ONLINE FIRST

Multivitamins in the Prevention of Cancer in Men

The Physicians' Health Study II Randomized Controlled Trial

J. Michael Gaziano, MD, MPH
Howard D. Sesso, ScD, MPH
William G. Christen, ScD
Vadim Bubes, PhD
Joanne P. Smith, BA
Jean MacFadyen, BA
Miriam Schvartz, MD
JoAnn E. Manson, MD, DrPH
Robert J. Glynn, ScD
Julie E. Buring, ScD

Context Multivitamin preparations are the most common dietary supplement, taken by at least one-third of all US adults. Observational studies have not provided evidence regarding associations of multivitamin use with total and site-specific cancer incidence or mortality.

Objective To determine whether long-term multivitamin supplementation decreases the risk of total and site-specific cancer events among men.

Design, Setting, and Participants A large-scale, randomized, double-blind, placebo-controlled trial (Physicians' Health Study II) of 14 641 male US physicians initially aged 50 years or older (mean [SD] age, 64.3 [9.2] years), including 1312 men with a history of cancer at randomization, enrolled in a common multivitamin study that began in 1997 with treatment and follow-up through June 1, 2011.

Intervention Daily multivitamin or placebo.

Main Outcome Measures Total cancer (excluding nonmelanoma skin cancer), with prostate, colorectal, and other site-specific cancers among the secondary end points.

Results During a median (interquartile range) follow-up of 11.2 (10.7-13.3) years, there were 2669 men with confirmed cancer, including 1373 cases of prostate cancer and 210 cases of colorectal cancer. Compared with placebo, men taking a daily multivitamin had a statistically significant reduction in the incidence of total cancer (multivitamin and placebo groups, 17.0 and 18.3 events, respectively, per 1000 person-years; hazard ratio [HR], 0.92; 95% CI, 0.86-0.998; $P=.04$). There was no significant effect of a daily multivitamin on prostate cancer (multivitamin and placebo groups, 9.1 and 9.2 events, respectively, per 1000 person-years; HR, 0.98; 95% CI, 0.88-1.09; $P=.76$), colorectal cancer (multivitamin and placebo groups, 1.2 and 1.4 events, respectively, per 1000 person-years; HR, 0.89; 95% CI, 0.68-1.17; $P=.39$), or other site-specific cancers. There was no significant difference in the risk of cancer mortality (multivitamin and placebo groups, 4.9 and 5.6 events, respectively, per 1000 person-years; HR, 0.88; 95% CI, 0.77-1.01; $P=.07$). Daily multivitamin use was associated with a reduction in total cancer among 1312 men with a baseline history of cancer (HR, 0.73; 95% CI, 0.56-0.96; $P=.02$), but this did not differ significantly from that among 13 329 men initially without cancer (HR, 0.94; 95% CI, 0.87-1.02; $P=.15$; P for interaction $=.07$).

Conclusion In this large prevention trial of male physicians, daily multivitamin supplementation modestly but significantly reduced the risk of total cancer.

Trial Registration clinicaltrials.gov Identifier: NCT00270647

JAMA. 2012;308(18):doi:10.1001/jama.2012.14641 www.jama.com

MULTIVITAMINS ARE THE most common dietary supplement, regularly taken by at least one-third of US adults.[1,2] The traditional role of a daily multivitamin is to prevent nutritional deficiency. The combination of essential vitamins and minerals contained in multivitamins may mirror healthier dietary patterns such as fruit and vegetable intake, which have been modestly and inversely associated with cancer risk in some,[3] but not all,[4,5] epidemiologic studies. Observational studies of long-term multivitamin use and cancer end points have been inconsistent.[6-12] To date, large-scale randomized trials testing single or small numbers of higher-dose individual vitamins and minerals for cancer have generally found a lack of effect.[13-18]

According to the 2010 Dietary Guidelines for Americans, "For the general, healthy population, there is no evidence to support a recommendation for the use of multivitamin/mineral supplements in the primary prevention of

Author Affiliations: Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Drs Gaziano, Sesso, Christen, Bubes, Schvartz, Manson, Glynn, and Buring and Mss Smith and MacFadyen); VA Boston Healthcare System, Boston, Massachusetts (Dr Gaziano); and Departments of Epidemiology (Drs Sesso, Manson, and Buring) and Biostatistics (Dr Glynn), Harvard School of Public Health, Boston, Massachusetts. Dr Gaziano is also Contributing Editor, *JAMA*.
Corresponding Author: J. Michael Gaziano, MD, MPH, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont St, Boston, MA 02120 (jmgaziano@partners.org).

chronic disease."[19] A National Institutes of Health–sponsored State-of-the-Science Conference also concluded that the present evidence is insufficient to recommend either for or against the use of [multivitamins] to prevent chronic disease.[20] Despite the lack of definitive trial data regarding the benefits of multivitamins in the prevention of chronic disease, including cancer, many men and women take them for precisely this reason.[21]

Thus, definitive information on the potential benefits, risks, or lack thereof, related to taking a daily multivitamin may have substantial effects on personal and clinical decision making and policy making. The Physicians' Health Study II (PHS II) represents the only large-scale, randomized, double-blind, placebo-controlled trial testing the long-term effects of a common multivitamin in the prevention of chronic disease. We present the findings for multivitamin use on total and other common site-specific cancers; the effects of a multivitamin on cardiovascular events, eye disease, and cognitive decline are being published separately.

METHODS

Design

The PHS II was a randomized, double-blind, placebo-controlled, 2×2×2×2 factorial trial evaluating the balance of risks and benefits of a multivitamin (Centrum Silver or its placebo daily; Pfizer [formerly Wyeth, American Home Products, and Lederle]), vitamin E (400-IU synthetic α-tocopherol or its placebo on alternate days; BASF Corporation), vitamin C (500-mg synthetic ascorbic acid or its placebo daily; BASF Corporation), and beta carotene (50-mg Lurotin or placebo on alternate days; BASF Corporation) in the prevention of cancer, cardiovascular disease, eye disease, and cognitive function among 14 641 male physicians aged 50 years or older.[22] The beta carotene component was terminated on schedule in March 2003. Treatment and follow-up of the vitamin E and vitamin C components continued through August 31, 2007, their scheduled end, with findings of no overall association reported for cancer[18] and cardiovascular disease.[23]

The study design of PHS II has been previously described in detail.[18,22,23] The recruitment, enrollment, and randomization of men into PHS II occurred in 2 phases (FIGURE 1). Beginning in July 1997, during phase 1, we invited 18 763 living participants from PHS I, a randomized trial of low-dose aspirin and beta carotene among 22 071 male physicians,[14,24] to participate in PHS II. Men were ineligible if they reported a history of cirrhosis, active liver disease, were taking anticoagulants, or reported a serious illness that might preclude participation. Men also must have been willing to forego the use of multivitamins or individual supplements containing more than 100% of the recommended dietary allowance of vitamin E, vitamin C, beta carotene, or vitamin A. Those men with a history of cancer, as well as myocardial infarction or stroke, remained eligible to enroll into PHS II. We randomized 7641 willing participants (41%) from PHS I into PHS II and retained their original PHS I beta carotene treatment assignment.

Beginning in July 1999, during phase 2, invitational letters and baseline questionnaires were mailed to 254 597 US male physicians aged 50 years or older identified from a list provided by the American Medical Association. Through July 2001, 42 165 men responded, of whom 11 128 were willing and eligible. A 12-week placebo, run-in period excluded men who were nonadherent.[25] Of 11 128 physicians who entered the run-in phase, 7000 (63%) willing and eligible men took at least two-thirds of their pills and were randomized into PHS II, resulting in a total of 14 641 participants.

Men were randomized in blocks of 16, stratified by age (in 5-year age groups), prior cancer, prior cardiovascular disease, and, for the 7641 participants in PHS I, their original beta carotene treatment assignment. There were 1312 men (9.0%) with a history of cancer (excluding nonmelanoma skin cancer) before randomization into PHS II through either confirmed events among PHS I participants or self-reports among new PHS II participants. All participants provided written informed consent and the institutional review board at Brigham and Women's Hospital, Boston, Massachusetts, approved the PHS II research protocol.

Treatment, Follow-up, and Adherence

Participants were sent monthly calendar packs containing a multivitamin or placebo (taken daily) every 6 months for the first year, then annually thereafter. We also sent participants annual questionnaires asking about adherence, adverse events, new end points, and risk factors. A National Death Index search was performed for any participants with unknown vital status. Blinded treatment and follow-up continued through June 1, 2011, the scheduled end of the multivitamin component of PHS II, for a median (interquartile range) follow-up of 11.2 (10.7-13.3) years. Data analyses included validated end points that occurred during randomized treatment and were reported by August 2012. Morbidity and mortality follow-up in PHS II were extremely high, at 98.2% and 99.9%, respectively. Furthermore, morbidity and mortality follow-up as a percentage of person-time each exceeded 99.9%, with only 2991 and 79 person-years of morbidity and mortality follow-up lost out of 164 320 person-years of follow-up through June 1, 2011.

Confirmation of Cancer End Points

For the multivitamin component, the primary end points were total cancer (excluding nonmelanoma skin cancer) and major cardiovascular events. Prespecified secondary cancer end points included prostate, colorectal, and other site-specific cancers. Epithelial cell cancer, total and cancer mortality, and cancer-specific death were other end points examined in the analysis. Epithelial cell cancer was limited to car-

cinomas, which included all cancers except for lymphoma and leukemia. Because prostate cancer comprised more than half of all confirmed cancers in PHS II most likely due to increases in screening for prostate-specific antigen levels and detection of less aggressive cancer, we also evaluated the end point of total minus prostate cancer.

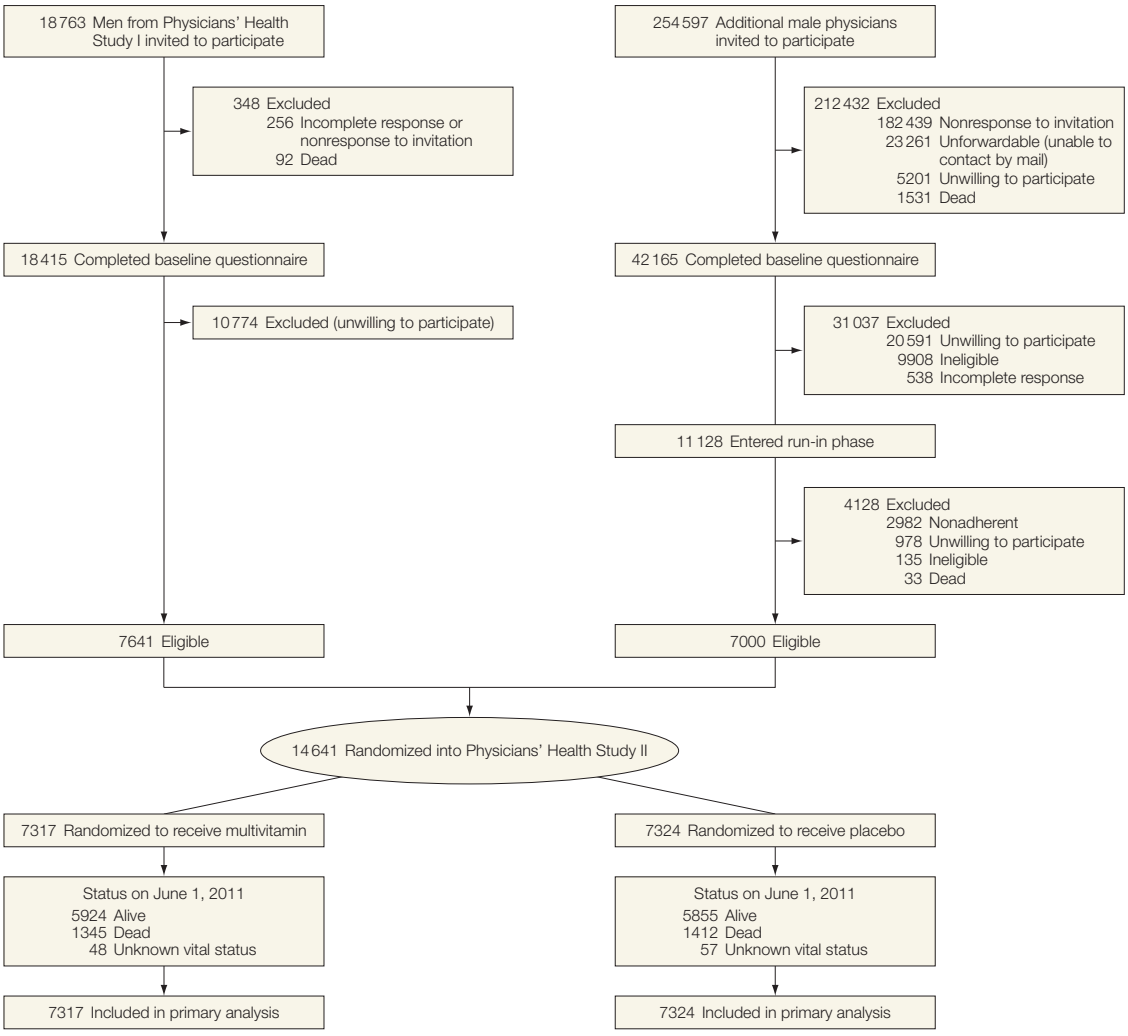
All cancer and mortality end points were assessed and validated by medical record review by the PHS II Endpoints Committee composed of physicians blinded to treatment assignment; 96.9% of confirmed total cancers were based on pathology or cytology reports. Cases of cancer were otherwise confirmed based on strong clinical and radiological or laboratory marker evidence. Total mortality was confirmed by the PHS II Endpoints Committee or by obtaining a death certificate. Only confirmed cancer and mortality end points are included herein.

Statistical Analyses

All primary analyses classified study participants based on the intention-to-treat principle, in which all 14 641 randomized participants were classified according to their randomized multivitamin treatment assignment and followed up until the occurrence of cancer, death, loss to follow-up, or the end of the multivitamin component of PHS II on June 1, 2011, whichever came first. We used SAS version 9.2 (SAS Institute Inc) and S-Plus (Insightful Corporation), with statistical significance set at $P < .05$ using 2-sided tests. The PHS II was estimated to have 80% power to detect a 10% reduction of the multivitamin on the primary end point of total cancer based on event rates among trial participants, with an average adherence of 75% during the entire treatment period and no interaction with other randomized components.

Initial analyses displayed distributions of baseline characteristics by multivitamin treatment assignment. Con-

Figure 1. Flow Diagram of Participants From Screening to Completion of the Multivitamin Component of the Physicians' Health Study II



sistent with previous PHS II trial analyses,[18,23] we used Cox proportional hazards regression models to estimate the hazard ratios (HRs) and 95% CIs comparing event rates in the multivitamin and placebo groups. For each prespecified end point, Cox proportional hazards regression models were stratified on the presence of cancer at randomization and adjusted for PHS II study design variables for age (in years), PHS cohort (original PHS I participant, new PHS II participant), and randomized vitamin E, vitamin C, and beta carotene assignments.

Only first cancer events after randomization were considered for analyses of total cancer, epithelial cell cancer, and total minus prostate cancer. For analyses of total cancer, all new cancers were included, regardless of whether the participant had a baseline history of cancer. For analyses of each site-specific cancer, we excluded participants if they had a baseline history of cancer of that site. Thus, these analyses included 13 980 men initially without prostate cancer, 14 519 initially without colorectal cancer, and 14 610 initially without lung cancer. Analyses of each site-specific cancer did not censor men on occurrence of cancer at another site. In addition, for analyses of site-specific cancer deaths, total cancer mortality, and total mortality, we included all 14 641 participants, and for total mortality, we additionally stratified on the presence of cardiovascular disease at randomization.

We tested the Cox proportional hazards regression assumptions by including an interaction term for treatment with the logarithm of time; this assumption was not violated for total cancer, prostate cancer, colorectal cancer, or other site-specific cancers (each $P > .05$). Cumulative incidence curves compared the overall effect of the multivitamin intervention on total and major site-specific cancers over time using a crude log-rank test. We then investigated whether multivitamin adherence affected our primary results through sensitivity analyses.

Additional exploratory analyses examined the effect of the multivitamin intervention on total cancer excluding the first 2 or 5 years of follow-up to explore a possible early vs late benefit associated with long-term multivitamin use. In addition, we conducted subgroup analyses stratified by major cancer risk factors, parental history of cancer, selected dietary factors, and other PHS II interventions. We also evaluated treatment effects within the prespecified subgroups of 1312 men

Table 1. Self-reported Baseline Characteristics According to Multivitamin Treatment Assignment in 14 641 Men From the PHS II[a]

Characteristics	Multivitamin	
	Active (n = 7317)	Placebo (n = 7324)
Age, y		
Mean (SD), y	64.2 (9.1)	64.3 (9.2)
50-59	2944 (40.2)	2947 (40.2)
60-69	2348 (32.1)	2348 (32.1)
≥70	2025 (27.7)	2029 (27.7)
BMI, mean (SD)	25.9 (3.4)	26.0 (3.4)
Cigarette smoking		
Never	4145 (56.7)	4107 (56.1)
Former	2908 (39.8)	2944 (40.2)
Current	255 (3.5)	269 (3.7)
Exercise ≥1 time/wk		
No	2699 (37.8)	2806 (39.3)
Yes	4444 (62.2)	4328 (60.7)
Alcohol consumption		
Rarely or never	1391 (19.2)	1339 (18.4)
≥1 drink/mo	5874 (80.9)	5942 (81.6)
Current aspirin use		
No	1625 (22.5)	1636 (22.7)
Yes	5602 (77.5)	5565 (77.3)
Parental history of cancer[b]		
No	2956 (47.1)	2881 (45.9)
Yes	3319 (52.9)	3402 (54.1)
Parental history of prostate cancer[b]		
No	5759 (89.4)	5746 (90.0)
Yes	682 (10.6)	642 (10.0)
Parental history of colorectal cancer[b]		
No	5559 (88.7)	5485 (87.8)
Yes	708 (11.3)	759 (12.2)
Self-reported history of cancer		
No	6669 (91.1)	6660 (90.9)
Yes	648 (8.9)	664 (9.1)
Self-reported history of prostate cancer		
No	6988 (95.5)	6992 (95.5)
Yes	329 (4.5)	332 (4.5)
Self-reported history of colorectal cancer		
No	7255 (99.2)	7264 (99.2)
Yes	62 (0.8)	60 (0.8)
Servings per d, median (IQR)[c]		
Fruit and vegetable intake	4.26 (2.95-5.75)	4.19 (2.94-5.77)
Whole grain intake	1.13 (0.49-2.00)	1.07 (0.49-1.99)
Red meat intake	0.63 (0.29-1.05)	0.57 (0.29-1.00)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; PHS, Physicians' Health Study.

[a] Data are No. (%) unless otherwise indicated. The numbers do not always sum to group totals due to missing information for some variables. $P > .05$ for all comparisons between active and placebo multivitamin groups.

[b] Excludes 2083, 1812, and 2130 men with missing information on parental history of cancer, prostate cancer, and colorectal cancer, respectively.

[c] Among 13 310, 13 280, and 13 268 men with available dietary data on fruit and vegetable, whole grain, and red meat intake, respectively.

with and 13 329 men without a baseline history of cancer. Effect modification was assessed by using interaction terms between subgroup indicators and multivitamin assignment.

RESULTS

A total of 14 641 male physicians were randomized with a mean (SD) age of 64.3 (9.2) years. All baseline characteristics had comparable distributions between the multivitamin and placebo groups (TABLE 1). Participants had a mean (SD) body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) of 26.0 (3.6), with a large proportion of former smokers (40.0%) and a very low proportion of current smokers (3.6%). Current aspirin use at baseline was high (77.4%) in this population of physicians, in part reflective of their previous participation and results of the PHS I randomized trial testing aspirin and cardiovascular disease.[24] There were 1312 men (9.0%) with a baseline history of cancer and 754 men (5.1%) with a baseline history of cardiovascular disease.

Participants in the PHS II were followed up for a mean of 11.2 years (median [interquartile range], 11.2 [10.7-13.3] years; maximum, 13.8 years), with follow-up totaling 164 320 person-years. For active multivitamin and its placebo, adherence at 4 years was 76.8% and 77.1%, respectively ($P=.71$); at 8 years, adherence was 72.3% and 70.7%, respectively ($P=.15$); and at the end of follow-up, adherence was 67.5% and 67.1%, respectively ($P=.70$). There were also no differences between the active (81.0%) and placebo (80.3%) groups comparing the percentage of men reporting avoidance of individual nontrial multivitamin use (<30 days per year) at the end of multivitamin follow-up ($P=.35$). During multivitamin treatment, we confirmed that 2669 men had cancer, including 1373 cases of prostate cancer and 210 cases of colorectal cancer, with some men experiencing multiple events. A total of 2757 men (18.8%) died during follow-up, including 859 (5.9%) due to cancer.

Multivitamin Use and Cancer

Overall in PHS II, the rates of total cancer, which included only first cancer events during follow-up, were 17.0 and 18.3 per 1000 person-years in the multivitamin and placebo groups, respectively. Men taking multivitamins had a modest reduction in total cancer incidence (HR, 0.92; 95% CI, 0.86-0.998; $P=.04$) (TABLE 2). The cumulative incidence curves are shown in FIGURE 2 (crude log-rank, $P=.05$).

Men taking a multivitamin had a similar modest reduction in total epithelial cell cancer (HR, 0.92; 95% CI, 0.85-0.997; $P=.04$). Approximately half of all incident cancers were prostate cancer, many of which were early stage. We found no effect of a multivitamin on prostate cancer (multivitamin and placebo groups, 9.1 and 9.2 events, respectively, per 1000 person-years; HR, 0.98; 95% CI, 0.88-1.09; $P=.76$), whereas a multivitamin significantly reduced the risk of total cancer excluding prostate cancer (HR, 0.88; 95% CI, 0.79-0.98; $P=.02$). There were no statistically significant reductions in individual site-specific cancers, including colorectal cancer (multivitamin and placebo groups, 1.2 and 1.4 events, respectively, per 1000 person-years; HR, 0.89; 95% CI, 0.68-1.17; $P=.39$), lung cancer (HR, 0.84; 95% CI, 0.61-1.14; $P=.26$), and bladder cancer (HR, 0.72; 95% CI, 0.48-1.07; $P=.10$), although power was limited with fewer events. There was no statistically significant difference in the risk of cancer mortality (multivitamin and placebo groups, 4.9 and 5.6 events, respectively, per 1000 person-years; HR, 0.88; 95% CI, 0.77-1.01; $P=.07$). Total mortality was not significantly reduced (HR, 0.94; 95% CI, 0.88-1.02; $P=.13$).

In secondary analyses, the exclusion of the first 2 or 5 years of follow-up did not appreciably alter the results for total cancer. We also considered the effect of adherence during follow-up on our results. In analyses accounting for adherence, we did not detect any material impact on the effect of the multivitamin on risk of total cancer.

Modifiers of the Effect Between Multivitamin Use and Cancer

In subgroup analyses, we examined whether selected baseline characteristics—including clinical, lifestyle, familial, and dietary factors—plus the other 3 randomized interventions from PHS II modified the effect of a daily multivitamin on total cancer (eTable 1, available at http://www.jama.com). For age, the effect of a daily multivitamin on total cancer among men aged 70 years or older revealed an HR of 0.82 (95% CI, 0.72-0.93), but the test for heterogeneity across age groups with men aged 50 to 59 years (HR, 0.96) and 60 to 69 years (HR, 1.01) did not reach significance (P for interaction = .06).

There was significant effect modification by parental history of cancer (P for interaction = .02); men with no parental history of cancer had a beneficial effect of a daily multivitamin on total cancer (HR, 0.86, 95% CI, 0.76-0.98; $P=.02$), although men with a parental history of cancer did not (HR, 1.05; 95% CI, 0.94-1.17; $P=.37$). No significant heterogeneity by other clinical, lifestyle, and selected dietary factors, or by the previously terminated randomized vitamin C, vitamin E, and beta carotene interventions of PHS II was found (all P for interaction > .05).

Based on prespecified hypotheses, daily multivitamin use was associated with a reduction in total cancer among the 1312 men with a baseline history of cancer (HR, 0.73; 95% CI, 0.56-0.96; $P=.02$), but this result did not significantly differ from that observed among 13 329 men initially without cancer (HR, 0.94; 95% CI, 0.87-1.02; $P=.15$; P for interaction = .07) (TABLE 3). The overall rates of total cancer were 18.4 and 17.6 per 1000 person-years, respectively, in men with or without baseline cancer. Based on the cumulative incidence curve (FIGURE 3), a reduction in total cancer among men with a history of cancer at baseline emerged early during multivitamin treatment and follow-up (crude log-rank, $P=.02$). Furthermore, the effect of a daily multivitamin on total epithelial cancer was stronger among men with a history of cancer at baseline (HR,

0.66; 95% CI, 0.50-0.88; *P*=.004) than men with no history of cancer (HR, 0.95; 95% CI, 0.87-1.03; *P*=.21; *P* for interaction=.02).

Among 1312 men with a baseline history of cancer, information on the number of years since their last cancer diagnosis was reported in 1279 men (97.5%), with 620 men (77 cases of total cancer) last diagnosed less than 5 years before PHS II baseline and 659 men (138 cases of total cancer) last diagnosed 5 years or more before PHS II baseline. A daily multivitamin did not have differential effects among men with more recent diagnoses less than 5 years ago (HR, 0.80; 95% CI, 0.50-1.26; *P*=.33) vs men with more distant diagnoses of 5 years or more before baseline (HR, 0.70; 95% CI, 0.50-0.98; *P*=.04; *P* for interaction=.70). Furthermore, no effect modification by the most recent type of cancer was found for prostate cancer (114 men; HR, 0.66; 95% CI, 0.34-1.27; *P*=.21) vs non–prostate cancer or unknown (1165 men; HR, 0.78; 95% CI, 0.58-1.05; *P*=.10) diagnosed before PHS II baseline (*P* for interaction=.62).

Adverse Effects

In addition to the main primary and secondary end points, we assessed a number of potential adverse effects of daily multivitamin use and found no significant effects on gastrointestinal tract symptoms (peptic ulcer, constipation, diarrhea, gastritis, and nausea), fatigue, drowsiness, skin discoloration, and migraine (all $P>.05$). Those men taking the multivitamin were more likely to have rashes (2125 men in multivitamin group vs 2002 men in placebo group; HR, 1.07; 95% CI, 1.01-1.14; *P*=.03). In addition, there were inconsistent findings for daily multivitamin use on minor bleeding, with a reduction in hematuria (1194 men in multivitamin group and 1292 men in placebo group; HR, 0.91; 95% CI, 0.84-0.98; *P*=.02), an increase in epistaxis (1579 men in multivitamin group and 1451 men in placebo group; HR, 1.10; 95% CI, 1.02-1.18; *P*=.01), and no effect on easy bruising and/or other bleeding (2786 men in multivitamin group and 2806 men in placebo group; HR, 0.99; 95% CI, 0.94-1.05; *P*=.77).

COMMENT

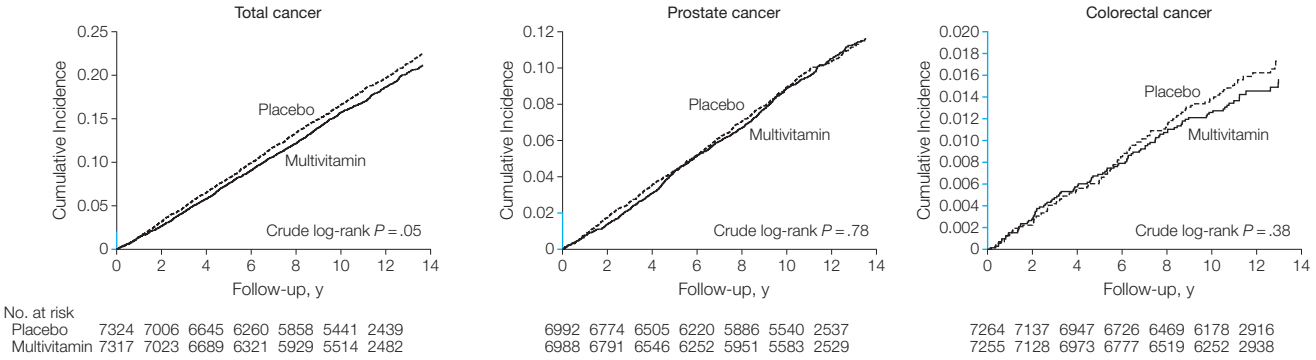
In this large-scale, randomized, placebo-controlled trial among middle-aged and older men, long-term daily multivita-

Table 2. Association Between Randomized Multivitamin Assignment and the Risk of Total Cancer, Site-Specific Cancer, and Mortality in the PHS II[a]

		Multivitamin					
		Active		Placebo			
Outcome	Total Men in Analysis[b]	No. of Men	No. of Events	No. of Men	No. of Events	Adjusted HR (95% CI)[c]	*P* Value
Total cancer	14 641	7317	1290	7324	1379	0.92 (0.86-0.998)	.04
Total epithelial cell cancer[d]	14 641	7317	1158	7324	1244	0.92 (0.85-0.997)	.04
Total cancer minus prostate cancer[e]	14 641	7317	641	7324	715	0.88 (0.79-0.98)	.02
Prostate cancer	13 980	6988	683	6992	690	0.98 (0.88-1.09)	.76
Prostate cancer death	14 641	7317	70	7324	78	0.91 (0.66-1.26)	.58
Colorectal cancer	14 519	7255	99	7264	111	0.89 (0.68-1.17)	.39
Colorectal cancer death	14 641	7317	37	7324	39	0.95 (0.60-1.48)	.81
Lung cancer	14 610	7300	74	7310	88	0.84 (0.61.1.14)	.26
Lung cancer death	14 641	7317	65	7324	73	0.89 (0.64-1.25)	.50
Bladder cancer	14 570	7276	41	7294	57	0.72 (0.48-1.07)	.10
Bladder cancer death	14 641	7317	15	7324	18	0.84 (0.42-1.67)	.62
Pancreatic cancer	14 638	7315	43	7323	36	1.19 (0.76-1.85)	.45
Pancreatic cancer death	14 641	7317	39	7324	39	0.99 (0.64-1.55)	.97
Lymphoma	14 595	7296	100	7299	88	1.13 (0.85-1.51)	.40
Lymphoma death	14 641	7317	38	7324	33	1.15 (0.72-1.84)	.55
Leukemia	14 612	7296	50	7316	60	0.83 (0.57-1.21)	.33
Leukemia death	14 641	7317	22	7324	37	0.59 (0.35-1.01)	.053
Melanoma	14 483	7238	108	7245	96	1.12 (0.85-1.47)	.42
Melanoma death	14 641	7317	9	7324	10	0.91 (0.37-2.25)	.84
Total mortality[f]	14 641	7317	1345	7324	1412	0.94 (0.88-1.02)	.13
Cancer mortality	14 641	7317	403	7324	456	0.88 (0.77-1.01)	.07

Abbreviations: HR, hazard ratio; PHS, Physicians' Health Study.
[a] Mean follow-up of 11.2 years for all 14 641 men through June 1, 2011.
[b] For total cancer, site-specific mortality, total mortality, and cancer mortality, analyses included all 14 641 participants. For the incidence of site-specific cancers, analyses were restricted to men without that site-specific cancer at baseline.
[c] Adjusted for age, PHS cohort (original PHS I participant, new PHS II participant), and randomized treatment assignment (beta carotene, vitamin E, and vitamin C), and stratified on baseline cancer.
[d] Epithelial cell cancer was limited to carcinomas, which included all cancers except for lymphoma and leukemia.
[e] Includes all cancers other than prostate cancer.
[f] Additionally stratified on baseline cardiovascular disease.

Figure 2. Cumulative Incidence Rates of Total Cancer, Prostate Cancer, and Colorectal Cancer by Randomized Multivitamin Assignment in the Physicians' Health Study II



No. at risk

Placebo	7324	7006	6645	6260	5858	5441	2439
Multivitamin	7317	7023	6689	6321	5929	5514	2482

6992	6774	6505	6220	5886	5540	2537	
6988	6791	6546	6252	5951	5583	2529	

7264	7137	6947	6726	6469	6178	2916	
7255	7128	6973	6777	6519	6252	2938	

Y-axis range shown in blue indicates cumulative incidence from 0 to 0.02. The reduction in the numbers at risk from 10 to 12 years reflects the 2 phases of Physicians' Health Study II recruitment; men in the Physicians' Health Study I initially enrolled in phase 1 starting in 1997 were followed up longer on average (mean, 13 years) than the men recruited in phase 2 starting in 1999 (mean, 10 years).

min use had a modest but statistically significant reduction in the primary end point of total cancer after more than a decade of treatment and follow-up. We found no evidence that this effect was driven by any individual site-specific cancers. In prespecified analyses, we found that the effect of a daily multivitamin in reducing cancer appeared stronger among men for secondary vs primary prevention of cancer in PHS II, although this difference was not significant for total cancer but was for total epithelial cell cancer. Approximately half of those men with baseline cancer in PHS II were last diagnosed 5 years or more ago, and we found no suggestion that more remote vs proximate diagnoses affected cancer risk.

Total cancer rates in our trial were likely influenced by the increased surveillance for prostate-specific antigen and subsequent diagnoses of prostate cancer during PHS II follow-up starting in the late 1990s.[26] Approximately half of all confirmed cancers in PHS II were prostate cancer, of which the majority were earlier stage, lower-grade prostate cancer with high survival rates. The significant reduction in total cancer minus prostate cancer suggests that daily multivitamin use may have a greater benefit on more clinically relevant cancer diagnoses.

In the Cancer Prevention Study II, which followed up more than 1 million US adults beginning in the early 1980s, multivitamin use was not associated with cancer mortality.[27] The Women's Health Initiative found that multivitamins had little or no relationship with the risk of breast, colon, or other cancers in more than 160 000 women followed up for a mean of 8 years.[9] Among 35 000 Swedish women, however, multivitamin use was associated with a 19% increased risk of breast cancer (95% CI, 1.04-1.37) during a 10-year period compared with women not using these vitamins.[8] How these results for breast and other cancers in women extend to our trial of men in PHS II remains unclear.

Other observational studies suggest protective relationships of multivitamins with various cancers,[28,29] no association,[30,31] and possible harm.[32] Studies with an association between multivitamins and specific cancers are typically of long duration, allowing for either a long latent period[11,12,33,34] or increased statistical power. For example, increasing duration of multivitamin use was strongly associated with a reduced risk of colon cancer in 88 756 participants in the Nurses' Health Study followed up for 15 years.[12] A long latency period was also noted in the Cancer Prevention Study II, with an inverse association between multivitamin use with both colon cancer incidence[34] and mortality[11] after more than a decade of multivitamin use; however, these findings were not supported in PHS II.

Only a few large-scale, long-term chemoprevention trials have considered combinations of selected vitamins or minerals, although not with the typical diversity of common multivitamin formulations with recommended dietary allowance levels of vitamins and minerals such as that tested in PHS II. The Linxian Chinese Cancer Prevention Trial,[35] targeting 29 584 adults with low baseline nutrient status, tested a combination of beta carotene, vitamin E, and selenium for 6 years and found significant reductions of 9% in total mortality, 13% in cancer mortality, and 21% in gastric cancer mortality. After 10 years of posttrial follow-up, the beneficial effects on total and cancer mortality remained.[36] The Heart Protection Study[37] tested higher doses of those 3 nutrients among individuals with adequate dietary intake and found no reductions in total or site-specific cancers. A meta-analysis[38] of 8 large randomized trials of folic acid and vitamin B supplementation found no effect on total cancer. In addition, the Supplementation en Vitamines et Mineraux Antioxydants (SU.VI.MAX) pri-

mary prevention trial[39] of 13 017 participants randomized to a low-dose combination of vitamin C, vitamin E, beta carotene, selenium, and zinc found no overall effect on total cancer, but there was a significant interaction with sex with a reduction in risk of total cancer in women only (relative risk, 0.69; 95% CI, 0.53-0.91).

Although numerous individual vitamins and minerals contained in the PHS II multivitamin study have postulated chemopreventive roles, it is difficult to definitively identify any single mechanism of effect through which individual or multiple components of our tested multivitamin may have reduced cancer risk. The reduction in total cancer risk in PHS II argues that the broader combination of low-dose vitamins and minerals contained in the PHS II multivitamin (eTable 2), rather than an emphasis on previously tested high-dose vitamins and mineral trials, may be paramount for cancer prevention. For example, in the Women's Health Initiative calcium and vitamin D trial, women not taking personal supplements randomized to vitamin D (400 IU/d) and calcium (1000 mg/d) had a reduction in total cancer similar to that observed in PHS II.[40] The role of a food-focused cancer prevention strategy such as targeted fruit and vegetable intake remains promising[41] but unproven given the inconsistent epidemiologic evidence[42] and lack of definitive trial data.

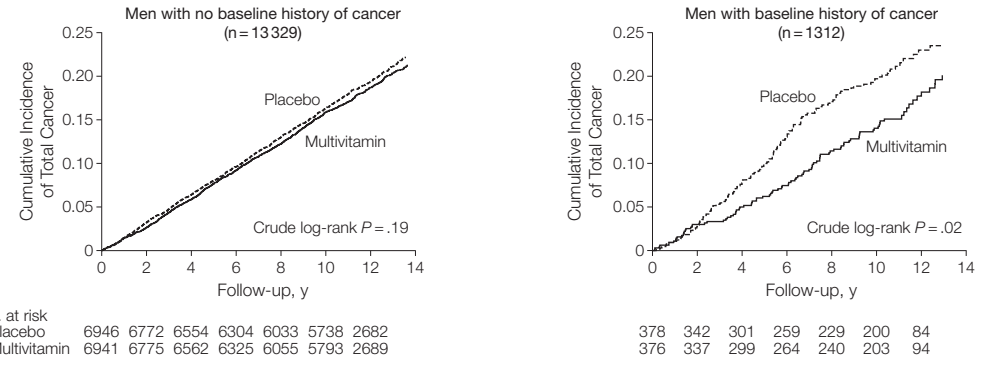
One explanation for results of some previous trials of supplements has been that the trial populations are already well-nourished.[43] This may also be particularly true in PHS II, composed of male physicians, although population-based clinical trials also recruit healthier

Table 3. Association Between Randomized Multivitamin Assignment and the Risk of Total Cancer, Site-Specific Cancer, and Mortality Among Men Without and With Baseline Cancer in the PHS II[a,b]

	No Baseline History of Cancer							Baseline History of Cancer							
		Active		Placebo					Active		Placebo				
Outcome	Total Men in Analysis[c]	No. of Men	No. of Events	No. of Men	No. of Events	Adjusted HR (95% CI)[d]	*P* Value	Total Men in Analysis[c]	No. of Men	No. of Events	No. of Men	No. of Events	Adjusted HR (95% CI)[d]	*P* Value	*P* for Interaction
Total cancer	13 329	6669	1195	6660	1253	0.94 (0.87-1.02)	.15	1312	648	95	664	126	0.73 (0.56-0.96)	.02	.07
Total epithelial cell cancer[e]	13 329	6669	1077	6660	1125	0.95 (0.87-1.03)	.21	1312	648	81	664	119	0.66 (0.50-0.88)	.004	.02
Total cancer minus prostate cancer[f]	13 329	6669	561	6660	615	0.90 (0.80-1.01)	.07	1312	648	80	664	100	0.78 (0.58-1.04)	.09	.38
Prostate cancer	13 329	6669	667	6660	662	1.00 (0.90-1.11)	.98	651	319	16	332	28	0.56 (0.30-1.04)	.07	.07
Colorectal cancer	13 329	6669	88	6660	95	0.92 (0.69-1.23)	.58	1190	586	11	604	16	0.70 (0.32-1.52)	.37	.52
Lung cancer	13 329	6669	67	6660	73	0.91 (0.65.1.27)	.57	1281	631	7	650	15	0.48 (0.20-1.19)	.11	.19
Melanoma	13 329	6669	100	6660	89	1.12 (0.84-1.49)	.44	1154	569	8	585	7	1.16 (0.42-3.21)	.78	.97
Total mortality[g]	13 329	6669	1092	6660	1134	0.94 (0.87-1.03)	.17	1312	648	253	664	278	0.93 (0.78-1.10)	.40	.98
Cancer mortality	13 329	6669	289	6660	313	0.91 (0.78-1.07)	.26	1312	648	114	664	143	0.81 (0.63-1.04)	.10	.51

Abbreviations: HR, hazard ratio; PHS, Physicians' Health Study.
[a] Mean follow-up of 11.4 years for 13 329 men without baseline cancer through June 1, 2011.
[b] Mean follow-up of 9.8 years for 1312 men with baseline cancer through June 1, 2011.
[c] For total cancer, site-specific mortality, total mortality, and cancer mortality, analyses included all 14 641 participants. For the incidence of site-specific cancers, analyses were restricted to men without that site-specific cancer at baseline.
[d] Adjusted for age, PHS cohort (original PHS I participant, new PHS participant), and randomized treatment assignment (beta carotene, vitamin E, and vitamin C).
[e] Epithelial cell cancer was limited to carcinomas, which included all cancers except for lymphoma and leukemia.
[f] Includes all cancers other than prostate cancer.
[g] Additionally stratified on baseline cardiovascular disease.

Figure 3. Cumulative Incidence Rates of Total Cancer Among 13 329 Men With No Baseline History of Cancer and 1312 Men With a Baseline History of Cancer in the Physicians' Health Study II



individuals.[44-46] Participants in PHS II represent on average a well-nourished population for whom the effect of a daily multivitamin on cancer outcomes may be less applicable to those of poorer nutritional status. Additional studies need to evaluate how the range of baseline nutritional status modifies the effect of a daily multivitamin on cancer.

Strengths of PHS II include the long duration of treatment and follow-up and consistently good adherence to taking a daily multivitamin. The inclusion of physician participants provided high-quality reporting of health information. We are unaware of other long-term clinical trials testing a common multivitamin in the prevention of cancer and chronic disease. We selected a commonly used multivitamin formulation, Centrum Silver, at the time we initiated PHS II in 1997 to increase the potential generalizability of our findings.

Several limitations should also be considered. The formulations of the multivitamin preparation used in our trial and other multivitamin preparations have changed over time, reflecting evolving perspectives and priorities in nutrition. For example, since PHS II was initiated, in the commercial form of this multivitamin, vitamin D increased from 400 to 500 IU, vitamin A (% as beta carotene) decreased from 5000 IU (50%) to 2500 IU (40%), and 250 µg of lutein and 300 µg of lycopene were added. However, the formulation of the multivitamin used throughout PHS II (eTable 2) remained the same, resulting in a consistent intervention in our trial. An improved understanding of the effects of single vs combined nutrients—at usual levels of dietary intake—on intermediate mechanisms leading to cancer is critically needed.

It is unclear how easily our trial results for cancer outcomes may be replicated given the high prevalence of multivitamin use in adults and difficulty of conducting a long-term, blinded clinical trial. This is especially important given the potential challenge of generalizing to younger men and women and racial and ethnic groups not included in PHS II. It remains possible that more effective chemoprevention via multivitamins may occur with longer treatment or follow-up than conducted to date in PHS II, given the apparent latent results on colon cancer and mortality in some cohorts.[11,12,34] This is particularly salient in our analyses of site-specific cancers, for which continued PHS II follow-up would increase statistical power and detect any emergent latent effects. Adherence remains of concern as in any long-term trial, but adherence with the multivitamin component of PHS II remained consistently good during a mean follow-up of 11 years. Drop-in rates of outside multivitamin use did increase during follow-up, paralleling general population trends of increased vitamin supplement use in the United States,[2,47] but there were no differences in rates in active vs placebo multivitamin groups and analyses accounting for adherence did not greatly affect the HRs of total and site-specific cancers.

As in any trial, the role of chance must be considered. This is particularly important when multiple hypotheses are being addressed. In PHS II, we had only 2 primary outcomes—total cancer and major cardiovascular events. However, there are additional secondary outcomes that include eye disease, cognitive function, and a number of prespecified secondary analyses. Caution must be applied in the interpretation of these analyses.

In this large-scale randomized trial of 14 641 middle-aged and older men, a daily multivitamin supplement significantly but modestly reduced the risk of total cancer during a mean of 11 years of treatment and follow-up. Although the main reason to take multivitamins is to prevent nutritional deficiency, these data provide support for the potential use of multivitamin supplements in the prevention of cancer in middle-aged and older men.

Published Online: October 17, 2012. doi:10.1001/jama.2012.14641

Author Contributions: Drs Gaziano and Sesso had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. Drs Gaziano and Sesso contributed equally to this manuscript.

Study concept and design: Gaziano, Sesso, Christen, Manson, Glynn, Buring.

Acquisition of data: Gaziano, Sesso, Christen, Bubes, Smith, MacFadyen, Schvartz, Manson, Glynn, Buring.

Analysis and interpretation of data: Gaziano, Sesso, Christen, Bubes, Manson, Glynn, Buring.

Drafting of the manuscript: Gaziano, Sesso.

Critical revision of the manuscript for important intellectual content: Gaziano, Sesso, Christen, Bubes, Smith, MacFadyen, Schvartz, Manson, Glynn, Buring.

Statistical analysis: Gaziano, Sesso, Bubes, Glynn.

Obtained funding: Gaziano, Sesso, Buring.

Administrative, technical, or material support: Gaziano, Sesso, Bubes, Smith, MacFadyen, Schvartz, Manson, Glynn.

Study supervision: Gaziano, Sesso, Bubes, Smith, MacFadyen, Glynn.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Gaziano reported receiving investigator-initiated research funding from the National Institutes of Health (NIH), the Veterans Administration, and the BASF Corporation; assistance with study agents and packaging from BASF Corporation and Pfizer (formerly Wyeth, American Home Products, and Lederle); and assistance with study packaging provided by DSM Nutritional Products Inc (formerly Roche Vitamins). Dr Sesso reported receiving investigator-initiated research funding from the NIH, the Tomato Products Wellness Council, and Cambridge Theranostics Ltd. Dr Christen reported receiving research funding support from the NIH, Harvard University (Clinical Nutrition Research Center), and DSM Nutritional Products Inc (formerly Roche Vitamins). Dr Manson reported receiving investigator-initiated research funding from the NIH, and assistance with study pills and packaging from BASF and Cognis Corporations for the Women's Antioxidant and Folic Acid Cardiovascular Study and from Pronova BioPharma and Pharmavite for the *VIT*amin D and Omeg*A*-3 Tria*L*, and funding from the nonprofit Aurora Foundation. Dr Glynn reported receiving investigator-initiated research funding from the NIH, Bristol-Meyers Squibb, AstraZeneca, and Novartis; and signed a consulting agreement with Merck to give an invited talk. Dr Buring reported receiving investigator-initiated research funding from the NIH, and assistance with study pills and packaging from Natural Source Vitamin E Association and Bayer Healthcare for the Women's Health Study. No other authors reported any financial disclosures.

Funding/Support: This work was supported by grants CA 097193, CA 34944, CA 40360, HL 26490, and HL 34595 from the NIH and an investigator-initiated grant from BASF Corporation. Study agents and packaging were provided by BASF Corporation and Pfizer (formerly Wyeth, American Home Products, and Lederle) and study packaging was provided by DSM Nutritional Products Inc (formerly Roche Vitamins).

Role of the Sponsors: The NIH, BASF Corporation, Pfizer, and DSM Nutritional Products Inc had no role in the study design and conduct of the study; in the collection, management, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Data and Safety Monitoring Board: Voting members over the course of the PHS II trial included Lawrence Cohen, Rory Collins, Theodore Colton, I. Craig Henderson, Andrea LaCroix, Ross Prentice, and Nanette Wenger (chair); ex-officio members included Mary Francis Cotch, Jeffrey Cutler, Frederick Ferris, Jerome

Fleg, Peter Greenwald, Natalie Kurinij, Howard Parnes, Marjorie Perloff, Eleanor Schron, and Alan Zonderman.
Disclaimer: Dr Gaziano, a contributing editor for *JAMA*, was not involved in the editorial review of or decision to publish this article.
Online-Only Material: eTables 1 and 2 are available at http://www.jama.com.
Additional Contributions: We thank the 14 641 physician participants for their long-standing dedication and conscientious collaboration. We also thank Charles Hennekens, MD, DrPH (Florida Atlantic University), for the long-term contributions to the PHS, and the exemplary contributions of the staff of the PHS at Brigham and Women's Hospital, under the leadership of Joanne Smith: Charlene Belanger, Eileen Bowes, Kenneth Breen, Mary Breen, Mary G. Breen, Jose Carrion, Shamikhah Curry, Colleen Evans, Ivan Fitchorov, Natalya Gomelskaya, Cindy Guo, Delia Guo, Jasmah Hanna, Beth Holman, Andrea Hrbek, Gregory Kotler, Tony Laurinaitis, Hannah Mandel, Chandra McCarthy, Geneva McNair, Annie Murray, Leslie Power, Philomena Quinn, Harriet Samuelson, Fred Schwerin, Andromache Sheehey, Sara Tower, Martin Van Denburgh, Diana Walrond, Phyllis Johnson Wojciechowski, and Angela Zhang. In addition, we thank the PHS Endpoints Committee, including Samuel Goldhaber, Carlos Kase, Meir Stampfer, and James Taylor, over the course of PHS II. Each named individual was compensated for his or her contribution as part of the grant support.

REFERENCES

1. Bailey RL, Gahche JJ, Lentino CV, et al. Dietary supplement use in the United States, 2003-2006. *J Nutr*. 2011; 141(2):261-266.
2. Gahche J, Bailey R, Burt V, et al. Dietary supplement use among U.S. adults has increased since NHANES III (1988-1994). *NCHS Data Brief*. 2011;(61):1-8.
3. Boffetta P, Couto E, Wichmann J, et al. Fruit and vegetable intake and overall cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst*. 2010;102(8):529-537.
4. Löf M, Sandin S, Lagiou P, Trichopoulos D, Adami HO, Weiderpass E. Fruit and vegetable intake and risk of cancer in the Swedish women's lifestyle and health cohort. *Cancer Causes Control*. 2011;22(2):283-289.
5. Hung HC, Joshipura KJ, Jiang R, et al. Fruit and vegetable intake and risk of major chronic disease. *J Natl Cancer Inst*. 2004;96(21):1577-1584.
6. Li K, Kaaks R, Linseisen J, Rohrmann S. Vitamin/mineral supplementation and cancer, cardiovascular, and all-cause mortality in a German prospective cohort (EPIC-Heidelberg). *Eur J Nutr*. 2012;51(4):407-413.
7. Park SY, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Multivitamin use and the risk of mortality and cancer incidence: the multiethnic cohort study. *Am J Epidemiol*. 2011;173(8):906-914.
8. Larsson SC, Akesson A, Bergkvist L, Wolk A. Multivitamin use and breast cancer incidence in a prospective cohort of Swedish women. *Am J Clin Nutr*. 2010; 91(5):1268-1272.
9. Neuhouser ML, Wassertheil-Smoller S, Thomson C, et al. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. *Arch Intern Med*. 2009;169(3):294-304.
10. Stevens VL, McCullough ML, Diver WR, et al. Use of multivitamins and prostate cancer mortality in a large cohort of US men. *Cancer Causes Control*. 2005; 16(6):643-650.
11. Jacobs EJ, Connell CJ, Patel AV, et al. Multivitamin use and colon cancer mortality in the Cancer Prevention Study II cohort (United States). *Cancer Causes Control*. 2001;12(10):927-934.
12. Giovannucci E, Stampfer MJ, Colditz GA, et al. Multivitamin use, folate, and colon cancer in women in the Nurses' Health Study. *Ann Intern Med*. 1998;129 (7):517-524.
13. 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. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. *N Engl J Med*. 1994; 330(15):1029-1035.
14. Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996;334(18):1145-1149.
15. Lee IM, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA*. 2005;294(1):56-65.
16. Lonn E, Bosch J, Yusuf S, et al; HOPE and HOPE-TOO Trial Investigators. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: a randomized controlled trial. *JAMA*. 2005;293(11):1338-1347.
17. Lin J, Cook NR, Albert C, et al. Vitamins C and E and beta carotene supplementation and cancer risk: a randomized controlled trial. *J Natl Cancer Inst*. 2009; 101(1):14-23.
18. Gaziano JM, Glynn RJ, Christen WG, et al. Vitamins E and C in the prevention of prostate and total cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2009;301(1):52-62.
19. US Department of Agriculture and US Department of Health and Human Services. Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans, 2010. http://www.cnpp.usda.gov/DGAs2010-DGACReport.htm. Accessed October 8, 2012.
20. NIH State-of-the-Science Panel. National Institutes of Health State-of-the-science conference statement: multivitamin/mineral supplements and chronic disease prevention. *Ann Intern Med*. 2006;145(5): 364-371.
21. Ervin RB, Wright JD, Kennedy-Stephenson J. Use of dietary supplements in the United States, 1988-94. *Vital Health Stat 11*. 1999;(244):i-iii, 1-14.
22. Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II--a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. *Ann Epidemiol*. 2000;10(2):125-134.
23. Sesso HD, Buring JE, Christen WG, et al. Vitamins E and C in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA*. 2008;300(18):2123-2133.
24. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med*. 1989;321(3):129-135.
25. Lang JM, Buring JE, Rosner B, Cook N, Hennekens CH. Estimating the effect of the run-in on the power of the Physicians' Health Study. *Stat Med*. 1991;10 (10):1585-1593.
26. Neppl-Huber C, Zappa M, Coebergh JW, et al; EUNICE Survival Working Group. Changes in incidence, survival and mortality of prostate cancer in Europe and the United States in the PSA era: additional diagnoses and avoided deaths. *Ann Oncol*. 2012; 23(5):1325-1334.
27. Watkins ML, Erickson JD, Thun MJ, Mulinare J, Heath CW Jr. Multivitamin use and mortality in a large prospective study. *Am J Epidemiol*. 2000;152(2):149-162.
28. Asgari MM, Chren MM, Warton EM, Friedman GD, White E. Supplement use and risk of cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 2011; 65(6):1145-1151.
29. Kwan ML, Greenlee H, Lee VS, et al. Multivitamin use and breast cancer outcomes in women with early-stage breast cancer: the Life After Cancer Epidemiology study. *Breast Cancer Res Treat*. 2011;130(1): 195-205.
30. Chan AL, Leung HW, Wang SF. Multivitamin supplement use and risk of breast cancer: a meta-analysis. *Ann Pharmacother*. 2011;45(4):476-484.
31. Pocobelli G, Peters U, Kristal AR, White E. Use of supplements of multivitamins, vitamin C, and vitamin E in relation to mortality. *Am J Epidemiol*. 2009; 170(4):472-483.
32. Zhang Y, Coogan P, Palmer JR, Strom BL, Rosenberg L. Vitamin and mineral use and risk of prostate cancer: the case-control surveillance study. *Cancer Causes Control*. 2009;20(5):691-698.
33. White E, Shannon JS, Patterson RE. Relationship between vitamin and calcium supplement use and colon cancer. *Cancer Epidemiol Biomarkers Prev*. 1997; 6(10):769-774.
34. Jacobs EJ, Connell CJ, Chao A, et al. Multivitamin use and colorectal cancer incidence in a US cohort: does timing matter? *Am J Epidemiol*. 2003;158(7):621-628.
35. Blot WJ, Li JY, Taylor PR, et al. Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. *J Natl Cancer Inst*. 1993;85(18):1483-1492.
36. Qiao YL, Dawsey SM, Kamangar F, et al. Total and cancer mortality after supplementation with vitamins and minerals: follow-up of the Linxian General Population Nutrition Intervention Trial. *J Natl Cancer Inst*. 2009; 101(7):507-518.
37. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360 (9326):23-33.
38. Clarke R, Halsey J, Lewington S, et al; B-Vitamin Treatment Trialists' Collaboration. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: Meta-analysis of 8 randomized trials involving 37 485 individuals. *Arch Intern Med*. 2010;170(18):1622-1631.
39. Hercberg S, Galan P, Preziosi P, et al. The SU.VI.MAX Study: a randomized, placebo-controlled trial of the health effects of antioxidant vitamins and minerals. *Arch Intern Med*. 2004;164(21):2335-2342.
40. Cauley JA, Chlebowski RT, Wactawski-Wende J, et al. The Women's Health Initiative (WHI) calcium plus vitamin D supplementation trial: health outcomes 5 years after trial completion [abstract]. *J Bone Miner Res*. 2012; 27(suppl 1).
41. Boeing H, Bechthold A, Bub A, et al. Critical review: vegetables and fruit in the prevention of chronic diseases. *Eur J Nutr*. 2012;51(6):637-663.
42. Riboli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr*. 2003;78(3)(Suppl):559S-569S.
43. Morris MC, Tangney CC. A potential design flaw of randomized trials of vitamin supplements. *JAMA*. 2011; 305(13):1348-1349.
44. Sesso HD, Gaziano JM, VanDenburgh M, Hennekens CH, Glynn RJ, Buring JE. Comparison of baseline characteristics and mortality experience of participants and nonparticipants in a randomized clinical trial: the Physicians' Health Study. *Control Clin Trials*. 2002;23 (6):686-702.
45. Block G, Jensen CD, Norkus EP, et al. Usage patterns, health, and nutritional status of long-term multiple dietary supplement users: a cross-sectional study. *Nutr J*. 2007;6(1):30.
46. Sebastian RS, Cleveland LE, Goldman JD, Moshfegh AJ. Older adults who use vitamin/mineral supplements differ from nonusers in nutrient intake adequacy and dietary attitudes. *J Am Diet Assoc*. 2007;107(8):1322-1332.
47. Park K, Harnack L, Jacobs DR Jr. Trends in dietary supplement use in a cohort of postmenopausal women from Iowa. *Am J Epidemiol*. 2009;169(7):887-892.

