

Vitamin E in the Primary Prevention of Cardiovascular Disease and Cancer

The Women's Health Study: A Randomized Controlled Trial

I-Min Lee, MBBS, ScD

Nancy R. Cook, ScD

J. Michael Gaziano, MD

David Gordon, MA

Paul M Ridker, MD

JoAnn E. Manson, MD, DrPH

Charles H. Hennekens, MD, DrPH

Julie E. Buring, ScD

FREE RADICALS CAN CAUSE LIPID peroxidation and DNA damage, contributing to the development of cardiovascular disease (CVD) and cancer.¹⁻⁵ Vitamin E has antioxidant properties, including inhibition of oxidation of low-density lipoprotein cholesterol in plasma, leading to the hypothesis that it can prevent these chronic diseases.⁵ In some, but not all, basic research reports, vitamin E supplementation retarded atherogenesis.⁶ In descriptive data, investigators noted a strong inverse relation between plasma vitamin E concentrations and death rates from ischemic heart disease in men in several European countries.⁷ Additionally, several large cohort studies observed decreased CVD rates among individuals who self-selected for higher intakes of vitamin E through diet and/or supplements.⁸⁻¹⁰ By 1997, despite a lack of randomized trials, 44% of US cardiologists reported routine use of antioxidant supplements,

See also pp 47 and 105.

Context Basic research provides plausible mechanisms and observational studies suggest that apparently healthy persons, who self-select for high intakes of vitamin E through diet or supplements, have decreased risks of cardiovascular disease and cancer. Randomized trials do not generally support benefits of vitamin E, but there are few trials of long duration among initially healthy persons.

Objective To test whether vitamin E supplementation decreases risks of cardiovascular disease and cancer among healthy women.

Design, Setting, and Participants In the Women's Health Study conducted between 1992 and 2004, 39 876 apparently healthy US women aged at least 45 years were randomly assigned to receive vitamin E or placebo and aspirin or placebo, using a 2 × 2 factorial design, and were followed up for an average of 10.1 years.

Intervention Administration of 600 IU of natural-source vitamin E on alternate days.

Main Outcome Measures Primary outcomes were a composite end point of first major cardiovascular event (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) and total invasive cancer.

Results During follow-up, there were 482 major cardiovascular events in the vitamin E group and 517 in the placebo group, a nonsignificant 7% risk reduction (relative risk [RR], 0.93; 95% confidence interval [CI], 0.82-1.05; *P* = .26). There were no significant effects on the incidences of myocardial infarction (RR, 1.01; 95% CI, 0.82-1.23; *P* = .96) or stroke (RR, 0.98; 95% CI, 0.82-1.17; *P* = .82), as well as ischemic or hemorrhagic stroke. For cardiovascular death, there was a significant 24% reduction (RR, 0.76; 95% CI, 0.59-0.98; *P* = .03). There was no significant effect on the incidences of total cancer (1437 cases in the vitamin E group and 1428 in the placebo group; RR, 1.01; 95% CI, 0.94-1.08; *P* = .87) or breast (RR, 1.00; 95% CI, 0.90-1.12; *P* = .95), lung (RR, 1.09; 95% CI, 0.83-1.44; *P* = .52), or colon cancers (RR, 1.00; 95% CI, 0.77-1.31; *P* = .99). Cancer deaths also did not differ significantly between groups. There was no significant effect of vitamin E on total mortality (636 in the vitamin E group and 615 in the placebo group; RR, 1.04; 95% CI, 0.93-1.16; *P* = .53).

Conclusions The data from this large trial indicated that 600 IU of natural-source vitamin E taken every other day provided no overall benefit for major cardiovascular events or cancer, did not affect total mortality, and decreased cardiovascular mortality in healthy women. These data do not support recommending vitamin E supplementation for cardiovascular disease or cancer prevention among healthy women.

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primarily vitamin E, compared with 42% who routinely used aspirin for the primary prevention of CVD.¹¹

Author Affiliations are listed at the end of this article.
Corresponding Author: I-Min Lee, MBBS, ScD, Brigham and Women's Hospital, 900 Commonwealth Ave E, Boston, MA 02215 (ilee@rics.bwh.harvard.edu).

With regard to cancer, several observational studies, particularly case-control studies, also reported reduced rates of cancer among persons who self-selected for high antioxidant intakes.¹²

For small to moderate effects, however, the amount of uncontrolled and uncontrollable confounding inherent in observational studies can be as large as the postulated benefit, so randomized clinical trials represent the most reliable study design strategy.¹³ Several trials were therefore initiated beginning in the late 1980s to directly test the vitamin E hypothesis.¹⁴⁻³⁸ To date, data from randomized trials have largely demonstrated no significant benefit of vitamin E supplementation on the incidence of CVD or cancer and, indeed, raised the question of possible adverse effects on total mortality with high doses.³⁹⁻⁴⁴ However, these trials have been conducted primarily among participants with cardiovascular risk factors and/or CVD or at high risk for cancer. Few trials have recruited apparently healthy persons, with most designed to examine ophthalmologic outcomes.^{30,33,37} Only one trial, testing a combination of antioxidant vitamins and minerals, has investigated CVD and cancer prevention among healthy persons not selected based on risk factors.³⁵ Additionally, the treatment duration in previous trials has generally been limited to 5 years or shorter, with 6 trials having a longer duration.^{14-16,30,35,38} One possible explanation for the largely null results of randomized trials is that the duration of supplementation has been insufficient for an effect.⁴⁵

To provide further information, the Women's Health Study (WHS) tested whether vitamin E supplementation for 10 years decreased risks of CVD and cancer in a large group of healthy women.

METHODS

Study Design

The WHS was a randomized, double-blind, placebo-controlled, 2 × 2 factorial trial evaluating the balance of risks and benefits of low-dose aspirin (100 mg

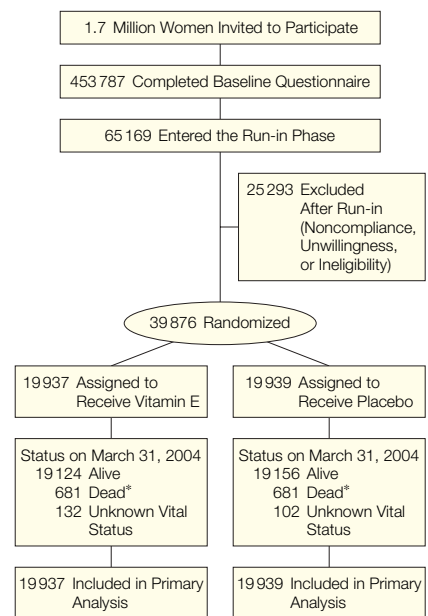
every other day; Bayer Healthcare) and vitamin E (600 IU of α -tocopherol every other day; Natural Source Vitamin E Association) in the primary prevention of CVD and cancer.^{46,47} Originally, a third component, beta carotene, was also included. However, this component was terminated early in January 1996 after a median treatment duration of 2.1 years.⁴⁸ Written informed consent was obtained from all participating women. The trial was approved by the institutional review board of Brigham and Women's Hospital and monitored by an external data and safety monitoring board.

Detailed methods of the design have been described previously.^{46,47} Briefly, between September 1992 and May 1995, letters of invitation to participate in the trial and baseline health questionnaires were mailed to more than 1.7 million female health care professionals throughout the United States (FIGURE 1). A total of 453 787 women completed the questionnaires and 65 169 were willing and eligible to participate. Eligibility criteria included the following: age 45 years or older; no previous history of coronary heart disease, cerebrovascular disease, cancer (except nonmelanoma skin cancer), or other major chronic illnesses; no history of adverse effects from aspirin; no use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) more than once a week, or willingness to forgo their use; no use of anticoagulants or corticosteroids; and no use of individual supplements of vitamin A, E, or beta carotene more than once a week. Eligible women were enrolled into a 3-month run-in period with placebo medications to identify likely long-term compliers to pill taking. Following the run-in period, 39 876 women remained willing, eligible, and compliant, and they were randomized in blocks of 16 within 5-year age strata to vitamin E (n = 19 937) or placebo (n = 19 939).

Study Treatment and Follow-up

Each year, women received calendar packs that contained amber capsules

Figure 1. Flow Diagram of the Vitamin E Component of the Women's Health Study



*The numbers of deaths are higher than those in Table 2 because this figure includes all reported deaths in the WHS, whereas the deaths in Table 2 include only reported deaths confirmed by the Endpoints Committee or by a death certificate.

(vitamin E or placebo) and white pills (aspirin or placebo) on alternate days. Every 6 months for the first year and annually thereafter, they also received follow-up questionnaires inquiring about compliance with pill-taking, potential adverse effects, occurrence of end points, and risk factors. Study medications and end point ascertainment were continued in blinded fashion through the scheduled end of the trial (March 31, 2004). Follow-up and validation of reported end points were completed in February 2005. Morbidity and mortality follow-up were 97.2% and 99.4% complete, respectively.

Using the information provided on questionnaires, compliance, defined as taking at least two thirds of the study capsules, was 78.9% at 5 years and 71.6% at 10 years. Averaged throughout the trial, it was 75.8% with no difference between active and placebo groups ($P = .64$). Nontrial use of individual supplements of vitamin E for at least 4 days per month ("drop-ins") was

10.0% at 5 years and 10.9% at 10 years. Averaged throughout the trial, outside use was somewhat lower in the active (8.6%) than in the placebo group (8.9%) ($P=.07$).

Confirmation of End Points

The primary end points were a composite of first major cardiovascular event (nonfatal myocardial infarction [MI], nonfatal stroke, or cardiovascular death) and total invasive cancer (apart from nonmelanoma skin cancer). Secondary end points were the individual cardiovascular events—total MI, total stroke, and cardiovascular death—and the main site-specific cancers in women: breast, lung, and colon cancers. We also collected information on coronary revascularization procedures (bypass surgery or percutaneous coronary angioplasty), transient ischemic attacks (TIAs), and total mortality.

Women reported the occurrence of relevant end points via follow-up questionnaires, letters, or telephone calls. Deaths were usually reported by family members or postal authorities or ascertained through the National Death Index. After obtaining written consent, we acquired medical records from hospitals and physicians, which were reviewed by the WHS Endpoints Committee of physicians blinded to randomized treatment assignment. The committee confirmed a diagnosis of MI if symptoms met World Health Organization criteria and the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiograms. The use of coronary revascularization procedures was confirmed by medical record review. Stroke was confirmed if the participant had a new neurologic deficit of sudden onset that persisted for more than 24 hours or until death within 24 hours. Clinical information and computed tomographic scans or magnetic resonance images were used to distinguish hemorrhagic from ischemic strokes.⁴⁹ A confirmed TIA was defined as a neurologic deficit of sudden onset lasting less than 24 hours. Cardiovascular deaths were confirmed by autopsy reports, death certificates, medical records, and

information from next of kin or family members. The vast majority (96.8%) of cancers were confirmed with pathology or cytology reports. Rarely, the committee confirmed a reported case of cancer based on strong clinical and radiological or laboratory marker evidence (eg, elevated CA-125) when pathology or cytology review was not conducted. Total mortality was confirmed by the committee or by obtaining a death certificate. Only confirmed end points are included in this report.

Statistical Analysis

All primary analyses were performed on an intention-to-treat basis (ie, based on all randomized persons, as randomized), using the SAS statistical software package (release 8.2; SAS Institute Inc, Cary, NC). We used Cox proportional hazards regression models to calculate the relative risks (RRs) and 95% confidence intervals (95% CIs), comparing event rates in the vitamin E and placebo groups, after adjustment for age and randomized aspirin and beta carotene assignments. Statistical significance was set at $P<.05$, using 2-sided tests. To test the proportionality assumption (ie, that of nonchanging RRs over time), we included an interaction term of vitamin E with the logarithm of time in the Cox models. The proportionality assumption was not violated for major cardiovascular events ($P=.16$), total invasive cancer ($P=.72$), or total mortality ($P=.81$). We conducted subgroup analyses stratified by major risk factors for CVD and cancer, and assessed effect modification using interaction terms between subgroup indicators and vitamin E assignment, testing for trend when subgroup categories were ordinal. To investigate the effect of compliance, we carried out a sensitivity analysis that censored follow-up for any participant at the time when she reported taking less than two thirds of study medications over the previous year.

RESULTS

The mean (SD) age of participants at baseline was 54.6 (7.0) years; other clinical characteristics are shown in

TABLE 1. As expected in this very large sample, randomization was effective in balancing the characteristics of women in the vitamin E and placebo groups. The average duration of follow-up from randomization to the end of the trial was 10.1 years (range, 8.2-10.9 years).

Cardiovascular Disease

By the end of the trial, 999 major cardiovascular events (253 per 100 000 person-years) had occurred: 482 in the vitamin E group and 517 in the placebo group (TABLE 2). This corresponded to a nonsignificant 7% risk reduction with vitamin E (RR, 0.93; 95% CI, 0.82-1.05; $P=.26$). For the individual cardiovascular events, vitamin E had no effect on total MI (RR, 1.01; 95% CI, 0.82-1.23) or total stroke (RR, 0.98; 95% CI, 0.82-1.17). For stroke subtypes, there was no reduction in ischemic or increase in hemorrhagic stroke rates. There was a significant 24% reduction in cardiovascular deaths among women in the vitamin E group (RR, 0.76; 95% CI, 0.59-0.98). This was largely attributable to fewer sudden deaths in the vitamin E group (38 vs 51 among women assigned to placebo) and fewer deaths from other cardiovascular disease (ie, deaths due to cardiovascular diseases other than ischemic heart disease and cerebrovascular disease, 20 vs 34, respectively). There was no significant effect of vitamin E on coronary revascularization procedures (394 vs 369, respectively) or TIA (212 in each group).

FIGURE 2 shows the cumulative incidence rates of major cardiovascular events among women in the 2 groups by year of follow-up. An apparent benefit of vitamin E on major cardiovascular events, as well as on the individual end points of MI, stroke, and cardiovascular death, was observed early in the trial. The effect on major cardiovascular events diminished over time and disappeared for MI and stroke by the end of the trial. In contrast, the difference in cardiovascular death rates between active and placebo groups appeared to increase over time; however, the change in RRs over time was not significant ($P=.59$). Because com-

pliance diminishes over time, we examined whether the observed trends might have been due to this tendency. In a sensitivity analysis that censored noncompliant (taking less than two thirds of study medications) follow-up time, there was no evidence that noncompliance influenced the findings (RR for major cardiovascular events, 0.96; 95% CI, 0.82-1.11; $P=.56$).

As reported previously, aspirin was associated with a nonsignificant 9% reduction in major cardiovascular events.⁴⁷ We therefore examined whether random assignment to aspirin modified the effect of vitamin E. There was no modification of the effect of vitamin E by random assignment to aspirin (TABLE 3). Beta carotene also did not modify the effect of vitamin E on the primary or secondary end points (data not shown).

We examined whether cardiovascular risk factors modified the relation between vitamin E and major cardiovascular events (Table 3). In particular, we were interested in whether levels of oxidative stress may modify the effect of vitamin E.⁵⁰ We did not have a direct measure of oxidative stress; however, smoking and diseases such as hypertension, hyperlipidemia, and diabetes are associated with increased production of reactive oxygen species in the vascular wall.⁵¹ Using these indirect markers (all self-reported), we found no evidence of benefit of vitamin E among persons with increased oxidative stress. Additionally, no benefit was observed among both users and non-users of multivitamins, who would presumably have lower and higher levels of oxidative stress, respectively.

There also was no statistically significant effect modification by any of the other factors considered, except age ($P=.008$). In subgroup analyses, women aged at least 65 years comprised 10% of study participants but contributed 31% of end points. A significant 26% reduction in major cardiovascular events was observed among women aged at least 65 years assigned to vitamin E (RR, 0.74; 95% CI, 0.59-0.93; $P=.009$) due to a 34% reduction in MI (RR, 0.66; 95% CI, 0.45-

0.98; $P=.04$) and 49% reduction in cardiovascular death (RR, 0.51; 95% CI, 0.33-0.77; $P<.001$) rates. However, no reduction in stroke rate was observed (RR, 0.88; 95% CI, 0.64-1.21; $P=.44$). Among women aged 45 through 54 and 55 through 64 years, the RRs for major

cardiovascular events were 1.13 (95% CI, 0.91-1.41; $P=.26$) and 0.95 (95% CI, 0.77-1.16; $P=.61$), respectively.

Cancer

During the trial, 2865 women developed invasive cancer (741 events per

Table 1. Baseline Characteristics of Women by Group, Women's Health Study

Characteristic	No. (%) [*]			P Value
	Vitamin E (n = 19 937)	Placebo (n = 19 939)	Total (N = 39 876)	
Age, y				
Mean (SD)	54.6 (7.0)	54.6 (7.0)	54.6 (7.0)	.94
45-54	12 016 (60.3)	12 009 (60.2)	24 025 (60.2)	.98
55-64	5878 (29.5)	5876 (29.5)	11 754 (29.5)	
≥65	2043 (10.3)	2054 (10.3)	4097 (10.3)	
Smoking status				
Current	2590 (13.0)	2645 (13.3)	5235 (13.1)	.42
Past or never	17 328 (87.0)	17 277 (86.7)	34 605 (86.9)	
Alcohol intake				
Never/rarely	9057 (45.4)	8925 (44.8)	17 982 (45.1)	.18
At least 1/mo	10 873 (54.6)	11 011 (55.2)	21 884 (54.9)	
Multivitamin use	7807 (39.2)	7661 (38.4)	15 468 (38.8)	.13
Body mass index [†]				
Mean (SD)	26.04 (5.07)	26.03 (5.06)	26.04 (5.06)	.94
<25	9885 (50.7)	9964 (51.0)	19 849 (50.8)	.75
25-29	6069 (31.1)	6012 (30.8)	12 081 (30.9)	
≥30	3557 (18.2)	3569 (18.3)	7126 (18.2)	
Physical activity, kcal/wk				
<1000	13 030 (66.2)	12 964 (65.8)	25 994 (66.0)	.37
≥1000	6645 (33.8)	6738 (34.2)	13 383 (34.0)	
Menopausal status and hormone therapy use				
Premenopausal	5458 (27.5)	5515 (27.7)	10 973 (27.6)	.88
Uncertain	3568 (17.9)	3581 (18.0)	7149 (18.0)	
Postmenopausal, current hormone therapy use	5981 (30.1)	5967 (30.0)	11 948 (30.0)	
Postmenopausal, never or past hormone therapy use	4880 (24.5)	4824 (24.3)	9704 (24.4)	
Hypertension [‡]				
Yes	5103 (25.6)	5214 (26.2)	10 317 (25.9)	.20
No	14 832 (74.4)	14 718 (73.8)	29 550 (74.1)	
Hyperlipidemia [§]				
Yes	5842 (29.3)	5903 (29.6)	11 745 (29.5)	.50
No	14 089 (70.7)	14 026 (70.4)	28 115 (70.5)	
Diabetes				
Yes	517 (2.6)	510 (2.6)	1027 (2.6)	.83
No	19 411 (97.4)	19 414 (97.4)	38 825 (97.4)	
Parental history of myocardial infarction before age 60 y				
Yes	2321 (13.0)	2312 (12.9)	4633 (12.9)	.83
No	15 583 (87.0)	15 627 (87.1)	31 210 (87.1)	

^{*}Numbers do not always sum to group totals due to missing information for some variables.

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

[‡]Hypertension was defined as a self-reported systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or physician-diagnosed hypertension.

[§]Hyperlipidemia was defined as a self-reported total cholesterol ≥240 mg/dL (6.2 mmol/L) or physician-diagnosed high cholesterol.

^{||}Diabetes was defined by self-report.

Table 2. Relative Risks of Cardiovascular Disease, Cancer, and Total Mortality by Group, Women's Health Study

Outcome	No. of Events		Relative Risk (95% CI)	P Value
	Vitamin E (n = 19 937)	Placebo (n = 19 939)		
Major cardiovascular event*	482	517	0.93 (0.82-1.05)	.26
Myocardial infarction	196	195	1.01 (0.82-1.23)	.96
Nonfatal	184	181	1.02 (0.83-1.25)	.87
Fatal	12	14	0.86 (0.40-1.85)	.70
Stroke	241	246	0.98 (0.82-1.17)	.82
Nonfatal	220	222	0.99 (0.82-1.19)	.93
Fatal	21	24	0.88 (0.49-1.57)	.66
Ischemic†	194	197	0.99 (0.81-1.20)	.88
Hemorrhagic†	44	48	0.92 (0.61-1.38)	.68
Cardiovascular death	106	140	0.76 (0.59-0.98)	.03
Total invasive cancer	1437	1428	1.01 (0.94-1.08)	.87
Breast	616	614	1.00 (0.90-1.12)	.95
Lung	107	98	1.09 (0.83-1.44)	.52
Colon	107	107	1.00 (0.77-1.31)	.99
Cancer death	308	275	1.12 (0.95-1.32)	.17
Total mortality	636	615	1.04 (0.93-1.16)	.53

Abbreviation: CI, confidence interval.

*Defined as a composite end point comprising the first of any of these events: nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.

†Stroke type was not known for 3 women in the vitamin E group and 1 in the placebo group.

100 000 person-years): 1437 in the vitamin E group and 1428 in the placebo group (RR, 1.01; 95% CI, 0.94-1.08; $P = .87$; Table 2). Further analyses that excluded the first 2 or 5 years of follow-up did not change the findings (data not shown). For the main site-specific cancers, there were no significant differences between the vitamin E and placebo groups (breast cancer: RR, 1.00; 95% CI, 0.90-1.12; lung cancer: RR, 1.09; 95% CI, 0.83-1.44; and colon cancer: RR, 1.00; 95% CI, 0.77-1.31). There also was no significant difference in rectal cancer rates (22 vs 33 cases in the vitamin E and placebo groups, respectively). A previous study in a poorly nourished population reported lower rates of stomach cancer among those randomized to a vitamin and mineral cocktail including vitamin E.¹⁴ We did not observe this in our healthy population (14 vs 6 cases of stomach cancer, respectively). Cancer death rates also were not significantly influenced by vitamin E (308 vs 275 cancer deaths, respectively; RR, 1.12; 95% CI, 0.95-1.32; $P = .17$).

Including in situ and invasive cancers in the analysis led to virtually unchanged findings (1626 vs 1615 cases,

respectively; RR, 1.01; 95% CI, 0.94-1.08; $P = .84$).

When we examined cumulative incidence rates of invasive cancer by year of follow-up, the curves were almost identical in the vitamin E and placebo groups (FIGURE 3). Additional analyses that censored noncompliant (taking less than two thirds of study medications) follow-up time continued to show a lack of effect of vitamin E on total invasive cancer (RR, 1.01; 95% CI, 0.93-1.09; $P = .88$).

As with major cardiovascular events, random assignment to neither aspirin nor beta carotene modified the effect of vitamin E on the primary or secondary cancer end points. Additionally, there was no significant effect modification by any of the cancer risk factors shown in Table 3.

Total Mortality

By the end of the trial, 636 women in the vitamin E group had died, as had 615 women in the placebo group (RR, 1.04; 95% CI, 0.93-1.16; $P = .53$). The main causes of death, apart from cardiovascular and cancer deaths, were pulmonary diseases (32 vitamin E, 22

placebo); violent deaths, excluding suicide (31 vs 21); and suicide (9 vs 6). None of these causes of deaths was significantly related to vitamin E.

In analysis that censored noncompliant follow-up time, there also was no significant effect of vitamin E (RR, 1.08; 95% CI, 0.90-1.29; $P = .42$).

There was no effect of random assignment to either aspirin or beta carotene on the effect of vitamin E on total mortality. There also was no significant effect of any of the cardiovascular and cancer risk factors in Table 3 on the association of vitamin E with total mortality.

Adverse Effects

We examined whether vitamin E increased adverse effects due to bleeding (gastrointestinal bleeding, hematuria, easy bruising, epistaxis) because of the potential for vitamin E to inhibit platelet function,⁵² gastrointestinal symptoms (gastric upset, nausea, diarrhea, constipation), or fatigue. There were no differences between reported adverse effects for any of these variables among women in the 2 groups, apart from a small, but significant, increase in the risk of epistaxis (RR, 1.06; 95% CI, 1.01-1.11; $P = .02$).

COMMENT

The WHS—the largest randomized trial of vitamin E supplementation to date with the longest duration of treatment—adds important information regarding whether vitamin E plays any role in CVD and cancer prevention. In this trial, 600 IU of natural-source vitamin E every other day for 10 years did not provide any statistically significant benefits on the primary end points of major cardiovascular events or cancer in almost 40 000 healthy women. There was, however, a significant 24% reduction in the secondary end point of cardiovascular deaths and a significant 26% reduction in major cardiovascular events among the subgroup of women aged at least 65 years. We observed no significant effect of vitamin E on total mortality.

The finding of no overall effect of vitamin E on CVD is congruent with data

from previous randomized trials. In 2 recent meta-analyses, the pooled RR of CVD with vitamin E treatment was 1.0 (95% CI, 0.94-1.07) in a 2003 analysis⁴⁰ and 0.98 (95% CI, 0.94-1.03) in a 2004 analysis.⁴¹ These trials, however, recruited participants at high risk either because of CVD risk factors or preexisting disease. There are few data on populations comparable with the healthy women in the WHS. A recently published trial not included in either meta-analysis, the SU.VI.MAX study,³⁵ like the WHS, enrolled primarily healthy persons. After 7.5 years, the SU.VI.MAX trial also reported no effect of randomized treatment using a combination of vitamins and minerals, including 30 mg/d of vitamin E, on CVD (RR, 0.97; 95% CI, 0.77-1.20).

With regard to the individual cardiovascular end points, we found a significant 24% reduction in cardiovascular deaths. This finding differs from the overall data; in the 2003 meta-analysis, the pooled RR for this end point was 1.0 (95% CI, 0.94-1.06)⁴⁰ and 1.00 (95% CI, 0.94-1.05) in the 2004 meta-analysis.⁴¹ The addition of the WHS data (106 cardiovascular deaths in the vitamin E group, 140 in the placebo group) to the latter and larger meta-analysis (2683 and 2689 cardiovascular deaths, respectively) should not have an appreciable impact on the pooled RR. In the WHS, the single largest contribution to the reduction in cardiovascular deaths was fewer sudden deaths among women assigned to receive vitamin E. One plausible explanation that we considered was whether omega-3 fatty acids in the treatment capsules may have played a role.²⁴ This is unlikely, however, because both active and placebo capsules were identically formulated with soybean oil, the only difference being the addition of vitamin E to the active capsules. It is possible that the observed reduction in cardiovascular deaths was due to chance, arising from multiple comparisons.

An interesting finding in subgroup analyses was the observation of a significant 26% reduction in major cardiovascular events, primarily cardiovascu-

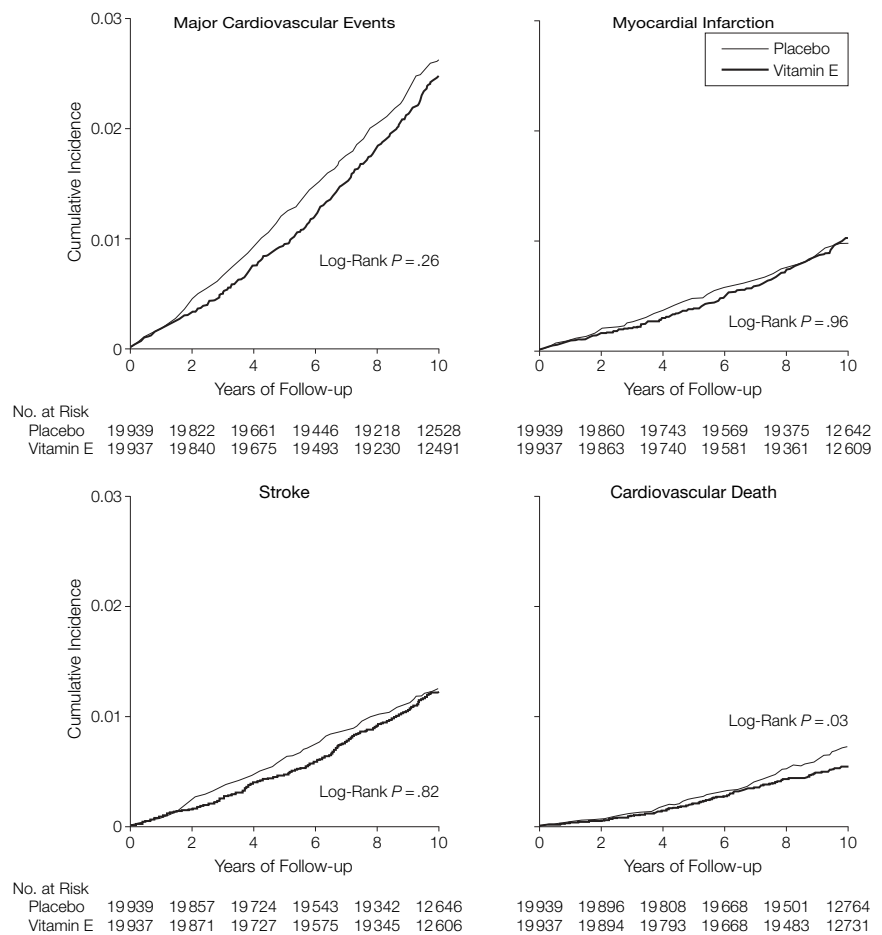
lar deaths, among women aged at least 65 years. Few previous trials of vitamin E have reported findings by age. The one that did, the HOPE trial, enrolled participants aged at least 55 years with CVD, or diabetes and one other risk factor, and reported no overall effect of vitamin E on CVD and no heterogeneity of results by age.²⁶ Several large observational studies that noted inverse associations between vitamin E intake and CVD rates did not provide findings by age.⁸⁻¹⁰ Existing trials of vitamin E can help clarify this by providing findings regarding any age effects.

A recent trial, HOPE-TOO, noted a possible adverse effect of 400 IU/d of vitamin E on the risk of heart failure.³⁸ This

was not a prespecified end point in the WHS; however, we did collect self-reported information, which did not demonstrate any association between random assignment to vitamin E use and incidence of heart failure. These self-reports are currently being validated against medical records.

In view of the lack of overall benefit of vitamin E on cardiovascular events in the WHS, we considered several factors. First, was the dose of vitamin E sufficient? Previous observational studies have reported significant benefits in women⁸ with a median intake of as little as 17 IU/d and 25.2 IU/d in men.⁹ The WHS used a far higher dose of 600 IU every other day. Second, the lack of

Figure 2. Cumulative Incidence Rates of Cardiovascular Disease



The composite cardiovascular end point (the first of any of the individual end points) is reported as well as the individual end points of myocardial infarction, stroke, and cardiovascular death.

Table 3. Relative Risks of Cardiovascular Disease and Cancer According to Baseline Characteristics, Women's Health Study

Group	Major Cardiovascular Event*				Total Invasive Cancer			
	No. of Events		RR (95% CI)	P Value	No. of Events		RR (95% CI)	P Value
	Vitamin E	Placebo			Vitamin E	Placebo		
Age, y†								
45-54	172	152	1.13 (0.91-1.41)	.26	645	673	0.96 (0.86-1.07)	.44
55-64	180	189	0.95 (0.77-1.16)	.61	518	509	1.02 (0.90-1.15)	.79
≥65	130	176	0.74 (0.59-0.93)	.009	274	246	1.12 (0.94-1.33)	.20
Smoking status								
Current	139	145	0.99 (0.78-1.25)	.91	238	228	1.07 (0.89-1.29)	.45
Past or never	341	370	0.92 (0.79-1.06)	.25	1199	1199	1.00 (0.92-1.08)	.95
Alcohol intake								
Never/rarely	252	263	0.96 (0.80-1.14)	.61	643	615	1.04 (0.93-1.16)	.52
At least 1/mo	230	254	0.90 (0.76-1.08)	.26	794	813	0.98 (0.89-1.09)	.75
Multivitamin use								
Yes	201	194	1.02 (0.84-1.25)	.81	577	531	1.07 (0.95-1.21)	.24
No	281	323	0.88 (0.75-1.03)	.10	860	897	0.97 (0.88-1.06)	.48
Body mass index‡								
<25	186	221	0.85 (0.70-1.03)	.09	709	728	0.98 (0.89-1.09)	.75
25-29	164	169	0.96 (0.77-1.19)	.69	429	403	1.05 (0.92-1.21)	.46
≥30	113	114	1.00 (0.77-1.30)	.99	269	272	0.99 (0.84-1.18)	.95
Physical activity, kcal/wk								
<1000	328	357	0.92 (0.79-1.07)	.28	949	967	0.98 (0.89-1.07)	.64
≥1000	147	153	0.95 (0.76-1.20)	.68	473	445	1.08 (0.94-1.22)	.27
Menopausal status and hormone therapy use								
Premenopausal	59	59	1.01 (0.71-1.45)	.94	294	300	1.00 (0.85-1.17)	.96
Uncertain	75	67	1.13 (0.81-1.57)	.46	173	211	0.82 (0.67-1.00)	.06
Postmenopausal, current hormone therapy use	145	154	0.95 (0.76-1.20)	.68	507	461	1.11 (0.98-1.26)	.11
Postmenopausal, never or past hormone therapy use	201	234	0.84 (0.70-1.02)	.08	460	453	1.00 (0.88-1.14)	.97
Hypertension§								
Yes	242	263	0.93 (0.78-1.11)	.41	408	424	0.97 (0.85-1.11)	.68
No	239	254	0.94 (0.78-1.12)	.46	1028	1003	1.02 (0.94-1.11)	.63
Hyperlipidemia								
Yes	189	221	0.86 (0.71-1.05)	.14	493	460	1.09 (0.96-1.23)	.20
No	293	296	0.98 (0.83-1.15)	.82	944	968	.97 (0.89-1.06)	.50
Diabetes¶								
Yes	62	58	1.05 (0.73-1.50)	.79	48	35	1.39 (0.90-2.15)	.14
No	420	458	0.92 (0.80-1.04)	.19	1388	1393	1.00 (0.93-1.07)	.93
Randomized to receive aspirin								
Yes	232	245	0.95 (0.79-1.13)	.55	716	722	0.99 (0.89-1.10)	.86
No	250	272	0.92 (0.77-1.09)	.32	721	706	1.02 (0.92-1.13)	.67
Parental history of MI before age 60 y								
Yes	73	62	1.16 (0.82-1.62)	.40				
No	352	391	0.90 (0.78-1.04)	.16				
10-Year risk of CHD, %#								
<5.0	179	148	1.19 (0.96-1.48)	.12				
5.0-9.9	98	95	1.10 (0.83-1.46)	.50				
≥10.0	53	68	0.81 (0.56-1.16)	.24				

Abbreviations: CHD, coronary heart disease; CI, confidence interval; MI, myocardial infarction; RR, relative risk.

*Defined as a composite end point comprising the first of any of these events: nonfatal MI, nonfatal stroke, or cardiovascular death.

†P value for interaction <.05 for major cardiovascular event. No other interactions are significant.

‡Calculated as weight in kilograms divided by the square of height in meters.

§Hypertension was defined as a self-reported systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or physician-diagnosed hypertension.

||Hyperlipidemia was defined as a self-reported total cholesterol ≥240 mg/dL (6.2 mmol/L) or physician-diagnosed high cholesterol.

¶Diabetes defined by self-report.

#Calculated using the Framingham risk score among 28 345 women who provided a blood sample at baseline.

effect was unlikely to be due to insufficient treatment duration, since this averaged 10 years in the WHS, representing the longest duration of any vitamin E trial. Third, we considered whether the source of vitamin E used, a natural source, influenced the findings. This was unlikely; 2 previous trials of secondary prevention that reported a benefit of vitamin E also used a natural source.^{21,27} On the other hand, a previous trial of secondary prevention, which included high-risk primary prevention patients, used natural-source vitamin E and found no benefits on CVD,²⁶ as did another secondary prevention trial testing natural-source vitamin E combined with other vitamins and minerals.³¹

Fourth, declining compliance over time in the WHS may have diluted the findings. However, in sensitivity analyses in which follow-up time was censored among women taking less than two thirds of their study pills, the finding for cardiovascular events was little changed. Additionally, accounting for outside use of vitamin E also did not make a difference.

Fifth, the hypothesis has been raised that antioxidants may adversely interact with simvastatin and niacin treatment.³¹ We did not systematically collect information on lipid-modifying therapy, but we did so for hyperlipidemia. Among women who remained normolipemic throughout the trial and who were unlikely to have taken lipid-modifying drugs, we observed no significant effect of vitamin E on major cardiovascular events, providing little support for an influence of lipid therapy on the WHS findings.

Finally, the possibility exists that γ -tocopherol, rather than vitamin E (or α -tocopherol), may be the relevant compound for CVD prevention.⁵³ γ -Tocopherol appears to have similar or greater efficacy than α -tocopherol at inhibiting lipid peroxidation under oxyradical systems and much more potency using nitration systems.⁵³

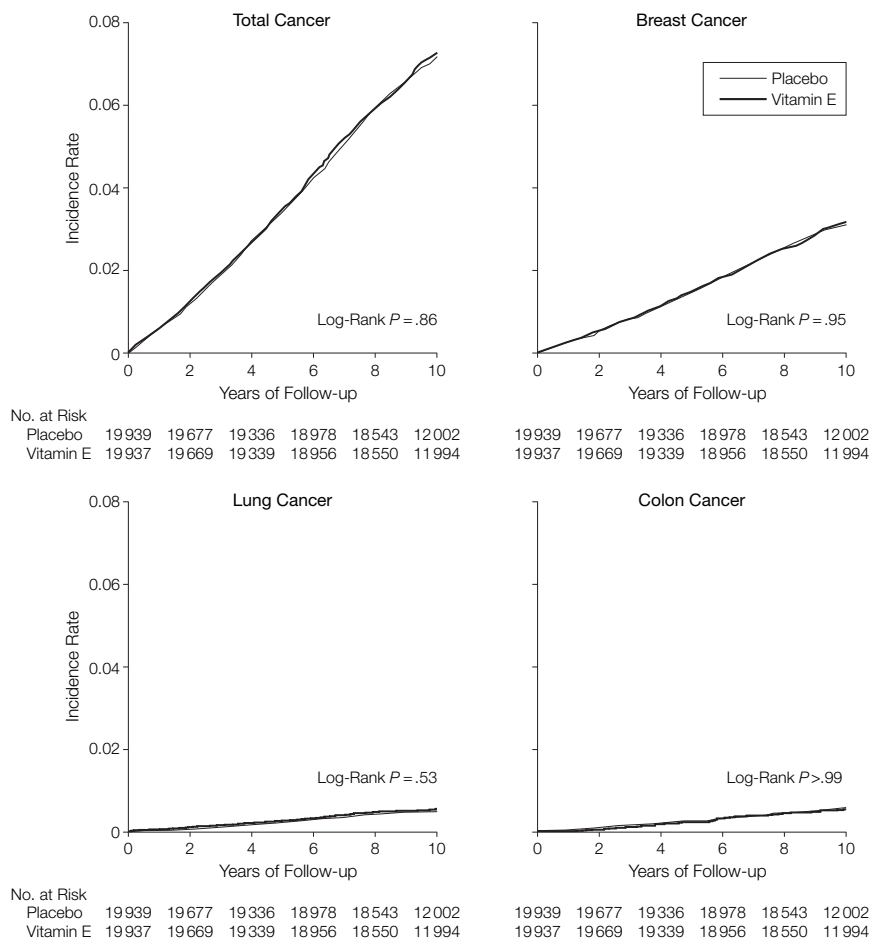
With regard to the cancer end points, there are few data from randomized trials of vitamin E.^{43,44,54} The ATBC trial,

conducted among men, observed a lower incidence of prostate cancer among men assigned to receive 50 mg/d of vitamin E, but no effect on lung or colon cancers.^{16,17} In the HOPE-TOO trial, there was no significant effect of 400 IU/d of vitamin E on cancer incidence or deaths, as in the WHS.³⁸ There was a lower incidence of lung cancer with vitamin E in HOPE-TOO, not reaching the predefined level of statistical significance. We did not observe any effect of vitamin E on lung cancer in the WHS. The SU.VI.MAX study reported significantly lower cancer rates among men, but not women, randomized to a combination of vitamins and minerals (including 30 mg/d of vitamin E).³⁵ Among poorly nourished persons randomized to a vitamin and min-

eral cocktail (including 30 mg/d of vitamin E), lower rates of stomach cancer occurred.¹⁴ This was not seen in the WHS, but the number of stomach cancers was small. Taken as a whole, the available data do not provide strong evidence for a role of vitamin E in cancer prevention, particularly in well-nourished persons.

A recent meta-analysis raised concern for increased mortality with vitamin E, especially in doses of 400 IU/d or greater.⁴² In the WHS, using 600 IU every other day, there was no significant effect of vitamin E on total mortality. There was no excess of cardiovascular (and, indeed, fewer such deaths) or cancer deaths, the main causes of mortality, in the vitamin E group. For the other main causes of

Figure 3. Cumulative Incidence Rates of Cancer



death, there were more deaths (but not statistically significant) from pulmonary disease, violent deaths, and suicides in the vitamin E group.

Vitamin E was well tolerated in the WHS with no significant differences in adverse effects between groups, except for epistaxis. This is likely to be a chance finding because there were no differences in other adverse effects from bleeding. Noteworthy was the observation of no increase in hemorrhagic strokes with vitamin E, in contrast to the ATBC trial with an excess of deaths from such strokes.¹⁶

CONCLUSIONS

In conclusion, the WHS does not support recommending vitamin E supplementation for CVD or cancer prevention among healthy women. This large trial supports current guidelines stating that use of antioxidant vitamins is not justified for CVD risk reduction.^{55,56} The WHS finding of a decreased cardiovascular death rate with vitamin E, as well as decreased major cardiovascular events among women aged at least 65 years, differs from the totality of evidence and should be explored further. The WHS findings should be viewed in the context of the available randomized evidence, as well as data that should be available over the next several years from ongoing trials, including the Physicians' Health Study, which will provide data on primary prevention in men.⁵⁷ At present, in the primary prevention of CVD and cancer, therapeutic lifestyle changes including a healthy diet and control of major risk factors remain important clinical and public health strategies.

Author Affiliations: Divisions of Preventive Medicine (Drs Lee, Cook, Gaziano, Ridker, Manson, and Buring and Mr Gordon), Cardiovascular Medicine (Drs Gaziano and Ridker), and Aging (Drs Gaziano and Buring), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass; Department of Epidemiology, Harvard School of Public Health, Boston (Drs Lee, Cook, Ridker, Manson, and Buring); Veterans Affairs Boston Healthcare System (Dr Gaziano); Department of Ambulatory Care and Prevention, Harvard Medical School, Boston (Dr Buring); and the Departments of Medicine and Epidemiology and Public Health, University of Miami School of Medicine, Miami, Fla, and Department of Biomedical Science, Center of Excellence, Florida Atlantic University, Boca Raton (Dr Hennekens).

Author Contributions: Dr Lee had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lee, Cook, Gaziano, Gordon, Ridker, Manson, Hennekens, Buring.

Acquisition of data: Lee, Gaziano, Gordon, Hennekens, Buring.

Analysis and interpretation of data: Lee, Cook, Gaziano, Ridker, Manson, Hennekens, Buring.

Drafting of the manuscript: Lee.

Critical revision of the manuscript for important intellectual content: Lee, Cook, Gaziano, Gordon, Ridker, Manson, Hennekens, Buring.

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