



NHS News



Dear Colleagues,

We're excited to announce that we recently received funding to continue the Nurses' Health Study for another five years. This was a major accomplishment, but it was not without challenge. Our primary funder, the National Cancer Institute (NCI), has an increasingly tight budget, which limits the amount of support they can give us.



As we move forward with the study, we'll need to identify other sources of funding to supplement our NCI grants. Although this is not an immediate issue (since we do have adequate funding right now), we're in the process of forming an advisory board to help us secure resources in the future. The board will consist of volunteers, and we sincerely hope that NHS participants will consider serving. For more information, please see page 2.

We're also pleased to announce that all of our published research articles will soon be available online at <http://www.ncbi.nlm.nih.gov/>. This website is part of a government initiative to ensure that the public, as well as the scientific community, has access to key study findings. We think that this is an important effort and are pleased to be supporting it. As always, you can also learn more about our study findings at www.NursesHealthStudy.org.

Thank you for your ongoing commitment to the Nurses' Health Studies.

Sincerely,

Graham A. Colditz, MD, DrPH
Principal Investigator, Nurses' Health Study

Walter C. Willett, MD, DrPH
Principal Investigator, Nurses' Health Study II

Premenopausal breast cancer

Breast cancer typically develops after menopause, but it's especially worrisome when it develops earlier. It seems to be more aggressive in younger women, and the underlying causes are largely unknown. Although we've learned much about postmenopausal breast cancer, not all the lessons apply to premenopausal disease. This remains one of our greatest challenges: understanding the factors that influence risk at various points in women's lives. The Nurses' Health Studies have been — and will continue to be — instrumental in furthering this understanding because we have a wealth of data that span both the pre- and postmenopausal years.

Reproductive Factors

Many reproductive factors influence the risk of both pre- and postmenopausal breast cancer, but we've identified two that are more strongly related to premenopausal disease: birth control pills and childbearing patterns.

Birth control pills have been a major focus of our work since the Nurses' Health Study began. We've found that the pill has only a modest and temporary effect on a woman's risk of breast cancer. Women have a slightly increased risk while they're on the pill, but this subsides soon after they stop taking it. This means that overall, birth control pills exert their largest influence during the premenopausal years but have little or no effect later on. We are currently investigating whether different types of pills have different effects on risk.

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INSIDE THE NHS

Our Advisory Board

Throughout NHS history, we've enjoyed strong and continuous financial support from the National Institutes of Health (NIH) and, more specifically, the National Cancer Institute (NCI). Although we hope that NCI will continue funding our work for many years to come, we can't be confident that we'll receive the same level of support that we have in the past. Federal funding is being cut back for many areas of health-related research, and it would be unwise of us to not to seek alternative sources of support for the future.

We are strongly committed to the Nurses' Health Studies and are doing everything we can to assure their long-term stability. In addition to seeking grants from major foundations and government institutes (as we have in the past), we're also planning to solicit support from private donors. This is a new direction for us, and so we're creating an advisory board to help us move forward with it. The board's role will be to assist us in securing major gifts that support the continued operation of the Nurses' Health Studies. Although we would obviously like to have board members who are familiar with private funding sources, we would also like people who are simply enthusiastic and have time to commit to this important cause. If you or someone you know is interested in serving on the board, please contact Graham Colditz, the Principal Investigator of the Nurses' Health Study, at 617-525-2258 or by e-mail at advisory@channing.harvard.edu.

Our Approach to Data Sharing

All recipients of NIH funding have been asked by the U.S. Congress to do a better job of sharing our data with other scientists. However, the best approach for doing this — while also maintaining the privacy of study participants — has not yet been determined. Our approach has always been to collaborate with scientists who have high standards and who are pursuing issues that we agree are important. Together we analyze any shared data and prepare joint reports for publication (see page 4 for an example). Notably, we never allow these scientists to access personally identifiable information: confidentiality is of the utmost importance to us, and we only work with scientists who value your privacy as much as we do. Over the past five years, we've participated in more than 50 collaborative projects and are proud that NHS data have helped to advance science in so many ways. As NIH continues to develop its data-sharing recommendations, we'll keep you abreast of any changes in how we approach our collaborative efforts.

Your Privacy

As an NHS participant, you provide us with very personal information through your questionnaires and biological specimens. We're grateful for the trust you've shown in us and want to assure you that we hold ourselves to the highest standards in the safekeeping and use of your data. For example, only authorized study personnel are granted access to your personal information, and all genetic results are coded so that they are never stored 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 could 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 your faith in us. Thank you for your continued commitment.

* To learn more about how Brigham and Women's Hospital and its affiliates use protected health information, visit www.partners.org and click on Patient Privacy.



Continued from cover

Childbearing patterns are another important risk factor for breast cancer. In the ten years after women first give birth, they experience a temporary increase in the risk of breast cancer, possibly because of the high hormone levels associated with a first pregnancy. Eventually, though, women gain protection from having given birth.

Overall, women who have children are at lower risk of breast cancer than women who do not, and the younger women are when they start their families, the lower their risk.

Weight and Activity

In one of the most surprising findings in the Nurses' Health Study, we found in the 1980s that being overweight has opposite effects on pre- and postmenopausal breast cancer: though it appears to reduce risk before menopause, it increases risk afterward. More recently, we've seen a reduced risk among women who were overweight before their first menstrual period. Although these findings have been confirmed in other studies, we still don't completely understand them and are exploring possible explanations.

Physical activity also seems to have different effects on pre- and postmenopausal breast cancer. Before menopause, it appears to have little effect on risk, but after menopause, it seems to modestly reduce risk.

Even though being active doesn't seem to offer women much protection against premenopausal breast cancer — and being lean actually seems to increase risk — we still encourage women to be both lean and active throughout their lives. The health benefits of regular exercise and a low body mass far outweigh the risk of developing premenopausal breast cancer. Furthermore, when premenopausal breast cancers do develop, they tend to be smaller and less aggressive in lean women than in overweight women.

Diet

Research on diet and breast cancer has been abundant, but we still have very few definitive answers. In the Nurses' Health Study II, we're currently evaluating the effects of diet during early adulthood. So far, we've seen a moderate increase in the risk of premenopausal breast cancer among women with higher intakes of animal fat (mainly from high-fat dairy products). Because this finding is related primarily to tumors that are sensitive to estrogen, we're



exploring the possible role of hormones in these foods. We've also observed a lower risk of premenopausal breast cancer with higher intakes of vegetable oils during high school. Finally, we've seen some suggestion that higher intakes of vegetables and vitamin D may be related to a lower risk of premenopausal (but not postmenopausal) disease.



Family History

Family history is another well-known risk factor for breast cancer: in general, women have an increased risk of the disease if their mother or sister ever had it. For premenopausal breast

cancer, the risk appears to be especially high for women whose relatives were diagnosed at a young age. In the Nurses' Health Study, we found a two- to threefold increase in risk among premenopausal women whose mothers were diagnosed before age 45.

Conclusion

Despite our best efforts, premenopausal breast cancer remains something of a mystery, and women understandably feel frustrated when they've "done everything right" and still develop this disease. Clearly, the usual advice to exercise and eat well is not enough to prevent breast cancer. Although we don't yet have answers on what does prevent this disease, we now have several good leads and expect to know more in the next several years. For example, we now have blood samples from 30,000 women in the Nurses' Health Study II and will be using them to study how premenopausal hormone levels influence breast cancer risk. We will keep you informed as results become available and promise that we will not rest until we know how to protect women from this disease.

— WALTER C. WILLETT, MD, DRPH

NHS Snapshot

- More than 238,000 women participate in the Nurses' Health Studies.
- The youngest women were 25 when they joined the studies, and the oldest are now in their 80s.
- Every state has at least 20 NHS participants. Pennsylvania has the most (32,000) and North Dakota the fewest (20).
- About two-thirds of the women in the Nurses' Health Studies are married.
- About 65% of NHSII participants and about 20% of original NHS participants are still in nursing.

RECENT FINDINGS

During the past year, the Nurses' Health Studies have produced nearly 90 publications on women's health. Below are some of our most important findings. A complete list of articles can be found by visiting www.NursesHealthStudy.org and clicking on Publications.

Alcohol and Risk of Colorectal Cancer

Although the link between alcohol and colorectal cancer has been assessed in several studies, results have been inconsistent. To address this issue, we teamed up with researchers from other large follow-up studies and combined our data with theirs. (For more on data sharing, see page 2.) Together, we found that alcohol modestly increased the risk of colorectal cancer: men and women who drank at least two alcoholic beverages a day were about 25% more likely to develop colorectal cancer than those who abstained from alcohol. Beer, wine, and liquor all had similar effects. (Cho E et al. *Ann Intern Med* 2004; 140:603)

Walking and Memory

Walking is one of the most common forms of exercise and has many health benefits: it can help lower the risk of cardiovascular disease, osteoporosis, and some types of cancer. Now data from the Nurses' Health Study suggest that walking can also help women maintain memory. We found that the more women walked during their late 50s and 60s, the better their memory was at age 70 and older. Those who walked at least 90 minutes a week had cognitive function similar to that of women 1.5 years younger. (Weuve J et al. *JAMA* 2004; 292:1454)

Physical Activity, Weight, and Mortality

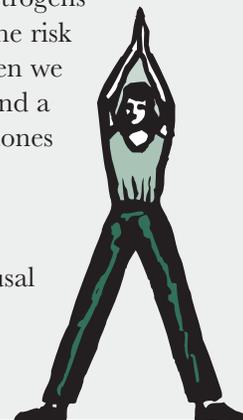
Does being fit counteract the health consequences of being overweight? Is it okay for women to be sedentary as long as they're lean? Not according to recent data from the Nurses' Health Study. We found that weight and exercise are both important predictors of longevity, and their effects are independent of each other. Being lean helps protect against premature death and so does being active, but it's best to be both. During a 24-year period of our study, mortality rates were lowest for women who were lean and active, moderate for women who were one or the other, and highest for women who were obese and sedentary. (Hu FB et al. *N Engl J Med* 2004; 351:26)

Sugar-Sweetened Beverages, Weight Gain, and Diabetes Risk

Soft drinks are the main source of added sugar in the American diet, leading many people to speculate that these beverages might contribute to weight gain and diabetes risk. When we examined this in the Nurses' Health Study, we took into account all of the other factors that could be affecting women's weight, including their age, activity patterns, and diet. Still, we found that over an 8-year period, women gained an average of 17 pounds if they started drinking at least one sugar-sweetened soft drink per day. In addition, daily consumption of these beverages nearly doubled the risk of diabetes. These results suggest that women can better maintain their weight — and their overall health — by cutting back on sugar-sweetened soft drinks. Notably, this appears to be true for children as well: in the Growing Up Today Study, we found a direct link between sugar-sweetened beverages and weight gain. (Schulze et al. *JAMA* 2004; 292:927 and Berkey CS et al. *Obes Res* 2004; 12:778)

Endogenous Hormones and Breast Cancer Risk

Endogenous hormones include estrogens, androgens, progesterone, and other hormones that are naturally produced by women's bodies. To determine whether these hormones influence the risk of postmenopausal breast cancer, we evaluated blood samples from women who eventually developed breast cancer and women who did not. (None of the women were taking postmenopausal hormones at the time of blood collection.) We found that having high levels of estrogens and androgens in the blood doubled the risk of postmenopausal breast cancer. When we looked at specific cancer types, we found a strong link between endogenous hormones and those tumors that had hormone receptors on their surfaces. Our next step is to investigate the effects of endogenous hormones in premenopausal women, using blood samples from NHSII participants. (Missmer SA et al. *J Natl Cancer Inst* 2004; 96:1856)



The NHS Memory Study

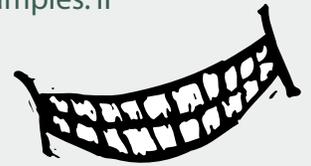
For the past eight years, we've been studying how lifestyle and diet influence memory in older women. Nearly 20,000 NHS participants have completed telephone interviews as part of this ongoing study, and we've learned a tremendous amount. For example, we've found that physical activity, moderate alcohol intake, and high vegetable consumption all help maintain memory (see page 4). We've also seen that type 2 diabetes is associated with worse memory, although diabetes treatment seems to help. We're grateful to the women who have contributed to this study and will continue to call them every couple of years to learn about any changes in memory.

We're also exploring whether some nurses might be able to come in for full neurologic consultations, including optional brain scans with magnetic resonance imaging (MRI). So far, about 15 nurses have come to Boston as part of this pilot study. We're not sure yet whether we'll be able to expand it (because of the cost involved), but we'll keep you updated on our progress.

NHSII Cheek Cell Collection

Over the past several years, Nurses' Health Study participants have generously provided us with thousands of cheek cell samples. These samples are an invaluable resource for investigating how differences in genes influence the risk of cancer, cardiovascular disease, and other chronic diseases.

We're now expanding our cheek cell collection to the Nurses' Health Study II and are asking participants who have not given us a blood sample to provide us with a cheek cell sample. Fortunately, this is an easy process: women simply swish with Scope® mouthwash, spit into a cup we provide, and then mail the cup back to us in a postage-paid envelope. So far, thousands of NHSII participants have already agreed to do this, and we are thankful for their participation. We plan to continue the collection throughout 2005 and hope to receive over 30,000 samples. If you're in NHS II and haven't previously submitted a blood sample, please watch the mail for your invitation letter.



The Growing Up Today Study

When we started the Growing Up Today Study (GUTS) in 1996, our goal was to learn about predictors of adolescent weight gain. Today the GUTS participants are 18 to 23 years old, and we look forward to following them into adulthood. However, we still have much to learn about adolescent diet, activity, and weight — and so we're starting a new study, GUTSII, with children who were born to NHSII participants between 1988 and 1994.

More than 11,000 boys and girls have already responded to our first GUTSII questionnaire, and we'd like to thank their mothers for allowing them to participate. As with the Nurses' Health Studies, we'll be sending out GUTSII questionnaires every other year to track participants' activity, diet, and growth. In addition, we're starting a pilot study with a group of GUTSII mothers who have agreed to measure and record their child's height and weight for us every six months.



Understanding the Risks and Benefits of Aspirin

With the recent controversy surrounding COX-2 inhibitors, many people are now reconsidering a tried-and-true pain reliever: aspirin. In addition to relieving pain, inflammation, and fever, aspirin offers several other health benefits, including positive effects on heart health and cancer risk. Of course, like most medications, it also has some side effects, such as bleeding ulcers. Here's what we currently know about balancing the risks and benefits of aspirin.

Protection against heart attack and stroke

Aspirin can hamper the development of blood clots, thereby reducing the risk of heart attack and stroke. However, its specific effects depend on a woman's medical history. Women who have already had a heart attack or ischemic stroke can lower their risk of a second event by taking aspirin every day. They can also lessen the damage caused by a heart attack by taking aspirin during the attack.

Whether healthy women (without a history of heart disease) can gain the same benefits from aspirin has been an area of longstanding controversy, but definitive answers recently came from a large clinical trial sponsored by the federal government. In this trial, researchers randomly assigned healthy women to receive placebo or 100 mg of aspirin every other day for 10 years. The aspirin didn't have any effect in preventing heart attacks or cardiovascular deaths, but it did reduce women's risk of developing stroke, particularly ischemic stroke.

Protection against cancer

Although researchers aren't sure why, aspirin also lowers the risk of colorectal cancer and adenomatous polyps (the lesions that often precede this type of cancer). In the Nurses' Health Study, taking aspirin reduced the risk of colorectal cancer by about 30%, but women had to take the drug regularly for at least 10 years to get this benefit. Fortunately, aspirin appeared to lower the risk of adenomatous polyps much more quickly, within only about two years. Researchers are still trying

to figure out which aspirin dose works best for preventing colorectal cancer, but they think it's probably higher than the dose required for cardiovascular benefits. Whether aspirin protects women against other types of cancer remains unclear. Some studies suggest that it might lower the risk of ovarian cancer and breast cancer, but this hasn't been proven.

Increased risk of bleeding ulcers

Despite its advantages, aspirin does have side effects, the most common of which is bleeding ulcers. In the clinical trial mentioned above, gastrointestinal bleeding occurred in about 50 out of every 1000 women who used aspirin. Serious bleeding (requiring a transfusion) occurred in about 6 out of every 1000 women.

Increased risk of high blood pressure

Aspirin might also increase the risk of hypertension, according to data from the Nurses' Health Study. We found that women who used aspirin only once or twice a week had about a 10% increase in risk, and those who used it almost every day had about a 20% increase in risk. This finding needs to be confirmed in other large studies.

Conclusion

Many women in the U.S. take aspirin regularly for pain relief, but it's important to be aware of aspirin's other health effects. Before taking this drug for anything other than minor aches and pains, talk to your health care provider. Together you can decide whether regular aspirin use is right for you.



visit us online at

www.NursesHealthStudy.org

- Complete list of all NHS research publications
- Detailed history of the Nurses' Health Studies
- Past newsletters and questionnaires
- Medical record release forms
- Photo gallery

FOCUS ON OUR RESEARCH TEAM



For more than a decade, we've been studying NHS blood samples to better understand how biomarkers (such as hormone and nutrient levels) and genetic markers influence the development of disease. Like every NHS project, this is a team effort, but it couldn't be done without **Helena Judge Ellis**, the Senior Project Manager in our blood lab.

Helena joined our group in 2001, having spent 13 years in a nutrition research lab at the Harvard School of Public Health. There she studied lipid metabolism, plasma fatty acids, and carotenoids — and sometimes found herself analyzing blood samples from the Nurses' Health Study. In her current role, she oversees the storage, safety, and preparation of more than 60,000 of those samples.

When the NHS blood samples arrived at Helena's lab, they were immediately separated into plasma (for biomarkers), white blood cells (for DNA), and red blood cells (for fatty acids, folate, etc.). About 70% of our work focuses on plasma, and the other 30% on white blood cells. Helena and her team store all of the samples in liquid nitrogen freezers and ensure that they remain frozen at all times, since temperature can dramatically affect biomarker levels.

When one of our studies requires blood samples, Helena and her team pull them from the freezer, prepare them for analysis, and send them out to be analyzed by either commercial labs or research collaborators. As with all of the NHS data, the blood samples are kept completely confidential and are labeled only with ID numbers. None of the labs (including Helena's) can link the samples back to the women who provided them, and individual test results are never shared with anyone. For any given study, only a selection of samples are analyzed, and we use only a very small portion of each selected sample. Our goal is to preserve the samples for as long as possible, so that we'll always have enough to study new biomarkers and genetic markers as they're discovered. As we learn more, we'll continue to share our findings with you, as we have on page 4.

Helena's commitment to the blood lab is part of what helps ensure the continued success of the Nurses' Health Studies. On a personal level, she is also committed to saving stray cats in her hometown, serving as both president and treasurer for a local nonprofit feline rescue group.

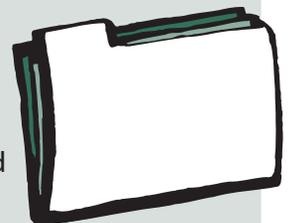


Keeping Us Up to Date

As members of the Nurses' Health Study get older, some will unfortunately become disabled or develop conditions that make it difficult to respond to future mailings. Should you become disabled, it would greatly help our research if someone could notify us of your health status and subsequently allow your pertinent medical records to be released to us. To help facilitate this process, we've developed an Authorization for Release of Medical Records and mailed it to every NHS participant. Copies can also be downloaded at www.NursesHealthStudy.org. Completing this form and keeping it with your will or personal papers will help make your wishes known in the event that you are not able to personally notify us about changes in your health status.

Medical Records Review

Participants who report a new diagnosis in their biennial questionnaires often receive a letter from our study, requesting permission to review their pertinent medical records. This review is important because it allows us to obtain specific information about treatment and diagnosis that only original records can provide. We want to extend a special thank-you to all of the nurses who have helped our work by allowing us to confidentially review their records. We would also like to encourage participants who receive these requests to complete and sign the release forms and then mail them back to us (not directly to the physician). This allows us to keep study information together in an organized and secure manner.



QUESTIONS & ANSWERS

I'm not sure how accurate I am about my diet when I fill out the NHS questionnaire. Can you still use my information?

You're probably more accurate than you think! We've tested our questionnaire against two different measures to make sure we're collecting good information. First, we asked a small group of people to weigh and record everything they ate for four weeks so that we could compare these detailed diet records with their questionnaire responses. Second, we asked women to provide blood samples so that we could compare the amount of nutrients in the blood with the amount of nutrients consumed according to their questionnaires. In both cases, we found that the questionnaire was giving us a good overall picture of what women were eating. We realize it's not perfect, but it is accurate enough to help us understand how diet affects health. For some recent findings related to diet, see page 4.

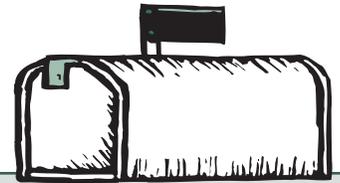
What have you learned so far about the effects of the nursing profession on women's health?

So far, we've looked at two aspects of the nursing profession: rotating night shifts and work-related stress. Rotating night shifts are of concern because exposure to light at night suppresses the body's production of melatonin, which researchers think could influence the risk of cancer. In the Nurses' Health Study, we found an increased risk of both breast cancer and colorectal cancer among women who worked rotating night shifts at least three nights per month for 15 or more years.

Work-related stress is another important issue. We've observed significant declines in physical function and mental health among women who have demanding jobs but little control and social support in their workplaces. On the positive side, we've seen no connection between work-related stress and the risk of either breast cancer or heart disease.

When you look at medical records after a cancer diagnosis, what information are you looking at, and is it being kept confidential?

Thousands of women have allowed us to review their medical records, and we're grateful for this privilege. With a cancer diagnosis, we generally look at where the tumor is located, how advanced the disease is, and what treatments are being used. We also get samples of cancerous tissue and examine these for molecular clues about how cancer develops. As with all of the information you provide to NHS, your medical records and tissue samples are reviewed in complete confidentiality. They will never be released to outside parties such as insurance companies, pharmaceutical companies, or employers. For more information on our privacy measures, see page 2.



NHS MAILBOX

“ Another questionnaire — Can't believe I've been doing this since 1976! It's like hearing from an old friend each year. It seems to help me reflect over the years, and it makes me so thankful I have been blest with such good health. Yes, one has to work at it, but it is also a blessing. Thank you for reminding me each year. May I spend more healthy years answering you. ” — MH

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THE NURSES' HEALTH STUDY

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Collect calls are accepted;
letters & feedback are welcome.

To report name or address changes,
visit www.NursesHealthStudy.org
& click Contact Us.

Donations & bequests to the Friends
of the Nurses' Health Study Fund can
be sent to the Channing Laboratory.

With sincere thanks,
Frank E. Speizer, MD
Founding Principal Investigator