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Physicians' Health Study Newsletter

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The PHS Turns Twenty-Five!

As the PHS celebrates its 25th anniversary, let's take a look back and a look ahead.

A look back … The Physicians' Health Study was initiated in the fall of 1982 to test the benefits and risks of aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer. Twenty-five years and approximately 300 published research reports later, it is still going strong. The original randomized trial, the Physicians' Health Study I, which enrolled 22,071 male physicians between 1982 and 1984, ended in 1995. It found that daily low-dose aspirin cut the risk for a first myocardial infarction by 44%, a result that led to changes in practice guidelines for the primary prevention of coronary heart disease in men. It also showed no benefit or harm from beta-carotene supplements. Although that *trial* is over, the physicians who took part in it continue to help advance our knowledge about the prevention of cardiovascular disease, cancer, and other chronic diseases by completing annual questionnaires. A second randomized trial, the Physicians' Health Study II, was started in 1997 to test the balance of benefits and risks of vitamin E, vitamin C, and a multivitamin—and to test long-term use of beta carotene—in the primary prevention of cardiovascular disease, cancer, and age-related eye disease. A total of 14,641 physicians participated, including 7,641 from the original PHS I cohort. The beta-carotene component ended in March 2003. The vitamin C and vitamin E components of the PHS II ended as planned in late 2007, but the multivitamin component will continue for a few more years. Since the study's inception, dedicated PHS participants have taken their study pills all over the world—for photos of recent travelers, see page 4.

And a look ahead … PHS investigators expect to analyze the data and announce the results for vitamin C and vitamin E by the end of this year. The multivitamin component of the PHS II trial will continue for several more years to allow an examination of long-term use of multivitamins in relation to a myriad of health outcomes, including cardiovascular disease, cancer, age-related eye disease, and cognitive decline. Half of U.S. adults take vitamins (primarily multivitamins)—and spend $23 billion on them each year—yet definitive data on the health effects of

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Dear Doctor,

As the Physicians' Health Study marks its 25th anniversary, we wish to thank each of you for your continuing contributions and extraordinary commitment to this landmark research endeavor. The rates of questionnaire completion remain very high, with approximately 90% of physician participants continuing to provide annual updates on their health, even after a quarter century! The rates of pill taking and follow-up among those enrolled in the PHS II vitamin trial have also been superb. As of December 31, 2007, the average length of participation in this trial was 8.8 years. As you are aware, the PHS II recently transitioned from a trial of three agents (vitamin C, vitamin E, and a multivitamin) to a trial of only one agent (the multivitamin). Your uninterrupted participation in the multivitamin trial is critical to ensure that the PHS II will yield the most definitive information possible on the benefits and risks of long-term multivitamin use.

We'd also like to appeal to those of you in the PHS II who have stopped taking your study pills. If (and only if!) you are medically able to do so, we would greatly appreciate your resuming the pills. Now that only one pill per day is being tested, you may find it much easier to adhere to the pill-taking requirement. Greater compliance will result in greater statistical power for the PHS II trial to draw definitive conclusions about the efficacy of multivitamins in preventing cardiovascular disease, cancer, eye disease, and cognitive decline. If you wish to resume taking the study pills and need calendar packs, please call us toll-free at 1-800-633-6907 or drop us an e-mail at phs@rics.bwh.harvard.edu.

With warm regards,
Drs. J. Michael Gaziano and Julie Buring, PHS Principal Investigators

Recent findings from the PHS

■ **Beta carotene and cognitive function.** Although much research has been done on medications that may prevent further cognitive decline among persons with dementia, fewer studies have tested interventions that may keep the brains of healthy individuals sharp. In 1998, researchers initiated a study among PHS participants aged 65 and older to determine whether use of vitamin supplements prevents aging-related cognitive decline. Nearly 6,000 men completed a 10-minute telephone interview consisting of standard tests of memory and thinking. Among PHS II participants who were also in PHS I—and who took beta carotene or its placebo for an average of 18 years—beta carotene was associated with better cognitive performance. On the other hand, among PHS II participants who were not in PHS I—and who took beta carotene or its placebo for an average of just one year—beta carotene was not related to cognitive performance. This pattern of findings suggests that long-term but not short-term use of beta-carotene supplements may help to preserve cognitive function. *Archives of Internal Medicine 2007;167:2184-90.*

■ **Secular trends in heart failure.** In the U.S., one in five 40-year-old adults will develop heart failure in his or her lifetime, and this condition is the leading cause of hospitalization among the elderly. Over the past two decades, there has been little change in the incidence of heart failure among PHS participants, but the likelihood of survival after such a diagnosis has increased dramatically. Compared with men diagnosed in 1985-1989, men diagnosed in 1990-1994, 1995-1999, and 2000-2004 were 41%, 64%, and 90% less likely to die prematurely, respectively. One possible explanation for this trend is improved treatment of heart failure itself or of coronary risk factors that may have averted severe heart failure with a high case-fatality rate. Another is that participants in more recent periods may be more likely to report milder cases of heart failure that were detected through new diagnostic methods, such as brain natriuretic peptide testing or imaging studies. *American Heart Journal 2007;154:855-60.*

■ **Blood levels of polyunsaturated fatty acids and prostate cancer.** Although the findings are not entirely consistent, epidemiologic studies suggest that long-chain polyunsaturated omega-3 fatty acids, found mainly in seafood, may protect against the development of prostate cancer. In a 13-year follow-up of PHS participants, men in the top quintile of blood level of long-chain omega-3 fatty acids were 41% less likely to develop prostate cancer than men in the bottom quintile. Men with high blood levels of linoleic acid, a polyunsaturated omega-6 fatty acid found mainly in nonhydrogenated vegetable oils, also had a reduced risk of prostate cancer. On the other hand, men with high blood levels of gamma-linolenic and dihomo-gamma-linolenic acids, which are linoleic acid metabolites, had an increased risk of prostate cancer, a finding that requires further investigation. *Cancer Epidemiology, Biomarkers & Prevention 2007;16:1364-70.*

Ongoing research projects in the PHS

■ **Prostate cancer and survival.** Prostate cancer, the most common cancer among U.S. men, has a variable course: in some individuals, the disease progresses slowly or not at all, while in others, the cancer is more aggressive. Initiated in 2003, the PHS Prostate Cancer Survivors Study aims to identify factors that affect survival after a prostate cancer diagnosis. To date, more than 2,000 men in PHS have participated by completing annual questionnaires regarding clinical course (clinical stage and grade of the cancer, treatments, prostate-specific antigen [PSA] levels, and evidence of progression) and post-diagnostic lifestyle factors such as diet, supplement use, and physical activity. PHS researchers have also assembled a biobank of tumor tissue specimens from 1,100 of these men and are now analyzing these specimens for expression of the androgen receptor gene and for markers of angiogenesis, apotosis, and cellular proliferation. Together with the data from the questionnaires and baseline blood samples, the biobank data will provide a powerful resource for investigating genetic, hormonal, and lifestyle determinants of survival in prostate cancer.

■ **Diet and health.** You may recall filling out a comprehensive dietary assessment known as a food frequency questionnaire several years ago. PHS researchers have finished coding these questionnaires and are initiating new studies on the relation between diet and health, and on how diet and supplemental vitamin use may interact to affect health. Of particular interest is the role of dietary fat—e.g., omega-3 fats or trans fats—in the development of cardiovascular disease and cancer.

■ **Beta carotene and lung cancer pathology.** There has been controversy regarding the relation between the use of beta-carotene supplements and risk for lung cancer. Although beta carotene was not associated with lung cancer risk in the PHS, it has been linked to an increased lung cancer risk among smokers or asbestos workers in two other large randomized trials. To examine whether beta carotene affects lung pathology, PHS researchers are measuring molecular markers—specifically, protein levels of total p53, cyclin D1, proliferating cellular nuclear antigen, retinoic acid receptor beta, and cytochrome p450 enzyme 1A1—in archival lung tissue samples from PHS participants with lung cancer. They will then compare the molecular marker profile of lung cancer patients who had been assigned to beta carotene to that of lung cancer patients who had been assigned to placebo.

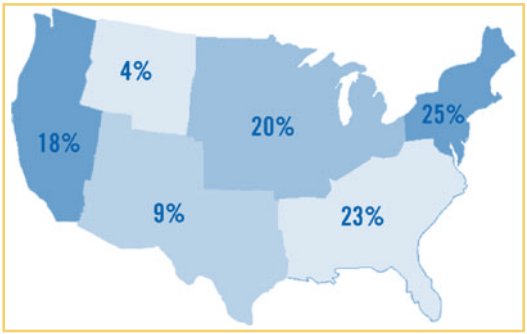
Demographic and health profile of men currently enrolled in the PHS

Data from the most recent set of questionnaires completed by PHS respondents have shed light on the characteristics of the more than 19,000 physicians currently participating in the study. As of December 2007, the average age of study respondents was 73 years. Five percent were age 58 or 59, 35% were in their 60s, 38% were in their 70s, 20% were in their 80s, and 3% were 90 or older. Five participants were centenarians!

PHS participants are geographically diverse, residing in all 50 states, Puerto Rico, and Guam. Indeed, more than 80 respondents live abroad, with one or more men mailing their questionnaires to us from (in alphabetical order) Argentina, Australia, Bermuda, Bolivia, Canada, Chile, Colombia, Ecuador, England, France, Germany, Greece, the Grenadines, Hungary, Ireland, Israel, Italy, Japan, Kenya, Mexico, Morocco, New Zealand, Pakistan, Peru, the Philippines, Spain, St. Maarten, Sweden, Switzerland, Tanzania, and Turkey.

Overall, PHS respondents appear more health conscious and are in better cardiovascular health than the general population of similarly aged men in the United States. Only 2% of participants are current smokers, a figure that compares favorably with the 24% of U.S. men who smoke. An impressive 76% of PHS respondents reported having had a physical exam in the prior year. Of men who knew their cholesterol level, 76% had a cholesterol level below 200 mg/dl (desirable), 19% had a level between 200 and 239 (borderline high), and 5% had a level of 240 or more (high). For comparison, roughly 20% of U.S. men aged 60 and older have a high cholesterol level. Participants' average systolic and diastolic blood pressures were 126 mm Hg and 76 mm Hg, respectively. Normal blood pressure is typically defined as a systolic blood pressure less than 120 and a diastolic pressure less than 80; prehypertension as a systolic pressure of 120 to 139 or a diastolic pressure of 80 to 89; and hypertension as a systolic pressure of 140 or more or a diastolic pressure of 90 or more, or, alternately, current use of a blood pressure medication. By these criteria, 20% of participants have normal blood pressure, 65% have prehypertension, and 14% have hypertension. For comparison, 65% of U.S. adults aged 60 or older have hypertension.

Body mass index calculations show that the average BMI is 27 kg/m^2. Two percent of PHS respondents are underweight (BMI less than 18.5) and 35% are at a healthy weight (BMI 18.5 to 24.9), while 40% are overweight (BMI 25 to 29.9) and 23% are obese (BMI 30 or more). For comparison, 43% of U.S. men aged 60 and older are overweight, and 30% are obese. If your BMI places you in the overweight or obese category, don't despair. Losing as little as 5% of your body weight—even if you aren't able to achieve a BMI below 25—favorably affects cholesterol, blood pressure, blood sugar, and other risk factors for cardiovascular disease.



Distribution of PHS participants, by region.

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daily vitamin use do not exist. Because the PHS II is the *only* existing large-scale randomized clinical trial of multivitamins for chronic disease prevention, the results are expected to have a substantial impact on personal and clinical decision making. And, of course, all participants will continue to receive yearly questionnaires to update information on health events and risk factors for disease. This will allow PHS investigators to build upon the wealth of data participants have already provided to explore new hypotheses and resolve existing uncertainties about health promotion and disease prevention in men.

Q&A

■ Although the multivitamin component of the PHS II trial is continuing for a few more years, the vitamin C and E components are not. What can I infer about the health effects of vitamins C and E?

The vitamin C and E components ended right on schedule. This means that the trial has provided enough data to allow PHS investigators to determine with a high degree of certainty what the health effects of vitamin C and E supplements are. It does *not* imply anything—either positive or negative—about the health effects of these supplements.

■ How will people be notified of the PHS II trial results for vitamins C and E?

We plan to present the trial results at a national scientific meeting and to publish them in a major medical journal. We will work with various media outlets to ensure widespread dissemination of the results. We will also summarize the findings in a future letter or newsletter to participants.

J. Michael Gaziano

Julie E. Buring

If you have questions about the PHS, please let us know. J. Michael Gaziano, MD, MPH, and Julie Buring, ScD, the study's Principal Investigators, will answer them in upcoming issues of the newsletter. Answers to frequently asked questions will also be posted on our website at http://phs.bwh.harvard.edu.