HEALTH PROFESSIONALS FOLLOW-UP STUDY
NEWSLETTER
SPRING 2011 • HARVARD SCHOOL OF PUBLIC HEALTH

Cardiovascular Disease Research

CARDIOVASCULAR DISEASE IS THE LEADING CAUSE of death among men and women in the United States. Using our data from the Health Professionals Follow-Up Study (HPFS) and Nurses' Health Study (NHS), we hope to identify the effects that both risk factors and healthy lifestyle choices have on such a common disease.

Recently, we assessed the risk of coronary heart disease (CHD) associated with excess weight among men and women with and without associated comorbid conditions of hypertension, high cholesterol, and diabetes (Flint et al, Obesity. 2010;18(2):377-83). Overall, among the men, we found the risk of CHD associated with body mass index (BMI) of 30 or higher (categorically obese) was more than twice that associated with a healthier BMI of 18.5-22.9. Thus the risk of CHD increased with BMI, both with and without comorbid conditions. Our results suggest that more than a third of all incident CHD in US men and women may be attributed to excess weight.

We also examined healthy or "low-risk lifestyle" choices (which include a prudent diet, regular exercise, weight management, moderate alcohol consumption, and not smoking). We thought it was particularly important to look at a low-risk lifestyle among healthy men and also among men taking medications for hypertension or high cholesterol (Chiuve et al, Circulation. 2006;114(2):160-7). We were concerned that some men may give up on healthy lifestyle choices once they were prescribed medication for high cholesterol and hypertension. Men who achieved all 5 healthy lifestyle factors had an 87 percent lower risk of subsequent CHD compared with men who had achieved none of these factors. We saw a similar benefit even among the men on medications for high cholesterol or hypertension. For these men, we estimate that a low-risk lifestyle would have prevented 57 percent of all coronary events. Moreover, even those who adopted two or more additional low-risk lifestyle factors had a 27 percent lower risk of CHD compared with men who made no lifestyle changes. Consequently, a majority of CHD events among US men may be preventable through adherence to healthy lifestyle practices, even among those taking medications for hypertension or high cholesterol.

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What's Inside

DEAR COLLEAGUES, Happy 25th anniversary of the Health Professionals Follow-Up Study! Thanks to your invaluable contributions, HPFS remains the largest, detailed long-term study of men's health. Just a few months ago, we submitted our application to the National Cancer Institute (NCI) for another five years of funding, so we hope to keep working with you to learn more about the effects of various diet and lifestyle choices on disease. This newsletter includes some of the recent results; we hope you will find them interesting.

As an HPFS participant, you provide us with very personal information through your questionnaires, medical records, and biological samples. 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 allow only authorized personnel to access your personal information, and we also code all of our biochemical and genetic results so that they are never stored together with individual identifying information. 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.

Again, thank you for your tireless support; we could not have made it to 25 years without you!

Best regards,

Walter Willett

Walter C. Willett, MD, DrPH
Principal Investigator,
Health Professionals Follow-Up Study

Chronic Fatigue Syndrome Epidemiology Initiative

WE RECENTLY LAUNCHED A NEW PROGRAM at the Harvard School of Public Health called the Chronic Fatigue Syndrome Epidemiology Initiative. This program, funded by the Chronic Fatigue Initiative and run by clinicians, epidemiologists, and infectious disease experts, aims to identify the causes of – and cure for – Chronic Fatigue Syndrome (CFS).

Enclosed with this newsletter, you will find a brief CFS questionnaire. If you suffer from severe unexplained fatigue or have ever been diagnosed with CFS, we ask you to please fill out and return this questionnaire. If you do not suffer from CFS or any type of chronic fatigue, please do NOT return the questionnaire.

CFS is a very important problem to address. This condition afflicts up to four million people in the US alone, and the vast majority of CFS sufferers cannot function at work or at home as well as they did before they became ill, and some are unable to work at all. The Centers for Disease Control and Prevention (CDC) estimates that CFS causes $9 billion in lost productivity each year.

The CFS Epidemiology Research Initiative will take advantage of the unique prospective epidemiological data collected in the HPFS and Nurses' Health Studies. We hope to identify a large number of people with CFS and to conduct an integrated investigation of genetic, infectious, and other determinants of CFS risk. The HPFS offers a unique scientific opportunity, because for the first time we will be able to access blood samples collected from people with CFS before they became ill and compare them to blood samples after the onset of the disease. If, as is believed by many in the field, CFS is often caused by the combination of a genetic vulnerability and the presence of a new infectious agent, these 'before and after' blood samples may be critically important in identifying both the nature of the vulnerability (which can be examined using analyses of specific genetic variants or whole genome scans) and the identity of the infectious agent. Further, we will study a variety of nutritional, environmental, and other risk factors for CFS, by comparing the exposures of participants with CFS to those without, many years before the onset of the disease.

We look forward to a fruitful and exciting collaboration with HPFS participants that we hope will lead us closer to finding the cause of and cure for CFS.

Aspirin Therapy for Colon Cancer

A COMPELLING BODY OF EVIDENCE, including data from the HPFS, demonstrates that aspirin can reduce the risk of colorectal adenoma and cancer (Chan et al, Gastroenterology. 2008;134:21-8). However, concern about aspirin's side effects has engendered limited enthusiasm about recommending widespread, long-term aspirin use for colorectal cancer (CRC) prevention in the general population. Because a US individual's lifetime risk of developing CRC is 6 percent, implementation of widespread aspirin chemoprevention would needlessly expose 94 percent of the general population to the potential risk of aspirin-related toxicities, such as gastrointestinal bleeding. Thus, the US Preventative Task Force recently recommended against such widespread use but did suggest that aspirin may be appropriate for

specific subgroups of high-risk individuals (Dube et al, Ann Intern Med. 2007;146:365-75).

One possible subgroup would include individuals with a high risk of developing CRC and then dying from the disease. Perhaps the most definable such population is patients with established CRC that underwent a resection for curative intent. Although such patients generally receive a favorable prognosis compared to those diagnosed with unresectable disease, they remain at high risk of recurrence. For example, approximately 30 percent of CRC patients with lymph node involvement at the time of resection develop a recurrence within five years, and nearly all such recurrences lead to death. Thus, these patients would stand to benefit considerably if aspirin therapy could lower the risk of recurrence and improve the odds of survival.

Aspirin therapy may provide other benefits as well. In animal models, aspirin or similar drugs have been shown to inhibit tumor growth and metastases, as well as prolong survival (Yao et al, Clin Cancer Res. 2005;11:1618-28. Lundholm et al, Cancer Res. 1994;54:5602-6). In addition, one randomized trial demonstrated a 35 percent reduction in risk of colorectal adenoma after approximately 30 months of standard-dose aspirin (325-mg) treatment (Sandler et al, N Engl J Med. 2003;348:883-90). Unfortunately, studies specifically examining the influence of aspirin use on the prognosis of patients with established CRC are lacking.

To investigate this potential to influence prognosis, we embarked on an analysis of 1,279 patients with established stage I, II, or III CRC enrolled in the HPFS and our companion study of women, the Nurses' Health Study (Chan et al, JAMA. 2009;302:649-58). We found that use of aspirin after diagnosis of non-metastatic CRC is associated with a 29 percent improved survival rate from the disease. Regular aspirin use after diagnosis was also associated with a lower risk of dying from the disease among participants in whom primary tumors overexpressed cyclooxygenase-2 (COX-2), a key enzyme in the pathway underlying aspirin's anti-cancer effect (Chan et al, N Engl J Med. 2007;356:2131-42). Although we had limited data on specific dose or frequency categories, it appeared that the optimal dose of aspirin was at least one standard tablet (325-mg) per day.

Our results suggest that aspirin may indeed influence the progression of established CRCs in addition to preventing their occurrence. Moreover, our data underscore the potential for using COX-2 or related genetic biomarkers to tailor aspirin use among patients with newly diagnosed CRC. If confirmed in other prospective studies, testing tumors for COX-2 status could identify patients who are relatively responsive to the anti-cancer effect of aspirin and should be considered for treatment (after an examination of the risks and benefits). In contrast, patients with COX-2 negative tumors may be relatively aspirin-resistant and could be spared unnecessary exposure to aspirin's potential side effects.

Randomized trials are now needed to confirm these results. Recently a large trial examining daily aspirin (200-mg, or smaller than a standard dose) has begun enrolling patients with stage III CRC in several centers in Southeast Asia and India. We hope to see results from this trial by 2015. In addition, we recently launched a trial of the COX-2 inhibitor celecoxib (brand name Celebrex) for adjuvant treatment through the US National Cancer Institute Cooperative Groups. Until then, a patient at high risk for colon cancer recurrence might consider closely monitored aspirin therapy, after a careful discussion with their physician of the potential risks and benefits.

Genetic Analysis Update

RECENT ADVANCES IN GENOTYPING TECHNOLOGIES AND ANALYTIC METHODS have had a dramatic impact on the field of human genetics. With blood samples obtained from a subset of HPFS participants, we have successfully applied these advances toward gene discovery for a variety of diseases and associated risk factors. In collaboration with researchers world-wide, we have identified over 20 genes underlying obesity and another 30 genes related to type 2 diabetes (Heid et al, Nat Genet. Nov 2010;42(11):949-960,937-948). In less than five years, we have contributed to the discovery of genes underlying major cancers including prostate, pancreatic, lung and colorectal cancer (Saccone et al, PLoS Genet. 2010;6(8). Penny et al, Cancer Epidemiol Biomarkers Prev. Nov 2010;19(11):2869-2876). Your continued participation has been essential to extending this research to cancer severity and prognosis.

In addition to learning about genes directly related to disease, we are uniquely poised to lead the search for genes that influence complex human behaviors, many of which are risk factors for common disease. Indeed, we have already discovered genes associated with smoking and caffeine consumption (Cornelis et al, PLoS Genet. 2011; in press). We are currently leading genetic studies of energy intake, alcohol and nutrient intake, food preferences and moderate to vigorous leisure activities. We know more about genes underlying other human traits including skin pigmentation and height (Nan et al, Int J Cancer. Aug 15 2009;125(4):909-917. Lango et al, Nature. Sep 29 2010). Such traits influence the risk or severity of several common human diseases and conditions, such as skin cancer and cardiovascular disease. Through the identification of previously unknown and often unanticipated genes, we hope to gain biological insight into human behavior and disease pathogenesis.

In less than five years, we have contributed to the discovery of genes underlying major cancers

Our research has yielded some unexpected findings and challenges. We were surprised to learn that common genetic alterations usually confer only a very small added risk of disease, although the risk may increase with more of these alterations. Additionally, one of our challenges is to identify dietary and other factors that can modify genetic predisposition to disease. We anticipate that the combination of information on diet and lifestyle factors together with genetic information will inform us how to best prevent disease and improve outcomes for those who develop cancers and other serious illnesses. Our work will continue to present new challenges as technology in genetics advances rapidly, and we anticipate that in the near future we will be assessing nearly all of the billion elements in the whole genome through DNA sequencing, compared to measuring several million at present.

As we and our collaborators further our research in assessing these elements in the whole genome, participant confidentiality continues to be of utmost importance. Due to the value of combining data from multiple studies, National Institutes of Health (NIH) has mandated that data from these studies be deposited in a controlled-access database. Of course,

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What is a Healthy Weight?

ALTHOUGH SERIOUS OBESITY IS CLEARLY RELATED TO MANY ADVERSE HEALTH OUTCOMES, the healthiest body weight has remained a topic of investigation and debate for decades. The HPFS recently joined with 18 other prospective studies (together including 1.46 million men and women) to provide the most detailed look at this question (Berrington de Gonzalez A, N Engl J Med. 2010; 63:2211-9). As has become standard, weight was expressed as body mass index (BMI), which adjusts for the fact that a taller person would be expected to weigh more. (To calculate your own BMI, please visit **www.nhlbisupport.com/bmi/bminojs.htm**). To avoid distortion by cigarette smoking, which tends to reduce weight but greatly increases risk of dying, most of the analyses focused on people who never smoked, although the results were similar for those who stopped smoking several decades earlier. Those with a healthy BMI of 20 to 24.9 at baseline saw the lowest mortality rate, and the risk of death increased progressively with a higher BMI through both the overweight range (BMI of 25 to 29.5) and obese range (BMI over 30). For example, for those with an obese BMI of 30 to 34.9, the risk of death was approximately 2.5 times greater than those with a healthier BMI of 22.5 to 24.9.

These findings highlight the importance of both overweight and obesity (each about one-third of the US population) as negative predictors of long-term health. Also, these results are consistent with many earlier HPFS publications documenting increases in risks of heart disease, diabetes, some cancers, and other conditions in both the overweight and obese ranges of BMI. Although BMI is a remarkably good indicator of excess body fat, it is not perfect for every individual. Some very muscular people have a BMI a bit over 25, and some people who have excess fat have a BMI of 23 or 24.

In addition to BMI, two other numbers are important to watch: weight gain and increases in waist circumference after age 21. Because these two factors take into account an individual's own frame size and almost always indicate an accumulation of fat, minimizing increases in these numbers with regular physical activity and keeping an eye on calories is a good lifetime objective.

Research Questions in Prostate Cancer

IN THE UNITED STATES, PROSTATE CANCER IS THE MOST COMMON CANCER DIAGNOSED AMONG MEN. Although prostate cancer is the second leading cause of cancer death, most men diagnosed are not likely to die of their disease. Indeed, many men have a slow growing cancer that likely could be left untreated. Some of the important questions in current prostate cancer research revolve around improving cancer survival rates through lifestyle changes. We have generated several key findings during this past year.

Physical activity after cancer diagnosis

The beneficial health effects of physical activity are diverse, although no study had previously examined whether physical activity after a prostate cancer diagnosis could improve survival. We report for the first time a striking finding whereby the most physically active men with prostate cancer had a significantly lower risk of dying of any cause, as well as a lower risk of cancer death (Kenfield et al, J Clinical Oncology. 2011; Feb 20;29(6):726-32. Epub 2011 Jan 4.). Moreover, participating in both non-vigorous forms of activity like brisk walking, as well as vigorous activities such as running, were associated with both lowered overall mortality and improved prostate cancer survival. These data, which need to be confirmed by additional studies, suggest that men can alter lifestyle practices after cancer diagnosis and substantially improve health. We are now investigating other aspects of physical activity as well as studying additional lifestyle and dietary patterns after prostate cancer diagnosis.

Vitamin D receptor in prostate tumors

We have assembled a collection of tumor tissue specimens from men in the HPFS who have been diagnosed with prostate cancer. This collection allows researchers to investigate a variety of markers in prostate tumors in order to understand the mechanisms of cancer development and progression. One such marker is the vitamin D receptor (VDR), a protein encoded by the VDR gene which plays a role in the vitamin D pathway. We measured protein levels of VDR in the prostate tumors, and found that men whose tumors had the highest levels of VDR had an almost three-fold lower risk of dying of prostate cancer compared to men whose tumors had the lowest protein levels (Hendrickson et al, J Clinical Oncology. 2011; in press). Of note, this lower risk was observed even when accounting for differences in extent the cancer had spread or tumor cell histology. These results suggest that aspects of the vitamin D pathway may be important in the prevention of lethal prostate cancer. In addition, information on VDR levels, in combination with other markers in prostate tumors, could be used clinically to help guide treatment choices. Our analyses also show that men with lower vitamin D levels may be more likely to develop lethal prostate cancer.

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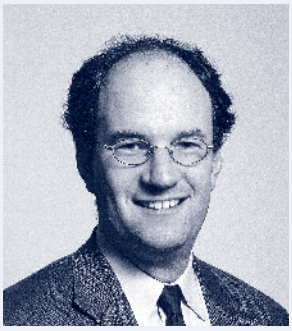
any data we send to this database are completely devoid of any personal identifiers (e.g., your year of birth, address, or zip code). NIH also restricts access to only qualified researchers who can show an appropriate scientific use for the data, and who commit to maintaining the confidentiality of the de-identified data.

If you have questions about these NIH/GWAS studies, or if you wish not have your information provided to the GWAS database, please send an email to hpfs@hsph.harvard.edu or write us at HPFS NIH/GWAS Studies, Walter C. Willett, 677 Huntington Ave., Boston, MA 02115. One of our researchers can answer any questions you many have.

FOCUS ON OUR ResearchTeam

Two of our HPFS investigators, Drs. Eric Rimm and Alan Flint, focus their research on the diet, lifestyle characteristics, and biomarkers of cardiovascular conditions such as coronary heart disease (CHD). With a particular interest on the effects of micro and macro nutrients and novel food components on cardiovascular disease, both investigators strive to understand the metabolic complexities of diet and lifestyle choices on the leading cause of death in the United States.



ERIC RIMM, ScD, serves two roles at the Harvard School of Public Health (HSPH): associate professor of epidemiology and nutrition as well as director of the program in cardiovascular epidemiology. He is a longtime collaborator with the HPFS, serving as project director for 20 years before taking on more recent projects. Dr. Rimm just finished serving as one of the 13-member advisory committee for the new *2010 Dietary Guidelines for Americans*. He also serves as an associate editor for the American Journal of Clinical Nutrition and the American Journal of Epidemiology.

ALAN FLINT, MD, DrPH, has been the project director for the HPFS for four years. Dr. Flint moved from practicing clinical medicine in pediatrics and public health in order to focus on disease prevention at HSPH. He conducts various research projects on CHD and other obesity-related studies with such organizations as the National Cancer Institute and one of our partner studies, the Growing Up Today Study, which involves children and adolescents.

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We also looked at the relationship between multiple lifestyle factors and the risk of stroke (Chiuve et al, Circulation. 2008;118(9):947-54). Men with all five low-risk factors had a 69 percent lower relative risk of ischemic stroke, compared with men who had none of these factors. We estimated that 35 percent of total strokes and 52 percent of ischemic strokes were preventable.

Finally, we studied the relationship between intake of whole grains and the risk of incident hypertension (Flint et al, Am J Clin Nutr. 2009;90(3):493-8). Whole grains are an important component of the diet and have now become an essential foundation for the new *2010 Dietary Guidelines for Americans*. In HPFS, over 9,000 men have been newly diagnosed with hypertension since the beginning of the study in 1986.

Because hypertension is a strong risk factor for ; and stroke, the identification of dietary components (in addition to lower salt intake) that could be beneficial was very important. Men in the top 20 percent of whole grains intake had a 20 percent lower risk of hypertension compared to men in the bottom 20 percent of intake. We found that the benefit was attributable to more than just the dietary fiber; other components of the bran, germ, and endosperm in whole grains may be beneficial.

In conclusion, our findings have broad implications for CHD and stroke risk assessment (in both clinical practice and epidemiologic studies) as well as future dietary guidelines and prevention of chronic disease. By reducing risk factors and increasing healthy lifestyle choices, individuals have a greater likelihood of warding off disease later in life.

Interested in Nutrition Updates?

www.hsph.harvard.edu/nutritionsource

MUCH OF WHAT WE NOW UNDERSTAND ABOUT DIET AND HEALTH comes from the Health Professionals Follow-Up Study, and we make a point of communicating through this newsletter the most important findings as they emerge. However, if you are interested in additional information on nutrition and health, we invite you to visit the website maintained by the Department of Nutrition at Harvard School of Public Health called The Nutrition Source: **www.hsph.harvard.edu/nutritionsource**. In addition to research from the HPFS, this site includes findings from other studies around the world, including our cohorts of women, the Nurses' Health Studies. The website also contains reviews on controversial topics in nutrition and helpful articles on how to put newfound knowledge into practice, such as recent features on healthful beverages ("How Sweet Is It?") and salt reduction. We also provide healthful recipes for foods served in our food service at Harvard, including those developed by the famous cookbook writer, Mollie Katzen. In reading this website, we hope you will feel good that much of the information would not be available without your many contributions as a member of the Health Professionals Follow-Up Study.

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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