NURSES' HEALTH STUDY NEWSLETTER

VOLUME 6, JUNE 1999

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Nurses' Health Study II Celebrates Tenth Anniversary



By the mid 1980s, the original Nurses' Health Study had become established as the single most important source of information on lifestyle factors and women's health. However, some important issues could not be answered in that study because we did not have information on diet and contraceptive use early in adult life. In recognition of the importance of these issues and the remarkable record of continued participation by women in the Nurses' Health Study, the National Institutes of Health provided funds to launch the Nurses' Health Study II. Thus, in 1989, 116,680 women aged 25 to 42 years completed a detailed questionnaire and thereby became members of this new cohort.

The admirable tradition of commitment to research on women's health established in the Nurses' Health Study has continued in the Nurses' Health Study II. In each of the two-year follow-up cycles, more than 90% of participants have returned questionnaires, thus ensuring the validity of the findings. Because this is the only large group of women enrolled relatively early in adult life, this information will, over the years, be a unique resource to guide personal and medical decisions. As expected, the number of major medical conditions has remained relatively low in the Nurses' Health Study II, and has allowed us to give attention to other less well studied conditions, such as infertility, uterine fibroids, asthma, and gestational diabetes. In most instances, these analyses have been by far the largest investigations of these topics, and considerable new information has been gathered already. In this newsletter, we include abstracts of some of these papers and describe how the blood and urine specimens from Nurses' Health Study II participants will provide data not available from any other source.

This is a moment to celebrate both the achievements of the last decade and the opportunities of the future. Our application to the National Institutes of Health for continued funding of the Nurses' Health Study II was recently approved with an outstanding score. This assures another five years of support, the longest period granted by the Institutes, and we are confident that this will be an extremely productive period for discovering new ways to enhance the health and well-being of women. From all of us who work on the Nurses' Health Studies, we salute you and all of the participants who make this possible!



Drs. Frank Speizer and Walter Willett *Photo by David Temelini*

Recent Findings



In every issue of our newsletter, we like to share with you summaries of recent publications. These selected papers present results from both Nurses' Health Study populations and provide findings that we believe are of particular public health importance.

Dietary carotenoids and vitamins A, C, and E and risk of breast cancer.

Among 83,234 Nurses' Health Study participants, we examined associations among intakes of specific carotenoids (α-carotene, β-carotene, and lutein/zeaxanthin), vitamins A, C, and E, consumption of fruits and vegetables, and breast cancer risk. During 14 years of follow-up, 2,697 incident cases of invasive breast cancer occurred. We found that consumption of fruits and vegetables high in these specific carotenoids and vitamins may reduce premenopausal breast cancer risk. (Zhang et al. J Natl Cancer Inst 1999; 91:547-556.)

Multivitamin use, folate, and colon cancer in women.
We studied the relationship between folate intake and colon cancer incidence in the Nurses' Health Study, where 442 new cases of colon cancer had occurred during 14 years of follow-up. We found that long-term use (15+ years) of multivitamins may substantially reduce colon cancer risk, and that this effect may be related to the folic acid contained therein. (Giovannucci et al. Ann Intern Med 1998; 129:517-524.)

Epidemiology of interstitial cystitis.
Interstitial cystitis is a chronic debilitating syndrome characterized by irritative voiding symptoms and suprapubic and/or pelvic pain. Sufferers of this condition may experience the need to void as frequently as every 30 minutes during the day and several times at night. Among 184,583 Nurses' Health Study and Nurses' Health Study II participants, 110 cases were confirmed by medical record review. This finding indicates that the prevalence of interstitial cystitis in the U.S. is more than 50% greater than previously reported and 3 times greater than that reported in Europe. (Curhan et al. J Urol 1999; 161:549-552.)

Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women.
Using blood samples collected from Nurses' Health Study participants in 1989 and 1990, we prospectively evaluated the relationships between sex steroid hormone levels in plasma and the risk of breast cancer. Our data, in conjunction with past epidemiologic and animal studies, provide strong evidence for a causal relationship between circulating postmenopausal estrogen levels and risk of breast cancer. (Hankinson, et al. J Natl Cancer Inst 1998; 90:1292-1299.)

Association of dietary intake of fat and fatty acids with risk of breast cancer.
Among 2,956 Nurses' Health Study participants who developed breast cancer between 1980 and 1994, we found no evidence that lower intake of total fat or specific major types of fat was associated with a decreased risk of breast cancer. (Holmes et al. J Am Med Assoc 1999; 281:914-920.)

Relationship of a polymorphism in *CYP17* to plasma hormone levels and breast cancer.
A variant form of *CYP17*, a gene encoding an enzyme involved in steroid hormone production, has been associated with elevated steroid hormone levels in premenopausal women and increased breast cancer risk. We prospectively assessed the association between this variant form (*A2* allele) of *CYP17* and breast cancer risk in the Nurses' Health Study. Our data suggest that the *A2* allele of *CYP17* modifies endogenous hormone levels but is not a strong independent risk factor for breast cancer. (Haiman et al. Can Res 1999; 59:1015-1020.)

Race, reproductive factors, and oral contraceptive use in relation to risk of uterine leiomyomata.
Among 95,061 premenopausal Nurses' Health Study II participants, 3,006 cases of uterine leiomyomata (fibroids) were confirmed by ultrasound or hysterectomy. Risk of this very common condition was significantly inversely associated with age at menarche, parity, age at first birth, and recent birth(s). The risk of developing fibroids was positively associated with history of infertility among women who first used oral contraceptives at ages 13-16. Even after adjusting for these risk factors, African-American women had a 2.5-fold increase in incidence of fibroids; the reasons for this increase remain the subject of future research (Marshall et al. Fertil Steril 1998; 70:432-439 and Marshall et al. Obstet Gynecol 1997; 90:967-973.)

Additional papers that may be of interest:

- Curhan et al. Beverage use and risk for kidney stones in women. Ann Intern Med 1998;128:534-540.
- Coakley et al. Lower levels of physical functioning are associated with higher body weight among middle-aged and older women. Int J Obes 1998;22:958-965.
- Rexrode et al. Abdominal adiposity and coronary heart disease in women. JAMA 1998;280:1843-1848.
- Achat et al. Social networks, stress and health-related quality of life. Qual Life Res 1998;7:735-750.
- Feskanich et al. Vitamin K intake and hip fractures in women: a prospective study. Am J Clin Nutr 1999;69:74-79.
- Sacks et al. Effect on blood pressure of potassium, calcium, and magnesium in women with low habitual intake. Hypertension 1998;31:131-138.

During the next year, we plan to create a website that would include a complete listing of our publications, as well as interesting information on our research team and links to other health-related sites. Stay tuned for this exciting new development!

Question and Answer

Q *I am no longer working as a nurse and I do not use birth control pills. Do you still want me in the Nurses' Health Study?*

A Yes, absolutely! You need not currently be a practicing nurse to continue to be an important part of the Nurses' Health Studies. A growing percentage of our participants are no longer employed as nurses or have retired (see the *"Did you know"* sections on pages 4 and 5). As original members of the study, you are unique and irreplaceable!

While it's true that one of our primary aims is to study the long-term effects of oral contraceptives, it's not necessary to be taking them currently (or to have ever used them). We follow current, former, and "never" users to evaluate the effects their use may have on women's health.

Q *Why do I sometimes get more than one questionnaire per year?*

A The vast majority of participants receive only one questionnaire every two years. Nurses who don't return their questionnaires promptly are mailed additional forms. Occasionally, some women may also be asked to participate in small sub-studies or to complete a questionnaire providing details about a specific medical condition. It's essential to the validity of our research that we maintain as high a follow-up rate as possible.

Q *How many of the original members are still active participants in the studies?*

A The Nurses' Health Study began in 1976 with 121,701 participants; the Nurses' Health Study II enrolled 116,680 women in 1989. In each questionnaire cycle since 1990, we obtained follow-up information on over 90% of each group. We must also report that about 10,000 members of the Nurses' Health Study and 450 participants in the Nurses' Health Study II have died.

The Nurses' Health Studies are the largest investigations of women's health to collect and maintain repeated follow-up information. This research depends on your continued willingness to complete our often lengthy surveys. Maintaining current information on each participant provides a strong database from which new insights into women's health can emerge.

Studies of Cognitive Function

Most people are worried about their memory as they get older. This is a particularly important issue for women, who live longer than men and have a higher frequency of memory loss in most age groups. Although research has examined memory in subjects with established dementia, virtually nothing is known about prevention of memory loss in healthy women.

In the Nurses' Health Study, we have just completed a pilot study investigating the incorporation of telephone-administered memory assessments into our research; these will allow us to explore lifestyle changes women might make to prevent or delay memory loss. For this pilot, 3,000 participants agreed to complete a brief telephone interview. The pilot project was so successful and the participants so enthusiastic that we are expanding its scope to include all participants aged 70 years and older. Over the next year, we will telephone these women to ask if they are willing to complete a 15-minute interview that will consist of several standard assessments of memory. Two follow-up interviews will be conducted at two-year intervals to evaluate any changes in memory.



The Nurses' Health Study offers a unique opportunity to understand how lifestyle and diet may affect memory, thanks to the informative and detailed lifestyle data you have provided over the past 23 years.

Keeping Us Up to Date

As members of the Nurses' Health Study continue to age, some will unfortunately become disabled or develop conditions such as Alzheimer's or Parkinson's that 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 identify possible causes of these illnesses, along with ways in which they may one day be prevented.



Beyond the Questionnaire

As you know, the information you have provided on your biennial questionnaires has been immensely valuable in evaluating what lifestyle factors are associated with increased or decreased disease risk. However, for many of you, we have also requested blood, urine, tissue, or other "body parts." We sincerely appreciate your willingness to provide these samples and would like to explain their importance to our research effort.

First, what samples have you provided to date? Many thousands of you provided a blood and/or urine sample either ten years ago or in the last few years. Over 60,000 women provided toenail clippings in 1982 (surely, you haven't forgotten that!). Many women who have been diagnosed with benign breast disease have given us permission to collect pathology (tissue) samples from their diagnostic biopsies. And finally, over the next several years, we will ask some of you for either a cheek cell brushing (collected by swirling a small bristled brush on the inside of your cheek) or a second blood sample.

We collect blood and other tissue because it can provide answers to questions that the written survey cannot address. For example, we have examined the relationship between circulating hormone levels and breast cancer (see Hankinson abstract, page 2). Similarly, using DNA samples obtained from a blood sample or cheek cell brushing, we evaluated whether inherited variations in the genes involved in hormone metabolism influence levels of these circulating hormones and hence alter breast cancer risk (see Haiman abstract, page 2). Urine samples can be used to assess a number of additional hormones. The toenail samples have been used to study the relationship between trace elements (e.g., selenium or fluoride) and risk of diseases such as cancer and osteoporosis. Finally, benign breast biopsy tissue allows us to determine the exact type of benign breast disease. We (and others) have found that the relationship between benign breast disease and breast cancer varies according to type (e.g., atypical hyperplasia is associated with an increased risk of breast cancer, whereas nonproliferative benign breast disease is unrelated to breast cancer risk). Over the next several years we will ask some of you for a second blood sample, so that we may look at levels of hormones or nutrients at two points in time to determine *when* a particular exposure may be important to disease risk (e.g., is the most important exposure recent or ten or more years in the past?). It would be impossible to conduct any of these studies without the samples you have provided.

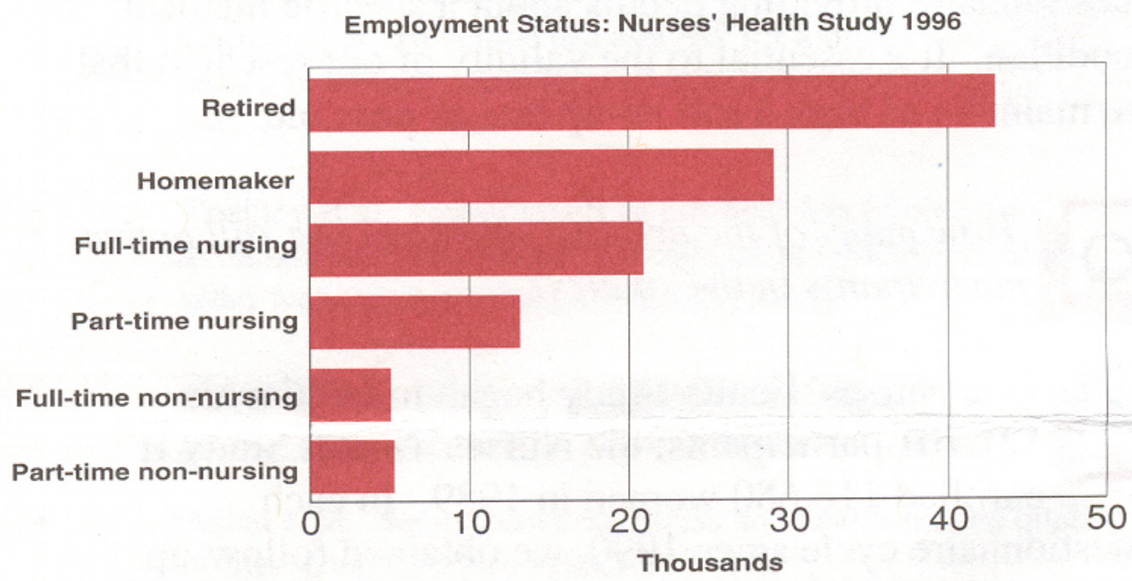
As a reminder, we are unable to provide you with individual results of genetic or plasma-based assays; there are several reasons why. Because of the considerable expense of the assays, we only evaluate samples from women who develop a disease and a small subset of those who remain disease-free. Hence, for most of you, it may be many years before we conduct a laboratory analysis of your sample. In addition, the clinical utility of many of these assays is still uncertain, particularly for genetic analyses where few studies have been conducted to date and the level of risk (or protection) associated with any one genetic alteration may be slight. However, as in the past, we will continue to provide you with up-to-date group results from these studies. If you have additional questions about any of these studies, please feel free to write or call us.

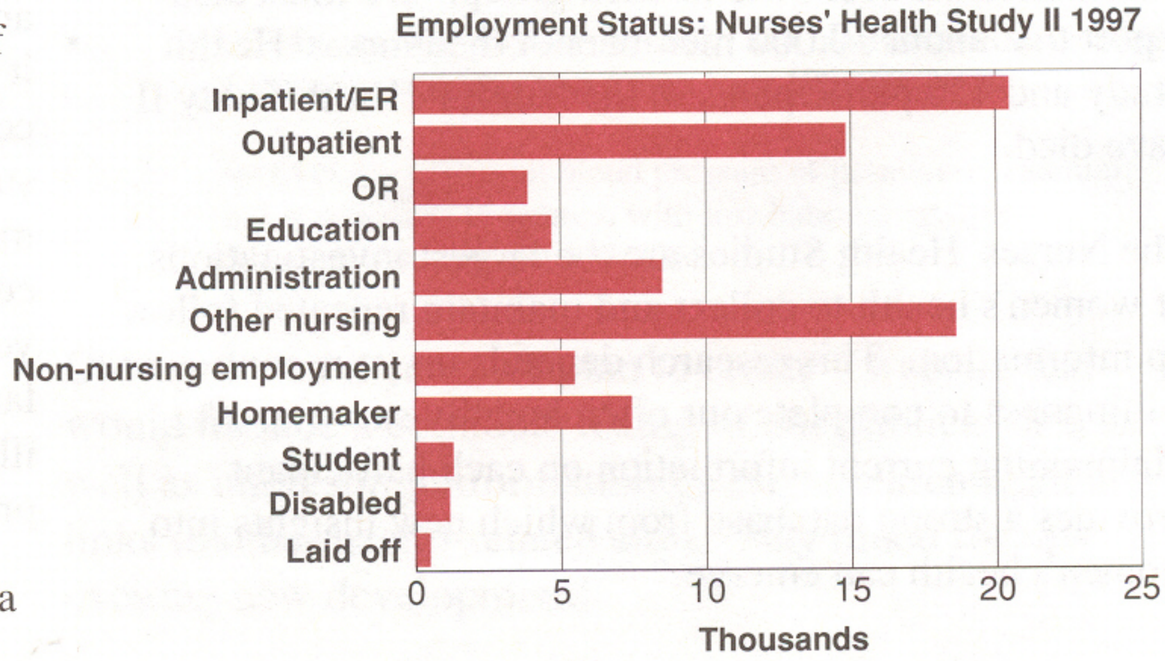
Issues of Confidentiality

Please remember that all results are kept under the highest standard of confidentiality. As part of this effort, we have received a Certificate of Confidentiality from the Department of Health and Human Services designed to render any results from this research immune from third-party legal challenge to obtain them (e.g., subpoena from an insurance company). We take the security of our data very seriously. This is just one more tool to help assure the complete confidentiality of your responses.

Did you know . . .

You often ask us if you should still be in the study if you aren't currently working as a nurse (see Q&A for more on this topic). The figures below demonstrate the wide range of employment choices you and your colleagues make.





Old Beliefs Challenged by New Data

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

Many of us working in health-related areas have believed that risk of colon cancer is reduced by high-fiber diets, and that heart disease can be greatly reduced by avoiding eggs (because they are high in cholesterol) and nuts (because they are high in fat). Indeed, many of us have counseled patients to eat fiber-rich foods and to avoid eggs and nuts for just these reasons. During the past year, three major publications from the Nurses' Health Study have challenged these beliefs. Specifically, we found that fiber intake was unrelated to colon cancer (Fuchs et al. N Engl J Med 1999;340:169-176), that egg consumption was not associated with risk of coronary heart disease (Hu et al. J Am Med Assoc 1999: 281:1387-1394), and that women who ate more nuts actually had a lower rate of coronary disease (Hu et al. BMJ 1998; 317:1341-1345). This has inevitably led to some confusion, with many people saying they don't know what to believe. Let's consider why there seems to be conflicting information.



In the case of fiber and eggs, the strong recommendations we have been taught were based on hypothesis and indirect evidence rather than direct data. For example, a physician working in Africa noted that fiber consumption was high and colon cancer rates were low, and thus concluded that these might be related. However, many other aspects of lifestyle besides fiber intake differ between peasant agriculturalists and populations living in affluent Western countries, including physical activity, obesity, and meat consumption. The hypothesis that egg consumption was an important risk factor for heart disease came mainly from evidence that increases in dietary cholesterol tend to raise blood cholesterol slightly, which is a risk factor for heart disease. However, dietary cholesterol also increases the beneficial HDL cholesterol fraction, which could off-set a small increase in risk. Eggs also contain other micronutrients that might counterbalance a small adverse effect of higher cholesterol. The important point is that strong recommendations were made without direct evidence that people who eat more fiber have lower future risk of colon cancer, or that those who eat more eggs have higher risk of coronary disease. The lack of direct evidence is just the reason that the dietary component of the Nurses' Health Study was launched in 1980, and why the current findings are now providing the best available evidence relating to these longstanding hypotheses. It is important to recognize that these findings are **not** in conflict with a strong preexisting body of data; as often occurs in science, the original hypotheses were simply not supported by subsequent evidence. One study, even one as large as the Nurses' Health Study, does not completely settle an issue. However, since virtually identical findings for fiber and eggs were seen in our parallel study among men, these results can be viewed with substantial confidence.

The origin of the belief that nuts are bad due to their high fat content is more troublesome. Virtually all nuts contain mainly unsaturated fats, which lower total and LDL cholesterol, and would therefore be expected to reduce coronary disease risk. Unfortunately, some experts felt that making distinctions between **types** of fat might confuse the public and therefore decided to focus educational efforts on reductions in **total** fat. The result has been that many foods high in unsaturated fats, including nuts, have been unjustifiably condemned. Our findings for nuts and heart disease, which have been confirmed in several other studies, are thus consistent with the expected benefit based on their nutrient composition.

What do these findings mean for those who wish to make healthy dietary decisions? Choosing foods high in fiber, such as whole grain breads and brown rice, is still important because evidence from the Nurses' Health Study and other investigations strongly supports benefits in reducing diabetes, heart disease, and diverticular disease of the colon. It appears that healthy people can consume up to one egg per day on average without any appreciable increase in heart disease. Notably, among men and women in our studies with diabetes, daily egg consumption did appear to increase risk of coronary heart disease. This finding will require confirmation in other studies, but for the moment diabetics may wish to be more cautious about egg consumption. Of course, working with your health provider to keep blood lipids under good control by diet, exercise, and possibly drugs is still important. Finally, incorporating nuts into daily diets is a good idea, especially when they are used to replace meat, such as in mixed dishes and salads.

Did you know . . .

Although all Nurses' Health Studies participants started out as registered nurses, over the years you have moved into a wide variety of other professions. In addition to many who are retired, we have "nurses" who are now :

- artists
- florists
- surgeons
- farmers
- psychotherapists
- real estate brokers
- internet consultants
- politicians

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 **Laura Sampson, Research Dietitian.**

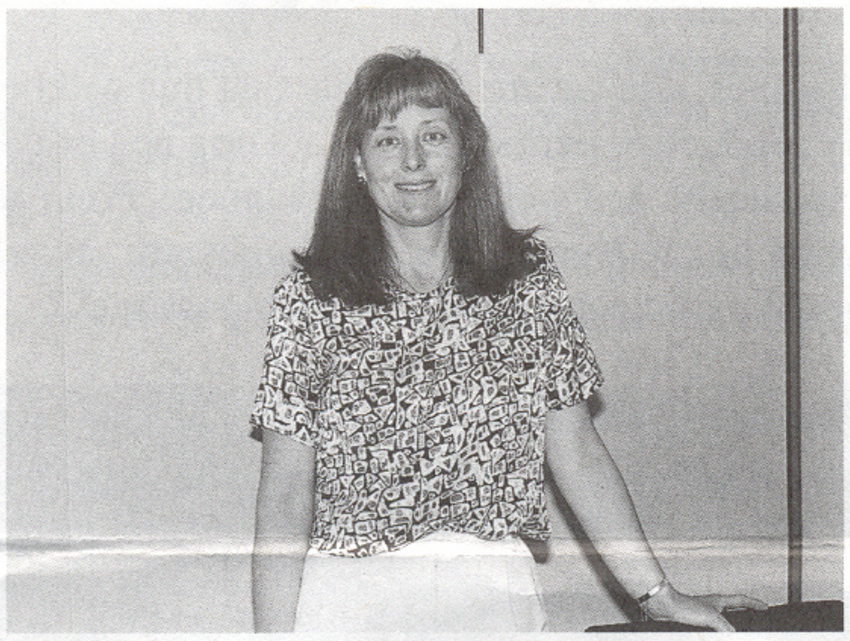


Photo by David Temelini

Laura attended the University of Massachusetts at Amherst and received a Bachelor of Science degree in Human Nutrition. She earned her advanced degree, a Masters in Science, at Framingham State College. Laura joined our research team in 1980 in the early development of the diet component of the Nurses' Health Study. She was responsible for the 1980 and 1986 diet validation studies in which 200 Boston-area nurses recorded two- and four-week diet records. She is also responsible for the nutrient database used to analyze the food frequency questionnaires. The dietetic staff now consists of four full-time dietitians and a nutrition assistant. The nutrient database is maintained for 162 variables: carbohydrate, protein, fat and fatty acids, energy, vitamins, minerals, amino acids, fiber, carotenoids, sugars, food contaminants, flavonoids, and glycemic index values. Future plans include adding other variables to the database such as ORAC, an antioxidant score.

The database established by Laura and her team of dietitians allows us to maintain nutrient information on brand-name multivitamins, margarines, cereals, and oils that participants write in on the food frequency questionnaires. The database contains information on 1,556 brand-name multivitamins, 104 margarines, 294 cereals, and 64 oils. The nutrition staff thanks those who have submitted label information for these items. Manufacturing information, journal articles, and the government's nutrient database (USDA SR12) are the primary sources for deriving your nutrient values for this year's questionnaire.

New Directions and Ongoing Research



The Cancer Risk Index: With colleagues at the Harvard Center for Cancer Prevention, we have developed a website that provides personal recommendations regarding risk reduction for colon cancer. The site builds on results from the Nurses' Health Study and gives tailored feedback that takes into account your responses to a set of ten to fifteen questions. In this way, you can see how much your risk would change if you modified your lifestyle. Please visit the website at http://www.hsph.harvard.edu/colonrisk

Quality of Life: Quality of life after cancer diagnosis is gaining increasing pubic attention. In September 1998, we were funded to investigate the changes in quality of life among women who completed a questionnaire in 1992-1993 and who subsequently were diagnosed with breast cancer. This work will continue for several years but already shows good response rates from women who received the supplementary survey. Early findings indicate that women with breast cancer experience lower quality of life than their peers of similar age, and that a considerable amount of decreased function is associated with lingering symptoms from breast surgery.

Growing Up Today Study: In our 1996 newsletter, we introduced you to the Growing Up Today Study, which includes nearly 17,000 children of Nurses' Health Study II participants. The main focus of the study is the relation among diet, activity, and excess weight gain in adolescence. Our findings on smoking contemplation and experimentation in relation to weight concerns and weight control behaviors are currently in press in the journal *Pediatrics*. Analyses are also underway to explore how diet and activity relate to weight gain. With obesity a major problem in the United States, our study of children as a major longitudinal resource will explore this and other issues.



Your Input

With every newsletter, our goal is to show you the broad scope of this study of which you are an integral part. We share stories about our research group and put faces with some of the names you may have heard or read. The newsletter, which is partially supported by the Friends of the Nurses' Health Study fund, is also our way of keeping in touch and giving a little something back to you. If there is a particular topic you would like to see in next year's newsletter, please let us know! All suggestions will be considered. Once again, many thanks for your participation.