

HEALTH PROFESSIONALS FOLLOW-UP STUDY

HPFS NEWS

Celebrating Thirty Years Strong!

A Brief History of the HPFS

The Health Professionals Follow-Up Study (HPFS) has been a pioneer in the study of men’s health for the past thirty years.

The data collected during this time have been exceptionally rich, combining long-term lifestyle and health-related information while also creating and maintaining an extensive repository of biological specimens. Thanks to the dedication of our participants, the HPFS maintains a response rate of 90% or more for each questionnaire cycle.

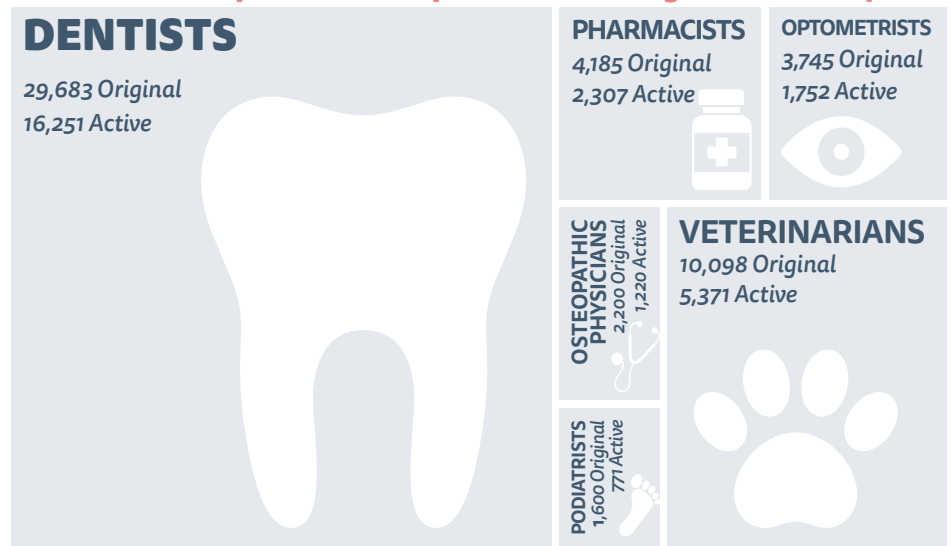
The primary purpose of the study is to evaluate a series of hypotheses about men’s health relating nutritional and lifestyle factors to the incidence of serious illnesses, such as cancer, heart disease, diabetes, neurodegenerative conditions, and other chronic diseases. This all-male study is designed to complement the all female Nurses’ Health Study, which examines similar hypotheses. The HPFS is sponsored by the Harvard T.H. Chan School of Public Health and is funded by the National Cancer Institute.



In 1986, Walter Willett, Principal Investigator, Meir Stampfer, Co-Investigator, and colleagues enlisted 51,529 men in health professions to participate in the study. Currently we have approximately 28,000 participants who are still living and actively participating in the study. The researchers selected

health professionals in the belief that men who chose these types of careers (see graphic below) would be motivated and committed to participating in a longterm project and would appreciate the necessity of accurately answering the survey questions. Every two years, members of the study receive questionnaires inquiring about diseases and health-related topics such as smoking, physical activity, and medications taken. The questionnaires that ask detailed dietary information are administered in four-year intervals. We have expanded the HPFS research scope by founding a biorepository of blood, toenails, and tissue samples from new cases of cancer. Taken together, the HPFS is one of the largest and longest running cohorts of men’s health in the world. The HPFS is also instrumental in training new generations of researchers who have advanced to leadership positions in epidemiological, medical, and nutritional research around the world.

How are health professions represented among HPFS Participants?



Prostate Cancer Update

Prostate Cancer Survival Study

In 2000, the HPFS began a prostate cancer survivors sub-study to collect updated information from men diagnosed with prostate cancer regarding their diagnosis, treatment, quality of life, and disease progression. We currently follow the entire course of disease, in detail, for every participant who reports having prostate cancer. To ascertain treatment, quality of life and disease progression, research staff validates and generates data from over 7,000 men in the cohort who have been diagnosed with prostate cancer. The data gathered from these men have been instrumental in developing our understanding of risk factors that impact prostate cancer survival, otherwise known as secondary prevention of prostate cancer. Notably, we have published research in top journals such as the *Journal of Clinical Oncology* and the *Journal of the National Cancer Institute* among others about the potential role that a healthy diet, engaging in regular vigorous exercise as well as maintaining a healthy body weight, can play in reducing a man's risk of dying from prostate cancer. (Zu K et al. *J Natl Canc Inst.* 2014 Feb; 106 (2): dtj430)

Prostate Cancer Tissue Collection

Over the last several years, the HPFS has collected prostate tissue specimens from participants in the study who have been diagnosed with cancer of the prostate. To date, we have collected over 1,700 radical prostatectomy tissue specimens and over 800 biopsy tissue specimens, making this one of the largest tumor tissue biorepositories globally within a male cancer epidemiology cohort. We work with pathologists to evaluate tissue biomarkers on these

specimens and classify each cancer based on molecular subtypes, as well as to use this information to predict whether a man's prostate cancer will progress. We then link this information with lifestyle, medical and outcome information from HPFS participants. Combining this information we will be able to better identify factors that cause or prevent cancer and to determine the best treatment for individual prostate cancer patients.

Prostate Cancer Research Findings

Members of the prostate cancer epidemiology research team recently published an important paper about lethal prostate cancer prevention in the November issue of the *Journal of the National Cancer Institute* entitled "Development and Application of a Lifestyle Score for Prevention of Lethal Prostate Cancer." As

“**Results from the study suggest that adhering to a healthy lifestyle may substantially lower a man's risk of developing lethal prostate cancer.**

it is well-documented, prostate cancer is the prevailing cancer diagnosis in men, and accounts for the second-highest number of cancer-related deaths in the United States. While certain lifestyle factors, such as smoking and obesity, have previously been associated with increasing a person's risk of developing lethal prostate cancer, these factors

have not yet been studied together. Therefore, in this study, researchers created a "lifestyle score" in hopes of answering the question of whether or not an association exists between combined lifestyle factors and lethal prostate cancer risk. The factors included in the score were smoking history, body mass index (BMI), physical activity, and dietary intake of tomatoes; fatty fish, and

processed meat. Points were awarded for healthy habits such as maintaining a healthy BMI and fitness level, having a high intake of tomatoes and fatty fish and a low intake of processed meats, and not smoking. The researchers studied the associations using survey data collected from men in HPFS, and applied it to data

from the Physicians’ Health Study (PHS). Results from the study suggest that adhering to a healthy lifestyle may substantially lower a man’s risk of developing lethal prostate cancer. (Peish et al. *World J Urol* (2016). doi:10.1007/s00345-016-1914-3)

Introducing Dr. Lorelei Mucci

NEW CO-PRINCIPAL INVESTIGATOR OF HPFS



Dr. Lorelei Mucci, Associate Professor of Epidemiology at the Harvard T.H. Chan School of Public Health, recently took over the role of Project Director and Co-Principal Investigator for HPFS. She also serves as Leader of the Cancer Epidemiology Program at the Dana-Farber/Harvard Cancer Center.

Dr. Mucci has been a Co-Investigator in HPFS for the past 14 years, and has overseen the HPFS Tumor Repository for the past 5 years. She is a cancer epidemiologist whose research focuses on utilizing integrative molecular epidemiology approaches, including circulating biomarkers, inherited genetic alleles, and tumor biomarkers to study cancer risk and mortality. Her research is primarily focused on prostate cancer, which is the most commonly diagnosed cancer among men in HPFS. She has led several studies that investigate the association between lifestyle and dietary factors and risk of advanced or fatal prostate cancer. These studies aim to identify biological markers that may accurately predict a man’s outcome after prostate cancer diagnosis, and factors associated with quality of life among prostate cancer patients.

In addition to her role in the HPFS, Dr. Mucci serves on Executive Committees for the Transdisciplinary Prostate Cancer Partnership (ToPCaP, www.topcapteam.org), an international, multidisciplinary effort whose objective is to integrate prostate cancer tissue biomarkers to address questions in etiology, prognosis and treatment as well as the Nordic Twin Study of Cancer (NorTwinCan, www.nortwincan.org), a population-based cohort of 300,000 twins from Sweden, Norway, Denmark and Finland. Dr. Mucci additionally serves as Co-Principal Investigator of IRONMAN: An International Registry to Improve Outcomes in Men with Advanced Prostate Cancer, which aims to create an international disease registry of 5,000 men with advanced prostate cancer. Through the collection of comprehensive treatment information, demographic, clinical, lifestyle, and outcomes data, and the formation of a biorepository, the registry will arguably be *the* most-equipped in the world to understand patterns of care for men with advanced prostate cancer. This information will help us to identify optimal treatment sequences that improve survival and quality of life and to identify biomarkers for subgroups of men who will respond well (or poorly) to specific therapy combinations.

Research Updates

Consuming Healthy Fats Instead of Saturated Fat Linked with Lower Mortality

There has been confusion in the biomedical community and the general public in the last few years about the health effects of fat in the diet. In a recent study in the HPFS and NHS, we examined the relation between specific types of fat and mortality rates.

Over the last three decades we have collected dietary information on 126,233 participants between NHS and HPFS. During this follow-up, we have had 33,304 deaths between the two studies. We examined the relationship between types of fats in diets and overall deaths, as well as deaths due to cardiovascular disease (CVD), cancer, neurodegenerative disease and respiratory disease.

We found that different types of dietary fat had different

““ We found that different types of dietary fat had different associations with mortality. Trans fats ... had the most significant adverse impact on health. ””

associations with mortality. Trans fats, which are largely being phased out of foods, had the most significant adverse impact on health. Every 2% higher intake of trans fat was associated with a 16% higher chance of premature death. A higher consumption of saturated fats was also linked with mortality risk.

When compared with the

same number of calories from carbohydrates, every 5% increase in saturated fat intake was associated with an 8% higher risk of overall mortality.

Conversely, intake of high amounts of unsaturated fats, both polyunsaturated and monounsaturated, was associated with between 11% and 19% lower overall mortality compared with the same number of calories from carbohydrates. Among the polyunsaturated fats,

both omega-6, found in most plant oils, and omega-3 fatty acids, found in fish and soy and canola oils, were associated with lower risk of premature death.

The research also showed that the health effects of specific types of fats depended on the replacement fat. For example, if saturated fats were replaced with unsaturated fats, especially polyunsaturated fats, there was a significantly lower risk of death overall, as well as lower risk of death from CVD, cancer, neurodegenerative disease and respiratory disease, compared with those who maintained high intakes of saturated fats. The findings for cardiovascular disease are consistent with many earlier studies showing *reduced total and LDL (“bad”) cholesterol* when unsaturated fats replace trans or saturated fats.

People who replaced saturated fats with carbohydrates had only slightly lower mortality risk. In addition, replacing total fat with carbohydrates was associated with modestly higher mortality. This was not surprising, since carbohydrates in American diet tend to be primarily refined starch and sugar, which have a similar influence on mortality risk as saturated fats.

This study is the most detailed and powerful examination to date on how dietary fats impact health. This study provides further support for the 2015-2020 Dietary Guidelines for Americans that emphasize the types of fat rather than total amount of fat in the diet. (Wang et al. *JAMA Intern Med.* 2016 Aug 1; 176(8):1134-45)

Consuming High Amounts of Saturated Fats Linked to Increased Heart Disease Risk

Another recent study has also shown the benefits of replacing saturated fats with unsaturated fats in relation to coronary heart disease. Previous studies have shown that individual saturated fatty acids have different effects on blood lipids, but little is known

about associations between individual saturated fatty acid intake and coronary heart disease risk. A recent study in the HPFS and NHS found that consuming high amounts of four major saturated fatty acids—found in red meat, dairy fat, butter, lard, and palm oil—may increase risk of coronary heart disease. Our findings also suggest that replacing these fats with healthier fats, whole grains, and plant proteins may reduce coronary heart disease risk.

Analyzing data provided by HPFS and NHS, we found that a higher intake of the most commonly consumed major saturated fatty acids—lauric acid, myristic acid, palmitic acid, and stearic acid—was associated with a 24% increased relative risk of coronary heart disease.

Replacing just 1% of daily consumption of these fatty acids with equivalent calories from polyunsaturated fats, monounsaturated fats, whole grain carbohydrates, or plant proteins, was estimated to reduce relative coronary heart disease risk by 4%-8%. Replacing palmitic acid—found in palm oil, meat, and dairy fat—was associated with the strongest risk reduction.

These findings strongly corroborate what the current USDA Dietary Guidelines recommend. This includes reducing saturated fat intake to no more than 10% of total calories, and eating an overall healthful diet that includes fruits, vegetables, whole grains, vegetable cooking oils rich in polyunsaturated fats and monounsaturated fats, nuts, legumes, fish, and low-fat dairy. (Zong and al. *BMJ* 2016 November 23;335:i5796.)

Regular Aspirin Use Found to Protect Against Overall Cancer Risk

Many studies have supported the ability of regular aspirin use to prevent colorectal cancer but aspirin's effects on overall cancer risk have not been clear. A recent analysis among the HPFS and the NHS found that the regular use of aspirin significantly reduces the overall risk of cancer, a reduction that primarily reflects a lower risk of colorectal cancer and other tumors of the gastrointestinal tract. These findings suggest that the use of aspirin may complement, but not replace the preventive benefits of colonoscopy and other methods of cancer screening.

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Valuable Data from Cancer Registries

When a member of the Health Professionals Follow-Up Study reports a new cancer diagnosis, we generally contact the participant to request permission to review the medical records relating to this diagnosis. When this is not possible, we may request data from state cancer registries on diagnosis data and tumor characteristics such as site, type of tumor, stage of disease, and treatment. This detailed diagnostic information from the registry, combined with the extensive lifestyle, health and biological data that the study has collected across decades, is vital to understanding the causes of cancer and allows us to learn more about improving survival for a variety of cancers. Most states have cancer registries. In order to accurately locate the correct information, we securely send the patient's name, date of birth, address and social security number to the state's cancer registry to look for a match. If you do not wish to have your data linked with the state cancer registry data, in the event you are diagnosed with cancer, please send an email to hpfs@hsph.harvard.edu or write to HPFS, 677 Huntington Ave, Boston, MA 02115. If you have any questions, please call Ann Fisher at 617-384-8666.

If you would like to speak to someone not involved in this research about your rights as a research subject, or any concerns or complaints you may have about the research, contact the Harvard T.H. Chan School of Public Health Human Research Committee at 617-432-2157.

Road Trip!



This fall, Alberto Ascherio, Co- Investigator of HPFS and three colleagues from Massachusetts General Hospital in Boston hopped into a 32-foot-long RV and began motoring down the east coast in order to meet with fifty-one participants from the Health Professionals Follow-Up Study and Nurses' Health Study. Their aim was to conduct neurological examinations that will help them learn more about the early symptoms of Parkinson's disease.

The team: Dr. Alberto Ascherio, Neurologist Dr. Michael Schwarzschild of Harvard Medical School and Massachusetts General Hospital and Dr. Schwarzschild's research fellows, Jessica Baker and Christopher Stephen, met with study participants who had completed questionnaires on their sense of smell and color vision—the loss of either of which may be an early symptom of Parkinson's disease. Participants were chosen to represent a range of scores on the tests, with some having already received a Parkinson's diagnosis, and others serving as healthy controls. The team spent an hour with each individual, conducting in-depth tests of their sense of smell and color vision, in addition to observing their ability to rise from a chair, postural stability, speed of movement, and the presence of tremors. The researchers hope to return in two years to retest participants and observe any changes.

According to Dr. Ascherio, the data they gathered from the examinations will provide important validation of the information they have collected from participants

by other means. He said, "For example, several participants have reported in questionnaires that they had tremors or difficulty with movements, but to use this information properly we need to see objectively how people who report these symptoms differ from those who do not."

Schwarzschild added that their evaluations of people "who have multiple versus no risk factors for Parkinson's has demonstrated the feasibility and value of expanding such neurological assessments to a network of Parkinson's specialists who can examine a large proportion of these epidemiological cohorts."

Dodging Tree Branches and Meeting Enthusiastic Volunteers

The team started their journey in Harrisburg, Penn. They then traveled back east, making additional stops in Pennsylvania, New Jersey, New York, Connecticut, and Massachusetts. They bonded over pre-sunrise runs and worked as a team to maneuver their large vehicle around whatever obstacles the road threw in their way, from tight parking spaces to rogue tree branches. They even narrowly avoided the occasional fate of a new college student traveling to Boston for the first time—getting stuck under the low overhead bridge on Storrow Drive.



Allison Gordon, a Research Assistant with HPFS provided logistical support for the trip. She scheduled appointments and made calls to find locations near clusters of participants where the team could park

their vehicle and set up shop—mostly in suburban mall parking lots. In the weeks leading up to the trip, Gordon worried that she would not be able to schedule enough appointments with the study participants. However, she found that the participants were more than willing to arrange their schedules to accommodate the researchers timetable, demonstrating once again the level of commitment the HPFS participants provide in order to make the HPFS a success.

"Research Updates" continued from page 5

Using data from HPFS and NHS, we found that participants who reported regular aspirin use—defined as taking either a standard or a low-dose aspirin tablet at least twice a week—had a 3% absolute lower risk of any type of cancer than those not reporting regular aspirin use. Regular aspirin use reduced the risk of colorectal cancer by 19% and the risk of any gastrointestinal cancer by 15%. No reduction was seen in the risk of breast, prostate or lung cancer. Aspirin's protective benefit appeared after five years of continuous use at dosages ranging from 0.5 to 1.5 standard tablets a week or one low-dose tablet a day. (Cao et al. *JAMA Oncol* 2016 Jun 1;2 (6):762-769.)

Dietary Flavonoid Intake and Weight Maintenance

As public health professionals, we continue to search out better science that provides insight into how diet and lifestyle choices lead to weight gain. Among men in the Health Professionals Follow-Up Study, we continue to see steady weight gain over time that peaks at approximately 65 years of age and then dips as many men begin to lose muscle mass. In the

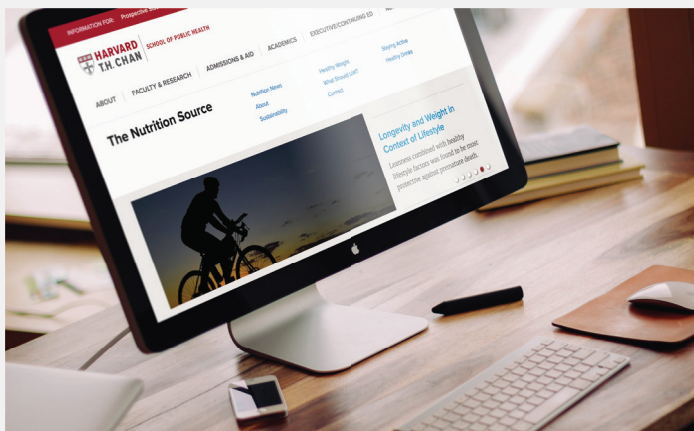
past we have highlighted the importance of aerobic physical activity and modest resistance training to limit weight gain over time. In our recent investigation of dietary factors that relate to weight change, we focused on bioactive compounds called flavonoids, found in high concentrations in berries, tea, apples and dark chocolate. Previous evidence suggests that these compounds may preferentially increase glucose uptake in muscle and decrease uptake in fat. When we pooled the data from the men's cohort with those of our sister cohort, the Nurses' Health Study, we found that those participants who consumed several servings a week of blueberries, strawberries or apples gained weight at a slower rate than non-consumers. Anthocyanins are the specific flavonoid that is highest in these food sources. We also found that flavan-3-ols found in dark chocolate and tea appeared beneficial to keeping weight gain minimal over time. As we concluded in our paper, current recommendations of two cups of fruit and 2.5 cups of vegetables per day are best for maximum health benefit, and ideally should include several foods high in flavonoids. (Bertoia et al. *BMJ* 2016 Jan 28; 352Li17.)

Your Privacy

Large studies will be the key to the success of these efforts to understand the role of genes. This highlights the importance of collaboration and careful data sharing with appropriate safeguards on participant confidentiality. Indeed, the National Institutes of Health (NIH) has mandated that data from studies of DNA and disease risk be deposited in a controlled-access database. Any data sent to this database will not contain any personal identifiers (e.g., your name, date of birth, address, zip code, or any trait information that could identify you).

Our participation in this NIH database will contribute to the large international effort to identify the genetic variants underlying the inherited predisposition to cancer, heart disease, diabetes, and other diseases. The goal is to develop more effective prevention and treatment strategies. However, we recognize that DNA sequence data are potentially sensitive. If you have any question about these studies (called GWAS or sequence studies), or you wish to withdraw from them in the future, please send an email to hpfs@hsph.harvard.edu or write to us at HPFS, 677 Huntington Avenue, Boston, MA 02115.

Interested in Nutrition Updates?



Much of what we understand about diet and health comes from the HPFS 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 T.H. Chan 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 replacing saturated fats and refined grains with polyunsaturated fats and whole grains. We also provide healthful recipes for foods served in our food service at Harvard, including those developed by the famous cookbook writer, Mollie Katzen.

Please note that much of the information would not be available without your MANY contributions as a member of HPFS. We are truly grateful for all you have provided.

Health Professionals Follow-Up Study

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To report name or address changes, please email the project coordinator at hpfs@hsph.harvard.edu or visit www.hsph.harvard.edu/hpfs. Letters and feedback are welcome.

Donations and bequests to the Friends of the Health Professionals Follow-Up Study Fund help to sustain our continued work. Donations may be sent to the Harvard T.H. Chan School of Public Health. For information on how to give or to make a secure gift online, please visit www.hsph.harvard.edu/give and indicate that the gift is in support of the Friends of the Health Professionals Follow-Up Study Fund.