Observational studies suggest that vitamin E, consumed through diet or supplements, may lower the risk of cardiovascular disease (CVD) and cancer. Yet critics have argued that these apparent benefits may simply reflect the fact that individuals with high vitamin E intake tend to have other health-promoting characteristics or habits, or that foods rich in vitamin E contain other nutrients that might account for the protective effect. Randomized trials such as the PHS II are less susceptible to these biases because the treatment status of participants is determined by chance rather than by the participants themselves.

Trial results published in the last several years indicate that supplementation with high doses of vitamin E does not protect against cardiovascular events among persons at high risk of such events (i.e., those with preexisting CVD or cardiovascular risk factors). The most recent of these trials, known as the HOPE-TOO study, included 7000 Canadian men and women aged 55 and older with heart disease, peripheral artery disease, stroke, or diabetes who took vitamin E or a placebo for 7 years. Myocardial infarctions (MI), strokes, and cardiovascular-related deaths were just as common in the vitamin E group as in the placebo group.

Fewer trials have tested whether vitamin E supplements can prevent CVD in initially healthy individuals. The ongoing PHS II and our recently completed Women’s Health Study, taken together, should provide a definitive answer to that question. As reported in the July 6, 2005 issue of JAMA, the Women’s Health Study found that 10 years of vitamin E supplementation did not reduce total CVD, MI, stroke, or total mortality in a cohort of nearly 40,000 healthy female health professionals aged 45 and older. However, vitamin E did reduce cardiovascular deaths among these women, as well as total CVD in the subgroup of women aged 65 and older, a group that comprised only 10% of the study population yet suffered one third of all cardiovascular events.

With respect to cancer outcomes, randomized trial data are more limited. Both the Women’s Health Study and HOPE-TOO found that vitamin E supplements did not reduce overall cancer incidence. However, the Alpha-Tocopherol, Beta-Carotene (ATBC) Trial, which studied 29,000 Finnish male smokers, suggested a benefit of vitamin E in the prevention of prostate cancer, and this hypothesis is being tested in PHS II and in the ongoing Selenium and Vitamin E Cancer Prevention Trial (SELECT).
than 35,000 healthy U.S. and Canadian men aged 50 and older have been assigned to take vitamin E, selenium (a mineral with antioxidant properties), both agents, or placebos for 7 to 10 years.

Several PHS participants have asked whether the use of vitamin E supplements carries any risks. In 2005, a much-publicized analysis of 19 vitamin E trials suggested that use of high doses (above 400 IU per day) slightly increased in size and included people with heart disease, cancer, or other chronic conditions, so E is to blame, or that these findings would also apply to initially healthy individuals. No such hazard was found in population. Preparing for this “aging revolution” requires understanding how to ensure good health and function during older years. Almost all 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; more than 860 participants have lived to age 90 or older, and 750 participants are now aged 87 to 89. Laurel Yates, MD, MPH, and her colleagues are seeking to determine the factors responsible for the exceptional survival of these men and, for many, their remarkably good health. Participants aged 90 or older will be contacted by phone or mail and asked about their current health and function, including mobility; memory and cognitive function; vision and hearing; quality of life; connections to family and friends; and emotional well-being. Combined with data from annual questionnaires and baseline blood samples, these assessments will allow researchers to determine physiologic and behavioral factors important for reaching exceptional age with good physical and cognitive function and sense of well-being. The results should help guide development of age-appropriate strategies to promote and maintain good health and robust function during later life.

Men and women aged 85 and older are the fastest growing segment of the U.S. population. Preparing for this “aging revolution” requires understanding how to ensure good health and function during older years. Almost all 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; more than 860 participants have lived to age 90 or older, and 750 participants are now aged 87 to 89. Laurel Yates, MD, MPH, and her colleagues are seeking to determine the factors responsible for the exceptional survival of these men and, for many, their remarkably good health. Participants aged 90 or older will be contacted by phone or mail and asked about their current health and function, including mobility; memory and cognitive function; vision and hearing; quality of life; connections to family and friends; and emotional well-being. Combined with data from annual questionnaires and baseline blood samples, these assessments will allow researchers to determine physiologic and behavioral factors important for reaching exceptional age with good physical and cognitive function and sense of well-being. The results should help guide development of age-appropriate strategies to promote and maintain good health and robust function during later life.

Ongoing research projects in the PHS

Thanks to your efforts, the PHS has advanced our understanding of health and disease in men in many ways. Although the primary goal of the trial is to determine whether various vitamins can prevent cardiovascular disease and cancer, data collected from PHS participants are also being used to address a wide variety of research questions concerning the influence of lifestyle, clinical, biochemical, and genetic variables on health and the development of chronic diseases.

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PHS researchers are collaborating with other cancer research groups in the U.S. and Europe in the “Cancer Consortium,” an initiative funded by the National Cancer Institute to accelerate research on the role of gene-environment interactions in the development of cancer. Data from the PHS have been combined with data from other large studies of men and women to create a dataset of nearly 800,000 participants. Using this dataset, David Hunter, MBBS, ScD, and his consortium colleagues are currently investigating how variations in genes that control hormone production and function interact with hormonal and lifestyle factors to influence the risk of developing prostate cancer and breast cancer. This research is expected to provide a deeper understanding of the fundamental biological pathways that underlie the onset of these cancers and may thus lead to better preventive and therapeutic strategies.

The prevalence of obesity in the U.S. has soared in recent decades, jumping from 15% in 1980 to 30% in 2002. This marked rise in obesity has been accompanied by a sharp increase in the incidence of type 2 diabetes, which now affects almost 8% of U.S. adults. In addition, an estimated 40% have “prediabetes” (i.e., impaired fasting glucose levels or impaired glucose tolerance). Emerging data suggest that sex steroid hormones, such as testosterone and estradiol, and hormones derived from fat cells, such as tumor necrosis factor-alpha and adiponectin, may be associated with risk of developing type 2 diabetes. Variation in genes related to hormone metabolism and to adiposity and insulin resistance may also be important in determining diabetes risk. To test these hypotheses, Simin Liu, MD, ScD, and colleagues will compare hormone and hormone-related gene profiles of 1200 PHS participants who develop diabetes during follow-up with the profiles of participants who do not.

Apart from nonmelanoma skin cancer, prostate cancer is the most common cancer among men in the U.S. Saw palmetto, an extract derived from the berry of the American palm tree, can dampen the activity of 5-alpha reductase, an enzyme that converts testosterone to dihydrotestosterone and that is thought to promote the development of prostate cancer. Saw palmetto has been shown to reduce symptoms of benign prostatic hyperplasia and to curb the growth of prostate cancer cells in vitro. However, no epidemiologic data are available regarding its association with risk of prostate cancer. To examine this question, I-Min Lee, MBBS, ScD, and colleagues have asked all PHS participants to provide details on their use of this plant extract.
Recent findings from the PHS

Plasma C-peptide and colorectal cancer. Colorectal cancer and type 2 diabetes share many risk factors, including a diet high in calories, animal fat, and refined carbohydrates, and low in fiber; physical inactivity; and obesity. In addition, individuals with type 2 diabetes have an increased risk of colorectal cancer. These observations have led to the hypothesis that hyperinsulinemia may promote the development of colorectal cancer. During 13 years of follow-up, PHS participants with elevated insulin production, as reflected by a C-peptide level in the top 20% of the sample distribution, were 2.7 times more likely to develop colorectal cancer than their counterparts with C-peptide levels in the bottom 20%, after adjustment for body mass index and other factors related to hormone resistance. Journal of the National Cancer Institute 2004;96:546-553.

Genes influence the relationship between beta-carotene supplementation and prostate cancer. An excellent example of how genes and the environment interact to influence the risk of disease is provided by a recent analysis of PHS data. Genetic variation in the gene coding for manganese superoxide dismutase (MnSOD), the primary antioxidant enzyme in mitochondria, has been linked to prostate cancer risk. Among men at high baseline risk of prostate cancer by virtue of their MnSOD genotype, beta-carotene supplementation significantly reduced the risk of developing prostate cancer. Among men with lower-risk MnSOD genotypes, however, beta-carotene supplementation had no effect on prostate cancer risk. Cancer Research 2005;65:2498-2504.

Analgesic use and renal function. Whether the use of aspirin or other nonsteroidal anti-inflammatory drugs increases the risk of chronic renal disease has long been debated. In the PHS, changes in creatinine levels and glomerular filtration rates over 14 years of follow-up were similar among men who did not use analgesics and those who did, even at total cumulative intakes of 2500 or more pills. These findings suggest that chronic analgesic use does not lead to a decline in renal function. American Journal of Kidney Diseases 2003;42:234-44.

PHS Fund

At the request of a few participants, the PHS is in the process of creating a special fund through which donations earmarked for research purposes can be made to the study. Details will be forthcoming in subsequent communications. Please contact us at 1-800-633-6907 or phs@rics.bwh.harvard.edu with any questions.