NURSES' HEALTH STUDY NEWSLETTER

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The past year has seen a record number of publications with important implications for women's health based directly on data from the Nurses' Health Studies. Below is a sampling of findings to which you have been a valuable contributor. Continuing high participation rates are essential to the validity of these results, regardless of your current employment or health status.

Dietary fat intake and the risk of coronary heart disease in women.
In the Nurses' Health Study, we found that replacing saturated and *trans* unsaturated fats with unhydrogenated monounsaturated and polyunsaturated fats is more effective in preventing coronary heart disease than reducing overall or total fat intake. (Hu et al. N Engl J Med 1997; 337:1491-1499.)

Oral contraceptives and ovulatory causes of delayed fertility.
In Nurses' Health Study II participants, we found that past oral contraceptive (OC) use transiently delayed return to fertility. However, there was no evidence of increased infertility with increasing duration of OC use or younger age at first use. In fact, 88% of the women reporting primary ovulatory infertility reported an eventual pregnancy in subsequent years, suggesting that absolute fertility was not impaired. (Chasan-Taber et al. Am J Epidemiol 1997; 146: 258-265.)

Leisure-time physical activity, body size, and colon cancer in women.
Our finding of a significant positive association between leisure-time physical activity and lower incidence of colon cancer among the Nurses' Health Study population is consistent with results in men. Recommendations to increase physical activity and maintain lean body weight should receive greater emphasis as part of a feasible approach to colon cancer prevention. (Martínez et al. J Natl Cancer Inst 1997; 89:948-955.)

Folate and vitamin B_6 from diet and supplements in relation to risk of coronary heart disease among women.
During 14 years of follow-up among Nurses' Health Study participants, we found that intakes of folate and vitamin B_6 above the current recommended dietary allowance (400 mcg for folate and 1.5 mg for B_6) may be important in the primary prevention of nonfatal myocardial infarction and fatal coronary heart disease. (Rimm et al. JAMA 1998; 279:359-364.)

Menstrual cycle characteristics and history of ovulatory infertility in relation to breast cancer risk.
Among Nurses' Health Study II participants, we found that having fewer ovulatory menstrual cycles appeared protective against breast cancer. Further study is needed to investigate the age-specific associations between menstrual cycle characteristics and the underlying hormonal environment and to examine the separate effects of infertility and its treatment on breast cancer risk. (Garland et al. Am J Epidemiol; 1998:147:636-643.)

Body weight, weight change, and risk of hypertension in women.
Our findings among Nurses' Health Study participants showed that excess weight and even modest adult weight gain substantially increased the risk for hypertension. Sustained weight loss significantly reduced the risk of hypertension. (Huang et al. Ann Intern Med 1998; 128:81-88.)

Dual effects of weight and weight gain on breast cancer risk.
We examined body mass index at age 18 and at midlife and adult weight in relation to breast cancer incidence and mortality in the Nurses' Health Study. We found that, among women who do not use postmenopausal hormones, avoiding weight gain may contribute importantly to the prevention of postmenopausal breast cancer. Women who use postmenopausal hormones appear to be at higher risk of breast cancer than women who do not, and leanness does not appear protective in this higher-risk group of hormone users. (Huang et al. JAMA 1997; 278:1407-1411.)

Milk, dietary calcium, and bone fractures in women: a 12-year prospective study.
Among Nurses' Health Study participants, we found no evidence that high consumption of milk or other food sources of calcium protects against hip or forearm fracture. These findings and those from other large prospective studies raise questions about current recommendations to increase dietary calcium intake. Further follow-up will help us address this issue in more detail and thus inform future dietary guidelines. (Feskanich et al. Am J Public Health 1997; 87:992-997.)

Prospective study of *NAT2* acetylation genotype, cigarette smoking, and risk of breast cancer.
Differences in the *N*-acetyltransferase 2 *(NAT2)* gene among individual women determine the rates at which they metabolize various carcinogenic compounds. On the basis of this gene's DNA sequence, women are categorized as either "rapid" acetylators (i.e., they metabolize carcinogens quickly) or "slow" acetylators. Among Nurses' Health Study participants who provided a blood sample in 1989-90, we found little evidence of an association between *NAT2* genotype and breast cancer; furthermore, cigarette smoking was not appreciably associated with breast cancer among either slow or fast *NAT2* acetylators. (Hunter et al. Carcinogenesis 1997; 18:2127-2132.)

Postmenopausal hormone therapy and mortality.
Postmenopausal hormone therapy has both benefits and hazards, including decreased risks of osteoporosis and cardiovascular disease and an increased risk of breast cancer. We examined the relation between the use of postmenopausal hormones and mortality among Nurses' Health Study participants. On average, mortality among postmenopausal hormone users is lower than among nonusers; however, the survival benefit diminishes with longer duration of use and is less for women already at low risk of coronary disease. (Grodstein et al. N Engl J Med 1997; 336:1769-1775.)

Friends of the Nurses' Health Study

As we reported last year, at the suggestion of some of the nurses who attended the Update on Women's Health Symposium in February 1997, we established the Friends of the Nurses' Health Study Fund at Harvard Medical School. The fund will be used to promote health education opportunities for women and to support new and emerging research opportunities that would otherwise be delayed or difficult to start. Because we believe it is important for this fund to grow, we thus far have not used any of the monies. The fund has increased since last year mostly due to the generous contributions of interested individuals. In addition, we have met with Development Office personnel from both Harvard Medical School and Brigham and Women's Hospital to develop strategies for obtaining support from potentially interested philanthropic organizations. We assure you that we will continue to maintain the confidentiality of your names and thus **will not** release them to **anyone** for **any** reason, without your specific permission.

Nurses' Health Study II Blood and Urine Collection

The blood and urine collection project is an exciting opportunity for us to gain vital information that cannot be acquired through questionnaires, namely levels of premenopausal sex hormones (i.e., estrogens, androgens, prolactin), urinary estrogen metabolites, and antioxidants in the body. These "biomarkers" are worth investigating in depth because previous studies have suggested a potential link between them and breast cancer. Specifics such as which hormones have the greatest impact and at what levels various biomarkers increase or decrease risk have yet to be established. Blood samples from this Nurses' Health Study II collection, along with samples provided by Nurses' Health Study participants in 1989-90 will help us address these issues.

The Nurses' Health Study II is particularly suited to such an investigation. One obvious strength is the long-term prospective design of the study. Because all participants in the blood and urine collection project have been enrolled since 1989 and continue to complete biennial questionnaires, your specimens will be a far more valuable resource than if they were collected at the time of initial recruitment and without long-term follow-up.

Secondly, you and your colleagues are the most motivated, medically aware, and generous group of study subjects we could hope to find. We have been most impressed by the great efforts participants have made to contribute and with the many positive letters and comments we've received about the project. Finally, this study is the first of its kind to collect a large number of blood and urine samples that have been timed according to the menstrual cycle (i.e., in the follicular and luteal phases). Pinpointing samples to these specific times in the cycle, when hormone levels differ substantially, will allow us to determine the relationships between individual cyclic variations and long-term health.

Women who cannot time their specimen collections because they are peri- or postmenopausal or have had a hysterectomy are also extremely valuable participants in this project. With their random samples, we will work to explore the relationships between nutrient and growth factor levels and later risks of both breast and colon cancer, as always, with the goal of developing disease prevention strategies.

The collection is still going on.

We continue to send weekly batches of kits to collect both timed and random samples, and have so far received specimens from more than 19,000 women. Our sincerest thanks go to all of you! To reach our goal and address the many important women's health issues that are currently unanswered, we still need to receive over 10,000 additional samples. If you are currently enrolled in the Nurses' Health Study II blood and urine collection project and have a question, or would like to become part of this project, please call our toll-free line at 1-800-644-6472 (644-NHS2). Someone on our blood collection team will gladly assist you.



Rachel Meyer, Project Coordinator (right); Julie Farris, Senior Research Assistant (second from left); and Research Assistants Todd Reid and Tina Thompkins.

Photo by David Temelini

Inherited Susceptibility to Cancer

In addition to the immensely valuable information Nurses' Health Studies participants have contributed over the years via questionnaire, those of you who provided a blood sample in the 1989-90 collection are also making a unique contribution to our understanding of inherited susceptibility to cancer and other diseases.

Using tiny amounts of DNA, we can now assess the presence of inherited alterations in the sequence of genes. Using the statistical power afforded by the large number of specimens available for diseases such as breast and colon cancer, we can assess whether these gene sequence alterations are more frequent in women who have been diagnosed with the diseases than they are in women who have not. In most instances, we do not observe a difference between the proportion of women who are in the "case" group and women in the "control" or comparison group. For example, last year we were unable to confirm preliminary findings from another study, which received much publicity, suggesting that common variants in the *N*-acetyltransferase 2 gene, in conjunction with cigarette smoking, were associated with higher risk of breast cancer (see summary on page 2). It is likely that many of these preliminary reports, usually from much smaller studies, will not be confirmed as so much work is being done in this area and so many combinations of genes, lifestyle and environmental exposures, and potential diseases are being studied. Your blood samples serve as a valuable reference bank from which these preliminary reports can be assessed.

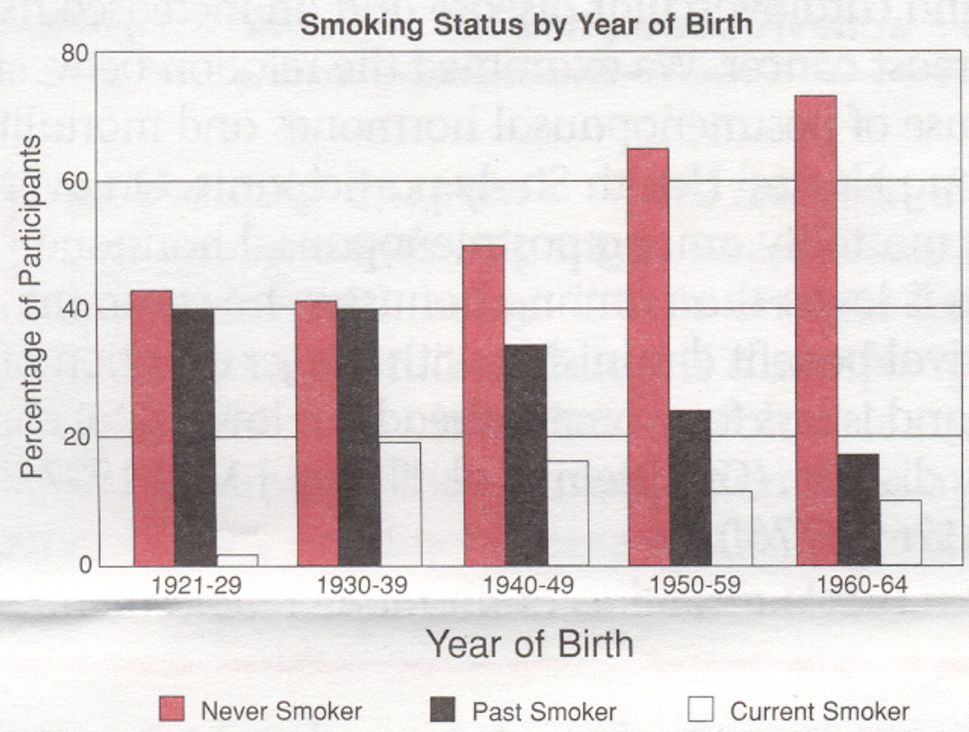
We are unable to provide results of these assays to individual participants, and the reasons for this are numerous. We only analyze samples from participants who have already developed a particular disease, and a matched sample of participants who have remained disease-free, in order to minimize the cost of the research. Thus, for most participants, we will never have individual results. Additionally, the clinical utility of much of this information is still very uncertain, particularly for inherited polymorphisms that may confer subtle degrees of risk or protection. Furthermore, almost all of the assays that determine DNA sequence are done in **research** laboratories, which, although we are confident of their quality, do not meet the accreditation criteria required of **clinical** labs; many states legally prohibit provision of results from research labs. Finally, it is a sad fact in today's society that knowingly undergoing genetic testing may put a study participant at risk of losing health or other insurance. Insurers may assume that having a test done suggests some clinical indication, not recognizing that an individual could be in a research study.

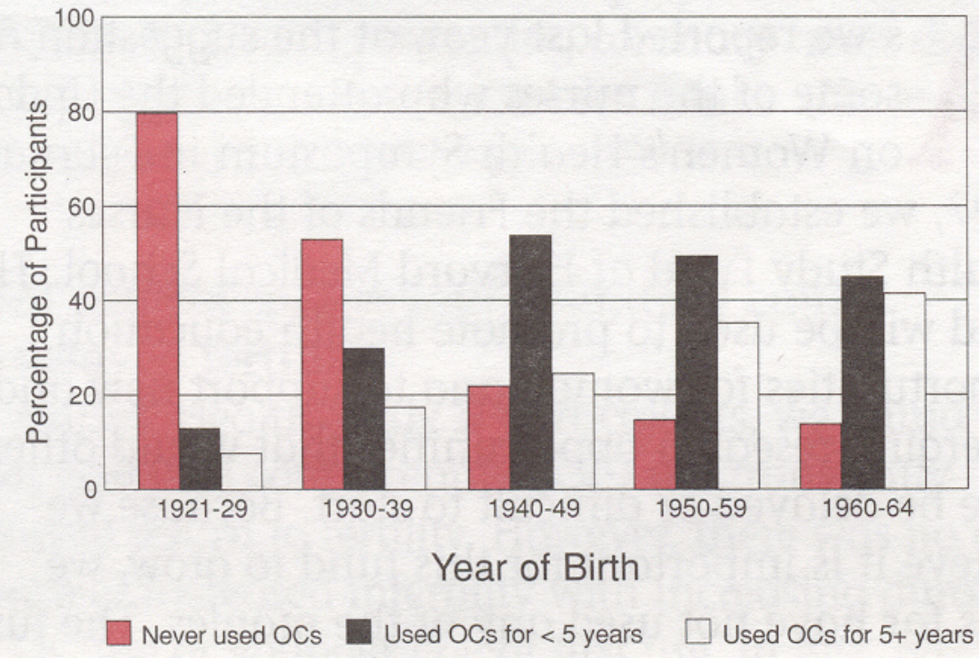
All results are kept under the highest standards of confidentiality, and we have received a Certificate of Confidentiality from the Department of Health and Human Services designed to render genetic research results immune from any third-party legal challenge to obtain them (e.g., a subpoena from an insurance company). Again we thank you for your participation in this important research. We will continue to report to you the conclusions of this genetic research as they become available.

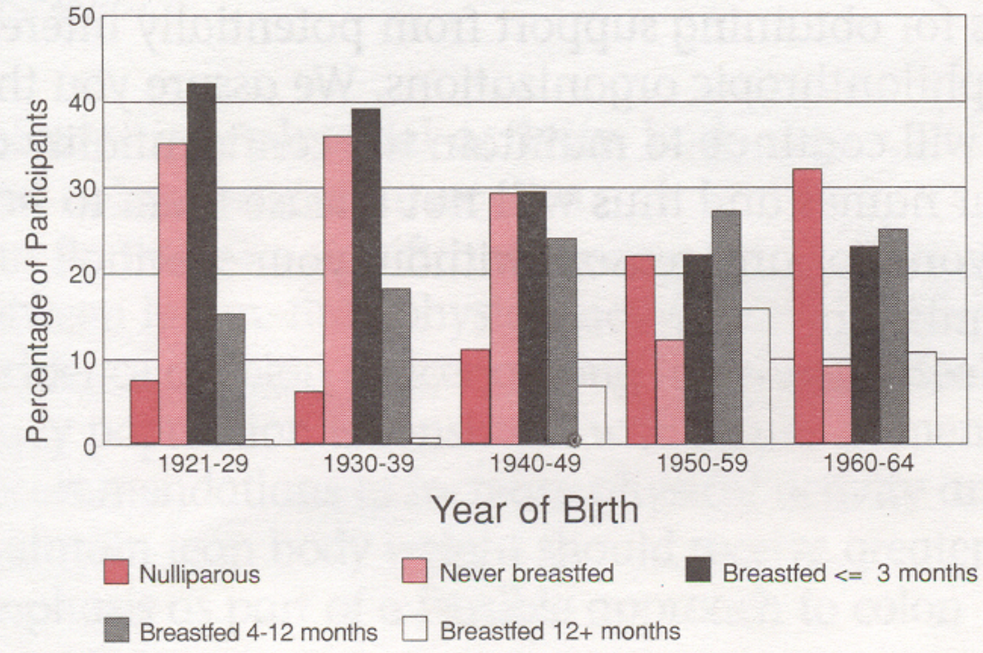
Keeping Us Up-to-Date

As members of the Nurses' Health Study continue to age, we can unfortunately expect that some will eventually develop conditions such as Alzheimer's or Parkinson's, which may make it difficult to respond to future mailings. We hope to examine these and other serious illnesses and learn more about their causes. Thus, we encourage you to discuss your participation in the Nurses' Health Study with your family and your doctor. Should you become disabled in the future, it would greatly help our research if someone could notify us of your health status and subsequently assist us by allowing your pertinent medical records to be released to us. By combining the long medical and dietary histories you have provided over the years with details of later illness, we can evaluate possible causes of these illnesses as well as ways in which they may one day be prevented.

Characteristics of Participants in the Nurses' Health Studies







Focus on Our Research Team

Once again we'd like to introduce you to one of our staff members whose behind-the-scenes work is essential to the successful conduct of the Nurses' Health Studies. Please meet Stefanie Parker, Project Coordinator.



Photo by David Temelini

Stefanie won a full scholarship to the State University of New York at New Paltz and earned a Bachelor of Arts degree in Biology. She joined our research team in 1987 and has seen the study grow dramatically in scope since that time. Stefanie was largely responsible for creating the color photo booklet of oral contraceptives used in the 1989 Nurses' Health Study II questionnaire. She works closely with study investigators to develop the biennial questionnaires, and each year she designs the study newsletter.

Stefanie plays an important administrative role in overseeing the submission of scientific grants to various funding agencies (e.g., National Institutes of Health, American Cancer Society, American Lung Association), as well as managing the financial accounts of grants that have been awarded. The successful submission of these applications allows us to secure funding and thus continue to answer important questions about the impact of lifestyle factors on women's health.

Risks and Benefits of Oral Contraceptives and Postmenopausal Hormones

The risks and benefits of oral contraceptive use have been a major focus of the Nurses' Health Study. Though originally designed to document the relations between OCs and major illnesses, particularly breast cancer, the Nurses' Health Study has also examined the relation between OC use and total mortality. In that analysis, we observed no increase or decrease in total mortality among women who have ever used OCs compared with women who never used them.

OC use for five or more years significantly reduces the risk of ovarian and endometrial cancers. Balancing this reduction in risk is a modest elevation in the risk of heart disease, stroke, and breast cancer, which is present only in women currently using OCs. As the rates of heart disease, stroke, and breast cancer are extremely low at the time most women use OCs, the number of excess cases is low. As women age, rates (of breast cancer, for example) rise, and the excess number of cases due to current use of OCs also rises. One estimate based on a combined analysis of many studies, including data from the Nurses' Health Study, is that the cumulative excess number of breast cancer cases is 4.5 cases per 10,000 women using OCs from age 25 to 29, and 10 excess cases per 10,000 women using OCs from age 30 to 35. Because risk is largely limited to current OC users, the excess breast cancer risk is balanced by the benefits from protection against other cancers and the potential adverse consequences associated with pregnancy and childbirth.

The Nurses' Health Study has provided much of our current knowledge on the long-term effects of postmenopausal hormone use. On the basis of information you have contributed over many years, we have found that hormone therapy after menopause can provide substantial protection against heart disease and possibly stroke (specifically death from stroke). In our most recent work, colorectal cancer risk appeared to be 35% lower in current estrogen users than in non-users. Although Nurses' Health Study participants are still somewhat young for fractures to be common, osteoporosis is also decreased by 25% in hormone users. The primary increase in disease risk is for breast cancer and is seen among long-term hormone users, with an increase of approximately 50% after five years of use. We have also found an elevated risk of pulmonary embolism for current hormone users, although pulmonary embolism is a very rare occurrence. Many risk-benefit studies have concluded that the benefits of hormone replacement therapy outweigh the risks; these are based mostly on the high overall mortality rates due to cardiovascular disease in industrialized countries and often do not take into account the increasing risk of breast cancer with increasing duration of hormone use.

In an analysis of all-cause mortality in the Nurses' Health Study, there was a 37% decrease in the risk of mortality for current hormone users; however, the primary benefit was for women with cardiovascular risk factors. In addition, the benefits diminished somewhat after ten years of hormone use because of the excess mortality due to breast cancer. Thus, the risk factor profile of a woman is important in her decision whether to take hormones, and this decision should be re-evaluated over time because the balance of risks and benefits may change with longer duration of hormone use. Women should also consider that lifestyle modifications, such as exercising regularly, avoiding weight gain, reducing saturated and *trans* fat consumption, increasing intake of fruits and vegetables, and quitting smoking, can provide many of the benefits of estrogen without any health risks. More information is needed to assess the risks and benefits of new estrogen substitutes, such as Raloxifene (now approved to prevent osteoporosis) and Tamoxifen.