PHYSICIANS' HEALTH STUDY *NEWSLETTER* **SUMMER 2009**

Dear Doctor,

As the Physicians' Health Study enters its 28th year, we wish to thank you for your extraordinary commitment to this landmark research endeavor. The PHS started in 1982 as a randomized trial testing the benefits and risks of aspirin and beta carotene in the primary prevention of cardiovascular disease and cancer. The trial found that aspirin dramatically cut the risk for a first myocardial infarction, 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. That trial ended in 1995, and many of you entered the ongoing PHS II, which recently reported no benefit or harm for vitamin E or C supplements on cardiovascular disease and cancer, and continues to test a standard daily multivitamin. We continue to send all PHS participants periodic questionnaires to update information on health events and risk factors. By completing these questionnaires, you allow us to build upon the wealth of data you have already provided to explore important new hypotheses and resolve existing uncertainties about health promotion and disease prevention in men. Indeed, the PHS has greatly advanced our knowledge about the prevention of cardiovascular disease, cancer, and other chronic diseases in men—and, with your assistance, will continue to do so for the foreseeable future. We are pleased to report that questionnaire completion rates remain very high, with the majority of the original 22,071 physician participants providing periodic updates on their health! Below is a sampling of recent research findings and ongoing research projects within the PHS.

With warm regards,

J. Michael Gaziano Julie E. Buring

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

RECENT FINDINGS FROM THE PHS

Vitamin E and C supplements of no benefit for cardiovascular disease or cancer prevention. The Physicians' Health Study II was initiated in 1997 to test the balance of benefits and risks of vitamin E, vitamin C, and a multivitamin 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 trial of aspirin and beta carotene. The multivitamin component remains ongoing, while the vitamin E and vitamin C components ended as scheduled in 2007. PHS researchers recently reported that vitamin E and vitamin C supplements do not decrease—or increase—the risk for major cardiovascular events or cancer (Sesso HD et al., *JAMA* 2008; 300:2123-2133; Gaziano JM et al., *JAMA* 2009; 301:52-62).

Predictors of exceptional longevity. Most studies of healthy aging and exceptional longevity are dominated by data on women. The PHS is one of the largest cohorts of long-lived men; as of March 2009, 1556 participants had lived to age 90 or older. Men with healthy behaviors, including smoking abstinence, weight management, blood pressure control, and regular exercise, are not only more likely to survive to age 90 but also to have good health and function at an advanced age (Yates LB et al., *Archives of Internal Medicine* 2008; 168:284-290).

Vitamin D and prostate cancer. Data from the PHS suggest that many men have suboptimal vitamin D levels and that vitamin D may play a key role in preventing prostate cancer. In the winter and spring, an estimated 77% of PHS participants had vitamin D insufficiency (i.e., plasma 25-hydroxyvitamin D_3 [25(OH)D] <32 ng/ml), and 36% had vitamin D deficiency (<20 ng/ml). In the summer and fall, these percentages dropped to 51% and 13%, respectively. Over 18 years of follow-up, men whose 25(OH)D and 1,25-dihydroxyvitamin D_3 levels were below the sample medians were twice as likely to develop aggressive prostate cancer as men whose levels were higher (Li H et al., *PLoS Medicine* 2007; 4:e103).

Fish intake and cancer. Fish is the main dietary source of marine omega-3 fatty acids, which may prevent cancer or delay its progression. During 22 years of follow-up in the PHS, men who ate fish five or more times per week were 37% less likely to develop colorectal cancer than were men who ate fish less than once per week (Hall MN et al., *Cancer Epidemiology, Biomarkers & Prevention* 2008; 17:1136-1143). Fish intake was unrelated to prostate cancer incidence but was associated with improved prostate cancer survival. Among men with prostate cancer, those who ate fish five or more times per week had a 48% lower risk for prostate cancer death than did men who ate fish less than once weekly (Chavarro JE et al., *American Journal of Clinical Nutrition* 2008; 88:1297-1303).

ONGOING RESEARCH PROJECTS IN THE PHS

Restless legs syndrome and cardiovascular disease. Restless legs syndrome (RLS) is a neurological disorder characterized by unpleasant sensations in the legs and an urge to move them for relief. Because symptoms tend to be most intense when lying down, patients are often so sleep deprived that their work, social, and family life suffers. Little is known about the disease, which affects an estimated 7 to 10% of the population. In cross-sectional studies, RLS is associated with multiple cardiovascular risk factors, including smoking, diabetes, hypertension, and nocturnal increases in blood pressure. However, it is not known whether RLS is a cause or a consequence of an unfavorable cardiovascular profile. If the former, it is plausible that RLS is also a risk factor for clinical cardiovascular disease. Using data from the PHS and a similar study of women, Tobias Kurth, MD, ScD, and colleagues are examining the interrelationships between RLS, cardiovascular risk factors, and cardiovascular disease.

Pathogenesis of pancreatic cancer. Pancreatic cancer is the fourth most common cause of cancer-related mortality. Charles Fuchs, MD, MPH, and colleagues have combined data from the PHS with data from four other large, long-term studies of men and women to study the pathogenesis of pancreatic cancer. Three pathways are of particular interest: (1) energy balance, insulin, and insulin-like growth factor signaling; (2) inflammation; and (3) vitamin D-related pathways. Lifestyle factors (e.g., diet, obesity, physical activity, and analgesic use), nutrient and hormonal biomarkers, and genetic factors related to these pathways will be examined as predictors of pancreatic cancer incidence as well as specific molecular alterations in pancreatic cancer specimens. A better understanding of underlying mechanisms should lead to strategies to reduce the incidence of and mortality from this highly lethal malignancy.

Genes, sex hormones, and prostate cancer. A gene translocation called the *TMPRSS2:ERG* fusion was recently identified in prostate cancer tumors, generating excitement for two reasons. First, until this discovery, translocations, although common in leukemias and lymphomas, were thought to be rare in solid tumors such as prostate cancer. It is now known that 40 to 50% of prostate tumors contain this translocation. Second, the translocation affects the gene *TMPRSS2,* which is regulated by testosterone and is also bound to a gene family involved in invasion and metastasis. It is possible that knowing about the *TMPRSS2:ERG* fusion will help clarify testosterone's role in prostate cancer progression and the reason for androgen deprivation therapy's effectiveness in slowing that progression. Lorelei Mucci, PhD, and colleagues will assay tumor tissues collected from PHS participants for the presence of this fusion, determine whether men whose tumors contain the fusion are at greater risk of prostate cancer progression, and examine whether levels of sex hormones or variation in genes involved in sex-hormone signaling or metabolism interact with the fusion to affect prostate cancer progression. More than 100,000 men diagnosed with prostate cancer each year are believed to have a fusion-positive tumor. If these tumors are indeed more aggressive, understanding the effect of the *TMPRSS2:ERG* fusion on prostate cancer survival in light of the hormonal milieu could illuminate opportunities for prevention or improve patient selection for specific therapeutic interventions.