



HEALTH PROFESSIONALS FOLLOW-UP STUDY NEWSLETTER

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PROSTATE CANCER SURVIVOR STUDY

WITH WIDESPREAD USE OF PSA SCREENING, many men are living with the diagnosis of prostate cancer. You may be aware of our studies looking at diet and the risk of developing prostate cancer, but it is also critical to identify dietary factors that promote or inhibit the cancer's growth after diagnosis. Despite its relevance to many men, this topic has received surprisingly little study.

The Health Professionals Follow-Up Study has started to look into this issue. To date, we have observed 392 progression outcomes among 1,202 men diagnosed with incident localized/regional prostate cancer between 1986 and 1996. Most of these outcomes were based on a rise in PSA after initial surgery or radiation treatment. At this point, our studies have shown an association between greater tomato sauce and fish consumption, especially fatty fish such as salmon, and a reduced risk of



progression. Conversely, higher milk intake was associated with a moderate increase in risk (Chan et al. *Cancer Causes Control* 2006;17:199-208). While our preliminary findings need to be confirmed with additional follow-up, they are promising and support our continued efforts in this area.

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VITAMIN D AND CANCER

VITAMIN D HAS RECEIVED CONSIDERABLE ATTENTION recently for its potential role in preventing some cancers and a number of other health conditions. There is a strong biologic basis for the association between vitamin D and cancer risk, which the Health Professionals Follow-Up Study has recently examined.

Based on your information, we considered multiple determinants of vitamin D exposure. These determinants include dietary and supplementary vitamin D, skin pigmentation (estimated by race), adiposity, geographic residence, and leisure-time physical activity (to estimate sunlight exposure) in relation to cancer risk. We found that men likely to have low levels of vitamin D had a higher risk of cancer incidence, and increased cancer mortality (Giovannucci et al. *J Natl Cancer Inst* 2006;98:428-430). These men had nearly twice the risk of developing cancers of the digestive system—the cancers most influenced by vitamin D—including those of the oral cavity, esophagus, stomach, pancreas, colon and rectum (Skinner et al. *Cancer Epidemiol Biomarkers Prev* 2006;15:1688-1695).

Our findings also suggested that the current recommendations for vitamin D (200 IU/day for those under 50 years of age, 400 IU/day for those 50 to 70, and 600 IU/day for those older than 60 years) might be inadequate to achieve optimal benefits, particularly for those with low sun exposure. Although the optimal dose still needs

to be worked out, it appears that 1,000 IU/day might be a minimum, especially for individuals in northern regions during the winter months. Current recommendations are not to exceed 2,000 IU/day, but new evidence suggests that this limit should be higher. In our continued follow-up of the study, we are working extensively to establish optimal vitamin D levels for cancers and other conditions, including diabetes, high blood pressure, osteoporosis and fractures, and heart disease.

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.

GALLSTONES

GALLBLADDER DISEASE, INCLUDING GALLSTONES, is prevalent in the United States, affecting 10 to 25 percent of adults. And although gallstone disease is more common in women, men are by no means immune. Since we began the Health Professionals Follow-Up Study in 1986, nearly 3,000 men have reported suffering from gallstone disease symptomatic enough to warrant gallbladder removal. While the actual prevalence of all gallstones is much higher, we have focused our studies for symptomatic gallstone disease.

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Obesity was the only previously accepted modifiable risk factor for gallstone disease, and we have further shown that the key is abdominal obesity, as measured by waist-to-hip ratio or simply waist circumference. Men with a waist circumference of 40 inches or more had 2.3 times the risk of gallstone disease compared with those whose waists measured approximately 34 inches or less. Not surprisingly, exercise was also associated with lower risk (Tsai et al. *Am J Clin Nutr* 2004;80:38-44).

In addition to obesity, we have shown that diet is a risk factor for gallstone disease, and our findings largely parallel what we observe for heart disease—that types of fats and carbohydrates are important. Specifically, high intake of polyunsaturated and monounsaturated fats in the context of an energy-balanced diet was associated with a reduced risk for gallstone disease in men (Tsai et al. *Ann Intern Med* 2004;141:514-522). Nuts are a particularly good source of these fats: men who consumed five one-ounce servings of nuts per week had a 30 percent lower risk of gallstone disease than men who rarely or never consumed nuts (Tsai et al. *Am J Epidemiol* 2004;160:961-968). However, trans-fat from partially hydrogenated oil appeared to be harmful (Tsai et al. *Arch Intern Med* 2005;165:1011-1015). Highly refined carbohydrates with a high glycemic index increased risk relative to less processed, high-fiber carbohydrate sources.

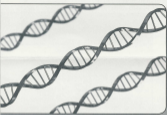
The strong similarities between risk factors for gallbladder and cardiovascular diseases should not be surprising, as high insulin and cholesterol production are strong risk factors for both, and are associated with diet, exercise, and obesity. This once again reinforces the idea that following a heart-healthy diet has many additional benefits.



DIABETES

A RESEARCH GROUP IN ICELAND RECENTLY DISCOVERED a new diabetes gene (transcription factor 7-like 2 (TCF7L2)). This discovery prompted us to examine whether this gene is associated with diabetes in a U.S. population. We evaluated a common variant on the gene in men from the Health Professionals Follow-Up Study and women from the Nurses' Health Study (Zhang et al. *Diabetes* 2006;55:2645-8). Consistent with the Icelandic study, we found that in both cohorts people who carried two copies of the risk allele had a nearly two-fold increased risk of diabetes. Although this association has also been replicated in other populations, our study represents the largest prospective cohort reporting on this gene and diabetes. Basic scientists are still exploring how this gene is associated with diabetes, but there is some evidence that it is related to reduced insulin secretion. Although this gene predicts diabetes risk, it is not ready to be implemented in genetic testing because its effects are relatively small compared to other known diabetes risk factors such as obesity, physical inactivity, and diet.

We also conducted a comprehensive study on another diabetes gene candidate (Interleukin 6 or IL-6) (Qi et al. *Hum Mol Genet* 2006; 15(11):1914-20). Unlike TCF7L2, variants on IL-6 gene do not appear to have an appreciable association with diabetes in either men or women. Studies like this are useful in ruling out genes that are not relevant to diabetes. Because of the considerable number of genes in the human genome, we plan to apply for NIH funds to simultaneously screen many thousands of genes.



We are also examining the interactions between genes and environmental factors. Our studies have shown that dietary factors such as saturated fat and alcohol use interact with the hepatic lipase gene to affect HDL (high-density lipoprotein) concentrations (Zhang et al. *Am J Clin Nutr* 2005;81(6):1429-35). Interestingly, obesity appears to modify the association between this gene and risk of coronary heart disease among diabetic men in the Health Professionals Follow-Up Study (Zhang et al. *Diabetologia* 2006; 49(7):1552-9). Specifically, obese men who carried a variant of the hepatic lipase gene had a nearly two and a half fold increased risk of heart disease compared to obese

men who did not carry the variant. This variant was not associated with heart disease in lean men. These analyses suggest that both genetic and environmental factors are important for diabetes and heart disease. In other words, these diseases are not simply caused by "nature" or by "nurture," but by complex interactions between our inherited genes and environment, including diet and lifestyle.

ERECTILE DYSFUNCTION

ERECTILE DYSFUNCTION IS A COMMON CONDITION IN OLDER MEN, with prevalence rates increasing dramatically after age 60. In the Health Professionals Follow-Up Study, 53 percent of men age 53 to 90 reported recent problems with erectile function, excluding men with prostate cancer. In our latest study, we found that fewer than two percent of men who reported current erectile dysfunction had symptoms before age 40, while 40 percent first showed symptoms between ages 60 and 69. Not surprisingly, there was a ten-fold difference in the risk for erectile dysfunction between the oldest and youngest men in the study (Bacon et al. *Ann Intern Med.* 2003;139:161-168).

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While this can be a frustrating condition, the good news is that several modifiable health behaviors are associated with maintaining good erectile function. We found the strongest associations in physical activity and body mass index. Obese men (body mass index of 30 kg/m² or greater) were nearly twice as likely to experience erectile dysfunction compared to men with an ideal body mass index (BMI less than 25 kg/m²) (Bacon et al. *J Urol.* 2006;176:217-221). We also found that physical activity significantly decreased the risk of erectile dysfunction: men who exercise frequently and vigorously are 30 percent less likely to experience erectile dysfunction compared with men who did not exercise or exercised very little. Any type and amount of exercise had a positive impact. This is encouraging news, showing that even small changes in habits can make a difference. In addition, we found that smoking, but not alcohol consumption, increases the risk of erectile dysfunction. And diabetes, especially duration of the disease, is associated with increased risk (Bacon et al. *Diabetes Care.* 2002;25:814-8).

It is well known that physical activity, maintaining a healthy weight and avoiding smoking are all linked to a reduced risk of diabetes, cardiovascular disease, cancer, and other chronic diseases. Adding erectile dysfunction to this list may be a new source of motivation for men to engage in health promoting behaviors. While nobody can stop the inevitable impact of age, our research suggests that there are many behavioral changes that men can make to delay the onset of erectile dysfunction.



FOCUS ON OUR RESEARCH TEAM



MORE THAN 20 YEARS AGO, **DR. WALTER WILLETT** and his colleagues started the Health Professionals Follow-Up Study to investigate how diet and lifestyle factors affect men's health. Dr. Willett focused much of his work developing methods, using both questionnaire and biochemical approaches, to study the effects of diet on major disease occurrence. He has applied these methods since 1980 with the Nurses' Health Studies I and II, and later in the Health Professionals Follow-Up Study. Together, these cohorts comprise nearly 300,000 men and women submitting repeated dietary assessments and providing the most detailed information on the long-term health consequences of food choices.

As the principal investigator of the Nurses' Health Study II and Health Professionals Follow-Up Study, Dr. Willett oversees all of the research conducted within these studies. He is also Professor of Epidemiology and Nutrition at the Harvard School of Public Health and Professor of Medicine at Harvard Medical School. He is a member of the Institute of Medicine of the National Academy of Sciences and the recipient of many national and international awards for his research. Among them, Dr. Willett received the 2001 Charles S. Mott Prize for most outstanding recent contribution related to the cause or prevention of cancer, the 2003 Linus Pauling Institute Prize for Health Research, and the 2005 Medal of Honor from the American Cancer Society.

Though it is hard to imagine that Dr. Willett has spare time, he enjoys spending it on his bicycle, in his kayak or garden, or with his family.



WE WOULD ALSO LIKE TO INTRODUCE YOU TO **JILL ARNOLD**, Staff Assistant for the Health Professionals Follow-Up Study. Ms. Arnold has been with the Harvard School of Public Health since 1979. She joined the Health Professionals Follow-Up Study team in 1994 and works closely with key study investigators. Ms. Arnold plays a crucial role in the preparation, coordination, and submission of grant applications, and manuscripts. She also helps with the management of the human subjects applications. Ms. Arnold is also who you will often reach when you call our office. She enjoys vacationing in Oregon and Washington, and especially enjoys ATV riding on the Oregon Coast dunes.

HPFS FUTURE DIRECTIONS

Throughout the Health Professionals Follow-Up Study's history, we have enjoyed strong and continuous financial support from the National Institutes of Health (NIH), and more specifically from the National Cancer Institute (NCI). Although we hope that NCI will continue funding our work for many years, we cannot be sure that we will receive the same level of support that we have in the past. Federal funding is being cut for many areas of health-related research, and so we are seeking alternative sources of support for the future. We are strongly committed to the Health Professionals Follow-Up Study and are doing everything we can to assure its long-term stability.

We are also currently in the preliminary stages of starting a younger Health Professionals Follow-Up Study (II) with a chief goal of looking at the effects of diet and lifestyle on health beginning earlier in adult life.

STUDY UPDATES & NEWS

Many of you have inquired about the status of your study colleagues. Today, nearly 74 percent of the initial 51,529 health professionals enrolled in 1986 are still living. Remarkably, we achieved more than a 90 percent response rate to the 2004 questionnaire. As of 2004, nearly half of you were still working part-time or full-time and 90 percent of you were married. Please find below a few more selected characteristics of active Health Professional Follow-Up Study participants (among professions) who answered the 2004 questionnaire.

	Dentists n=18,087	Pharmacists n=2,637	Optometrists n=2,225	Osteopaths n=1,243	Podiatrists n=793	Veterinarians n=6,512
MEAN AGE (yrs)	70.9	70.6	72.9	70.2	70.5	70.1
MEAN WEIGHT (lbs)	182	185	179	186	185	187
BODY MASS INDEX (BMI), kg/m²						
BMI under 25 (normal)	43.5%	38.6%	47.7%	37.0%	38.8%	36.4%
BMI 25 to 30 (overweight)	45.4%	46.7%	42.9%	47.7%	44.3%	49.4%
BMI over 30 (obese)	11.1%	14.7%	9.5%	15.4%	16.9%	14.2%
EXERCISE: % who exercise more than 40 minutes per week						
Walking	63.4%	59.2%	61.7%	56.2%	54.2%	60.2%
Jogging	9.0%	4.6%	7.4%	9.1%	7.2%	5.8%
Running	4.4%	1.9%	3.2%	5.2%	3.2%	3.1%
SMOKING:						
% smokers:	3.3%	3.1%	3.5%	3.9%	3.4%	3.2%
MULTIVITAMIN USE:						
% taking multivitamin	69.0%	75.0%	71.0%	64.0%	63.0%	69.0%
FLU VACCINE:						
% receiving flu vaccine	75.1%	79.7%	76.9%	79.5%	72.9%	73.9%
SLEEP PATTERNS:						
% who have difficulty falling asleep						
Most of the time	5.1%	4.2%	4.1%	7.2%	5.6%	4.1%
Sometimes	24.8%	25.9%	25.5%	24.5%	28.2%	25.2%
Rarely	70.1%	69.9%	70.4%	68.4%	66.2%	70.7%
% who have trouble waking up during the night						
Most of the time	27.2%	26.0%	27.0%	25.7%	22.1%	26.0%
Sometimes	44.4%	45.5%	44.2%	42.4%	43.4%	44.8%
Rarely	28.4%	28.5%	28.9%	31.9%	34.5%	29.2%

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 still would like you to remain part of the Health Professional 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
- Q. In the disease history section, why did you ask "Since January 1, 2004 have you had any of the following clinician diagnosed conditions", but then you provide "Before 2004" as an option to answer?**
- A.** Not all participants respond to every biennial questionnaire. To capture information from any missed questionnaires, we provide the earlier years for you to mark. If you respond to all of the questionnaires, you would not have to provide a previously reported disease—unless you wanted to report it again to be certain we have it.

19. Since January 1, 2004, have you had any of the following clinician diagnosed conditions?

	YEAR OF DIAGNOSIS			
	Before 2004	2004	2005	2006
Leave blank for NO, mark here for YES <input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
High blood pressure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



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:

Walter C. Willett, MD, DrPH
The Health Professionals Follow-Up Study
677 Huntington Ave.
Boston, MA 02115
(617) 998-1067

VISIT US ONLINE AT

WWW.HSPH.HARVARD.EDU/HPFS