

Physicians' Health Study

Spring/Summer 2004

Newsletter

PHS substudies utilize rich fund of data

The PHS has made enormous contributions to our understanding of health and disease in men in several ways, and, with your help, will continue to do so. The major goal of the trial is to understand the roles played by various vitamins in the prevention of cardiovascular disease and cancer. At the same time, data collected from all PHS participants will address other important questions about the impact of lifestyle, clinical, biochemical, and genetic variables on the development of chronic diseases. Here are some examples of substudies being conducted under the auspices of the PHS:

■ One substudy focuses on the prevention of **eye disease**. When pill taking is completed, William Christen, ScD, and colleagues will determine whether vitamin E, vitamin C, or multivitamin supplementation can help prevent cataract or age-related macular degeneration, the leading causes of vision loss and blindness in older people. A recent PHS report found no overall benefit or harm of 12 years of beta-carotene supplementation on the occurrence of cataract or cataract extraction (*Archives of Ophthalmology* 2003;121:372-378). Data from the PHS have already implicated

smoking as a risk factor for cataract (*JAMA* 1992;268:989-993) and macular degeneration (*JAMA* 1996;276:1147-1151).

■ As we grow older, many of us worry about **memory loss**. Although much research has been done on interventions that may prevent further cognitive decline among persons with dementia, relatively few studies have examined factors that may keep the brains of healthy individuals sharp. The PHS is in a unique position to understand how lifestyle and diet affect memory and cognitive function. PHS researchers, led by Fran Grodstein, ScD, are collecting data to investigate these connections by asking participants aged 65 years or older to complete a 10-minute telephone interview consisting of standard memory and cognitive function tests. More than 6000 men are taking part in these interviews.

■ Although factors such as obesity or physical inactivity have been associated with an increased risk of **hypertension**, data on the core biological underpinnings of this condition, which affects 50 million U.S. adults, are sparse. Using blood samples collected at the start of the PHS, Howard Sesso, ScD, and

colleagues will compare the biochemical profiles of 400 randomly selected men who develop hypertension during follow-up with those of 400 men who do not. The comparison is expected to yield a deeper understanding of the fundamental biological pathways that underlie the onset of hypertension and may thus lead to better preventive and therapeutic strategies.

■ **Prostate cancer** is the most common cancer in men. In some individuals, the disease progresses slowly, whereas in others, the cancer

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“Data collected from all PHS participants will address important questions about the development of chronic diseases.”

Dear Doctor,

As the Physicians' Health Study enters its 22nd year, we wish to express our gratitude to each of you for your continuing commitment and extraordinary dedication to this important research endeavor. The rates of questionnaire completion remain very high, with more than 95% of physician participants providing annual updates on their health, even after two decades. The rates of pill taking and follow-up among those enrolled in the PHS II vitamin trial have also been excellent. The average length of participation in this trial is approaching 5 years. The PHS II trial is funded through June 2007. Although pill taking will most likely not extend beyond that time, we hope to secure additional funding to continue sending all PHS participants yearly questionnaires to update information on health events and risk factors for disease. This will allow us to continue to use and to build upon the wealth of data already gathered to explore new hypotheses, as well as to resolve existing uncertainties, about health promotion and disease prevention in men. Thank you!

Drs. J. Michael Gaziano and Julie Buring
PHS Principal Investigators



Recent findings from the PHS

The importance of outcome information

The success of the PHS is contingent upon a sufficient number of participants reporting their health information. On annual questionnaires, we ask whether you have developed various outcomes, including cardiovascular disease and cancer, or have had medical procedures relating to these conditions. In addition, many of you notify us of changes in your health status via interim letters and telephone calls. Your assistance in the documentation and verification of health outcomes is a critical component of the PHS. This information enables us not only to test whether vitamin supplements reduce the risk of cardiovascular disease and cancer but also to examine many other hypotheses regarding disease prevention and health promotion in men.

What happens when you report a health event of interest? After obtaining your written permission to do so, we contact the hospital or attending physician and ask for a copy of the relevant medical records. Using standardized clinical criteria, a committee of four PHS physician researchers blinded to your treatment assignment then reviews the records to confirm the reported diagnosis or procedure. The committee is blinded to prevent knowledge of treatment status from consciously or subconsciously affecting the interpretation of the medical record data. All medical records are kept confidential (see related stories on page 3).

Thanks to your efforts, we have achieved very high confirmation rates for cardiovascular, cancer, and other outcomes among the medical records reviewed to date.

Cholesterol and ischemic stroke. Although clinical trials of statins indicate that these medications reduce the risk of developing ischemic stroke, observational studies have not found consistent associations between high cholesterol levels and subsequent stroke. Indeed, cholesterol and triglyceride levels were not predictive of ischemic stroke over 12 years of follow-up in the PHS, suggesting that statins may prevent stroke by a mechanism other than cholesterol reduction. *Stroke* 2003;34:2930-2934.

Inhibition of clinical benefits of aspirin by other nonsteroidal anti-inflammatory drugs (NSAIDs). The PHS and other clinical trials have demonstrated that aspirin greatly reduces the risk of having a first myocardial infarction. However, new analyses from the PHS suggest that the regular use of other NSAIDs may interfere with the cardioprotective effect of aspirin. In the cohort as a whole, men randomized to aspirin were 44% less likely to have a first MI than were men randomized to placebo. However, men in the aspirin group who also elected to use

other NSAIDs on a regular basis (i.e., more than 60 days per year) did not experience this benefit. *Circulation* 2003;108:1191-1195.

Breakfast cereals and mortality. Dietary guidelines recommend consumption of grain products to maintain health and prevent chronic disease. However, most grain products eaten in the U.S. are highly refined, which often leads to the loss of potentially beneficial micronutrients, antioxidants, minerals, and fiber. Although observational studies suggest that substituting whole-grain products for refined-grain products may lower the risk of cardiovascular and other diseases, there are few data on the association between consumption of breakfast cereal, a major source of whole and refined grains in this country, and premature mortality. Eating whole-grain breakfast cereals may reduce total and cardiovascular mortality, suggests a 5.5-year follow-up of PHS participants. No protective effect was observed for refined-grain cereals, however. *American Journal of Clinical Nutrition* 2003;77:594-59.

Genetics of myocardial infarction. Blood samples supplied by PHS participants are providing a unique database for genetic analyses. (As with all PHS studies approved by the Institutional Review Board of Brigham and Women's Hospital, participants are never identified and their information is held in the strictest confidence.) One such analysis examined mutations in the gene coding for peroxisome proliferator-activated receptor gamma-2, a protein involved in lipid metabolism, inflammation, and other processes that play a role in the development of atherothrombosis. Men with a common genetic mutation—an alanine for proline substitution—were about 25% less likely to develop myocardial infarction over 13 years of follow-up than were other men. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2003; 23:859-863. In another study, common genetic variations in the gene coding for apolipoprotein E, another protein that regulates lipid metabolism, were not related to risk of myocardial infarction in the PHS. *Atherosclerosis* 2003;166: 323-329.

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is more aggressive. PHS researchers, led by Meir Stampfer, MD, DrPH, and Jing Ma, MD, PhD, have initiated a study of genetic and cellular markers in prostate tumor specimens to better understand what factors may prolong

survival after prostate cancer diagnosis. All PHS participants diagnosed with prostate cancer will be contacted and asked for information about their cancer diagnosis and treatment and for permission to obtain their prostate cancer specimens from

hospitals. These samples will be analyzed using state-of-the-art genetic and tissue microarray techniques. The response from PHS participants to this substudy has been enthusiastic, with more than 95% of the 1000 physicians invited to date agreeing to take part.

■ Why was beta-carotene dropped from the PHS II trial?

We decided not to continue the beta-carotene component of the trial because the important scientific questions regarding the health effects of beta-carotene supplementation have been satisfactorily answered. Based on two decades' worth of data contributed by PHS participants, beta-carotene did not reduce the risk of total cardiovascular disease, total cancer, or total mortality. You will be reassured to learn that no serious adverse health effects of beta-carotene supplementation were observed in the PHS, even among men who took the vitamin for the longest periods of time.

■ I recently suffered a myocardial infarction. Am I out of the study?

No, you are definitely not out of the study! Although one of the main goals of the PHS is to test whether vitamin supplements can reduce the risk of developing MI, there are many other outcomes being examined in the study. While the health and risk factor information that we collect from you after your MI will not be used to study which factors predict the development of a first MI, this information will still be very important in analyzing the effect of vitamin supplements (as well as other exposures) on cardiovascular outcomes other than MI

(such as stroke) and on noncardiovascular outcomes (such as cancer and eye disease). It is therefore crucial that we continue to include your health experience as the study progresses.

■ I am a PHS II participant, but I haven't taken my study pills in a while. Is there any point in resuming now?

Yes! Every participant is irreplaceable. A fundamental principle of clinical trial research is summed up by the adage, "Once randomized, always analyzed." Restating this in everyday language, every single man who was randomized to take either active agent or placebo—even if he subsequently stopped taking his pills!—must be classified as a member of the group to which he was assigned, and analyzed as such, to maximize the chance of obtaining a valid study result. Participants who do not take their assigned pills dilute the observed health effects of the vitamins being tested. Resuming your study pills now will help enable the PHS II to determine whether these vitamins can prevent cardiovascular events, cancer, and other diseases in men. If you wish to resume taking the study pills and need calendar packs, please call us toll-free at 1-800-633-6907.

Julie E. Buring
J. Michael Gaziano

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>.

HIPAA: How new privacy regulations affect PHS

As a fellow healthcare provider, you are probably aware that the Health Insurance Portability and Accountability Act (HIPAA) went into effect on April 14, 2003. This federal law has two purposes: (1) to protect health insurance coverage for workers when they change or lose their jobs, and (2) to protect the privacy of individuals' healthcare information. Although many states already have more stringent measures in place than those introduced by HIPAA, the Act guarantees basic rights and protections for all Americans.

The HIPAA privacy rule has had a far-reaching impact in both clinical and research settings. However, we have not had to make any major changes in our rigorous privacy policies, and HIPAA will not materially affect your experience as a participant in the PHS. This is because we have always taken every available precaution to protect your privacy. We allow only authorized personnel to access your personal information, and we require your written permission before reviewing any pertinent medical records. When we do share study data with other scientists, we never include personal identifiers such as participants' names or social security numbers.

Because of these safeguards, the confidentiality of your PHS data has always been maintained. We remain committed to protecting your privacy as a study participant and will continue to take all necessary steps to shield your private information while advancing the study of men's health. We appreciate your continued collaboration and are grateful for the trust that you have placed in us.

“the confidentiality of your PHS data has always been maintained”

Certificate of Confidentiality

To help protect your privacy, we have obtained a Certificate of Confidentiality from the federal government. With this Certificate, PHS researchers cannot be forced to disclose your identity, or other information about you collected in PHS, in any legal proceedings at the federal, state, or local level. If needed, of course, you can ask us to disclose some of this protected information to your physician or insurance company without violating this Certificate of Confidentiality. In addition, federal agencies may review our records under limited circumstances, such as a request from the Department of Health and Human Services for a program evaluation or audit, or a request from the Food and Drug Agency under the Food, Drug, and Cosmetic Act. These agencies are also required to safeguard your privacy, however. Your trust is essential to the success of the study, and we would never do anything to risk losing your faith in us.

PHS out and about



■ **Irwin Weisbrot, MD**, of Norwalk, Connecticut, writes, "I'll keep flying as long as I can pass the FAA flight physical. Your pills keep me fit to fly!" The 74-year-old pilot is pictured in a Grob 115C aircraft at Bridgeport Airport.



■ **Michael Bornemann, MD**, of Honolulu, Hawaii, writes, "Thanks for the PHS tie! It goes well with my local attire." This photo was taken about a mile from his home.



■ **Arthur Frank, MD**, of Washington, DC, recently returned from a mountain-trekking trip in Ethiopia. During the trip, he writes, "I didn't miss a single pill."



■ **Harold Evans, MD**, of Grand Forks, North Dakota, recently took his pill packs on a 24-day cruise. The ship departed from Cape Town, South Africa, traveled across the Atlantic Ocean, and stopped at numerous islands off the coast of Antarctica and South America, before arriving at Santiago, Chile. This photo was taken at Tristan da Cunha, which, according to the Guinness Book of World Records, is "the remotest inhabited island in the world." Its nearest neighbors are the island of St. Helena, which is 1450 miles to the north, and Cape Town, which is 1726 miles to the east.



■ **Milam Cotten, MD** (on the left), and **Charles Parkman, MD**, who are next-door neighbors in Hattiesburg, Mississippi, are both enrolled in the PHS but were unaware of each other's participation in the study until, on a recent hiking trip in Yosemite National Park, they each started the day taking their pills on the trail. Thus, the two men are "quadruple bonded" as neighbors, hikers, physicians, and PHS participants.



■ **Robert Kan, MD**, of Towson, Maryland, pictured at the Pompidou Center in Paris, France, writes, "I am having an excellent time here, the city is gorgeous, the museums and exhibits are excellent, and the food is ...well, you know about that." To offset the culinary indulgence, "I'm getting plenty of exercise walking around and up and down the endless stairs of the Metro system (not disabled-friendly)!!"



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