Effects of Long-term Vitamin E Supplementation on Cardiovascular Events and Cancer

A Randomized Controlled Trial

The HOPE and HOPE-TOO Trial Investigators*

Context Experimental and epidemiological data suggest that vitamin E supplementation may prevent cancer and cardiovascular events. Clinical trials have generally failed to confirm benefits, possibly due to their relatively short duration.

Objective To evaluate whether long-term supplementation with vitamin E decreases the risk of cancer, cancer death, and major cardiovascular events.

Design, Setting, and Patients A randomized, double-blind, placebo-controlled international trial (the initial Heart Outcomes Prevention Evaluation [HOPE] trial conducted between December 21, 1993, and April 15, 1999) of patients at least 55 years old with vascular disease or diabetes mellitus was extended (HOPE–The Ongoing Outcomes [HOPE-TOO]) between April 16, 1999, and May 26, 2003. Of the initial 267 HOPE centers that had enrolled 9541 patients, 174 centers participated in the HOPE-TOO trial. Of 7030 patients enrolled at these centers, 916 were deceased at the beginning of the extension, 1382 refused participation, 3994 continued to take the study intervention, and 738 agreed to passive follow-up. Median duration of follow-up was 7.0 years.

Intervention Daily dose of natural source vitamin E (400 IU) or matching placebo.

Main Outcome Measures Primary outcomes included cancer incidence, cancer deaths, and major cardiovascular events (myocardial infarction, stroke, and cardiovascular death). Secondary outcomes included heart failure, unstable angina, and revascularizations.

Results Among all HOPE patients, there were no significant differences in the primary analysis: for cancer incidence, there were 552 patients (11.6%) in the vitamin E group vs 586 (12.3%) in the placebo group (relative risk [RR], 0.94; 95% confidence interval [CI], 0.84-1.06; $P=.30$); for cancer deaths, 156 (3.3%) vs 178 (3.7%), respectively (RR, 0.88; 95% CI, 0.71-1.09; $P=.24$); and for major cardiovascular events, 1022 (21.5%) vs 985 (20.6%), respectively (RR, 1.04; 95% CI, 0.96-1.14; $P=.34$). Patients in the vitamin E group had a higher risk of heart failure (RR, 1.13; 95% CI, 1.01-1.26; $P=.03$) and hospitalization for heart failure (RR, 1.21; 95% CI, 1.00-1.47; $P=.045$). Similarly, among patients enrolled at the centers participating in the HOPE-TOO trial, there were no differences in cancer incidence, cancer deaths, and major cardiovascular events, but higher rates of heart failure and hospitalizations for heart failure.

Conclusion In patients with vascular disease or diabetes mellitus, long-term vitamin E supplementation does not prevent cancer or major cardiovascular events and may increase the risk for heart failure.

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OXIDATIVE INJURY HAS BEEN implicated in atherosclerotic cardiovascular disease and in cancer, the 2 leading causes of death. Low-density lipoprotein cholesterol is rendered more atherogenic by oxidative modification[1] and many carcinogens create free oxygen radicals that damage DNA and other cellular structures, initiating and promoting tumor development.[2] Therefore, antioxidant vitamins have been extensively evaluated in the prevention of cardiovascular diseases and cancer.

α-Tocopherol, the predominant and most active form of vitamin E in humans, is the major antioxidant in lipid phases.[3] In animal models, α-tocopherol has been shown to reduce atherosclerotic lesions,[4] smooth muscle cell proliferation,[5] platelet adherence and aggregation,[6] and protein kinase C activation.[7] In humans, it can improve endothelial function.[8] Epidemiological data indicate an inverse association between cardiovascular risk and vitamin E intake from dietary sources and/or supplements.[9] Vitamin E appears similarly attractive in cancer chemoprevention. Antioxidants can neutralize free radicals, thereby preventing cell damage and subsequent malignant transformation.[2] In addition, α-tocopherol may prevent cancer by inhibiting cell

For editorial comment see p 1387.

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proliferation and angiogenesis,[10] inducing apoptosis,[11] and enhancing immune function.[12] In observational studies, diets high in fresh fruits and vegetables were associated with reduced incidence of cancers,[13] and inverse associations between α-tocopherol levels or vitamin E intake and risk of lung,[14] prostate,[15] oral and pharyngeal,[16] and colorectal cancer[17] have been reported in some but not other studies.[18-20]

Despite these promising experimental and epidemiological data, most randomized controlled trials have failed to confirm a role for vitamin E supplementation in cardiovascular prevention.[21] With few exceptions,[22,23] trials of cancer chemoprevention have also been disappointing.[24,25] It has been suggested that this may be related to the relatively short period of treatment and observation (generally 3-5 years) of these trials and that longer studies are needed.[26,27]

The Heart Outcomes Prevention Evaluation (HOPE) trial conducted between December 21, 1993, and April 15, 1999, reported a neutral effect of vitamin E on cardiovascular outcomes after an average 4.5 years of treatment.[28] To assess whether longer duration of treatment would prevent cancer and/or cardiovascular disease, the HOPE study was extended (HOPE–The Ongoing Outcomes [HOPE-TOO]).

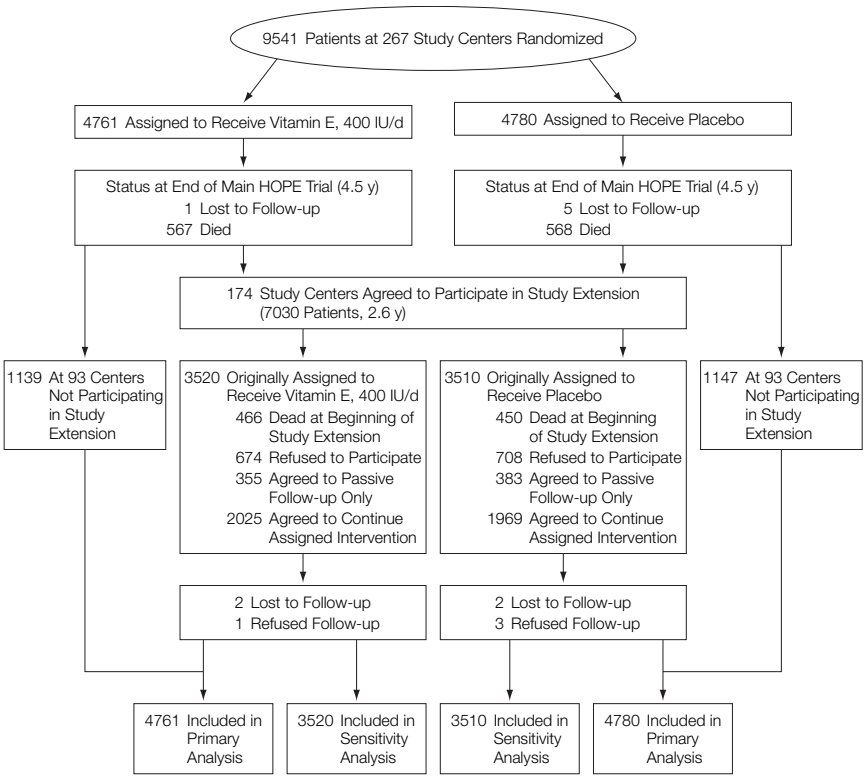
METHODS

Study Design and Participants

The design and organization of the main HOPE trial have been previously reported.[28,29] In summary, HOPE was an international, multicenter, double-blind, randomized, 2 × 2 factorial design trial that evaluated ramipril (10 mg/d) vs placebo and vitamin E (400 IU/d) vs placebo in 9541 patients at high risk for cardiovascular events. Patients were eligible if they were at least 55 years old, had a history of coronary or peripheral arterial disease, prior stroke, or diabetes mellitus plus at least 1 other cardiovascular risk factor and did not have heart failure, known low ejection fraction (<40%), uncontrolled hypertension or overt nephropathy, had not sustained myocardial infarction or stroke within 4 weeks before the study began, were not planned to undergo revascularization, and were not taking an angiotensin-converting enzyme inhibitor or vitamin E.

The initial HOPE study was conducted between December 21, 1993, and April 15, 1999. At the conclusion of the trial, all study centers were invited to participate in a trial extension (HOPE-TOO), which was conducted between April 16, 1999, and May 26, 2003. Of the initial 267 centers, 174 agreed to participate in the HOPE-TOO trial. These 174 centers had originally randomized 7030 patients. Of these, 916 were deceased at the beginning of the trial extension, 1382 (22.6% of those still alive) refused participation, 4732 agreed to extended observation and were evaluated every 6 months, 3994 of which (65.3% of those still alive) agreed to continuation of study intervention—vitamin E or matching placebo (FIGURE 1). To maximize the study power and duration of follow-up, the steering committee of the trial decided that the main study analyses will incorporate all randomized HOPE trial patients, including those who did and those who did not participate in the trial extension, with each patient contributing all available data for his/her duration of follow-up within the trial. All patients enrolled at the centers continuing in the trial extension

Figure 1. Flow Diagram of the Main HOPE Trial and the HOPE-TOO Trial Extension



The initial Heart Outcomes Prevention Evaluation (HOPE) trial included 267 centers and randomized 9541 study participants between December 21, 1993, and June 15, 1995. Mean follow-up was 4.5 years. Details regarding all stages of the initial HOPE trial have been previously published.[28,29] The trial extension, HOPE–The Ongoing Outcomes (HOPE-TOO), began on April 16, 1999, and extended for an average of 2.6 years. A total of 93 HOPE study centers that had randomized 2511 study participants refused participation in the HOPE-TOO trial. The primary analysis of the HOPE-TOO trial includes all available data from all HOPE study participants. The sensitivity analysis includes all available data from all patients at the centers continuing in the trial extension. Clinic visits occurred at 1 month postrandomization, at 6 months, and every 6 months thereafter during the initial HOPE trial and the HOPE-TOO trial. All patients lost to follow-up and/or those who refused follow-up completed at least 2 clinic visits and are included in the final analysis censored for duration of observation.

were included in a sensitivity analysis. The HOPE trial and HOPE-TOO trial were approved by the ethics boards of all participating institutions, and all patients provided separate written informed consent for each stage. Most study participants were white (8580 [89.9%]), followed by Hispanic (533 [5.6%]), Asian (155 [1.6%]), black (141 [1.5%]), native American (43 [0.5%]), and other (89 [0.9%]) ethnic groups. This information was based on self-declared race/ethnicity.

Interventions

The initial HOPE trial evaluated natural source vitamin E (RRR-α-tocopheryl acetate) (400 IU/d) vs placebo and ramipril (10 mg/d) vs placebo. During the HOPE-TOO trial, 3994 study participants continued to take daily vitamin E (400 IU) or matching placebo. Treatment allocation for the vitamin E group of the trial remained blinded for all study participants, including those who did not participate in the trial extension. Due to clear benefit of ramipril in the initial HOPE trial, at its completion, the ramipril group of the study was unblinded and angiotensin-converting enzyme inhibitor therapy was recommended for all patients.

Plasma vitamin E levels were measured by liquid chromatography (Waters 625 LC system; Millipore, Milford, Mass) at baseline and at 2 years postrandomization in 163 randomly selected patients in the vitamin E group and in 34 randomly selected patients in the placebo group.

Randomization and Allocation Concealment

The study used central telephone randomization. The randomization code was generated using a fixed block size of 4, stratified by center. The information about block size and whether it was random or fixed was kept confidential for all study investigators. The kit numbers were not sequential and were received by calling the central randomization number. The randomization sequence was concealed and all study personnel and study participants were blinded to treatment allocation for both study interventions during the initial HOPE trial and for vitamin E during the HOPE-TOO trial. The vitamin E and placebo pill formulations were manufactured (Banner Pharmacaps, High Point, NC) to be indistinguishable by size, color, weight, taste, or dissolution in water. There were no adverse events or changes in any physiological parameters that could be attributed to vitamin E or have unmasked blinding. No request was made to stop the blinding for vitamin E.

Study Objective and Main Outcome Measures

The main objective of the HOPE trial extension was to evaluate whether long-term supplementation with vitamin E decreases the risk of cancer, cancer death, and major cardiovascular outcomes.

For the initial HOPE trial, the primary outcome was the composite of myocardial infarction, stroke, and death from cardiovascular causes. For the HOPE-TOO trial extension, the primary outcome included the same composite cardiovascular outcome in addition to cancer incidence and cancer death.

The duration of the HOPE-TOO trial was calculated to allow for an average follow-up of 7 years, considering the fixed number of possible participants, and to allow the detection of a 15% to 20% reduction in incident cancers with vitamin E with more than 80% power, assuming a 1.5% to 2% yearly placebo incident cancer rate (2-sided $\alpha = .05$; this calculation was made after identifying the number of study participants willing to participate in the trial extension).

All cancer events from the beginning of the initial HOPE trial and those occurring during the trial extension were adjudicated and classified during the HOPE-TOO trial by an adjudication committee, with specific expertise in cancer. Classification was performed according to the *International Classification of Diseases, Ninth Revision (ICD-9)*. Source documentation, including pathology (or cytology) reports, discharge and other clinical summaries, and results of imaging, serum markers, and other diagnostic procedures were obtained. Clinical summaries were available for all reported cancers. In addition, microscopic confirmation was available for 70.1%, direct tumor visualization for 0.8%, and imaging reports, tumor markers, or other laboratory investigations for 10.7%. The final adjudication was based on clinical summaries alone for 18.5% of all cancers.

To further evaluate the validity of the cancer ascertainment, we compared the adjudication of cancers in the trial with the Cancer Care Ontario Registry (CCOR) in the subset of 2492 HOPE study participants from Ontario, Canada. A total of 2127 study participants (85.4%) did not have incident cancer, both in the trial and in the CCOR; 283 participants (11.4%) had cancer both in the trial and in the CCOR, all classified as involving the same major organ system in both databases. Only 52 study participants (2.1%) had an incident cancer identified in the trial but not in the CCOR, and for only 30 participants (1.2%), cancer was reported in the CCOR but not in the trial. The overall coefficient of agreement was $\kappa = 0.85$. Coefficients of agreement for the most common cancers, including lung, prostate, breast, colorectal, oral/pharyngeal cancers, and melanoma, were 0.92, 0.88, 0.84, 0.90, 0.86, and 0.95, respectively.

Cardiovascular outcomes were the same as in the initial HOPE trial and continued to be adjudicated by an adjudication committee with cardiovascular expertise and according to the definitions used in the initial HOPE trial.[28] The main cardiovascular outcome remained the composite of myocardial infarction, stroke, and death from cardiovascular causes. Each component of this composite was also evaluated. Secondary and other cardiovascular outcomes were all-cause death, hospitalization for unstable angina, revascularization or limb amputation, hospitalization for heart failure with clinical and radiological signs of congestion, and the development of heart failure regardless of the need for hospitalization.

Statistical Analysis

All analyses were by intention-to-treat (all randomized participants were analyzed in the treatment groups to which they were assigned at randomization) and stratified for assignment to ramipril or placebo, to account for the factorial study design; there was no interaction between ramipril and vitamin E for any outcomes analyzed. The predefined primary analysis in the HOPE-TOO trial used all available data on all 9541 HOPE trial participants, with each patient censored for his/her duration of observation. For this analysis, the median duration of follow-up was 7.0 years. A sensitivity analysis was conducted considering only patients at the centers continuing in the trial extension. This analysis included data from all 7030 patients at the centers continuing in the trial extension, with each patient censored for his/her duration of observation. The median duration of follow-up for the sensitivity analysis was 7.2 years. The decision to incorporate in the sensitivity analyses all patients at these centers, including those who declined further participation at the completion of the initial HOPE trial, was taken to minimize bias. Survival curves were estimated according to the Kaplan-Meier method and treatments were compared using the log-rank test. Subgroup analyses were conducted using tests for interaction in the Cox proportional hazards regression model; the Cox proportional hazards regression assumption was confirmed. For all predefined cancer and cardiovascular outcomes, the level of significance was predefined for 2-sided α=.05. All analyses were performed at the Population Health Research Institute, McMaster University, Hamilton, Ontario, by using SAS version 8.2 (SAS Institute, Cary, NC) and graphs were generated using S-Plus version 6 (Insightful, Seattle, Wash).

RESULTS

Patient Characteristics and Adherence

The baseline characteristics of the 9541 patients who participated in the initial HOPE trial were similar across the vitamin E and placebo groups and the baseline characteristics of the 7030 patients at the centers continuing in the trial extension were similar to those of the entire HOPE study population and were also well balanced (TABLE 1). Compliance was high throughout the initial HOPE trial, as previously reported.[28] In the subset of patients who had vitamin E levels measured, mean (SD) plasma vitamin E levels were similar at baseline (28.1 [9.7] mmol/L in the vitamin E group and 29.8 [15.2] mmol/L in the placebo group). At 2 years, mean (SD) plasma vitamin E levels increased to 48.7 (17.6) mmol/L in the vitamin E group ($P<.001$) and remained unchanged in the placebo group (30.4 [21.1] mmol/L). Among the 3994 patients who agreed to continue to take study intervention at the beginning of the trial extension, compliance as measured by pill count at 1 year, 1.5 years, and at study end was 96.7%, 95.7%, and

Table 1. Baseline Characteristics of All HOPE Study Patients and of the Patients at Centers Continuing in the Trial Extension (HOPE-TOO)*

	All HOPE Study Patients (N = 9541)		Patients at Centers Continuing in the HOPE-TOO Trial Extension (N = 7030)	
Characteristic	Received Vitamin E (n = 4761)	Received Placebo (n = 4780)	Received Vitamin E (n = 3520)	Received Placebo (n = 3510)
Age, mean (SD), y	66 (7)	66 (7)	66 (7)	66 (7)
Blood pressure, mean (SD), mm Hg				
Systolic	139 (20)	139 (20)	138 (20)	138 (19)
Diastolic	79 (11)	79 (11)	78 (10)	79 (10)
Heart rate, mean (SD), beats/min	69 (11)	69 (11)	68 (11)	68 (11)
Body mass index, mean (SD)†	28 (4)	28 (4)	28 (4)	28 (4)
Female sex	1263 (26.5)	1282 (26.8)	912 (25.9)	911 (26.0)
Cardiac history				
Coronary artery disease	3857 (81.0)	3832 (80.2)	2846 (80.9)	2818 (80.3)
Myocardial infarction	2499 (52.5)	2535 (53.0)	1851 (52.6)	1882 (53.6)
Stable angina pectoris	2653 (55.7)	2668 (55.8)	2047 (58.2)	2032 (57.9)
Unstable angina pectoris	1205 (25.3)	1246 (26.1)	967 (27.5)	980 (27.9)
CABG	1229 (25.8)	1251 (26.2)	948 (26.9)	965 (27.5)
PCI	851 (17.9)	863 (18.1)	662 (18.8)	678 (19.3)
Stroke or transient ischemic attack	530 (11.1)	500 (10.5)	392 (11.1)	384 (10.9)
Peripheral arterial disease‡	1991 (44.3)	1931 (40.4)	1490 (42.3)	1441 (41.1)
Hypertension	2219 (46.6)	2222 (46.5)	1602 (45.5)	1608 (45.8)
Diabetes mellitus	1838 (38.6)	1816 (38.0)	1356 (38.5)	1324 (37.7)
Known elevated total cholesterol	3109 (65.3)	3171 (66.3)	2279 (64.7)	2321 (66.1)
Known low HDL cholesterol	893 (18.8)	869 (18.2)	651 (18.5)	610 (17.4)
Current cigarette smoking	665 (14.0)	679 (14.2)	488 (13.9)	471 (13.4)
Medications				
β-Blockers	1901 (39.9)	1870 (39.1)	1414 (40.2)	1396 (39.8)
Aspirin or other antiplatelet agents	3665 (77.0)	3616 (75.6)	2700 (76.7)	2657 (75.7)
Lipid-lowering agents	1352 (28.4)	1401 (29.3)	997 (28.3)	1058 (30.1)
Diuretics	728 (15.3)	717 (15.0)	535 (15.2)	537 (15.3)
Calcium channel blockers	2249 (47.2)	2236 (46.8)	1645 (46.7)	1628 (46.4)
Left ventricular hypertrophy on ECG	411 (8.6)	382 (8.0)	271 (7.7)	278 (7.9)
Microalbuminuria	1014 (21.3)	981 (20.5)	694 (19.7)	683 (19.5)

Abbreviations: CABG, coronary artery bypass graft surgery; ECG, electrocardiogram; HDL, high-density lipoprotein; HOPE, Heart Outcomes Prevention Evaluation Study; HOPE-TOO, HOPE–The Ongoing Outcomes; PCI, percutaneous coronary intervention.

*Data are presented as No. (%) unless otherwise specified.

†Body mass index was calculated as weight in kilograms divided by the square of height in meters.

‡Included claudication, a history of peripheral arterial disease, or a ratio of blood pressure in the ankle to blood pressure in the arm of less than 0.90.

90.7%, respectively, in the vitamin E group, and 96.0%, 95.5%, and 90.9%, respectively, in the placebo group. Vitamin E was well tolerated and there were no serious adverse events related to its use.

At the end of the initial HOPE trial, vital status was ascertained for 9535 (99.9%) of 9541 randomized patients. At the end of the HOPE-TOO trial, vital status was ascertained for 4724 (99.8%) of 4732 patients who participated in the extension trial.

Effect of Vitamin E on Cancer

There were no significant differences in incident cancers and cancer deaths, both in the primary analysis of all HOPE study patients and in the sensitivity analysis, which included all patients in the centers continuing in the trial extension (TABLE 2 and FIGURE 2).

Additional exploratory analyses evaluated the effect of vitamin E on site-specific cancers by major organ systems (using *ICD-9* groupings) and for selected cancers with previous promising vitamin E data (TABLE 3). Due to the exploratory nature of these analyses and the large number of cancer groupings evaluated, the level of significance for these analyses was set for 2-sided α=.01. There was a reduction in lung cancers with vitamin E (relative risk [RR], 0.72; 95% confidence interval [CI], 0.53-0.98; P=.04) in the analysis that considered all HOPE study patients; however, this did not reach the predefined level of statistical significance (2-sided α=.01) and was not confirmed in the sensitivity analysis (RR, 0.78; 95% CI, 0.55-1.10; P=.16). No other differences were observed.

Table 2. Incidence and Relative Risks of Cancers and Deaths Due to Cancer*

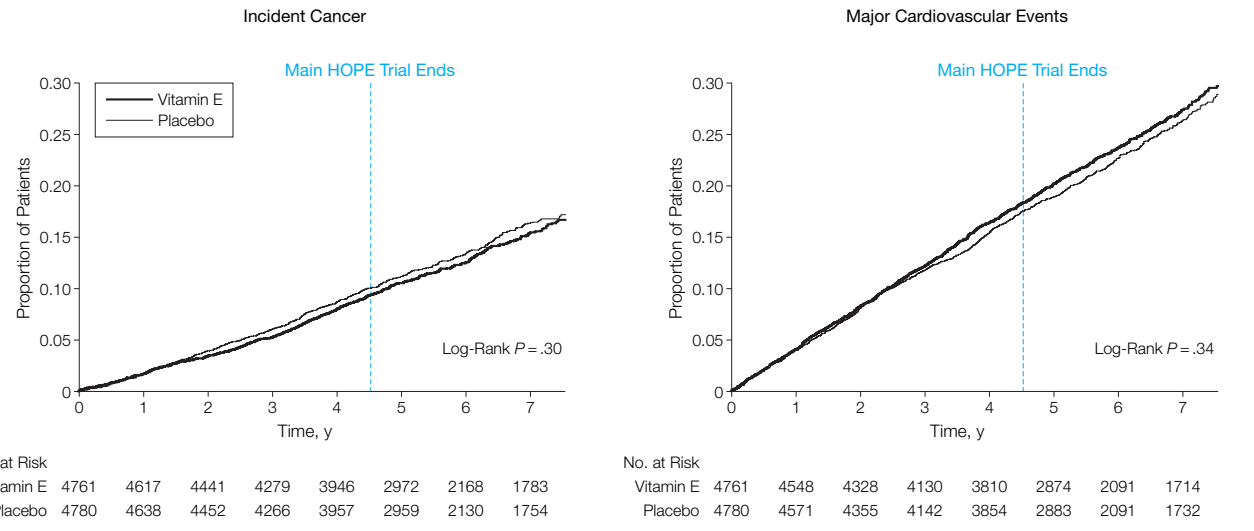
	No. (%) of Patients			
	Received Vitamin E	Received Placebo	Relative Risk (95% Confidence Interval)	*P* Value†
Primary analysis (all HOPE study patients, N = 9541)				
No. of patients	4761	4780		
Incident cancer	552 (11.6)	586 (12.3)	0.94 (0.84-1.06)	.30
Deaths due to cancer	156 (3.3)	178 (3.7)	0.88 (0.71-1.09)	.24
Sensitivity analysis (patients at centers continuing in the HOPE-TOO trial extension, N = 7030)				
No. of patients	3520	3510		
Incident cancer	464 (13.2)	482 (13.7)	0.96 (0.84-1.09)	.50
Deaths due to cancer	128 (3.6)	133 (3.8)	0.96 (0.75-1.22)	.75

Abbreviations: HOPE, Heart Outcomes Prevention Evaluation Study; HOPE-TOO, HOPE–The Ongoing Outcomes.
*In analyses excluding cancers and deaths due to cancer that occurred within the first 2 years following randomization and are less likely to be affected by the study intervention, there were also no significant differences in incident cancers and deaths due to cancer.
†Log-rank test.

Effects of Vitamin E on Cardiovascular Outcomes

Among all HOPE study patients as well as among patients in the centers participating in HOPE-TOO trial extension, there were no differences in the main composite cardiovascular outcome (Figure 2), or its components, in deaths, hospitalizations for unstable angina, and revascularizations (TABLE 4). Heart failure overall and hospital admissions for heart failure were more common in the vitamin E group (Table 4 and FIGURE 3). The increased risk for heart failure was consistent among subgroups defined by ramipril use, sex, baseline history of coronary artery disease, diabetes melli-

Figure 2. Kaplan-Meier Analysis of the Effects of Vitamin E on Incident Cancer and Major Cardiovascular Events for All 9541 Study Patients



tus and hypertension, systolic blood pressure, heart rate, and use of other drugs. A regression model, which considered all HOPE study patients and included all major baseline variables, identified treatment assignment to vitamin E as an independent predictor for heart failure (hazard ratio, 1.13; 95% CI, 1.01-1.26; $P=.04$).

An echocardiographic substudy evaluated the effects of ramipril and vitamin E on left ventricular mass, volumes, and function in 506 HOPE study patients.[30] Baseline left ventricular ejection fraction was similar (58% both in the vitamin E and placebo groups). During the period of 4 years, there was a mean (SD) decrease in left ventricular ejection fraction of 1.86% (0.58%) in the vitamin E group and 0.58% (0.61%) in the placebo group. The adjusted mean (SD) difference in left ventricular ejection fraction loss between the 2 groups was 1.66% (0.69%) ($P=.02$).

COMMENT

The major finding of the HOPE trial, including the initial trial and the trial extension, is the lack of benefit for vitamin E in preventing cancer or major cardiovascular events after a prolonged period of treatment and observation. Furthermore, our study raises concern about an increased risk of heart failure related to vitamin E.

No Clear Evidence of Benefit in Cancer Chemoprevention

After a median 7.0 years of follow-up for the entire study population and a median 7.2 years for patients at centers continuing in the trial extension, we observed no overall effect of vitamin E on the incidence of fatal and nonfatal cancers. There was also no apparent benefit for vitamin E in preventing most site-specific cancers, including selected cancers, for which some previous epidemiological studies or clinical trials had suggested particular promise.[14-17,22,23] Thus, there were no reductions in incident prostate, colorectal, oral/pharyngeal, and gastrointestinal cancers.

We did observe a lower incidence of lung cancer among patients receiving vitamin E vs those receiving placebo (69 [1.4%] vs 96 [2.0%]; $P=.04$). However, when applying more stringent statistical rules, which account for multiple comparisons when assessing the effect of vitamin E on site-specific cancers and which consider the exploratory post hoc nature of these analyses, the difference in lung cancer rates did not reach the predefined level of significance, and in the sensitivity analyses in patients at the centers continuing in the study extension (ie, those with longer duration of treatment and observation), the difference observed was not statistically significant ($P=.16$). As expected, most lung cancers (94.1%) occurred in current or previous smokers. Moreover, these findings need to be interpreted with caution, in light of the lack of benefit for vitamin E in preventing lung cancer in the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study[24] and the Heart Protection Study,[25] which were larger and had more lung cancer events. Combined data from these large randomized vitamin E trials do not show benefit for vitamin E in the prevention of lung cancer and suggest that the differences observed in our study are likely a chance finding (TABLE 5). Furthermore, 2 large randomized trials[24,31] using the antioxidant vitamin beta carotene reported increased rates of lung cancer, and a recent meta-analysis[32] found no benefit for antioxidant vitamin supplementation (including vitamin E) in the prevention of gastrointestinal cancers and raised concerns about an increase in total mortality.

The lack of benefit for prostate cancer is especially noteworthy, as the only prior evidence from randomized clinical trials supporting a potential benefit of vitamin E in cancer chemoprevention in a western population was provided by the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study,[24] which found a 34% lower rate of prostate cancer in middle-aged male Finnish smokers who were administered 50 mg of α-tocopherol daily for 6.1 years. However, similar to our study, the Heart Protection Study,[25] which involved more than 15 000 men, reported no significant impact of vitamin E on prostate cancer; this trial used a combina-

Table 3. Incidence and Relative Risks of Site-Specific Cancers*

	No. (%) of Patients			
	Received Vitamin E	Received Placebo	Relative Risk (95% Confidence Interval)	*P* Value
Primary analysis (all HOPE study patients, N = 9541)				
Prostate	116 (2.4)	119 (2.5)	0.98 (0.76-1.26)	.86
Lung	69 (1.4)	96 (2.0)	0.72 (0.53-0.98)	.04
Oral and pharyngeal	9 (0.2)	18 (0.4)	0.50 (0.24-1.18)	.09
Colorectal	69 (1.4)	57 (1.2)	1.22 (0.86-1.73)	.28
Breast	25 (0.5)	29 (0.6)	0.86 (0.50-1.47)	.58
Melanoma	15 (0.3)	18 (0.4)	0.84 (0.42-1.66)	.61
Sensitivity analysis (patients at centers continuing in the HOPE-TOO trial extension, N = 7030)				
Prostate	91 (2.6)	101 (2.9)	0.90 (0.68-1.19)	.46
Lung	58 (1.6)	74 (2.1)	0.78 (0.55-1.10)	.16
Oral and pharyngeal	8 (0.2)	15 (0.4)	0.53 (0.24-1.35)	.15
Colorectal	61 (1.7)	44 (1.3)	1.39 (0.94-2.04)	.10
Breast	19 (0.5)	26 (0.7)	0.73 (0.40-1.31)	.29
Melanoma	13 (0.4)	17 (0.5)	0.76 (0.37-1.57)	.46

Abbreviations: HOPE, Heart Outcomes Prevention Evaluation Study; HOPE-TOO, HOPE–The Ongoing Outcomes.
*A patient may have had more than 1 incident cancer; 50 patients in the vitamin E group and 58 in the placebo group had at least 2 cancers. The classification of cancer sites was based on the following *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes: prostate cancer, 185; lung cancer, 162; oral and pharyngeal cancer, 140-149; colorectal cancer, 153 and 154; breast cancer, 174 and 175; and melanoma skin cancer, 172.

tion of vitamin E (600 mg), vitamin C (250 mg), and beta carotene (20 mg) administered daily for 5 years. The ongoing Selenium and Vitamin E Cancer Prevention Trial[33] evaluates up to 12 years of supplementation with selenium and vitamin E in the prevention of prostate cancer among 32 400 men in North America, and will provide further information.

No Benefit on Cardiovascular Events and Potential for Excess HF

Vitamin E had no significant effect on myocardial infarction, stroke, cardiovascular death, unstable angina, revascularization, and total mortality. The long duration of treatment and observation and the large number of cardiovascular outcomes conclusively exclude any benefit for vitamin E in our study. Our results are also consistent with most previous large randomized controlled trials and a recent meta-analysis.[21,24,25,34-36]

We observed an unexpected and disturbing increase in heart failure rates in patients assigned to vitamin E. Although this finding could be due to chance, several factors persuade us to believe that it may be real. Heart failure was a predefined secondary study outcome and the excess in heart failure events in the vitamin E group was a robust and consistent finding in our study, present in all prespecified analyses. This finding was observed for all heart failure events and for heart failure needing hospital admission (an adjudicated event of greater seriousness); it was present both at the end of the initial HOPE trial (RR increased 17%, $P=.02$)[28] and after the extended follow-up (RR increased 13%, $P=.03$); it was observed in the primary analysis including all study participants and was more pronounced in the sensitivity analysis, which included patients randomized at the centers that continued in the trial extension. In the latter analysis of the study patients with longest duration of treatment and observation, the increase in risk was particularly striking (19% increase in the risk of all heart failure events [$P=.007$] and 40% increase in the risk of hospital admission for heart failure [$P=.002$]). These analyses are based on a large number of events, more than 1200 heart failure events and more than 400 hospitalizations for heart failure. A regression analysis identified vitamin E as an independent predictor of heart failure and supportive mechanistic evidence from an echocardiographic substudy of the HOPE trial found that vitamin E decreased left ventricular ejection fraction.

We did not identify any previous articles of an adverse effect of vitamin E on heart failure, and none of the previous large randomized trials of vitamin E published information about heart failure. A review of heart failure events in these trials is strongly recommended.

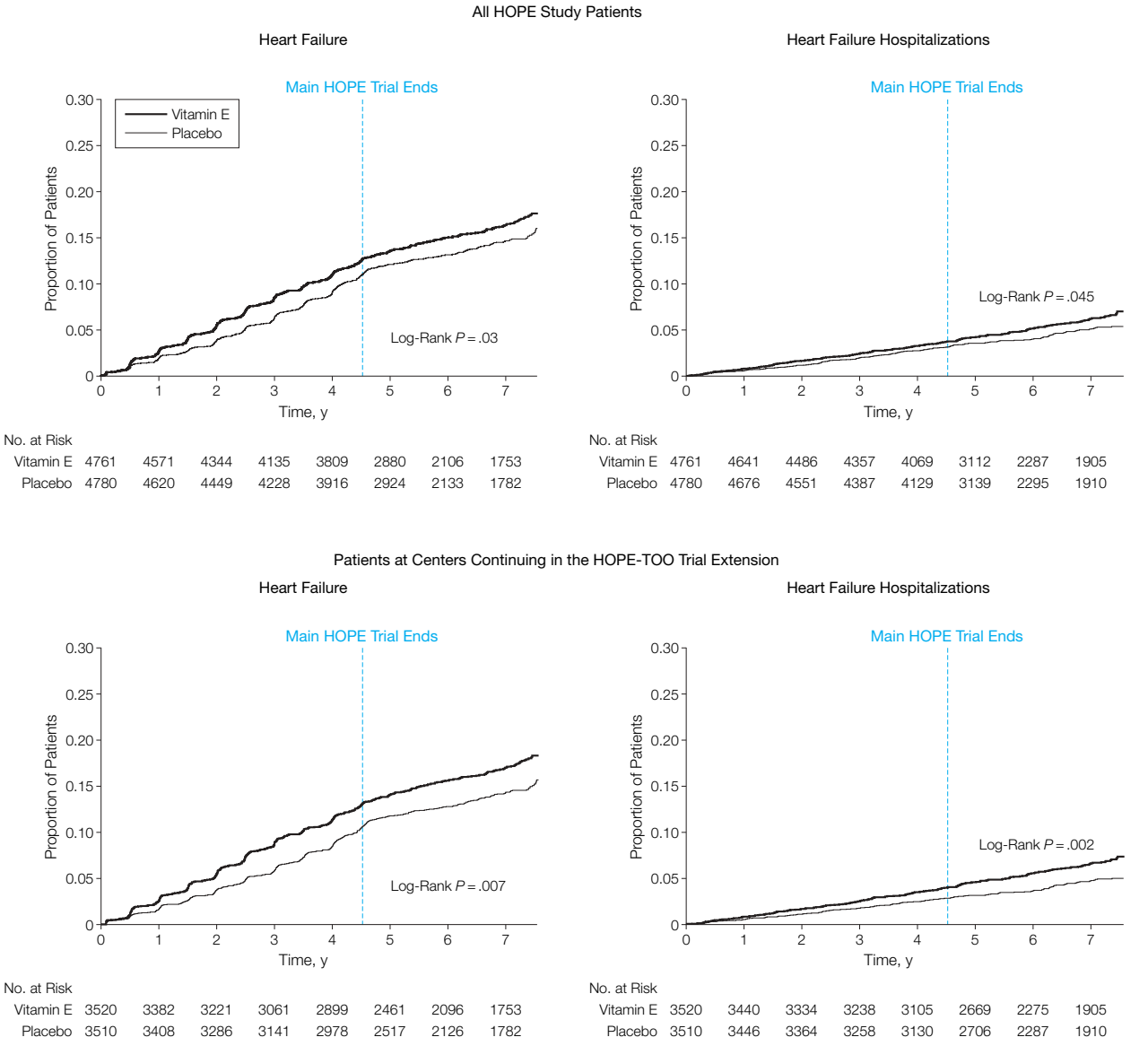
The mechanism for the observed harmful effect of vitamin E on heart failure is not clear but may relate to the potential for α-tocopherol to become a pro-oxidant in an oxidative milieu, thereby depressing myocardial function.[37] Other potential mechanisms of harm associated with vitamin E supplements in doses much higher than those provided by balanced diets may relate to displacement of other fat-soluble antioxidants, such as λ-tocopherol, disrupting the natural balance of antioxidant systems and a reduction in high-density lipoprotein (HDL_2)cholesterol.[38] Moreover, although the precise explanation for a possible harmful effect of vitamin E is not entirely clear, a recent meta-analysis reported increased

Table 4. Incidence and Relative Risks of Major Vascular Events, Deaths, and Secondary Cardiovascular Outcomes

	No. (%) of Patients		Relative Risk (95% Confidence Interval)	*P* Value*
	Received Vitamin E	Received Placebo		
Primary Analysis (All HOPE Study Patients, N = 9541)				
Major vascular events and deaths				
Myocardial infarction, stroke, or death from cardiovascular causes	1022 (21.5)	985 (20.6)	1.04 (0.96-1.14)	.34
Myocardial infarction	724 (15.2)	686 (14.4)	1.06 (0.96-1.18)	.27
Stroke	270 (5.7)	246 (5.1)	1.10 (0.93-1.31)	.27
Death from cardiovascular causes	482 (10.1)	475 (9.9)	1.02 (0.91-1.10)	.79
Death from any cause	799 (16.8)	801 (16.8)	1.00 (0.91-1.10)	>.99
Secondary cardiovascular outcomes				
Hospitalization for unstable angina	712 (15.0)	698 (14.6)	1.03 (0.92-1.47)	.63
Revascularization and limb amputation	1082 (22.7)	1013 (21.3)	1.08 (0.99-1.18)	.07
All heart failure	641 (13.5)	578 (12.1)	1.13 (1.01-1.26)	.03
Hospitalization for heart failure	236 (5.0)	196 (4.1)	1.21 (1.00-1.47)	.045
Sensitivity Analysis (Patients at Centers Continuing in the HOPE-TOO Trial Extension, N = 7030)				
Major vascular events and deaths				
Myocardial infarction, stroke, or death from cardiovascular causes	807 (22.9)	769 (21.9)	1.05 (0.95-1.16)	.31
Myocardial infarction	580 (16.5)	534 (15.2)	1.09 (0.97-1.22)	>.99
Stroke	208 (5.9)	191 (5.4)	1.09 (0.90-1.33)	.39
Death from cardiovascular causes	364 (10.3)	361 (10.3)	1.01 (0.87-1.16)	.93
Death from any cause	620 (17.6)	604 (17.2)	1.02 (0.92-1.15)	.67
Secondary cardiovascular outcomes				
Hospitalization for unstable angina	565 (16.1)	547 (15.6)	1.03 (0.92-1.16)	.57
Revascularization and limb amputation	882 (25.1)	822 (23.4)	1.09 (0.99-1.19)	.09
All heart failure	519 (14.7)	443 (12.6)	1.19 (1.05-1.35)	.007
Hospitalization for heart failure	203 (5.8)	146 (4.2)	1.40 (1.13-1.73)	.002

Abbreviations: HOPE, Heart Outcomes Prevention Evaluation Study; HOPE-TOO, HOPE–The Ongoing Outcomes.
*Log-rank test.

Figure 3. Kaplan-Meier Analysis of the Effects of Vitamin E on All Heart Failure Events and Hospital Admissions for Heart Failure in All 9541 HOPE Study Patients and in the 7030 Patients at Centers Continuing in the Study Extension (HOPE-TOO)



HOPE indicates Heart Outcomes Prevention Evaluation; HOPE-TOO, HOPE–The Ongoing Outcomes.

Table 5. Lung Cancer in Large Randomized Trials of Vitamin E*

Trial	Daily Dose of Study Drug	Duration, y	No. of Patients With Events/ Total No. (%) of Randomized Patients		Odds Ratio (95% Confidence Interval)	*P* Value
			Received Vitamin E	Received Placebo		
ATBC[24]	50 mg	6.1	433/14 564 (3.0)	443/14 560 (3.0)	0.98 (0.85-1.12)	.73
HPS[25]	600 mg	5	160/10 269 (1.6)	141/10 267 (1.4)	1.13 (0.90-1.43)	.27
HOPE†	400 IU	7.1	69/4761 (1.4)	96/4780 (2.0)	0.72 (0.53-0.98)	.04
Total			**662/29 594** (2.2)	**680/29 607** (2.3)	0.97 (0.87-1.08)	.62

Abbreviations: ATBC, Alpha-Tocopherol, Beta Carotene Cancer Prevention Study; HOPE, Heart Outcomes Prevention Evaluation Study; HPS, Heart Prevention Study.
*P for heterogeneity = .06.
†Includes the initial HOPE trial and HOPE–The Ongoing Outcomes trial extension.

mortality in trials using high-dose vitamin E (≥400 IU/d).[39]

Study Limitations

In the initial HOPE trial, data on cancers were collected prospectively, but reported cancers were not adjudicated. Adjudication of all cancer events (including those that occurred during the initial trial) was performed during the HOPE-TOO trial, when cancer was identified as a primary study outcome. Nevertheless, we believe that the ascertainment of cancer outcomes is accurate, as all events were adjudicated by an expert committee blinded to treatment assignment and using predefined criteria; histological confirmation was available for 70.1% of cardiovascular events and there was a high degree of agreement with an independent cancer registry.

Not all eligible centers and patients continued in the study extension, but this is unlikely to have biased the results, as the patient characteristics were similar among patients at centers continuing in the extension and those withdrawing. Moreover, our primary analyses considered all available data on all study participants, and sensitivity analyses in patients at the centers participating in the study extension provided similar results.

CONCLUSIONS

In the HOPE and HOPE-TOO trials, the daily administration of 400 IU of natural source vitamin E for a median of 7.0 years had no clear impact on fatal and nonfatal cancers, major cardiovascular events, or deaths. We observed an increase in the risk of heart failure, which is of concern. Although this adverse effect of vitamin E was unexpected and cannot be confirmed at this time by other trials, our data are internally consistent. Therefore, a meta-analysis of heart failure events including all completed large vitamin E trials is strongly recommended.

In conjunction with its lack of efficacy, the potential for harm suggested by our findings strongly supports the view that vitamin E supplements should not be used in patients with vascular disease or diabetes mellitus.

Our study also has wider implications. There is a tendency to accept "natural products" (eg, vitamins) as being safe, even if they have not been proven to be effective. However, our findings emphasize the need to thoroughly evaluate all vitamins, other natural products, and complementary medicines in appropriately designed trials before they are widely used for presumed health benefits.

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REFERENCES

1. Steinberg D, Parthasarathy S, Carew TE, Khoo JC, Witztum J. Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med*. 1989;320:915-924.
2. Prasad KN, Edwards-Prasad J. Vitamin E and cancer prevention: recent advances and future potentials. *J Am Coll Nutr*. 1992;11:487-500.
3. Traber MG, Sies H. Vitamin E in humans: demand and delivery. *Annu Rev Nutr*. 1996;16:321-347.
4. Verlangieri AJ, Bush MJ. Effects of d-α-tocopherol supplementation on experimentally induced primate atherosclerosis. *J Am Coll Nutr*. 1992;11:131-138.
5. Meydani M. Vitamin E. *Lancet*. 1995;345:170-175.
6. Steiner M. Influence of vitamin E on platelet function in humans. *J Am Coll Nutr*. 1991;10:466-473.
7. Bursell SE, King GL. Can protein kinase C inhibition and vitamin E prevent the development of diabetic vascular complications? *Diabetes Res Clin Pract*. 1999;45:169-182.
8. Skyrme-Jones RA, O'Brien RC, Berry KL, Meredith IT. Vitamin E supplementation improves endothelial function in type 1 diabetes mellitus: a randomized, placebo-controlled study. *J Am Coll Cardiol*. 2000;36:94-100.
9. Jha P, Flather M, Lonn E, Farkouh M, Yusuf S. The antioxidant vitamins and cardiovascular disease: a critical review of epidemiologic and clinical trial data. *Ann Intern Med*. 1995;123:860-872.
10. Shklar G, Schwartz JL. Vitamin E inhibits experimental carcinogenesis and tumour angiogenesis. *Eur J Cancer B Oral Oncol*. 1996;32B:114-119.
11. Sigounas G, Anagnostou A, Steiner M. dl-alpha-Tocopherol induces apoptosis in erythroleukemia, prostate, and breast cancer cells. *Nutr Cancer*. 1997;28:30-35.
12. Meydani SN, Beharka AA. Recent developments in vitamin E and immune response. *Nutr Rev*. 1996;56(suppl):S49-S58.
13. Ziegler RG, Mayne ST, Swanson CA. Nutrition and lung cancer [review]. *Cancer Causes Control*. 1996;7:157-177.
14. Woodson K, Tangrea JA, Barrett MJ, Virtamo J, Taylor PR, Albanes D. Serum α-tocopherol and subsequent risk of lung cancer among male smokers. *J Natl Cancer Inst*. 1999;91:1738-1743.
15. Huang HY, Alberg AJ, Norkus EP, Hoffman SC, Comstock GW, Helzlsouer KJ. Prospective study of antioxidant micronutrients in the blood and the risk of developing prostate cancer. *Am J Epidemiol*. 2003;157:335-344.
16. Gridley G, McLaughlin JK, Block G, Blot WJ, Gluch M, Fraumeni JF Jr. Vitamin supplement use and reduced risk of oral and pharyngeal cancer. *Am J Epidemiol*. 1992;135:1083-1092.
17. Longnecker MP, Martin-Moreno JM, Knekt P, et al. Serum alpha-tocopherol concentration in relation to subsequent colo-rectal cancer: pooled data from five cohorts. *J Natl Cancer Inst*. 1992;84:430-445.
18. Knekt P, Aromaa A, Maatela J, et al. Serum vitamin E and risk of cancer among Finnish men during a 10-year follow-up. *Am J Epidemiol*. 1988;127:28-41.
19. Ocke MC, Bueno-de-Mesquita HB, Feskens EJ, van Staveren WA, Kromhout D. Repeated measurements of vegetables, fruits, beta-carotene, and vitamins C and E in relation to lung cancer: the Zutphen Study. *Am J Epidemiol*. 1997;145:358-365.
20. Klein EA, Thompson IM, Lippman SM, et al. SELECT: the next prostate cancer prevention trial: Selenium and Vitamin E Cancer Prevention Trial. *J Urol*. 2001;166:1311-1315.
21. Vivekananthan DP, Penn MS, Sapp SK, Hsu A, Topol EJ. Use of antioxidant vitamins for the prevention of cardiovascular disease: meta-analysis of randomised trials. *Lancet*. 2003;361:2017-2023.
22. Heinonen OP, Albanes D, Virtamo J, et al. Prostate cancer and supplementation with α-tocopherol and β-carotene: incidence and mortality in a controlled trial. *J Natl Cancer Inst*. 1998;90:440-446.
23. Li J-Y, Taylor PR, Li B, et al. Nutrition intervention trials in China: multiple incidence and disease-specific mortality among adults with esophageal dysplasia. *J Natl Cancer Inst*. 1993;85:1492-1498.
24. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 1994;330:1029-1035.
25. Heart Protection Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20536 high-risk individuals: a randomized placebo-controlled trial. *Lancet*. 2002;360:23-33.
26. Steinberg D. Clinical trials of antioxidants in atherosclerosis: are we doing the right thing? *Lancet*. 1995;346:36-38.
27. Steinberg D, Witzum JL. Is the oxidative modification hypothesis relevant to human atherosclerosis: do the antioxidant trials conducted to date refute the hypothesis? *Circulation*. 2002;105:2107-2111.
28. The Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E supplementation and cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:154-160.
29. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med*. 2000;342:145-153.
30. Lonn E, Shaikholeslami R, Yi Q, et al. Effects of ramipril on left ventricular mass and function in cardiovascular patients with controlled blood pressure and with preserved left ventricular ejection fraction: a substudy of the HOPE trial. *J Am Coll Cardiol*. 2004;43:2200-2206.
31. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. *N Engl J Med*. 1996;334:1150-1155.
32. Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet*. 2004;364:1219-1228.
33. Klein EA, Thomson IM, Lippman SM, et al. SELECT: the Selenium and Vitamin E Cancer Prevention Trial: rationale and design. *Prostate Cancer Prostatic Dis*. 2000;3:145-151.
34. GISSI-Prevenzione Investigators (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infracto Miocardico). Dietary supplementation with n-e polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione Trial. *Lancet*. 1999;354:447-455.
35. Age-Related Eye Disease Study Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamin C and E and beta-carotene for age-related cataract and vision loss: AREDS Report No. 9. *Arch Ophthalmol*. 2001;119:1439-1452.
36. Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. *Lancet*. 2001;342:154-160.
37. Bowry VW, Ingold KU, Stocker R. Vitamin E in human low-density lipoproteins: when and how this antioxidant becomes a pro-oxidant. *Biochem J*. 1992;288:341-344.
38. Brown BG, Zhao XQ, Chait A, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med*. 2001;345:1583-1592.
39. Miller ER III, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. *Ann Intern Med*. 2005;142:37-46.