



NHS NEWS



Back row: S. Hankinson, W. Willett, F. Speizer
Front row: M. Stampfer, F. Grodstein

Dear Colleagues,

We are thrilled to announce that we recently received new funds from the National Institutes of Health (NIH) to continue the Nurses' Health Study II for another five years (see page 3 for further details)! This is especially gratifying given the challenging funding climate and government reductions in the funds devoted to medical research. We will soon apply to NIH to extend the original Nurses' Health Study as well.

Our lead article this year reviews our research on breast cancer, which has always been a primary focus of the studies. Though much more work remains, with your help we have made important strides in understanding risk factors for breast cancer.

We also highlight recent research on colorectal cancer and how regular aspirin use may help to increase survival after the diagnosis of certain types of colorectal tumors.

Thank you for your tremendous contributions to these studies. We look forward to many more years of collaboration.

Best regards,

The Nurses' Health Study Senior Team
Susan Hankinson, RN, ScD
Walter Willett, MD, DrPH
Meir Stampfer, MD, DrPH
Francine Grodstein, ScD
Frank E. Speizer, MD

New Insights on Breast Cancer

Over many years, the Nurses' Health Studies (NHS and NHS II) have helped us understand some of the factors that influence breast cancer risk. Recently, we have expanded our research on dietary and hormonal factors by combining our data with other studies to get a more complete picture of the causes of breast cancer, and importantly, identify ways to prevent the disease.

PLASMA CAROTENOIDS

We previously showed that higher levels of plasma carotenoids (compounds that give fruits and vegetables their rich colors) were associated with lower risk of breast cancer in the NHS. To evaluate this further, we established a large consortium with seven other cohort studies. This pooled data set included thousands of participants, comprising more than 80 percent of the world's data on carotenoids measured in blood and subsequent breast cancer risk. This allowed us to look at which carotenoids were most beneficial and whether the associations we observed differed by subtypes of breast cancers. We found that women with the highest levels of carotenoids had about a 15-20 percent lower risk of breast cancer compared to women with the lowest levels. (Eliassen et al. *J Natl Cancer Inst.* 2012; 104(24):1905-16)

We also found that several specific carotenoids were associated with a lower breast cancer risk, including alpha-carotene, beta-carotene, lycopene, and lutein/zeaxanthin. (Alpha- and beta-carotene are found in carrots and sweet potatoes, while lutein and zeaxanthin are found in leafy greens.) Interestingly, high levels of alpha- and beta-carotene were associated with a 40-50 percent lower risk of estrogen receptor-negative (ER-) tumors. This finding was especially important because these particular tumors are more aggressive and are notoriously harder to treat, so understanding prevention is critical. The pooled analysis was the only way to look at this association because ER- tumors are less common than ER+ cancers.

In a similar pooled consortium effort led by our team, we examined dietary intake of carotenoids in the NHS, NHS II, and 16 other studies. There were over one million participants and more than 33,000 cases of



Recent Findings

Red Meat and Type 2 Diabetes

People who eat red meat on a daily basis—especially processed red meats such as bacon and sausage—may be putting themselves at risk of developing type 2 diabetes. In a recent study in the NHS, NHS II, and Health Professionals Follow-Up Study (HPFS), we found that one daily serving of unprocessed red meat (e.g., three ounces of steak) was associated with a 12 percent increased risk of developing type 2 diabetes; one daily serving of processed red meat (e.g., one medium-size hot dog or two slices of bacon) was associated with a 32 percent increased risk. Our findings were confirmed with an updated meta-analysis including another six prospective cohort studies from around the world.

Frequent red meat consumption was also associated with obesity and weight gain, and processed red meat has high amounts of sodium and nitrites, which could lead to insulin resistance. Fortunately, individuals who chose more healthful protein sources in place of red meat (such as fish, unprocessed poultry, nuts, legumes, low-fat dairy, and whole grains) had a 10-35 percent lower risk of developing type 2 diabetes. (Pan et al. *Am J Clin Nutr.* 2011;94:1088-96)

Water, Sugar-Sweetened Beverages, and Weight Gain

In a recent study in the NHS, NHS II, and HPFS we confirmed that regular consumption of sugar-sweetened beverages can lead to weight gain and thus an increased risk of obesity. However, little is known about the long-term impact of other types of beverages (e.g., plain water or coffee) on body weight. We found that in each four-year

period, while people *gained* weight overall, adding one cup of plain water or coffee daily was associated with about 0.3 pounds *less* weight gain. More importantly, replacing one daily serving of sugar-sweetened beverages with water was associated with 1.1 pounds less weight gain; replacing fruit juices with water was associated with 0.8 pounds less weight gain. Taken together, these findings support current recommendations to limit consumption of sugar-sweetened beverages and fruit juices and increase consumption of water, tea, or coffee for the prevention of obesity. (Pan et al. *Int J Obes* (Lond). 2013 Jan 15. [Epub ahead of print])

Adolescent Alcohol Intake and Benign Breast Disease

Alcohol consumption during adulthood is a well-established risk factor for breast cancer. However, less research has been conducted about alcohol consumption during adolescence (when breast cells undergo rapid growth) and later risk of breast cancer.

In the NHS II, we found that higher levels of alcohol consumption between ages 18 and 22 was associated with increased risk of proliferative benign breast disease (BBD), a type of breast lesion that is a known risk marker for invasive breast cancer. Compared to non-drinkers, moderate drinkers (less than ½ drink per day) had an 11 percent greater risk of developing proliferative BBD, whereas heavier drinkers (more than ½ drink per day) had a 36 percent greater risk. Each additional drink consumed per day was associated with a 15 percent increase in risk of proliferative BBD. An assessment of alcohol consumption in young women in the Growing Up Today Study, or GUTS

Recent Findings continued from previous page

(children of the NHS II participants), also showed that drinking between ages 16 and 22 years was associated with increased risk of BBD. These results provide evidence that drinking alcohol during adolescence may increase the risk of BBD. (Liu et al. *Pediatrics*. 2012;129(5):e1192-8)

Oophorectomy and Mortality

Each year, over 600,000 American women have a hysterectomy for benign disease—such as fibroid tumors or severe endometriosis—and this is often accompanied by elective oophorectomy (ovary removal) in order to prevent ovarian cancer. However, ovarian cancer is relatively uncommon (except in some women who have a strong family history of breast or ovarian cancer), and oophorectomy may increase the likelihood of other diseases. Of over 50,000 NHS women who had a hysterectomy without a diagnosis of gynecologic cancer, 48 percent had both ovaries removed at the same time. Those who had both ovaries removed had a slightly higher mortality rate, mainly due to non-gynecologic cancer and coronary heart disease. Bilateral oophorectomy was not associated with lower overall mortality, regardless of the age at surgery. Thus, women having hysterectomy for benign disease may want to talk to their health care provider about ovarian conservation. Women who had a bilateral oophorectomy should be particularly encouraged to practice a healthy lifestyle to reduce their risk. (Parker et al. *Obstet Gynecol*. 2013;121(4):709-16)

Berries and Cognition: Did You Know?

Recent research in the NHS found that higher intakes of blueberries and strawberries were associated with slower rates of memory decline in older women. Women who ate ½ cup of blueberries at least once a week or ½ cup of strawberries at least twice a week appeared to have the best memory. Specifically, women who ate lots of berries had similar memory skills to those who were one to two years younger. These findings could be due to a specific type of flavonoid called an anthocyanidin, which has antioxidant properties and gives berries their rich color. Anthocyanidin can cross the blood-brain barrier, which may explain how it affects a person's memory. (Devore et al. *Ann Neurol*. 2012;72:135-43)



NHS II Grant Award

Since the inception of the NHS and NHS II, we have received funding from the National Cancer Institute (NCI) that we use to maintain our studies, including research and infrastructure costs. Our infrastructure costs include mailing, processing, scanning, and coding questionnaires; confirming reports of disease diagnoses; and compiling the information in our databases to be used for scientific analyses.

Recently, the NCI began a new funding process that focuses on maintaining the infrastructure of the cohort. Last summer we applied for this type of grant for the NHS II and received

a score that was only 1 point away from a perfect score! This ensures the continued existence of the NHS II cohort structure for five more years. We will continue to pursue funding opportunities to support our scientific projects.

We are now working on a similar application for the original NHS cohort and hope to have comparable success. While the funding is necessary to maintain the cohorts, none of this would be possible without your efforts as participants, and for that we are very grateful to you.

4 In Brief

Being Overweight Increases Mortality: No Surprise There!

You may have heard conflicting reports in the media about ideal weight and mortality. A controversial study released on New Year's Day suggested that being overweight is associated with a lower risk of premature death. However, in the NHS we have consistently seen that women who are overweight or obese are at increased risk of premature mortality.

How could this other study come to the opposite conclusion? That work combined results from many studies, though it excluded other large, well-conducted studies comprising over six million people. The controversial findings—that being overweight seemed beneficial—were influenced by the inclusion of people who already had serious illnesses including cancer and heart disease. Many of these people had lost weight due to their illness, which created the appearance of high mortality among the lean group and, by comparison, lower mortality among the overweight group. In addition, the reported study did not adequately take into account the effect of smoking on weight and health. Many smokers are lean due to the effects of nicotine, and of course tobacco smokers are at higher risk of disease and death. As a result, the lean groups disproportionately included smokers, which made being thin look harmful. When we look at nonsmokers in the NHS, there is a clear and steady increase in risk of premature death as a person's weight (expressed as body mass index, or BMI) increases.

To summarize, in the NHS and in most carefully conducted studies, a higher BMI is associated with an increased risk of diabetes, high blood pressure, heart disease, stroke, several types of cancer, and an overall increase in risk of premature mortality. The recent controversial paper, by including people with serious illnesses that cause weight loss, and not fully accounting for the effect of smoking, reached a conclusion that is not supported by the majority of research done by us and hundreds of other scientists.

To learn more about the limitations of this new study, which has received much undue media attention, and what we do know about obesity and mortality, you can watch a recent symposium on this topic at the Harvard School of Public Health: <http://hvr.d.me/XDbyv0>.



Aspirin and Colorectal Cancer

Colorectal cancer is a leading cause of cancer death worldwide. There will likely be over 142,000 individuals diagnosed with colorectal cancer and at least 50,000 deaths from this disease in the U.S. in 2013. For early-diagnosed colon cancers, the recommended treatment is surgical removal. However, once a colon cancer has spread to local lymph nodes the risk of cancer recurrence is high, even after all visible tumors have been removed by surgery. Thus, adjuvant treatment, or therapy given in addition to the initial treatment, is usually recommended.

Aspirin is an adjuvant therapy often prescribed for patients with colorectal cancer, but its effectiveness varies and physicians are unable to predict which patients will benefit most. Using tumor tissue and patient data in the NHS and a comparable study in the HPFS, we found that only those with colorectal cancer whose tumors carry a specific genetic mutation—in the PIK3CA gene—may benefit from aspirin therapy. Patients with this type of cancer had better survival rates if they took aspirin regularly after diagnosis. However, the medication appeared to have no effect on survival in cancers without the mutation.

These results, if confirmed, will have important clinical implications. For the first time, we have shown that a gene marker may help physicians pinpoint which colorectal cancer patients may benefit from aspirin therapy. Aspirin's low cost and easy accessibility may make it an effective and practical part of a treatment plan.

We anticipate that in the coming years, similar biomarkers will be discovered in many types of cancer, such as breast and lung cancers, and treatment of these cancers will become more targeted and thus more effective.

Genetic Research Update

Sugar-Sweetened Beverages and Predisposition to Obesity

We are currently investigating how our genes may interact with our lifestyle choices to influence body weight. Recently, genome-wide association studies (GWAS) around the world have identified 32 genetic regions associated with body mass index (BMI). These common genetic variants partly help to predict a person's susceptibility to obesity. However, we still do not understand whether a person's genetic predisposition to obesity can interact with diet and lifestyle to affect weight gain.

To explore this, we conducted a “gene-environment interaction test” among a small subset of participants from the NHS, HPFS, and another large cohort. We created a genetic risk score (on the basis of the 32 established BMI-related genetic regions) to estimate each person's overall genetic susceptibility to obesity. Notably, we found a significant interaction between the genetic risk score and intake of sugar-sweetened beverages. Among men and women who consumed at least one serving of sugar-sweetened beverages per day, the genetic predisposition to high BMI and obesity was much more pronounced. In contrast, the genetic susceptibility seemed less important among those consuming sugar-sweetened beverages less often. In other words, in those with low consumption of sugar-sweetened beverages, the genetic risk score had more limited impact on body mass index.

In addition, we also found that greater physical activity in one's leisure time could substantially lessen the effect of that person's genetic predisposition to obesity, whereas a sedentary lifestyle (like prolonged TV watching) may exaggerate the effect.

Taken together, our findings suggest that diet and lifestyle modifications hold promise in reducing the risk of obesity attributed to genetic susceptibility. Of course, more work will be necessary before any clinical recommendations can be made.



Data Sharing

The National Institutes of Health (NIH) has mandated that anonymized data from genetics studies be deposited in a controlled-access database so that they can be used by other scientists. In these studies—and all our studies—we practice careful data sharing with strict safeguards to protect participant confidentiality. Data sent to this database do 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 greatly contribute to the large international effort to identify the genetic variants underlying the inherited predisposition to cancer, heart disease, diabetes, and other diseases. However, we recognize that DNA sequence data are potentially sensitive. If you have any questions about these genetic studies, or you wish to withdraw from them in the future, please send an email to: nhsgwas@channing.harvard.edu or write to us at NHS NIH/GWAS Studies, 181 Longwood Avenue, Boston MA 02115. If you would like to speak to someone at Brigham and Women's Hospital who is not involved in this research, please contact the Partners Human Research Committee at 617-424-4100. As always, your decision to participate or not in any of these studies will not affect your status as a valued member of the Nurses' Health Studies.

Study Updates



DIABETES
& WOMEN'S HEALTH

Partnering with investigators from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD) and the State Serum Institute (SSI) in Denmark, we contacted women who have had a pregnancy affected by gestational diabetes among both NHS II participants and women throughout Denmark. Over 3,000 women have agreed to complete additional questionnaires for this study. Among this group, we are now completing the collection of additional biospecimens (blood, urine, and toenail samples).

Over the next few years, we will use these resources to understand more about women whose pregnancies have been affected by gestational diabetes, such as why they are at an increased risk of developing type 2 diabetes later in life, and what may be done to prevent this progression from gestational diabetes to type 2 diabetes. To learn more about the study, please visit www.dwhstudy.org.



We happily report that nearly 35,000 women have joined the NHS 3, the newest phase of the Nurses' Health Studies. We will continue recruiting female RNs, LPNs, and nursing students between the ages of 20 and 46 (who are living in the U.S. or Canada) to join the new Web-based study. Prominent features of the NHS 3 include a closer look at fertility and pregnancy, as well as adolescent diet and occupational nursing exposures in the development of chronic diseases.

While we are grateful that so many nurses have decided to join the NHS 3, we hope to reach our goal of 100,000 members, and we need your help! Many of the new participants decided to join after hearing from long-standing members like you; we hope you will continue encouraging your younger colleagues to join this new study by visiting www.nhs3.org. With your help we hope to make NHS 3 a success!



Our new yearly questionnaire cycle has begun for the Growing Up Today Study (GUTS): in January we sent our first combined questionnaire to your children in both GUTS I (born 1980-1987) and GUTS II (born 1988-1995). Impressively, we have already heard from a quarter of all GUTS participants! From now on, we will be sending out a shorter questionnaire every year to help GUTS participants find time in their busy lives to give us a regular update. Thank you for continuing to encourage your children to participate in this important study.

In 2011, we began collecting saliva samples from a subset of GUTS participants in hopes of establishing our first GUTS biorepository. We have now received samples from over 1,500 participants! These samples, along with those contributed by many GUTS moms in the NHS II, will allow us to examine biologic markers like cortisol to understand how stress is related to chronic disease risk.

Lastly, GUTS has a new Web site: www.gutsweb.org. Please visit to keep up with recent study findings and other GUTS news. As always, please send any questions or comments to: guts@channing.harvard.edu. We love to hear from you!



Have you ever wondered about the impacts of stress on your physical well-being? Or how methods of relaxation and mindfulness might protect your health? In an effort to help address these questions, we have formed a team of psychologists, psychiatrists, and chronic disease epidemiologists to develop the new NHS II Mind Body Study.

Over the next two years, nearly 300 study participants will be asked to provide biological samples and complete online surveys to help gauge emotional well-being. With the combi-

Karen Corsano & Jeanne Sparrow

After 27 years of service as the senior computer programmer for the Nurses' Health Studies, Karen Corsano retired last autumn, passing along her job responsibilities to Jeanne Sparrow. Our focus this year is on Karen and Jeanne.



K. Corsano and J. Sparrow

KAREN CORSANO began working with the NHS in 1985 as a programmer/analyst. She ran data analyses for several years before acquiring the role of manager of the programming team. Her job responsibilities widened even further over the years as more cohort studies were added (including NHS II, GUTS, and others) to include data management and employee training. Karen had a significant impact on the success of the NHS, overseeing many important initiatives that helped make this study what it is today.

Now that Karen is retired, she is as busy as ever! She and her husband, both medieval historians, are working on three books—one of which is about to be published. Somehow she also manages to squeeze in a drawing class, volunteer work at the Boston Ballet, and research trips to Paris and London.

In 1997, **JEANNE SPARROW** began her career with the NHS when she responded to a tiny advertisement for a programmer for a “major study of women’s health.” She originally worked with data associated with the biomarker collections (e.g., blood samples, cheek cells, and others), but when Karen retired she took over as director of cohort programming and data management. Jeanne and her team of 10 programmers are charged with the critical task of cleaning and organizing data from many sources—including the biennial questionnaires, medical records, tracking databases, and the biospecimen collections—and making the data available, but still secure and confidential, for use by our investigators. In her “free” time, she and her husband love to bike and ski with their children, a 14-year-old daughter and 10-year-old triplets. She had the pleasure of meeting five study nurses at a wedding many years ago—all of whom were coincidentally sitting at her table! She remarked, “I spent the whole event talking about my job!”

Study Updates continued from previous page

nation of biologic samples and women’s descriptions of their well-being, we will then focus on identifying new stress-related markers that can be measured in biologic samples. This will help us to explore how life experiences and emotional feelings may impact health and the risk of chronic disease.

We are grateful to our participants for their dedication, without which none of this would be possible! For more information about the study, please visit www.nhs2.org/mindbody.



Hearing loss affects 48 million Americans; up to one-third of women in their 50s and two-thirds in their 60s have some degree of hearing loss. Many people think this common and disabling condition is an unavoidable companion to aging. However, recent findings from the Nurses' Health Studies show that hearing loss may not be inevitable. Our research

illustrates a number of potentially modifiable factors—things that we can change in order to prevent hearing loss or delay its progression—such as limiting the use of over-the-counter pain relievers.

The Conservation of Hearing Study (CHEARS), currently underway, aims to identify additional factors that may influence hearing and to detect changes at an early stage in order to prevent further loss. We are collecting hearing-related information on a detailed Hearing Study Supplementary Questionnaire (HSSQ). In addition, the study includes free hearing tests for 3,300 NHS II women at 17 major medical centers across the country. Our hope is to obtain additional funding so that many more participants may have their hearing tested as part of this study. If you would like to learn more about the NHS CHEARS study, or if you are a participant and would like to complete the HSSQ, please visit www.chearsstudy.org.

breast cancer. Like the results in the plasma consortium, we found that higher intakes of alpha-carotene, beta-carotene, and lutein/zeaxanthin were associated with a significantly lower risk of ER- breast cancer. (Zhang et al. *Am J Clin Nutr.* 2012;95(3):713-25)

The results from these pooled studies strongly suggest that eating more—and more colorful—fruits and vegetables may help prevent ER- breast cancer in addition to providing many other health benefits.

ENDOGENOUS HORMONES

Endogenous hormones are those that our bodies synthesize on their own. Using the blood samples and questionnaire data you have provided, we recently conducted two analyses to better understand the role of these endogenous steroid hormones in the development of breast cancer. It is well established, thanks in part to early work done in the NHS, that higher circulating levels of estrogens and androgens (such as testosterone) are associated with higher risk of developing breast cancer in postmenopausal women. However, the interconnection of these hormones and the timepoint at which they influence breast cancer are unknown.

Recently, we evaluated the role of multiple hormones in postmenopausal breast cancer. We found that having high levels of multiple hormones at once (including estrogens, androgens and prolactin—a hormone involved in breast development and lactation) was associated with an almost three-fold higher risk of developing breast cancer, compared to women with lower levels of all of the hormones. As might be expected, high levels of hormones were most important in predicting later development of ER+ breast tumors. (Tworoger et al. *Breast Cancer Res.* 2011;13(5):R99) In future research we will examine how to lower the levels of these

hormones, although we know that maintaining a healthy weight with aging (especially after menopause) is one way to avoid high levels of estrogens.

Since we have two blood samples provided 10 years apart from approximately 18,000 NHS women, we have a unique resource for trying to understand the influence of endogenous hormones on breast cancer development over time. Interestingly, we found that measures of estrogens and androgens in blood samples collected 10 years apart were highly correlated. In addition, the hormone levels appeared to predict breast cancer risk up to 20 years later, whether they were measured from the first or the second timepoint. The bottom line is that endogenous hormone levels seem to play a key role in breast cancer throughout its development. (Zhang et al. *Breast Cancer Res.* 2013;137(3):883-92)

CONCLUSION

These studies were only possible because of your generous participation in the NHS for so many years. Over the decades, we have substantially expanded upon our original research within the NHS to better understand how carotenoids and endogenous hormones may alter breast cancer risk. While endogenous hormones are not easily modifiable—the best thing to do is avoid postmenopausal weight gain—eating more fruits and vegetables is likely to help lower your risk of breast cancer.



Nurses' Health Study

To report name or address changes, please visit www.nurseshealthstudy.org. Letters and feedback are welcome.

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Donations and bequests to the Friends of the Nurses' Health Study Fund help to sustain our continued work.

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