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STUDY METHODS & DESIGN

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

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PURPOSE: To assess the balance of benefits and risks of supplementation with beta-carotene, vitamin E, vitamin C, and multivitamins on cancer, cardiovascular (CVD), and eye diseases.
DESIGN: Physicians' Health Study II (PHS II) is a randomized, double-blind, placebo-controlled trial enrolling 15,000 willing and eligible physicians aged 55 years and older. PHS II will utilize a $2 \times 2 \times 2 \times 2$ factorial design to test alternate day beta-carotene, alternate day vitamin E, daily vitamin C, and a daily multivitamin, in the prevention of total and prostate cancer, CVD, and the age-related eye diseases, cataract and macular degeneration.
PRIOR RESULTS: The final results of the recently completed Physicians' Health Study I (PHS I), a randomized, double-blind, placebo-controlled trial in 22,071 healthy US male physicians, indicated that beta-carotene supplementation (50 mg on alternate days) had no significant benefit or harm on cancer or CVD during more than 12 years of treatment and follow-up. In regards to cancer, there were possible benefits on total and prostate cancer in those with low baseline levels assigned to beta-carotene, a finding compatible with the Chinese Cancer Prevention Study for combined treatment with beta-carotene, vitamin E, and selenium in a poorly nourished population. Further, with respect to CVD, there were apparent benefits of beta-carotene supplementation on subsequent vascular events among a small subgroup of 333 men with prior angina or revascularization. The currently available data from randomized trials of primary prevention are sparse and inconsistent for vitamin E and non-existent for vitamin C and multivitamins. For eye diseases, namely cataract and age-related macular degeneration, there are no completed large-scale randomized trials of antioxidant vitamins.
CONCLUSIONS: PHS II is unique in several respects. PHS II is the only primary prevention trial in apparently healthy men testing the balance of benefits and risks of vitamin E on cancer and CVD. In addition, PHS II is the only primary prevention trial in apparently healthy men to test the balance of benefits and risks of vitamin C, multivitamins, as well as any single antioxidant vitamin, alone and in combination, on cancer, CVD, and eye diseases. Finally, PHS II is the only trial testing *a priori* the hypotheses that beta-carotene and vitamin E may reduce the risks of prostate cancer. Thus, PHS II will add unique as well as importantly relevant and complementary information to the totality of evidence from other completed and ongoing large-scale randomized trials on the balance of benefits and risks of beta-carotene, vitamin E, vitamin C, and multivitamins alone and in combination on prevention of cancer, CVD and eye diseases.
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KEY WORDS: Randomized Trial, Antioxidant Vitamins, Cancer, Cardiovascular Disease, Age-Related Cataract, Age-Related Macular Degeneration.

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Selected Abbreviations and Acronyms

PHS I = Physicians' Health Study I
PHS II = Physicians' Health Study II
CARET = Beta-Carotene and Retinol Efficacy Trial
ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
CHAOS = Cambridge Heart Antioxidant Study
HOPE = Heart Outcomes Prevention Evaluation Study
SU.VI.M.AX = Supplementation en Vitamines et Mineraux Antioxydants Study
WHS = Women's Health Study
WACS = Women's Antioxidant Cardiovascular Study
AREDS = Age-related Eye Disease Study
CHD = coronary heart disease
CVD = cardiovascular disease
AMD = age-related macular degeneration

INTRODUCTION

Physicians' Health Study II (PHS II) is a randomized, double-blind, placebo-controlled trial utilizing a $2 \times 2 \times 2 \times 2$ factorial design to test alternate day beta-carotene, alternate day vitamin E, daily vitamin C, and a daily multivitamin, in the prevention of total and prostate cancer, CVD, and age-related eye diseases, namely, cataract and macular degeneration. PHS II will enroll 15,000 US male physicians aged 55 years and older including all willing and eligible participants from PHS I (1).

PHS I participants who enroll in PHS II (approximately 7500) will continue on their original randomized beta-carotene treatment assignment and will also be randomized to vitamin C, vitamin E, and a multivitamin, or their placebos. New physician participants in PHS II (approximately 7500), identified from a roster of all potentially eligible U.S. male physicians provided by the American Medical Association, will also be randomized to beta-carotene, vitamin E, vitamin C, and a multivitamin, or their placebos. All enrollment, randomization, and follow-up procedures in PHS II will be identical to those successfully employed in PHS I.

PHS II will provide the first randomized trial data in several important areas of antioxidant vitamin research testing alone and in combination: 1) beta-carotene on total and prostate cancer in those with low blood levels, as well as on CVD among those at high risk; 2) vitamin E on total and prostate cancer, CVD, and eye diseases in apparently healthy men; 3) vitamin C on total and prostate cancer, CVD, and eye diseases; and 4) multivitamins on total and prostate cancer, CVD, and eye diseases.

BACKGROUND

PHS II will test the balance of benefits and risks of several antioxidant vitamin supplements, alone and in combination, on cancer, CVD, and age-related eye diseases.

Cancer

Cancer is the second leading cause of death in the US, after coronary heart disease (CHD). Basic research has shown that free radical damage (oxidation) to cellular components likely plays an important role in carcinogenesis (2–4), and that antioxidants such as beta-carotene and vitamins E and C can help prevent this oxidative damage (5–7). Consistent evidence from observational epidemiologic studies indicate that individuals who consume high amounts of beta-carotene in fruits and vegetables tend to have reduced risks of cancer; less data are available for vitamin E, vitamin C, and multivitamins (8–22). Results from four completed large-scale randomized trials that tested supplements of beta-carotene and/or vitamin E, alone or in combination with each other or other antioxidant vitamin supplements, have not been consistent (Table 1).

In the Chinese Cancer Prevention Trial, conducted among 29,584 poorly nourished residents of Linxian, China, persons assigned to a combined daily treatment of beta-carotene (15 mg), vitamin E (30 mg), and selenium (50 μg) experienced statistically significant reductions of 9% in total mortality, 13% in cancer mortality, and 21% in gastric cancer mortality after nearly six years of treatment and follow-up (23). However, these results are likely to be not generalizable to well-nourished populations. Moreover, because three agents were tested in combination, the specific benefit of beta-carotene, vitamin E, or selenium cannot be determined.

In the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), there was no reduction in risk of cancer among 29,133 male smokers randomized to alpha-tocopherol (50 mg daily) and/or beta-carotene (20 mg daily) (24). In fact, assignment to beta-carotene was associated with statistically significant increases of 18% in lung cancer and 8% in total mortality, neither of which had been pre-specified. Results for vitamin E indicated no effect on lung or total cancer. However, for vitamin E, there was a non-prespecified but significant 34% decrease in prostate cancer.

The Beta-Carotene and Retinol Efficacy Trial (CARET) evaluated combined treatment with beta-carotene (30 mg daily) and retinyl palmitate (25,000 IU daily) among 18,134 men and women at high risk of lung cancer due to cigarette smoking and/or occupational exposure to asbestos (25). CARET was terminated early, after an average duration of treatment of four years, primarily because interim analyses suggested that no evidence of benefit could be demonstrated with longer treatment. There was also concern that the interim findings for combined treatment with beta-carotene and retinyl palmitate appeared to be compatible with the ATBC results for beta-carotene alone. Specifically, for lung cancer, the primary trial endpoint, there was a non-prespecified 28% increase among the combined treatment group ($p = 0.02$). This finding, however, did not reach the prespecified stopping boundary for early termination ($p < 0.007$).

TABLE 1. Completed large-scale, randomized, double-blind, placebo-controlled trials of antioxidants in the prevention of cancer and cardiovascular disease

Reference	Agent/population	Cancer findings	CVD findings
Chinese Cancer Prevention Study. Blot et al., 1993 (23)	Combination of beta-carotene, alpha-tocopherol, and selenium in 29,000 healthy Chinese men and women at high risk for gastric cancer and low risk for CVD	Significant reduction in gastric cancer (RR, 0.79 [0.64–0.99]) and total cancer (RR, 0.87 [0.75–1.00])	Nonsignificant trend toward reduction in cerebrovascular mortality
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group, 1994 (24)	Beta-carotene and vitamin E in 29,000 Finnish male smokers	Beta-carotene: significant increase in lung cancer (RR, 1.18 [1.03–1.36])[a] Vitamin E: no reduction in lung cancer or total cancer Significant reduction in prostate cancer (RR, 0.66 [0.51–0.85])[a,b]	Beta-carotene: Significant increase in ischemic heart disease mortality (RR, 1.12 [1.00–1.25])[a,b] Vitamin E: significant increase in mortality from cerebral hemorrahge (RR, 1.50 [1.02–2.20])[a,b]
Beta-Carotene and Retinol Efficacy Trial, 1996 (25)	Combined beta-carotene and retinyl palmitate in 18,000 men and women smokers and/or asbestos workers	Possible increase in lung cancer (RR, 1.28 [1.04–1.57])[a,c]	Nonsignificant trend toward increase in CVD mortality[a]
Physicians' Health Study I, 1997 (26)	Beta-carotene and aspirin in 22,000 U.S. male physicians	No reduction or increase in cancer	No reduction or increase in CVD
Cambridge Heart Antioxidant Study, 1996 (47)	Vitamin E in 2000 men and women with angiographically proven coronary atherosclerosis	Not evaluated	Significant reduction in non-fatal MI (RR, 0.23 [0.11–0.47]) Nonsignificant increase in CVD mortality

[a] Not pre-specified.
[b] Confidence interval estimated from data presented.
[c] Trial terminated early and *p*-value did not reach stopping boundary.

PHS I indicated that 12 years of treatment with beta-carotene (50 mg on alternate days, supplied as Lurotin by BASF) had no significant benefit or harm on risk of cancer (relative risk [RR] = 0.98; 95% confidence interval [95% CI] = 0.91 to 1.06) during the period of treatment (26). Subgroup analysis also indicated no significant evidence of benefit or harm among the 11% of participants who were current smokers at baseline. This finding of no overall effect is particularly reliable in view of the length of the trial (more than twice as long as any other trial of beta-carotene), and because the narrow confidence intervals exclude even small effects with a high degree of assurance. On the other hand, subgroup analyses of prerandomization bloods in PHS I are compatible with possible small benefits for beta-carotene supplementation on total and prostate cancer among those with the lowest blood levels at baseline (27), a finding consistent with the results of the Chinese Cancer Prevention Trial for combined treatment with beta-carotene, vitamin E, and selenium.

For beta-carotene and cancer, the totality of trial evidence contrasts with the totality of observational evidence which indicates clear and consistent benefits for those with high intakes. One possibility is that the apparent benefits in observational studies merely reflect confounding factors associated with self-selection to high intake of beta-carotene. These may include other nutritional factors in fruits and vegetables that are protective, or even non-dietary lifestyle differences. It is also possible that a protective effect of beta-carotene through diet or supplements requires very long exposure, of two decades or so as was achieved in all observational studies, but in none of the randomized trials completed to date. If, as the analogy with cigarette smoking and development of lung cancer suggests, extended exposure is required, even the 12 years in PHS I may have been inadequate. Thus, post trial follow-up of participants in all randomized trials should be particularly informative.

PHS II will also enable testing of the prespecified hypotheses that vitamin E reduces risk of prostate cancer, and that beta-carotene reduces total and prostate cancer among those with low baseline blood levels (27). In addition, PHS II will provide the first randomized trial data for vitamin C and multivitamins in the primary prevention of cancer. Finally, with respect to the issue of possible harm among current smokers randomized to beta-carotene in ATBC and combined treatment with beta-carotene and retinyl palmitate in CARET, PHS II will provide additional information from this closely monitored subgroup.

Cardiovascular Disease (CVD)

CVD is the leading cause of death in the US and most developed countries. Basic research has demonstrated sev-

eral plausible mechanisms through which antioxidant vitamins may prevent or retard atherogenesis (28–30). Numerous observational epidemiologic studies support the hypothesis that, in humans, those with high intakes of various antioxidant vitamins have decreased risks of CVD (31–46). Results from randomized trials conducted to date, however, are sparse and not consistent.

In the Chinese Cancer Prevention Study, subjects assigned to combined daily treatment of beta-carotene (15 mg), vitamin E (30 mg), and selenium (50 μg) had a nonsignificant 10% decrease in cerebrovascular mortality compared with those assigned placebo (RR = 0.90; 95% CI = 0.76 to 1.07) (23). However, these findings are likely to be not generalizable to well-nourished populations, and the specific effect of the individual agents cannot be determined.

In the Finnish ATBC study of male smokers, there was no apparent CVD benefit of either vitamin E (50 mg daily) or beta-carotene (20 mg daily); those assigned to beta-carotene had a non-prespecified but significant 12% increase in ischemic heart disease mortality, whereas those assigned to vitamin E experienced a non-prespecified but significant 50% increase in mortality from cerebral hemorrhage (24).

In CARET, among a high-risk population of smokers and asbestos workers, although not prespecified, those assigned to combined treatment with beta-carotene and retinyl palmitate had a nonsignificant 26% increased risk of cardiovascular mortality (RR = 1.26; 95% CI = 0.99 to 1.61, $p = 0.06$) at the time of the study's early termination, which required a more extreme significance level to declare a clear effect ($p < 0.007$) (25).

In the Cambridge Heart Antioxidant Study (CHAOS) (47), conducted among 2002 patients with angiographically proven coronary atherosclerosis, patients assigned to vitamin E (800 IU daily for 546 patients; 400 IU daily for 489 patients) had a 47% reduced risk of a combined endpoint of cardiovascular death and non-fatal MI (RR = 0.53; 95% CI = 0.34 to 0.83, $p = 0.005$) compared to those not assigned to this treatment, after a median treatment and follow-up of 1.4 years. This reduced risk was due to a significant benefit of vitamin E on non-fatal MI (RR = 0.23; 95% CI = 0.11 to 0.47, $p = 0.005$). For cardiovascular death, there was a possible but non-significant 18% increased risk for those assigned to vitamin E (RR = 1.18; 95% CI = 0.62 to 2.27, $p = 0.61$).

In PHS I (26), there was no significant evidence of benefit or harm of beta-carotene on total myocardial infarction (RR = 0.96; 95% CI = 0.84 to 1.09), total stroke (RR = 0.96; 95% CI = 0.83 to 1.11), cardiovascular death (RR = 1.09; 95% CI = 0.93 to 1.27), or the combined endpoint of nonfatal myocardial infarction, nonfatal stroke, and total cardiovascular death (RR = 1.00; 95% CI = 0.91 to 1.08). In subgroup analyses of current smokers, there was no significant evidence of benefit or harm but the confidence limits were wide.

Preliminary subgroup analysis using the PHS I five-year data at the time the aspirin component was terminated, had indicated that beta-carotene supplementation among 333 men with prior angina or revascularization procedures decreased the risk of subsequent important vascular events by 54% (48, 49). With 12 years of treatment and follow-up of this small subgroup, there was a possible reduced risk of important vascular events of 21%. Thus, PHS II will enable testing of the prespecified hypothesis that beta-carotene decreases risks of CVD among those at high risk. PHS II will also examine the balance of benefits and risks of supplementation with vitamin C and E, as well as multivitamins, alone and in combination, on CVD. At present, there are no long-term randomized trials of primary prevention for vitamin C or multivitamins on CVD. Finally, with respect to the observed possible increased risks among current smokers assigned to beta-carotene in ATBC and combined treatment with beta-carotene and retinyl palmitate in CARET, PHS II will provide valuable information on this closely monitored subgroup.

Age-related Eye Disease: Cataract and Age-related Macular Degeneration

Cataract and age-related macular degeneration (AMD) are two of the leading causes of visual impairment (50). Cataract extraction is now the most frequently performed surgical procedure among persons over age 60, with more than one million operations performed annually in the US (50). AMD is the leading cause of blindness in people age 65 and older (50). Basic research studies in animal models have demonstrated that supplementation with antioxidant vitamins can prevent or delay the formation of lens opacities (51, 52), and can reduce the damaging effects of reactive oxygen species on the retina (53–55).

Observational epidemiologic studies tend to demonstrate that individuals who self-select for high dietary intake of antioxidant vitamins have reduced risks of cataract (56–67) and AMD (68–75). At present, however, there are no completed large-scale randomized trials, but there are three ongoing trials of antioxidant vitamins and cataract or AMD, namely the Age-Related Eye Disease Study (AREDS) (76, 77), the Women's Health Study (WHS) (78), and the Women's Antioxidant Cardiovascular Study (WACS) (79).

STUDY DESIGN AND METHODS

PHS II is a randomized, double-blind, placebo-controlled trial of the balance of benefits and risks of beta-carotene, vitamin E, vitamin C, and a multivitamin in the prevention of total and prostate cancer, CVD, and the age-related eye diseases, cataract and macular degeneration. The trial utilizes a 2 × 2 × 2 × 2 factorial design (Figure 1) and participant recruitment and randomization will occur in two

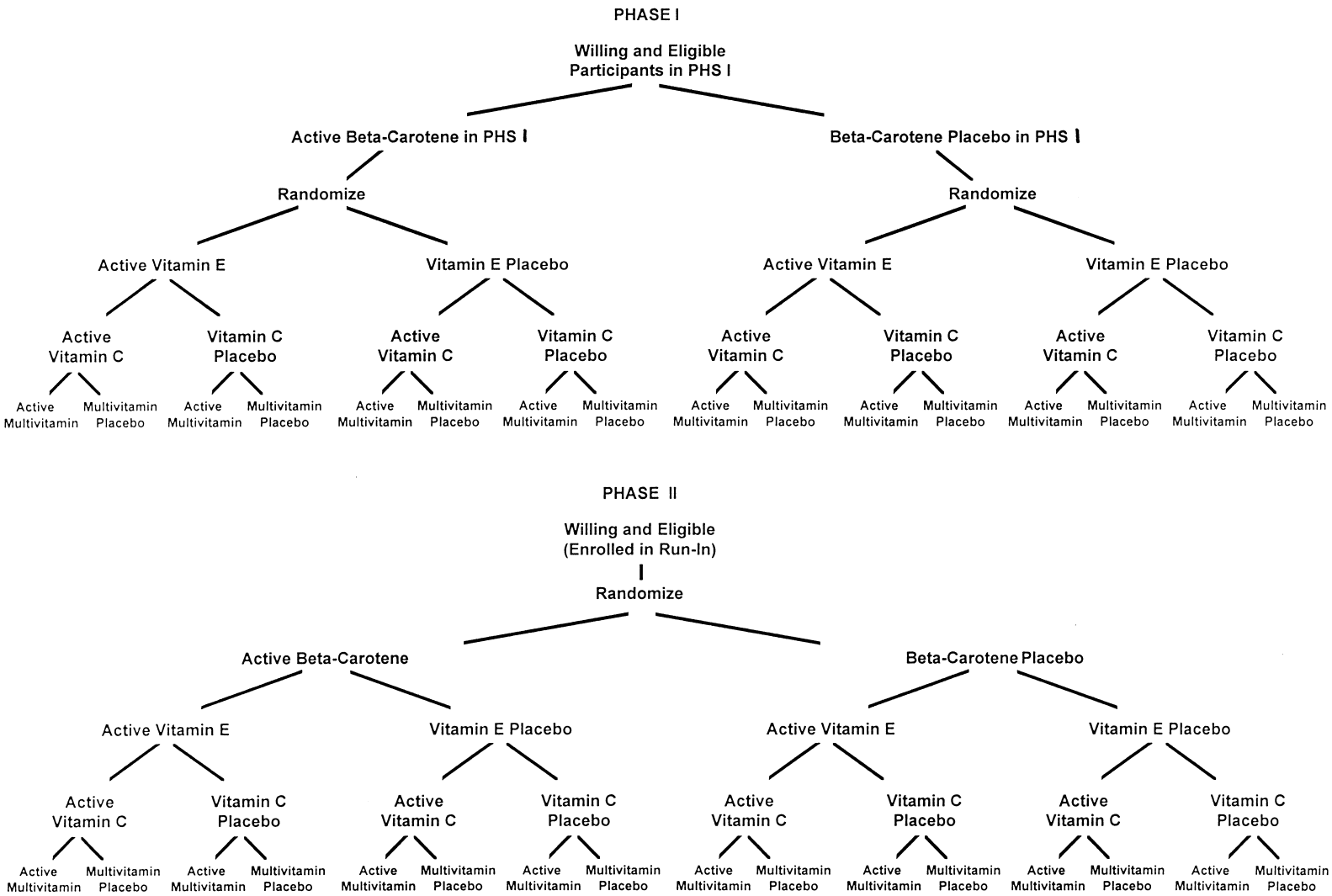

FIGURE 1. Physicians' Health Study II: Randomization Scheme for Phase I (willing and eligible participants in Physicians' Health Study I) and Phase II (willing and eligible new physician participants). In Phase II, potentially willing and eligible physicians will be enrolled in a 12-week prerandomization run-in to assess their willingness and ability to comply with the daily pill-taking regimen.

phases. In Phase I, PHS I participants who are willing and eligible for participation in PHS II will retain their randomized beta-carotene assignment from PHS I (50 mg Lurotin or placebo on alternate days, supplied by BASF), and will be also randomized to vitamin E (400 IU of synthetic alpha tocopherol or placebo on alternate days, supplied by BASF), vitamin C (500 mg synthetic ascorbic acid or its placebo daily, supplied by BASF), and a multivitamin (Centrum Silver, or its placebo daily, supplied by Lederle). In Phase II, new physician participants will be randomly assigned to the same interventions.

Thus, participants in PHS II will take three pills per day as follows: 1) either vitamin E or its placebo every other day with beta-carotene or its placebo on the alternate days; 2) vitamin C or its placebo daily; and 3) a multivitamin or its placebo daily. As was done in PHS I, calendar packs (supplied by BASF) will be used to facilitate the administration of three pills daily and to maintain high compliance. Intake of these agents in combination has no detectable effect on absorption of the other agents. The doses are designed to provide those assigned to beta-carotene, vitamin E, and/or vitamin C with a dose considerably above that usually achieved from diet alone. The multivitamin contains RDAs of most vitamins and minerals.

Recruitment

PHS II will enroll 15,000 US male physicians aged 55 years and older including: 1) willing and eligible participants in PHS I (about 7500); and 2) new physician participants (about 7500). Recruitment and enrollment of participants for PHS II will be conducted in two phases.

Phase I. All living participants in PHS I will be sent a detailed letter explaining the background and rationale for the PHS II trial. This initial mailing will also contain informed consent forms and questionnaires requesting information on the occurrence of relevant endpoints since the previous PHS I questionnaire, as well as use of various vitamin supplements over the past 12 months. Participants who indicate they are currently taking individual supplements of beta-carotene, vitamin A, vitamin C, or vitamin E, containing more than 100% of RDA, or a multivitamin, will be asked if they are willing to forego the use of such supplements for the course of the PHS II trial. Physicians unwilling to avoid using these outside supplements will be ineligible for PHS II.

PHS I participants who report a history of cirrhosis, or active liver disease in the past six months will also be ineligible. The questionnaire will also request detailed information on a large number of risk factors for cancer and CVD as well as current use of anti-hypertensive or cholesterol-lowering medications, and recent use of other prescription or over-the-counter medications. Venous blood samples collected after the completion of PHS I (beginning in July 1996) will be used for assessment of baseline levels of various antioxidant vitamins.

Phase II. Beginning in the summer of 1999, invitational letters and baseline questionnaires will be mailed to US male physicians ages 55 and older (excluding physicians who participated in PHS I), identified from a list provided by the American Medical Association, asking them to participate in PHS II. Physicians who respond to the invitational mailing by returning the baseline questionnaire will be screened for willingness to participate and for eligibility. Physicians will be eligible for PHS II if they do not report a personal history of cancer (except non-melanoma skin cancer), CVD (including myocardial infarction, stroke, or transient cerebral ischemia), current liver disease (active in the past six months), current renal disease, peptic ulcer, or gout. In addition, potentially eligible physicians will be required to indicate their willingness to avoid the use of nonstudy vitamin supplements.

As was the case in PHS I, potentially willing and eligible physicians will be enrolled in a 12 week prerandomization run-in to assess their willingness and ability to comply with the daily pill-taking regimen. During the run-in, they will receive calendar packs containing placebos of beta-carotene, vitamin C, vitamin E, and a multivitamin. Physicians will also be requested to provide a venous blood sample during the run-in period. Only physicians who comply with the pill-taking regimen at least two-thirds of the time and remain willing and eligible to participate will be subsequently randomized into one of the sixteen treatment groups. The pilot studies for PHS I demonstrated that most noncompliers become evident during the first several months of participation (80). Thus, the run-in will help to assure that nearly all participants randomized in PHS II are excellent compliers thereby greatly increasing the power of the trial to definitively test the hypotheses under study (81).

Randomization

PHS I participants who enroll in PHS II will retain their original beta-carotene assignment and new physicians will be assigned to beta-carotene at random. Randomization to the other agents, using a computer-generated list of random numbers, will be stratified according to age (55–59, 60–64, 65–69, 70–74, and 75+ years) in blocks of sixteen.

Follow-up

As in PHS I, all randomized participants will receive yearly questionnaires and calendar packs containing the study pills. Questionnaires will be used to obtain information on study endpoints, as well as side-effects of the study agents, use of non-study vitamins, compliance, and other risk factors. Close follow-up will be maintained with all participants through the questionnaires and annual newsletters. As in

PHS I, non-respondents will receive multiple letters and follow-up telephone calls.

Documentation of Endpoints

Procedures for validation of endpoints will be identical to PHS I. For each reported endpoint, the participant will be asked to sign an informed consent form releasing information about the diagnosis to the investigators. A request for records will be mailed to the hospital or attending physician. For eye endpoints, the treating ophthalmologist/optometrist will be requested to complete a questionnaire providing information about the reported diagnosis. The records will be reviewed initially by a single physician investigator for adequacy to document the presence or absence of an endpoint. An Endpoints Committee of physicians, blinded to the participants' treatment assignment, will review the medical records for final confirmation of a reported diagnosis.

Data Analyses

Because this trial includes participants from the PHS I cohort who have been treated with beta-carotene or placebo for over 12 years but who will also be randomized to the other study agents, methods of analysis will differ by intervention. For the vitamins E and C and multivitamin interventions, the data will be analyzed as a randomized factorial trial starting from the new study date. Analysis will be in terms of number of events per person-years of follow-up for each study agent, and will be conducted on an intent- to-treat basis. We will use the Cox proportional hazards model to compare event rates for each treatment group while controlling simultaneously for variable lengths of follow-up, other treatment assignments, and any risk factors that are unbalanced. We will also use this model to evaluate effect modification by other factors, including other study agents and risk factors for each outcome.

Analyses of beta-carotene supplementation will include the total experience of subjects who have been randomized to beta-carotene since the beginning of the PHS. Participants from PHS I will remain on their original assignment of beta-carotene or beta-carotene placebo. Thus, treatment groups for beta-carotene in PHS II are determined by an original randomization plus a willingness to continue with their original blinded beta-carotene assignment. Because of the overall lack of effect of beta-carotene on cancer and CVD during PHS I, the absence of notable side effects during this period, and the persistence of blinding, no differences between treatment groups in willingness to continue are expected. However, analyses of beta-carotene in PHS II will utilize analytic approaches to control for any factors associated with the decision to continue in PHS II, including an adjustment for propensity to continue.

For each of the outcomes, follow-up time for these participants will be accrued starting from their original time of randomization to the PHS. The Cox model will be used to also control for age at randomization and time of follow-up as well as other study agents and risk factors. We will also examine effect modification of the beta-carotene effect by age and by duration of treatment.

Sample Size and Power

The estimated statistical power to study the individual effects of beta-carotene, vitamin E, vitamin C, and multivitamins, on the various endpoints is calculated for a five-year prevention trial with a sample size of 15,000 men for each endpoint (Table 2). Anticipated rates for the various endpoints in PHS II are based on the observed rates in PHS I. PHS II will have over 80% power to detect: 1) a 20% reduction in the risk of total cancer and a 30% reduction in the risk of prostate cancer for each study agent; 2) a 25% reduction in a combined endpoint of important vascular events defined as a new occurrence of nonfatal myocardial infarction, nonfatal stroke, and all cardiovascular deaths; 3) a 25% reduction in the risk of cataract; and 4) a 50% reduction in the risk of AMD based on currently observed incidence rates. For beta-carotene, these power estimates are conservative as they do not take into account the accrual of 12 years of supplementation and follow-up that has already taken place for PHS I participants, which are estimated to comprise about 50% of the sample for PHS II.

Data and Safety Monitoring Committee

An independent Data and Safety Monitoring Committee will meet at least annually to examine the unblinded data for evidence of benefit or harm. This committee will consider any trial finding in light of the totality of evidence, and recommend whether to continue the trial uninterrupted, alter the protocol, or alter or terminate one or more of the arms.

COMMENTS

Although basic research and observational epidemiologic studies suggest possible benefits of antioxidant vitamins in cancer, CVD, and age-related eye disease, the only design strategy to detect the most plausible small to moderate effects (i.e., benefit or harm) is the large-scale, randomized trial. For cancer, the available data from four completed large-scale randomized trials, including PHS I, are inconsistent and inconclusive. Beta-carotene treatment for as long as 12 years has been shown to have no overall effect on cancer among a generally well-nourished sample of male physicians. However, a delayed effect, which emerges after the very long-term exposure to beta-carotene seen so far only in observational studies, remains plausible.

Data from PHS I indicate that men with low blood

TABLE 2. Predicted number of events and estimated power for study endpoints in a five-year trial of 15,000 participants in Physicians' Health Study II (PHS II)

Endpoint	Crude rate per 100,000[a]	Estimated no. of cases	Power to detect reduction of	
			20%	30%
Total cancer	5691.7	854	80.8	99.2
Prostate cancer	2511.0	377	45.7	81.3
Important vascular events	4279.7	642	68.4	96.3
Age-related macular degeneration	813.6	122	18.0	36.3
Cataract	4597.2	690	71.6	97.3

[a]Based on observed rates in Physicians' Health Study I.

levels at baseline have decreased total and prostate cancer if assigned at random to beta-carotene, a possibility compatible with the findings from the Chinese Cancer Prevention Study (23). Randomized trial data regarding other antioxidant vitamins and cancer are limited. For CVD, the available randomized trial data indicate that beta-carotene does not have a major beneficial or harmful effect on CVD among well-nourished individuals at usual risk. However, the data also suggest that beta-carotene treatment may have beneficial effects in the subgroup at high risk of CVD, namely those with chronic stable angina or revascularization procedures. Finally, the PHS II will add to the body of available data on possible harm in current smokers randomized to beta-carotene in ATBC and combined treatment with beta-carotene and retinyl palmitate in CARET. Randomized trial data for other antioxidant vitamins and CVD are sparse. For cataract and AMD, there are no large-scale randomized trial data regarding the effects of treatment with these antioxidant vitamins.

In conclusion, PHS II will provide importantly relevant and timely data on the possible role of antioxidant vitamins in disease prevention by directly assessing the balance of benefits and risks of supplementation with beta-carotene, vitamin C, vitamin E, and multivitamins, alone and in combination, on cancer, CVD, and age-related eye disease. Several other ongoing trials will also provide important data on the possible role of antioxidant vitamins in disease prevention. These trials include the Heart Protection Study (Richard Peto, personal communication), which is evaluating a cocktail of beta-carotene, vitamin E, and vitamin C among 20,000 high-risk patients in the United Kingdom; the Heart Outcomes Prevention Evaluation (HOPE) study (82), which is testing vitamin E among 9000 high-risk subjects in Canada; the Supplementation en Vitamines et Mineraux Antioxydants Study (SU.VI.M.AX) (83), which is testing beta-carotene, vitamin E, vitamin C, zinc, and selenium in 12,735 healthy French men and women; and the GISSI Prevention Trial (84), which is evaluating vitamin E among 11,000 high-risk patients in Italy.

PHS II, however, is the only trial testing *a priori* the possible benefits of beta-carotene on prostate and total cancer in those with low blood levels and vitamin E in prevention of prostate cancer. PHS II and WACS are testing *a priori* whether beta-carotene will show a CVD benefit among those at high risk. PHS II is also the only primary prevention trial in apparently healthy men testing the balance of benefits and risks of vitamin E on cancer and CVD. Finally, PHS II is the only primary prevention trial in apparently healthy men to test the balance of benefits and risks of vitamin C, multivitamins, as well as any single antioxidant vitamin, alone and in combination, on cancer, CVD, and eye diseases.

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