no interactions between beta-carotene and vitamin E.

Colonic Polyps

Studies of the efficacy of vitamin combinations to prevent colonic neoplasia had mixed results. The Polyp Prevention Study, a US multi-center trial, used a factorial design to evaluate beta-carotene (described above) and vitamin C plus vitamin E.[11] After 4 years on study (3 years between colonoscopies), the relative risk for polyp recurrence for the vitamin C plus vitamin E supplement vs placebo was 1.08 (95% CI, 0.91–1.29).

Two other trials examined the effect of vitamin combinations on colon polyps. In Canada, a randomized trial compared vitamin C plus vitamin E to lactulose and placebo.[25] After 2 years of follow-up, there was no significant effect on polyp recurrence in the group randomized to vitamins C plus E compared with placebo (RR, 0.86; 95% CI, 0.51–1.45). A small Italian trial evaluated a daily dose of vitamin A plus vitamin C plus vitamin E vs placebo in 150 participants.[26] After a 3-year follow-up, the relative risk for polyp recurrence in the intervention group compared with the control group was 0.16 (95% CI, 0.04–0.46).

Discussion

The main findings of this review are summarized in Table 2. The strongest finding is that beta-carotene supplements and combinations including beta-carotene are harmful in smokers and others at high risk for lung cancer. Another strong finding is that supplemental beta-carotene appears to have no effect on mortality or cancer incidence in the general population.

Historically, the results of randomized trials of vitamin supplements have not always confirmed those of epidemiological cohort studies. Even for well-designed, well-conducted cohort studies, it is never possible to be certain that the results do not reflect the influence of unrecognized confounders. Uncertainty about the adequacy of control for the "healthy user effect" and other potential confounders makes it difficult to decide how much weight to place on consistent results from cohort studies.

Limitations of the randomized trials may also be responsible for the discrepancy between trials and observational studies. The timeframe for prevention of chronic diseases may be longer than the follow-up period in the trials, or the trials may have examined the efficacy of supplements at the wrong time in the natural history of the disease. The trials of beta-carotene, for example, recruited subjects at high risk for developing lung cancer in order to increase statistical power. The subjects had smoked tobacco or been exposed to asbestos for many years before the efficacy of supplements was tested. This raises the possibility that the cohort studies observed a benefit from using beta-carotene earlier in the course of carcinogenesis, at a period that the trials have not examined.

The trials in nonsmokers may have the opposite problem: the subjects included in the trials may have been at lower risk than those observed to benefit in the cohort studies. In some of the epidemiological studies, supplements were associated with a reduced risk for cancer only in the subgroup of subjects who had low baseline intake or serum levels of antioxidant vitamins.[5, 27, 28] As noted earlier, a similar observation was made in the Physicians' Health Study, in which beta-carotene supplementation was associated with a reduced incidence of prostate cancer in subjects who were relatively deficient in beta-carotene at baseline.[17, 18] The trials may have limited the chance of finding a benefit by focusing on relatively well-nourished subjects selected by profession rather than by baseline nutritional measures.

Table 2. Summary of results of randomized trials

Vitamin(s)	Outcome(s)	Strength of evidence, comment
Beta-carotene *or* beta-carotene plus vitamin A	Increased incidence and mortality from lung cancer *in smokers*	Consistent results from good randomized trials
	Increased incidence and mortality from mesothelioma *in high-risk group*	One trial suggests harm
	No effect on lung cancer in the general population	Consistent results from good randomized trials
	No benefit for prostate cancer in the general population	Mixed results, requiring additional study
	No benefit for colon cancer in the general population	Consistent results from good randomized trials
	No effect on the incidence of colonic polyps in subjects at high risk for polyps	Results from two trials suggest no benefit. (One suggests harm.)
	No effect on breast cancer in the general population	Results from one good trial, requiring additional study
	No effect on all-cause mortality in the general population	Consistent results from good randomized trials
Vitamin E	No effect on lung cancer, colon cancer, cancer mortality, total mortality *in smokers*	Results from one good trial, requiring additional study
	Reduced incidence and mortality from prostate cancer and stomach cancer *in smokers*	Results from one good trial, confirmatory trial underway
	Effects in nonsmokers	No data from trials. Trials for prostate and breast cancer underway.
Vitamins C + E	No effect on polyp recurrence	Consistent results from two trials
Vitamins C + E + A	Reduction in polyp recurrence	Results from one fair-to-poor trial

Recommendations for Future Research

Among the vitamin-cancer combinations that have evidence from randomized trials, the most promising finding was that smokers who took vitamin E had a lower incidence of prostate cancer and lower mortality from prostate cancer than those who did not. A large US trial is underway to confirm the finding that vitamin E might reduce mortality from prostate cancer.

Among the vitamin-cancer combinations that do not yet have evidence from randomized trials, the strongest evidence from observational studies is for a possible beneficial effect of vitamin A for breast cancer (see Appendix I). The cohort studies also raise the possibility that vitamin A reduces the risk for colon cancer in women.

The cohort studies evaluating B vitamin supplementation in relation to breast cancer and colon cancer also show some evidence of benefit. A randomized controlled trial of the effect of long-term B vitamin supplementation on polyp recurrence is currently underway.

Three other trials are also in progress. The Physicians' Health Study II has re-randomized many of the original Physicians' Health Study participants and has recruited additional participants to a 2x2x2 factorial randomized controlled trial comparing

vitamin C, vitamin E, and a multivitamin (100% of RDA type) with placebo.[29] The Women's Health Study, focusing on health professionals, is a factorial study of beta-carotene, vitamin E, and aspirin; the beta-carotene arm has been closed, but the vitamin E and aspirin arms continue. Finally, the "Supplementation en Vitamines et Mineraux Antioxydants" study is a population-based, randomized trial of over 12,000 subjects. The SU.VI.MAX study is designed to test the efficacy of a daily supplementation with antioxidant vitamins (vitamin C, 120 mg; vitamin E, 30 mg; and beta-carotene, 6 mg) and minerals (selenium, 100 microg; and zinc, 20 mg) at nutritional doses in reducing mortality from cancers and cardiovascular diseases.[30, 31]

Epidemiological cohort studies will continue to be extremely important in providing guidance regarding the role of vitamin supplementation in the prevention of chronic disease. The largest established cohorts (Nurses' Health Study, Health Professionals' Follow-up Study, Iowa Women's Study, and Leisure World Study) are now reaching a stage of maturity in which they can provide information on risks and benefits associated with behaviors taking place early in the carcinogenesis process. A problem that will continue to plague the epidemiological studies, however, is the degree to which supplement users differ in other ways from non-users, ways that may not be fully accounted for in the multivariate analyses. Attempts by scientists to analyze the large cohort studies in ways that replicate, to the extent possible, clinical trial designs would be extremely useful in elucidating the sources of the differences in findings between clinical trials and cohort studies. Understanding the sources of these differences will permit us to better use the cohort study data and to better design long-term clinical trials.

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Appendix I. Longitudinal Cohort Studies

The results of observational cohort studies that met the inclusion criteria are summarized in Appendix Table 1. Major features of each study are summarized below. Additional information about most studies is available in: Morris CD and Carson S. Vitamin supplementation to prevent cardiovascular disease, summary of the evidence for the U.S. Preventive Services Task Force available at http://www.ahrq.gov/clinic/uspstfix.htm.

1. **The Netherlands Cohort Study.**[1,2] This study was designed to examine the association between intake of vitamins C and E, retinol, and beta-carotene and risk of breast cancer. Women from the general population aged 50–69 at baseline were eligible for enrollment. Of the 62,573 women enrolled, 96% continued for 3.3 years (median) of follow-up. The study found no relationship between the use of vitamin C supplements and breast cancer.

Appendix Table I. Summary of cohort studies evidence

Cancer	Vitamin A	Beta-carotene	Vitamin C	Vitamin E	Multi-vitamins containing folic acid
Lung Cancer	No effect in men and women (LWS)	No data	No effect in men and women (LWS)	Trend toward benefit but NS (LWS, HPFS)	No data
Breast Cancer	Four studies show NS RR estimates of 0.7–1.0; pooled analysis suggests possible benefit (RR 0.81; 95% CI 0.62–0.97).	No data	No effect shown in 4 studies (pooled OR .98; 95% CI 0.85–1.14) Harm shown in 1 study (OR 1.46)	4 studies show no effect	No effect overall (NHS) but reduced incidence in women who consumed > 15 g/d of alcohol (NHS)
Prostate Cancer	No effect (LWS)	No data	No effect (LWS)		No data
Colon Cancer	Benefit in women (LWS, IWHS)	No data	No effect (LWS, IWHS)		Lower incidence observed after 15 years in women (RR, 0.25; 95% CI, 0.13 to 0.51) (NHS)
Bladder Cancer	No effect (LWS)	No data	Benefit (LWS)		No data

Note: NS indicates not statistically significant; RR, relative risk; CI, confidence interval; LWS, Leisure World Study; NHS, Nurses, Health Study; IWHS, Iowa Women's Health Study; HPFS, Health Professionals, Follow-up Study.

2. **Nurses' Health Study I.**[3,4,5,6,7] This study was conducted in the United States and designed to determine whether vitamins A, C, E, folic acid, and multivitamin supplements are related to risk of colorectal adenomas. Female nurses aged 34–59 at baseline were eligible for enrollment. Of the 89,494 women enrolled, 96% continued for 8 years of follow-up participation.

3. **Canadian National Breast Screening Study.**[8] This study was conducted in Canada and designed to examine the relationships of vitamins A, C, and E to risk of breast cancer. Women aged 40–59 at baseline who were involved in an ongoing breast cancer screening study were eligible for enrollment. Of the 56,837 qualified study subjects, 96% continued for 5 years of follow-up participation.

4. **Leisure World Study.**[9,10] This U.S. study was designed to examine the relationships of vitamins A, C, and E to risk of lung, colon, bladder, prostate, and breast cancers. Males and females living in the Leisure World retirement community were eligible for enrollment. The average age of the 70,159 qualified study subjects (24,218 men and 45,941 women) was mid-70s. Four- to 8-year follow-up rates were 99% for vital status and 85% for incident cancers. Statistical adjustment was made for age and smoking but not for other confounders.

5. **Health Professionals' Follow-up Study.**[11,12] This study was conducted in the United States and designed to examine the relationships of folic acid, beta-carotene and vitamins C and E to risk of colon cancer. Male dentists, osteopaths, optometrists, podiatrists, pharmacists, and veterinarians aged 40–75 were eligible for participation. Of the 43,738 qualified study subjects, 96% continued for 4 years of follow-up participation.

6. **Iowa Women's Health Study.**[13,14,15] This study, conducted in the United States, was designed to investigate whether high intakes of antioxidant micronutrients (vitamins A, C, and E, and beta-carotene) protect against colon and breast cancers. Women living in Iowa in 1986 who were aged 55–69 years at baseline and did not have a history of cancer were eligible for participation following completion of a dietary questionnaire. Of the 34,486 qualified study subjects, 84% continued for 5 years of follow-up participation.

7. **National Health and Nutritional Examination Survey I.**[16] This U.S. study was designed to examine the relation between vitamin C intake and cancer and all-cause mortality. Noninstitutionalized U.S. adults aged 25–74 years at baseline who were nutritionally examined during 1971–1974 as part of an epidemiological follow-up study (NHANES I) were eligible for participation. Of the 14,407 qualified study subjects, 93% continued for 10 years (median) of follow-up participation.

8. **Established Populations for Epidemiologic Studies of the Elderly.**[17] This study was conducted in the United States and designed to examine vitamin E and vitamin C supplement use in relation to mortality risk and whether vitamin C enhanced the effects of vitamin E. Residents of 4 East Coast communities who were older than 65 at baseline (range 67–105) and who were involved in the Established Populations for Epidemiologic Studies of the Elderly in 1984–1993 were eligible for enrollment. Of the 11,178 qualified study subjects, 100% continued for 6 years of active participation and an additional 2–3 years for mortality follow-up. Adjustment was made for alcohol use, smoking history, aspirin use, and medical conditions.

9. **Cancer Prevention Study II.**[18] This study was conducted in the United States and designed to determine the relation between multivitamin use and cancer and all-cause mortality. American Cancer Society volunteers recruited men and women aged 30 years and older for participation. The percentage of the 1,063,023 (453,962 men and 609,061 women) eligible study subjects who continued for the 7-year follow-up participation period is unclear.

10. **Substudy of Polyp Prevention Study.**[19] Conducted in the United States, this study was

designed to determine the relation between folate and multivitamin use and adenomatous polyp recurrence. Adults who were involved in the Polyp Prevention Study were eligible for enrollment. Eligible study subjects were 79% male and an average age of 60 years. The percentage of the 709 participants that completed the 4-year follow-up colonoscopy is unclear.

11. **Nurses' Health Study and Health Professionals' Follow-Up Study.**[4] This analysis was designed to measure the association of folate and methionine to risk for colorectal adenoma. Female nurses aged 34–59 from the Nurses' Health Study started in 1976. Male dentists, osteopaths, optometrists, podiatrists, pharmacists, and veterinarians aged 40–75 from the Health Professionals Follow-up Study, all of whom had undergone an endoscopy, were eligible for participation, started in 1986. Combined 4-year follow-up rates for the 9,490 male subjects and 10-year follow-up rates for the 15,984 females subjects were 96% for standardized questionnaire completion and 91% for response to letter following adenomatous polyp recurrence.

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Appendix II. Excluded Trials

Appendix II. Excluded trials

Study	Population or nutrients	Reason for exclusion
Mackerras, 1999[1]	Women with CIN; beta-carotene, vitamin C	Wrong outcomes
Manson, 1995[2]	WACS; Combination	Wrong outcomes
Childers, 1995[3]	Patients with CIN; Folate	Wrong outcomes
Hercberg, 1999[4] Hercberg, 1998[5] SU.VI.MAX Study	Primary prevention; vitamin C, vitamin E, and beta-carotene, 6 mg	Results not available yet
Lonn, 1996[6] SECURE	Vitamin E	Wrong outcomes
DeMaio, 1992[7]	Post-PTCA vitamin E	Wrong outcomes
Christen, 2000[8] Physicians Health Study II	Alternate day beta-carotene, alternate day vitamin E, daily vitamin C, and a daily multivitamin in the prevention of total and prostate cancer	Results not available yet
Butterworth, 1992[9]	Patients with cervical dysplasia, folic acid	Wrong outcomes
Hofstad, 1992[10]	Patients with polyps: calcium, vitamins A, C, and E, and selenium	Wrong outcomes (polyp growth)
Stephens, 1996[11] CHAOS	Vitamin E	Wrong outcomes
Collaborative Group of the Primary Prevention Project[12]	Vitamin E	Wrong outcomes
McLarty, 1992[13]	Vitamin A	Wrong outcomes
Miller, 1997[14]	Vitamin E,C, and beta-carotene	Wrong outcomes
Paganelli, 1992[15]	Vitamins A,C, and E	Wrong outcomes
Tsubono, 1997[16]	Patients with atrophic gastritis	Results not available yet
Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico, 1999[17]	Vitamin E	Wrong outcomes
Hoogwerf, 2000[18] Lonn, 1996[6] Yusuf, 2000[19]	Vitamin E	Wrong outcomes
Munoz, 1985[20]	Vitamin A (esophageal dysplasia)	Wrong outcomes, population

Appendix II. Excluded trials (continued)

Study	Population or Nutrients	Reason for Exclusion
Stich, 1988[21] Stich, 1988[22]	Beta-carotene, vitamin A, and beta-carotene+vitamin A (leucoplakia)	Wrong outcomes
Zaridze, 1993[23]	Vitamin A, beta-carotene, and vitamin E (leucoplakia)	Wrong outcomes
Wang, 1994[24] Taylor, 1994[25] Dawsey, 1994[26] Li, 1993[27]	Retinol and zinc; riboflavin and niacin; vitamin C and molybdenum; and beta-carotene, vitamin E, and selenium	Wrong interventions and possibly wrong outcomes (gastric dysplasia and gastric cancer and esophageal cancer)
Heart Protection Study, 1999[28]	Vitamin E, vitamin C, and beta-carotene	Wrong outcomes
Wald, 2001[29]	Folic acid	Wrong outcomes
Skin Cancer Prevention Study, 1990[30]	Beta-carotene; skin cancer recurrence	Wrong outcomes (nonmelanoma skin cancer only)
Nambour Study[31, 32]	Beta-carotene; skin cancer (primary prevention)	Wrong outcomes (nonmelanoma skin cancer only)
Southwest Skin Cancer Prevention Study Group[33]	Retinol, isotretinoin; skin cancer recurrence	Wrong outcomes (nonmelanoma skin cancer only)

Note: CIN indicates cervical intraephithelial neoplasia; SU.VI.MAX, Supplementation en Vitamines et Mineraux Antioxydants; SECURE, Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E; post-PTCA, post-percutaneous transluminal coronary angioplasty; CHAOS, Cambridge Heart Antioxidant Study.

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Appendix III. Additional Information on Randomized Controlled Trials of Vitamin Supplementation to Prevent Cancer (Supplement to Table 1)

Appendix III. Additional information on randomized controlled trials of vitamin supplementation to prevent cancer (Supplement to Table 1)

Beta-Carotene

Study, Year	Treatment (n)	Control (n)	Exclusion criteria	# Enrolled/ # screened	Other nutrients supplemented	Compliance method, rate	Jadad score
Hennekens 1996[8] Physicians' Health Study	11,036	11,035	History of cancer, MI, stroke, cerebral ischemia	22,071 enrolled	Aspirin; 4% on placebo took BC or vitamin A	Pill count; 78% at year 12	4
Alpha-Tocopherol Beta-Carotene (ATBC) Study Group, 1994[9]	13,602	13,669	Prior MI, severe angina, proven malignancy, chronic renal insufficiency, cirrhosis, alcoholism, anticoagulant therapy, any current use of vitamin A, vitamin E, BC, other serious medical illness	42,957 screened; 29,246 enrolled; 29,133 randomized; 22,269 included	Co-intervention with vitamin E	Pill count 99%	5
Greenberg 1994[11] Polyp Prevention Study	BC, 184; vit C+E, 205; all, 175	187	FAP, history of cancer, malabsorption, renal calculi, thrombophlebitis	2,092 screened; 981 signed; 864 randomized	See Table 1	82% at year 4	5
MacLennan 1995[12] Australian Polyp Prevention Study	BC, 53; BC+low fat, 51; BC+C+ bran, 47; low fat+ bran+BC, 50	48	Chronic IBD, GI tract resection, FAP, cancer history, renal, liver, GB disease	2,780 cx; 1304 potential; 559 eligible; 424 randomized	See Table 1	No data	3
I-M Lee 1999[10] Women's Health Study	BC, 19,939	19,937	History of cancer, coronary heart disease, or cerebrovascular disease	65,169 eligible; 39,876 randomized	Vitamin E	After 2 years, 87% of active group reported taking at least 2/3 of capsules	4

Appendix III. Additional information on randomized controlled trials of vitamin supplementation to prevent cancer (Supplement to Table 1) (continued)

Beta-Carotene (continued)

Study, Year	Treatment (n)	Control (n)	Exclusion criteria	# Enrolled/ # screened	Other nutrients supplemented	Compliance method, rate	Jadad score
DeKlerk 1998[15] Mesothelioma Prevention Study	BC, 512; retinyl palmitate, 512	none		1,203 joined; 1,024 randomized		Pill counts at 1 year, 100%. Process discontinued	3

Vitamin E

***Vitamin E* ATBC Study[9]**	See above						

Multivitamin and antioxidant combinations

Greenberg 1994[11] Polyp Prevention Study	See above						
Omenn 1996[14] CARET	2,044 asbestos workers; 7,376 smokers	2,016 asbestos workers; 6,878 smokers	Limited vitamin A use and no BC supplement use	4,060 workers exposed to asbestos; 14,254 heavy smokers (44% female) randomized	Retinol and BC co-intervention; 2% took additional BC; 1% took vitamin A	Weighed capsules or self-report in 15%	4
McKeown-Eyssen 1988[25]	96	89	Unwilling to stop supplementation; no adenomatous polyps (n=15)	200 signed; 185 randomized	Intervention group more likely to have taken supplement prior to randomization	95% based on urinary ascorbate in intervention group; slightly fewer completed in placebo group	5
Ponz de Leon 1997[26] Italian Polyp Prevention Study	70	Lactulose 61; no treatment, 78		255 randomized	3 follow-up colonoscopies: 6–8 months, 12–18 months, 24–36 months		3

Note: n indicates number; ATBC, Alpha-Tocopherol Beta-Carotene; MI, myocardial infarction; BC, beta-carotene; FAP, familial adenomatous polyposis; GB, gall bladder; CARET, Beta-Carotene and Retinol Efficacy Trial.

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