



HEALTH PROFESSIONALS FOLLOW-UP STUDY NEWSLETTER

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Parkinson's Disease



Dr. Alberto Ascherio, leading investigator in Parkinson's Disease

IN THE PAST SEVERAL YEARS, the Health Professionals Follow-Up Study (HPFS) has made substantial progress in our search for risk factors for Parkinson's disease (PD). The most promising finding is that individuals with higher levels of serum urate have a markedly lower risk of developing Parkinson's disease—men in the top 25% of serum urate

distribution had about half the risk of PD than those in the bottom 25% (Weisskopf et al. *Am J Epidemiol.* 2007;166(5):561-567; Gao et al. *Am J Epidemiol.* 2008;167(7):831-838). Because urate is a potent antioxidant, and oxidative stress seems to be implicated in the pathogenesis of Parkinson's disease, this finding suggests that urate could exert a neuroprotective effect.

To further address this possibility, we collaborated with clinical colleagues to examine whether additional increases in urate could also contribute to predict the disease progression among individuals with Parkinson's disease. The results of these analyses have been

extremely promising (Schwarzschild et al. *Arch Neurol.* 2008;65(6):716-723). In fact, we are now conducting a randomized clinical trial to determine the safety and tolerability of urate elevation in patients with Parkinson's disease. It is important to remember that urate elevation may increase the risk of gout, kidney stones, and possibly cardiovascular disease, and therefore attempts to elevate urate should not be undertaken outside of a rigorously monitored trial.

Among other findings is the increased risk (about two-fold) of Parkinson's disease among individuals with red hair, which seems to be explained by the underlying variation in a gene called melanocortin-1 receptor (Gao et al. *Ann Neurol.* 2008, in press). This association suggests that the higher-than-expected frequency of melanoma observed among individuals with Parkinson's disease is not, as previous thought, an adverse effect of levodopa treatment.

Our research program on Parkinson's disease is now in rapid expansion and we expect within a few years to be able to translate some of our findings into new and better ways to prevent and treat Parkinson's disease.

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Vitamin D

IN THE PREVIOUS NEWSLETTER, we reported on our findings regarding vitamin D and cancer risk in the Health Professionals Follow-Up Study. We found that men low in vitamin D had a higher risk of cancer incidence, and especially cancer mortality (Giovannucci et al. *J Natl Cancer Inst.* 2006;98:428-430). The cancers most influenced—where the incidence risk was almost doubled—were those of the digestive system, including cancers of the oral cavity, esophagus, stomach, pancreas, colon and rectum.

In the past year, we extended our findings to include cancer survival. Combining data from the Health Professionals Follow-Up Study and the

Nurses' Health Study, we found that colorectal cancer patients with a better vitamin D status at the time of diagnosis had a significantly better survival than those with low vitamin D levels (Ng et al. *J Clin Oncol.* 2008;26(18):2984-91). This study was the first to suggest that vitamin D status may influence prognosis in addition to prevention. We also extended our interest in vitamin D beyond cancer to heart disease. Based on some suggestive evidence from other studies of a potential benefit of vitamin D in preventing cardiovascular events, we examined whether vitamin D level predicted risk of coronary heart disease and fatal cardiovascular disease. We found that men

with low vitamin D levels (<15 ng/ml) had double the risk of cardiovascular disease than did men with sufficient levels (>30 ng/ml) (Giovannucci et al. *Arch Intern Med.* 2008;168(11):1174-80). The increased risk was much higher for men whose cardiovascular event was fatal. Of note, this association existed after accounting for the major cardiovascular risk factors.

These results, which need to be confirmed, indicate that a low level of vitamin D may be an important additional risk factor for heart disease. Although the optimal dose still needs to be worked out, it now appears that 1000 IU/day might constitute an acceptable minimum dose. Obtaining at least this amount is thought to be an important part of one's health, especially for individuals living in northern regions during the winter months.

YOUR PRIVACY

As a HPFS participant, you provide us with very personal information through your questionnaires, medical records, and biological samples. We are grateful for your contributions and for the trust you have shown us in providing this information. We want to assure you that we protect your information in every possible way and hold ourselves to the highest standards in safekeeping and use of your data. We only allow authorized personnel to access your personal information, and we also code all of our genetic results so that they are never stored together with individual identifying information, among other security measures. We also have a Certificate of Confidentiality from the Department of Health and Human Services, which means that under current laws we cannot be forced to disclose information that may identify you in any legal proceedings.

Your trust is essential to the success of the study, and we would never do anything to risk losing that trust. Thank you for your continued commitment.

Prostate Cancer



Dr. Edward Giovannucci, leading investigator in Prostate Cancer

OVER THE YEARS, we have reported on a number of dietary and other lifestyle factors in relation to the development of prostate cancer in the Health Professionals Follow-Up Study. For some of the factors we have studied, our results are often, but not always,

in line with findings from other studies based in different populations of men. We suspect that part of the reason for the inconsistencies across studies lies in the methods of prostate cancer diagnosis and the considerable biologic heterogeneity of this disease. Since the onset of widespread PSA screening in the United States since the early 1990's, the nature of prostate cancer diagnosis has changed dramatically; specifically, many of the cancers are now diagnosed at a very early stage and are relatively less aggressive. Some important risk or preventive factors may influence primarily the progression of these lesions into advanced and fatal cancers, rather than the initiation of the tumors. Studies that examine only total prostate cancer, and not cancer progression defined by stage or mortality, may have missed these important factors, which influence mortality for prostate cancer.

We re-examined nine lifestyle and diet factors in relation to incident prostate cancer and fatal prostate cancer risk in order to understand the role of these in initiation and progression of prostate

cancer: cigarette smoking history, physical activity, body mass index, family history of prostate cancer, race, height, total energy consumption, and intakes of calcium and tomato sauce (Giovannucci et al. *Int J Cancer*. 2007;121(7):1571-8). In this analysis, only three factors had a clear statistically significant association with overall incident prostate cancer: African-American race, positive family history of prostate cancer, and higher tomato sauce intake (which was protective). In contrast, for fatal prostate cancer, recent smoking history, taller height, higher body mass index, family history, and high intakes of total energy and calcium were associated with a statistically significant increased risk, while higher vigorous physical activity level and higher tomato sauce intake were associated with lower risk, suggesting their involvement in disease progression.

This study confirms that many risk factors for prostate cancer affect the progression of the disease, rather than the occurrence. Smoking, obesity and physical inactivity had been considered relatively unimportant risk factors for prostate cancer, but now the evidence is strong that these increase mortality from prostate cancer. We are now examining in more detail whether changes in these risk factors after the diagnosis of prostate cancer can impact survival from this cancer. With the widespread use of PSA screening, the vast majority of men are living many years after the initial diagnosis of prostate cancer. Thus, it is critical to identify dietary factors that promote or inhibit the growth of the cancers after diagnosis.

Genetic Studies

IT IS WIDELY ACKNOWLEDGED in the scientific community that most chronic diseases have genetic components, or variations. However, until very recently, the genes implicated in most diseases have been poorly understood. The Health Professionals Follow-Up Study has started to look into this issue.

Revolutionary advances in genotyping technology and availability of a catalog of human genome variations enable scientists to search for relevant genes over the whole genome. Using the new research approach, we have successfully identified genetic variations in chromosome 8 that increase the risk of prostate cancer (Yeager et al. *Nat Genet.* 2007;39:645-9). Recently we have found four new genes/regions related to prostate cancer risk (Thomas et al. *Nat Genet.* 2008;40:310-5). Though the mechanisms underlying these findings have to be clarified further in functional tests, this information can be useful in distinguishing men who are at high risk for developing prostate cancer from those who are at low risk.

In 2007, UK scientists found the first obesity gene through a genome-wide scan. We confirmed that this gene, called the fat mass- and obesity-associated (FTO) gene, is related to a 20 percent increased risk of obesity in both men and women from the Health Professionals Follow-Up Study and from the Nurses' Health Study, respectively (Qi et al. *Diabetes.* 2008;57:3145-51). Interestingly, we found the genetic effects declined in men greater than 65 years old.

In related news, we found that the inflammatory marker C-reactive protein (CRP) gene is associated with CRP levels and up to a twofold increase in risk of coronary heart disease. The data provide evidence for the causal role of inflammation in coronary heart disease (Pai et al. *PLoS ONE.* 2008;3:e1395). Through funds from the National Institutes of Health and other resources, we are now simultaneously screening thousands of genes across the human genome for their relations to obesity, diabetes and coronary heart disease.

We also examined the interactions between genes and environmental factors. Alcohol consumption has shown protective effects on coronary heart disease, partly through increasing high-density lipoprotein cholesterol (HDL-C). Our recent study suggests that a lipid-related gene, cholesteryl ester transfer protein (CETP), modifies the relationship between alcohol intake and HDL-C and thus effects the risk of coronary heart disease (Jensen et al. *Eur Heart J.* 2008;29:104-12). This gene also interacts with consumption of animal fat, saturated fat, and monounsaturated fat in relation to HDL-C in diabetic men (Li et al. *Am J Clin Nutr.* 2007;86:1524-9). Our findings further demonstrate that environmental (diet and lifestyle) and genetic factors may act in tandem in determining complex diseases. This gene-environment interaction provides scientific rationale for tailoring future diet and lifestyle interventions from a one-size-fits-all approach to a more efficient, personalized one.

Dental/Oral Health

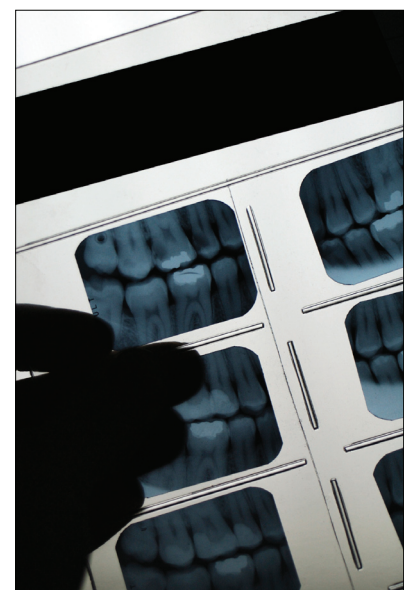
TO CLARIFY THE RELATIONSHIPS between dental infection and risk of coronary heart disease (CHD), root canal therapy (as a measure of pulpal inflammation) was studied as a risk factor for the onset of heart disease (Joshiyura et al. *JOE*. 2006; 32(2):99-103). We found that compared to men with no history of root canal therapy, those with one or more occurrences experienced a 21% greater rate of CHD. This association was limited to the dentists in the Health Professionals Follow-Up Study; studied separately, this group showed a 38% higher risk of CHD among those who had had root canal therapy. Dental caries was not associated with CHD.

We also studied intake of carotenoids and vitamins C, E, and A, and the risk of oral pre-malignant lesions, or OPLs (Maserejian et al. *Int J Cancer*. 2006; 120:970-977). There were 207 cases of OPLs among HPFS participants between 1986 and 2002. Total intake of vitamin C, vitamin A, or carotenoids was not associated with risk of OPLs, though dietary (non-supplement) intake of vitamin E was weakly associated with increased risk of OPLs, particularly among current smokers. Vitamin C from dietary sources was associated with lower risk of OPLs.

In related analyses, we found an inverse association between intake of some fruits and risk of OPLs; after adjusting for other

important risk factors, reduced risk of OPLs was observed among those with higher intake of citrus fruits and citrus fruit juices (Maserejian et al. *Am J Epi*. 2006; 164:556-566). Intake of vitamin C-rich fruits and vegetables was also associated with lower risk. No consistent associations were found for other vegetables.

Recently we reported on the relationships between periodontal disease, tooth loss, and the risk of overall and site-specific cancers (Michaud et al. *Lancet Oncol*. 2008;9:550-558). After adjustment for known risk factors, we found that a history of periodontal disease was associated with increased risk of lung, kidney, pancreatic, and hematological cancers. Having fewer teeth at baseline (0-16 vs. 25-32) was associated with increased risk of lung cancer. Among men who had never smoked, however, no association was observed between periodontal disease and lung cancer, suggesting that the association among current or former smokers may be largely or wholly due to a residual confounding effect of smoking.



FOCUS ON OUR Research Team



CURRENTLY, OVER TWO MILLION MEN IN THE UNITED STATES are prostate cancer survivors. Although our research group continues to study a number of diet and lifestyle factors in relation to the development of prostate cancer, we are also focusing on identifying factors that may reduce prostate cancer recurrence and progression and increase survival after a prostate cancer diagnosis. The Prostate Cancer Survivor's Study began in 2000 in order to accomplish these goals. We are following this cohort of survivors every two years to inquire about further treatments and prostate cancer recurrence and progression, in addition to asking about new factors that may be relevant to disease progression or survival. Our last biennial questionnaire included questions related to quality of life, and asked men to report urological symptoms and severity of these symptoms. We are also beginning to look at markers in the tumor tissue, blood, and DNA to explore relevant biological pathways that may lead to progression. To date, we have over 3,600 participants in our survivor's cohort, and have 1,052 progression outcomes.

There are many people at the Harvard School of Public Health who are involved with the Survivor's Study. **Dr. Meir Stampfer** and **Dr. Edward Giovannucci**, both Professors of Nutrition and Epidemiology, oversee the project. **Dr. Lorelei Mucci**, Assistant Professor of Epidemiology and Nutrition, is involved with tissue collection and biomarkers. Their efforts are joined by **Dr. Stacey Kenfield**, post-doctoral Research Fellow, as the Project Supervisor of the Survivor's Study. Data are coded by **Dr. Preet Dhillon**, post-doctoral Research Fellow, **Russ DeSouza**, doctoral student in Nutrition, and **Lauren McLaughlin**, Research Assistant for the Health Professionals Follow-Up Study.

About the Study

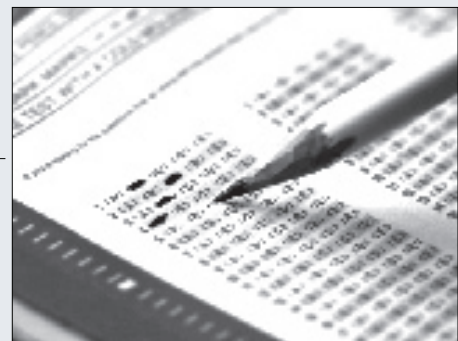
THE HEALTH PROFESSIONALS Follow-Up Study (HPFS) began in 1986. The purpose of the study is to evaluate a series of hypotheses about men's health relating nutritional factors to the incidence of serious illnesses, such as cancer, heart disease, and other vascular diseases. This all-male study is designed to complement the all-female Nurses' Health Study, which examines similar hypotheses. The HPFS is sponsored by the Harvard School of Public Health and is funded by the National Heart, Lung, and Blood Institute and National Cancer Institute.

In the beginning, Walter Willett, Principal Investigator, Meir Stampfer, and colleagues enlisted 51,529 men in health professions to participate in the study. This group is composed of 29,683 dentists, 4,185 pharmacists, 3,745 optometrists, 2,220 osteopathic physicians, 1,600 podiatrists, and 10,098 veterinarians. Among the study participants are 531 African-Americans and 877 Asian-Americans.

The researchers selected health professionals in the belief that men who chose these types of careers would be motivated and committed to participating in a long-term project and would appreciate the necessity of answering the survey questions accurately.

Every two years, members of the study receive questionnaires with questions about diseases and health-related topics like smoking, physical activity, and medications taken. The questionnaires that ask detailed dietary information are administered in four-year intervals.

Since its inception, more than 400 published research articles have been produced by scientists working with data from the study.



HPFS II

We are currently in the pilot phase for the Health Professionals Follow-Up Study II, which will be predominantly web-based. This study includes a new cohort of men ages 30-60, and its chief goal is to examine the effects of diet and lifestyle on health beginning earlier in adult life.

Frequently Asked Questions

Q: I have retired. Would you still like me to participate?

A: Your continued participation is still extremely important. We value your contribution regardless of your work status. If you have retired or changed professions, we would like you to remain part of the Health Professionals Follow-Up Study. Please inform us of any new addresses or other contact information changes so that we can keep you abreast of any new information and send you the most recent questionnaire and newsletter. To update your contact information, email the Project Coordinator at hpfs@hsph.harvard.edu

Q: Based on your results, what would you recommend as a healthy diet?

A: The Department of Nutrition at the Harvard School of Public Health has a good website to use as a reference. This website contains information regarding the food pyramid, fats and cholesterol, carbohydrates, protein, fiber, fruits and vegetables, and vitamins, as well as other nutrition information. Access the site at www.hsph.harvard.edu/nutritionsource



THANK YOU AGAIN for your valuable participation!
We are truly grateful for all you have provided.

To report an address change or make a comment or provide feedback, please email the Project Coordinator at hpfs@hsph.harvard.edu or contact us at the address or phone number below:

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