

# The Nurses' Health Study: 20-Year Contribution to the Understanding of Health Among Women

GRAHAM A. COLDITZ, M.D., Dr.P.H., JOANN E. MANSON, M.D., Dr.P.H.,  
and SUSAN E. HANKINSON, R.N., Sc.D.

## ABSTRACT

The Nurses' Health Study was designed as a prospective follow-up study to examine relations between contraception and breast cancer. With follow-up questionnaires mailed every 2 years, investigators have added extensive details of lifestyle practices. The study, currently in its 20th year, has maintained high follow-up with >90% of participants responding to each of the follow-up cycles since 1988. The relations between use of hormones, diet, exercise, and other lifestyle practices have been related to the development of a wide range of chronic illnesses among women. This review describes the methods used to follow up the study participants and summarizes the major findings that have been described over the first 20 years of the study. We highlight additional areas added to the study in recent years to address emerging issues in women's health. Special emphasis is placed on the recent findings from the study, including relations between weight gain and heart disease, diabetes, and mortality, the lack of relation between calcium and osteoporotic fractures, and the positive relation between postmenopausal use of hormones and risk of breast cancer.

## INTRODUCTION

THE NURSES' HEALTH STUDY COHORT initially comprised 121,700 female registered nurses who returned a mailed questionnaire in 1976. The nurses were 30–55 years of age, married, and resided in one of 11 U.S. states (California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania, or Texas) according to 1972 files provided by the state boards of nursing and the American Nurses' Association. In June 1976, under the direction of Frank E.

Speizer, M.D., principal investigator, an introductory letter, a two-page questionnaire, and a prepaid return envelope were sent to each nurse. Identical materials were mailed in September and December 1976 in an attempt to enlist the participation of previous nonrespondents. Overall, 70% of those invited to participate in the study returned questionnaires.<sup>1</sup>

Funded initially to examine relations between the use of oral contraceptives (OCs), cigarette smoking, and risk of major illnesses in women, the study has been broadened over time to include the evaluation of health conse-

Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

This work was supported by grant CA 40356 from the National Institutes of Health.  
This manuscript expands on work previously summarized in *J Am Med Wom Assoc* 1995;50:40.

quences of many lifestyle practices, including diet, physical activity, and specific forms of estrogen replacement therapy. Although the major source of funding remains the extramural program of the National Cancer Institute (NCI), the wide range of conditions studied has resulted in supplemental funding from the National Heart, Lung, and Blood Institute, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, and the National Eye Institute. A more recent addition is funding from the National Institute on Aging to study work stress and quality of life. In addition, funding for pilot studies has been received from several pharmaceutical firms and from the National Dairy Council and the Florida Citrus Commission/Florida Department of Citrus. The research effort is coordinated by a group of investigators at Harvard Medical School and Harvard School of Public Health, who meet every 2 weeks to review the progress of the component studies and plan analyses and further research questions.

The study was designed as a prospective cohort investigation to define the relation between OCs and cancer. Based predominantly on data on women's use of OCs marketed during the 1960s and 1970s, the cohort provides extensive data on the health effects of these early OC formulations. Nurses were chosen because of the higher accuracy of information that they would report than would a broader sample of women. Further, they were expected to understand some of the issues involved in research studies and so participate more readily than women in general. Information was collected from participants while they were free from disease, thus avoiding problems of recall of lifestyle factors that plague retrospective studies. Only participants free from disease are followed to examine disease incidence. In an incidence-based follow-up study, the histories of those who subsequently develop disease are compared with the histories of women the same age who remain free from disease. Because we mail follow-up questionnaires to all cohort members, women who have been diagnosed with cancer and other major illnesses also provide updated information. In the future, as numbers become sufficiently large, we

may be able to examine diet, activity, and other lifestyle factors after diagnosis and their relation to survival. After the cohort was established in the initial grant period, additional funding was obtained from the NCI to follow the women to study hypotheses relating cigarette smoking, hair dyes, and postmenopausal hormones to the risk of a range of cancers and cardiovascular diseases.

## FOLLOW-UP OF PARTICIPANTS

Follow-up questionnaires are mailed to all cohort members every 2 years. These questionnaires are mailed along with cover letters and a newsletter that updates participants on the progress of the study. Each follow-up questionnaire inquires about a number of exposures as well as the development of cancer, cardiovascular disease, and other major medical conditions diagnosed since the last follow-up. The first follow-up questionnaire is mailed in June of even-numbered years (1978, 1980, 1982, and so on), and those who do not respond are sent a second mailing in September. On average, 80,000 women respond to the first mailing. Subsequently, we send a third and fourth questionnaire to those who still have not responded. Finally, a fifth mailing of a short questionnaire that includes only a few key exposure variables and the list of major illnesses is sent. This fifth mailing, which includes a newsletter to update participants, is sent in June of odd-numbered years. This strategy ensures that any change of address is obtained from the post office (whose usual practice is to keep address forwarding orders for only 12 months).

Most deaths are reported by the subject's next of kin or by postal authorities. These reports are supplemented by searches of the National Death Index for deaths among the nonrespondents. Using these methods, we estimate that more than 98% of deaths in this cohort have been identified.<sup>2</sup>

In 1982, we added a telephone follow-up to reach those women who had not responded to any of the five mailings. More than 14,000 women were successfully contacted and completed a brief telephone interview focused on any newly diagnosed illness. Telephone fol-

low-up was repeated after the 1986 follow-up cycle. In 1988, we used a series of additional approaches, including sending questionnaires by UPS and certified mail,<sup>3</sup> and achieved a response of 88%. In 1990 and subsequently, using both telephone and certified mail to reach initial nonresponders, responses were received from just over 90% of the women in the study. Overall, participation has been very high, a tribute to the dedication of the women in the study.

Each year we are notified of more than 4000 address changes. In addition, some mail is returned to us as undeliverable. Using mechanisms developed over the last 20 years, we trace these women through direct contact with the local postmaster, the state boards of nursing, and a contact person designated by the study participant (contacts were identified by study members in 1978, 1982, 1986, 1988, and again in 1992). Through these approaches, we have successfully located the majority of participants with whom we have lost contact at some time.

### CONFIRMATION OF SELF-REPORTED ILLNESSES

For any report of cancer (except basal cell skin cancer), we seek written permission from study participants to review their medical records. We telephone nonrespondents to this request to obtain verbal confirmation of the information reported on the follow-up questionnaire (asking details of diagnosis and treatment, such as chemotherapy). All medical records are reviewed by trained physicians blinded to exposure information previously provided by the study participant.

For women reporting a myocardial infarction or stroke, we also seek the medical records pertaining to the initial diagnosis. Myocardial infarction is classified as confirmed if the records meet the criteria of the World Health Organization, including symptoms and either typical electrocardiogram changes or elevations of serum cardiac enzymes.<sup>4</sup> Stroke is classified according to the criteria developed by the National Survey of Stroke.<sup>5</sup>

On the 1982 questionnaire, we added an item seeking a history of fracture of the hip or fore-

arm and details regarding the diagnosis of gallstones and cholecystectomy. Diagnostic details of these major medical conditions have been included on subsequent follow-up questionnaires. Using a similar approach, we have added documentation of self-reported colon polyps and a range of eye conditions, including cataract surgery, macular degeneration, and glaucoma.

After the 1984 follow-up questionnaire cycle, we mailed supplementary questionnaires to all women who had ever responded affirmatively to the question "Have you ever been diagnosed as having diabetes mellitus?" on any of the previous questionnaires. This supplementary questionnaire included items on symptoms of diabetes at the time of diagnosis, fasting and random glucose levels, oral glucose tolerance testing, presence of glycosuria or ketonuria, history of ketoacidosis (including hospitalization), history of diabetes treatment, and gestational diabetes.

Earlier cohort studies conducted in the United Kingdom to document the health consequences of cigarette smoking used populations of doctors<sup>6</sup> to reduce the likelihood of error in the reporting of illnesses and to facilitate follow-up, as the professional register served as a means to trace the physicians. Similarly, in establishing a large cohort of women, a key consideration was the ability of participants to accurately report the diagnosis of major illnesses. Because each reported disease must be confirmed, even a small increase in documentation due to erroneous reporting would greatly increase the cost of the study. The extremely accurate reporting of major medical conditions by Nurses' Health Study participants has contributed greatly to the cost-effective nature of this large study.

After confirming illnesses reported on the 1978 and 1980 follow-up questionnaires, we reported the level of agreement. Overall, almost all self-reported cancers were confirmed by medical record review.<sup>7</sup> Application of strict criteria for cardiovascular end points may result in rejection of some true cases and a slight underestimate of the true incidence of disease, but with few false-positive diagnoses.

The reliability of reporting of hypertension, high blood cholesterol, fractures, and diabetes

has been confirmed in random samples of women. Agreement between self-report and medical records has been high, more than 98% for those conditions. In contrast, for classic connective tissue diseases, we were only able to document <20% of cases when applying standard diagnostic criteria as defined by the American College of Rheumatology to information contained in medical records.

### STATISTICAL ANALYSIS

We perform statistical analyses on data collected prospectively from participants in the Nurses' Health Study. All data are analyzed for statistical purposes only, and the confidentiality of participants is maintained by storing all questionnaire information by identification number only. Names and addresses are stored on a computer system separate from the computer that stores questionnaire response data. We use relative risk as a measure of association between exposure (lifestyle variables) and disease. The relative risk, or rate ratio, is calculated as the rate of disease among women in each category of an exposure (e.g., duration of use of OCs) divided by the rate of disease among women in the reference category (e.g., women who have never used OCs). Relative risks are adjusted for age in 5-year intervals. To control simultaneously for age and other potential confounding variables, we use either logistic regression or proportional hazards (Cox) models.

### LIFESTYLE EXPOSURES

The design of the Nurses' Health Study includes several unique features. Among these is the repeated assessment of lifestyle and other exposure variables. Such repeated assessment is needed, at least in part, because of the questions being asked by the study. For example, given a focus on OCs and health, we need to update the status of women who are using these or other exogenous hormones, such as those used in postmenopausal hormone therapy. The changing availability of products and their patterns of use, such as the addition of

progesterins to postmenopausal estrogen and varying number of days per month that these products are used, preclude the application of more controlled research designs to address risks associated with current prescribing patterns. Likewise, with >1% of smokers stopping every year, it is necessary to update smoking status on a regular basis to accurately estimate the relation between current smoking and disease as well as the benefits of quitting smoking. The repeated measurement of lifestyle allows for the study of many factors as they relate to health. Another benefit of repeated questionnaires has been the ability to add items to the follow-up questionnaires to address new and evolving hypotheses. Among the many additions have been some of the diseases and conditions discussed and such variables as diet, physical activity, and screening behaviors.

Several studies have grown out of the ongoing Nurses' Health Study: a study of mortality among spouses who use vasectomy as their form of contraception,<sup>8</sup> a new study of younger nurses to address questions that we cannot adequately answer with the ongoing study, and the establishment of a cohort of children of the younger participants to examine adolescent diet, activity, and excess weight gain. Each study is made possible by the many components that already exist, including our data processing methods, software for data management and analysis, and, for the study of spouses, a population of women already committed to health research.

In 1980, a dietary component was added to the follow-up questionnaire. A food frequency questionnaire was pilot tested among study participants during 1979, and based on the results, 61 food items were selected and included in the follow-up questionnaire mailed to all cohort members in 1980. For each food, a commonly used unit or portion (e.g., one egg or slice of bread) was specified, and the women were asked how often, on average over the past year, they had consumed that amount of each food. There were 10 possible responses, ranging from "never" to "six or more times per day." We also inquired in detail about the types of fat used in cooking and at the table and about the use of specific vitamin supplements. Nutrient intakes were compiled by multiplying

the frequency of consumption of each unit of food by the nutrient content of the specified portions.

This food frequency questionnaire has been evaluated extensively for reproducibility and validity. Nutrient intake assessed by this questionnaire was compared with detailed diet records kept by a sample of 194 participants who weighed or measured everything they ate or drank for 4 weeks over the course of a year.<sup>9-11</sup> In addition, various nutrients measured in the blood (vitamin E, beta carotene, omega-3 fatty acids) were found to be correlated with the questionnaire estimates of intake.<sup>12,13</sup> The instrument's reproducibility was assessed in 1614 women<sup>14</sup> and not found to be influenced by obesity or other personal characteristics, including cigarette smoking, alcohol intake, or age. These validation studies were crucial in establishing the validity of dietary questionnaires in large-scale studies and remain the standard for such studies in the field of epidemiology. Since 1980, the food frequency questionnaire has been expanded to include approximately 120 individual food items plus vitamin and mineral supplement use that collectively account for >90% of the major nutrient intakes being measured. This expanded questionnaire was completed by the cohort in 1984, 1986, 1990, and 1994.

## BIOLOGIC SPECIMENS

### Toenail samples

Because of evidence suggesting that selenium may be important in the etiology of cancer and heart disease, our research group was interested in obtaining selenium exposure levels from participants in the cohort. It is not possible to assess selenium intake from a food frequency questionnaire because of high variability of selenium values within specific grains and vegetables as a result of variability in soil selenium content.<sup>15</sup> After validation of the use of toenails as a means to measure body selenium levels integrated over an extended period,<sup>16</sup> we invited 92,000 participants to mail a set of 10 toenail clippings following the return of the 1982 follow-up questionnaire. In all,

68,213 women responded, and their nails are stored in a bank of toenail specimens that have been used in several analyses comparing women who have developed a serious illness during follow-up to a sample of those who have remained free from disease.

### Blood samples

In 1989, the Nurses' Health Study research group was awarded funds to undertake the collection of blood specimens from participants in the cohort to address hypotheses related to hormone levels, micronutrients, and risk of breast cancer. The collection of blood specimens was completed over a year-long period. The 1988 questionnaire asked participants if they would be willing to provide a blood sample, and those who indicated yes were sent a blood collection kit. More than 32,000 women participated in this additional phase of the study. Only about 6500 of the participants were premenopausal. Although their blood samples were not collected at a specific time in their menstrual cycle, the day their current cycle started was recorded on the study questionnaire. The women who provided blood samples were similar to those who did not in terms of both age and body mass index (BMI), although they were slightly less likely to be current cigarette smokers and more likely to be currently using postmenopausal hormones. Samples were sent by overnight delivery to our research laboratory, where they were centrifuged, labeled, and stored on liquid nitrogen for subsequent nested case-control analyses. We will identify the blood samples from women who subsequently develop breast cancer during follow-up and compare hormone levels with those of controls who have remained free from cancer and are the same age as the women with breast cancer (i.e., a nested case-control analysis). Likewise, when studying hormones and risk of fractures or antioxidant levels and risk of cataracts or cardiovascular disease, we will identify women who provided blood samples and subsequently developed these conditions and a group of women who remained free from these diseases as a comparison group.

Studies among a subset of postmenopausal participants who provided repeated blood

samples over 3 years have shown that a single blood sample, as obtained from the more than 30,000 women, is a good indicator of blood hormone levels over at least the previous 3 years.<sup>17</sup>

Analyses of hormone levels among postmenopausal participants in this study indicate that with increasing levels of obesity (BMI), higher levels of estrogens are present. For estrone and estrone sulfate, the correlation was 0.37, and for bioavailable estradiol, it was 0.67.<sup>18</sup> Prolactin was the only hormone analyzed that was unassociated with BMI. Height was unassociated with plasma estrogens or prolactin. Alcohol intake was positively associated with estrone sulfate concentration ( $r = 0.17$ ). These data suggest that the associations of BMI and alcohol intake with subsequent breast cancer risk might be mediated, at least in part, through influence on postmenopausal estrogen levels.

The possibility of exploring the genetic basis for cancer, as well as other diseases, by assessing the stored blood for candidate genes is being undertaken. This is a rapidly changing field, and, at present, it is not clear what the full extent of using blood samples from the cohort will be.

### QUALITY OF LIFE AND SOCIAL NETWORKS

Over the years, participants have indicated to us through letters returned with questionnaires that they have concerns beyond the more directly biologic exposures (such as cigarette smoking and menopause) that we routinely record. In response to their concern, in the fall of 1991 we identified a series of questions to assess quality of life using the Medical Outcomes Study SF-36,<sup>19</sup> work-related stress (including job demands and control),<sup>20</sup> caregiving outside of work, retirement, and other measures of social support or social networks.<sup>21</sup> In 1992, we included these questions in the initial June mailing to all participants in the study. More than 70,000 women completed and returned questionnaires with these additional items related to quality of life, thus forming the basis for detailed analyses relating these measures to changes over the life course as these women are followed through the next decade.

Comparing the mean score for each subscale on the SF-36 against the National Opinion Social Survey—General Social Survey,<sup>22</sup> we observe that for working women, the mean scores for nurses were quite comparable to U.S. working women in general. The main difference appears to be that the Nurses' Health Study participants reported higher levels of physical functioning compared with the general population of working women (Table 1). Initial analyses of the work stress questions show that there is substantial variability even within a single occupation. Inpatient and operating room nurses were more likely to be in high-strain jobs. Outpatient nurses in passive jobs and nurse educators were more likely to be in low-strain jobs or active jobs. Thus, although job demands and control do not measure unique aspects of nursing work, these data suggest that they are reasonably differentiating nursing work in expected ways. We also note that when we compare role functioning and vitality as measured by the SF-36 across categories of job strain, women with high strain have substantially and significantly lower role physical and role emotional functioning and also lower vitality than women in active jobs.

### MAJOR FINDINGS AND CONTRIBUTIONS TO WOMEN'S HEALTH

The major disease-related findings from the study over the first 18 years of follow-up are summarized in Table 2. Here we set forth the

TABLE 1. COMPARISON OF SF-36 SCORES ON THE NATIONAL OPINION RESEARCH CENTER'S GENERAL SOCIAL SURVEY AND THE NURSES' HEALTH STUDY

SF-36 Subscale	NORC-General Social Survey	Nurses' Health Study
Vitality	63.9 (60.7–67.1)	62.8 (62.5–63.0)
Role emotional functioning	85.9 (81.2–90.5)	83.9 (83.5–84.2)
Mental health	77.6 (75.0–80.3)	75.7 (75.3–75.9)
Bodily pain	74.7 (71.2–78.2)	76.6 (76.3–76.8)
Physical functioning	85.3 (82.5–88.1)	89.4 (89.2–89.6)
Role physical functioning	87.1 (82.1–92.2)	82.0 (81.6–82.4)

major lifestyle factors and their relations to major illnesses among women. For each association, a citation to the full published report is included. Of note, the study has also made major contributions to the methods of assessing diet and other lifestyle variables that are now incorporated into many of the more recently created cohort studies, both in the United States and elsewhere. Many of these have been summarized previously.<sup>23</sup>

The major new findings reported over the past 2 years include a lack of association between dietary calcium intake among postmenopausal women and risk of osteoporotic fractures. Higher intake of calcium from dietary sources was not protective against fractures of the hip or wrist. In addition, a positive relation was observed between protein intake and risk of fractures. Dairy products high in protein and calcium were not protective against fractures. However, we observed a trend toward lower risks among women who consumed higher levels of milk during adolescence.

We also reported that calcium intake does not protect against risk of colon cancer<sup>24</sup> and that the risk of pancreatic cancer falls rapidly after cessation from cigarette smoking.<sup>25</sup> Women who have used OCs for  $\geq 5$  years have under half the risk of ovarian cancer compared with women who never used OCs.<sup>26</sup> Importantly, we have made major contributions to the framing of the revised dietary guidelines for Americans. A series of articles addressed the adverse effects of weight gain during adult life. Women who gained substantial weight after age 18 are at significantly increased risk of coronary heart disease (CHD),<sup>27</sup> noninsulin-dependent diabetes mellitus,<sup>28</sup> and total mortality<sup>29</sup> compared with women who remained within 5 pounds of their weight at age 18. Based on these results and an extensive body of literature showing physiologic changes with weight gain, the dietary guidelines now place greater emphasis on avoiding weight gain and state "Balance the food you eat with physical activity. Maintain or improve your weight."<sup>30</sup>

With regard to the use of postmenopausal hormones, we observed that longer use of hormones ( $\geq 5$  years) was associated with increased risk of breast cancer incidence and

mortality.<sup>31</sup> Also, we reported that the addition of progestins to estrogen therapy did not reduce the risk of breast cancer. Consistent with many other studies, early menopause is associated with substantially lower risk of breast cancer among women who do not take postmenopausal hormones. Current use of postmenopausal hormones continues to protect women against CHD.<sup>32</sup> Within this cohort of women up to age 71, almost three cases of breast cancer are diagnosed for every heart attack.

Other major findings that may lead to greater prevention of chronic illnesses include a decrease in risk of colon cancer with longer durations of use of aspirin.<sup>33</sup> The risk reduction was substantial after  $\geq 10$  years of use. A decrease in risk of colon cancer with moderate levels of physical activity also offers an important avenue for prevention. We reported that coffee drinking is not related to risk of CHD. Women consuming  $\geq 6$  cups of coffee per day had a relative risk of CHD that was 0.95 (95% CI 0.73–1.26) compared with women who did not consume coffee.<sup>34</sup> Suicide is less likely among women as level of coffee intake increases.<sup>35</sup> Also with regard to risk of CHD, we observed that women who had worked rotating shifts for  $\geq 6$  years were at increased risk.

One important feature of the prospective cohort design is the ability to study total mortality. With this outcome, we can begin to balance the risks and benefits of lifestyle choices, such as use of OCs, smoking, alcohol consumption, and body weight. Other studies that focus on one disease at a time are typically not able to address these important (and, from an individual perspective, often difficult) tradeoffs. Recent analyses have shown that use of OCs is not related to any overall increase in mortality,<sup>36</sup> that increasing body weight is associated with increased risk of mortality from all causes and separately from CHD and from cancer,<sup>29</sup> that smoking is associated with increased mortality and that risk is reduced after stopping smoking,<sup>37</sup> that alcohol is associated with increased mortality among women under age 40, and for women over age 50, light to moderate alcohol intake was associated with significant reduction in mortality.<sup>38</sup> Importantly, death from breast cancer was elevated among women

TABLE 2. MAJOR FINDINGS FROM THE NURSES' HEALTH STUDY, 1976-1996

	Breast Ca	CHD <sup>a</sup> /stroke	Colon Ca	Fracture	Diabetes	Other diseases
Cigarette smoking	No relation with current or past smoking <sup>43</sup>	Smoking dominant cause of CHD; strong dose-response relation <sup>44</sup>	Current smoking related to polyps; strong relation with cancer after 30-year latent period <sup>42</sup>	Increased risk of hip fracture	Increased risk of NIDDM <sup>a48</sup>	Strong predictor of lung cancer suicide, <sup>49</sup> and cataracts; <sup>50</sup> risk of total mortality for ex-smokers approaches that of never smoker after 10-14 years <sup>37</sup>
	Risk of CHD reduced by 14% within 2 years of stopping <sup>45</sup>	Strong relation with stroke <sup>46</sup> reduced after stopping smoking <sup>47</sup>	Strong relation cessation associated with modest weight gain of about 6 pounds <sup>51</sup>	No relation with total mortality <sup>36</sup>	No relation with rheumatoid arthritis <sup>56</sup>	
Oral contraceptives	Current use increases risk <sup>52</sup>	Current use increases risk <sup>53</sup>	No association <sup>54</sup>	Not examined	No association <sup>55</sup>	
	Past use—little association	Past use—little relation				
Postmenopause hormones	Current use for >5 years increases risk <sup>31</sup>	Current use reduces risk of CHD <sup>57</sup>	Suggestive decrease in risk of colon cancer <sup>54</sup>	Reduces risk of hip fracture	Not related to risk of NIDDM <sup>58</sup>	Decreased risk of ovarian cancer <sup>26</sup>
	Progesterins added to estrogen therapy do not reduce risk <sup>31</sup>					No relation with rheumatoid arthritis
						No relation with systemic lupus erythematosus <sup>59</sup>
Obesity	Weak positive relation with incidence among postmenopausal women <sup>61</sup>	Strong relation, even average weight women at increased risk of CHD <sup>62</sup>	Increased risk <sup>63</sup>	Strong protection against hip fracture	Strong dose-response relation; average weight women at significantly increased risk <sup>64</sup>	Increasing risk of cholecystectomy with increasing duration of use <sup>59</sup>
						Strong relation with gallstones <sup>65</sup> and total mortality <sup>29</sup>
	Weight gain after age 18 associated with increased risk <sup>27</sup>					

Alcohol	Increasing risk with increasing drinks per day <sup>66</sup>	Strong inverse relation for CHD; positive relation for subarachnoid hemorrhage <sup>57</sup>	Weight gain after age 18 significantly increases risk <sup>28</sup>	Strong inverse dose-response relation <sup>67</sup>	Reduced risk of total mortality among older women <sup>38</sup>
Diet	Low vitamin A intake associated with increased risk <sup>70</sup> but no relation for vitamin C or E	Moderate intake increases risk of polyps <sup>68</sup>	Increased risk of hip fracture with moderate intake <sup>69</sup>	No reduction in risk with higher dietary calcium intake <sup>77</sup> ; dietary protein associated with increased risk <sup>78</sup>	Magnesium intake inversely related to risk <sup>79</sup>
	Vitamin E protects against CHD <sup>73</sup>	Red meat intake increases risk of cancer <sup>75</sup>	No reduction in risk with higher dietary calcium intake <sup>77</sup> ; dietary protein associated with increased risk <sup>78</sup>	No relation with fat intake or total carbohydrate	Dietary vitamin A intake associated with reduced risk of cataracts <sup>80</sup>
	Trans-fatty acids increase risk of CHD <sup>74</sup>	Folate intake associated with reduced risk of polyps <sup>68</sup>	Caffeine intake positively related to risk of hip and forearm fracture <sup>69</sup>	Vigorous activity at least once per week reduces risk <sup>93</sup>	Antioxidant supplements—no important relation to asthma <sup>81</sup>
	Monounsaturated fat intake inversely related to risk of breast cancer	Calcium intake not related to risk of polyps <sup>76</sup> or to colon cancer <sup>24</sup>	Taller women more likely to have hip fractures <sup>92</sup>	Tubal ligation halves risk of ovarian cancer <sup>93</sup>	Coffee intake inversely related to suicide <sup>35</sup>
	No relation for total fat intake <sup>71</sup>	Aspirin use ( $\geq 20$ years) reduces risk <sup>33</sup>			
Other exposures	No relation with selenium <sup>72</sup>				
	Atypical hyperplasia associated with increased risk <sup>82</sup>				
	Family history accounts for 6% of breast cancer <sup>83</sup>	History of adult-onset diabetes increases risk of CHD and stroke <sup>87</sup>	Family history increases risk up to 4-fold among women <50%	Leisure time physical activity reduces risk of colon cancer <sup>91</sup>	Number of blistering sunburns before age 20 positively related to risk of melanoma <sup>95</sup>
	Use of hair dyes not related to risk <sup>84</sup>	Taller women have lower risk <sup>88</sup>	Rotating shift work increases risk of CHD <sup>89</sup>	Breast implants not related to risk of connective tissue disease	Use of hair dyes not related to risk of hematopoietic cancers <sup>81</sup>
	First pregnancy increases risk of breast cancer in short term but decreases risk long term; closer spacing of births associated with lower risk <sup>85</sup>				

<sup>a</sup>CHD, coronary heart disease; NIDDM, noninsulin-dependent diabetes mellitus.

consuming more than a drink per day, and death from cardiovascular disease was reduced among women with this level of intake.

The contribution of genetics to most major chronic diseases remains small. For breast cancer, for example, perhaps 6%–10% can be attributed to inherited genetic factors.<sup>39</sup> A similar estimate may prevail for colon cancer and for heart disease. Thus, the study of lifestyle factors acting in the broader population is more useful in identifying areas for prevention in the general population than merely focusing on the high-risk subgroups for specific diseases.

With additional follow-up, the numbers of cases available for study has increased, allowing application of new biomathematical models to the analysis of breast and lung cancer. These analyses allow us to better understand the interrelationships between particular lifestyle habits or exposures, the timing of these exposures, and the subsequent risk of cancer.<sup>40</sup>

Among the methodologic advances made in the Nurses' Health Study, the repeated measures of diet, hormone use, physical activity, body weight, and cigarette smoking have become the standard for modern studies among women. Of particular note is the need for repeated measures when studying behaviors, such as postmenopausal hormone use, with changing products and patterns of use that preclude the application of more controlled research designs to address risks associated with current prescribing patterns.

One concern when interpreting the results from the Nurses' Health Study is their internal validity. This point has been addressed, as noted, through extensive validation of reported lifestyle measures and careful documentation of disease outcomes. Once internal validity is established, issues of generalizability must be considered. The participants are predominantly white women, reflecting the ethnic background of women who trained as registered nurses through the 1960s.<sup>41</sup> At entry, their level of cigarette smoking was comparable to U.S. national data for women, and their use of OCs is comparable to that of their birth cohorts.<sup>23</sup> Their experiences (and age distribution) of menopause could not conceivably be altered by their training as registered nurses. Further, their reproductive histories are similar to na-

tional census data, and correspondingly, their rates of breast cancer are very close to those expected based on the national Surveillance, Epidemiology, and End Results age-specific rates. Data on occupational work stress is comparable to that of other studies, and the quality of life measures reported in 1992 reflect the patterns observed in the national reference study. Based on data such as these, we conclude that the cohort reflects the relations between lifestyle and health of white women in general. Thus, although they come from a professional group, their training in large part serves as an advantage, in all likelihood removing socioeconomic and other barriers to access to health care. If such barriers existed, it would be possible that women with specific lifestyle characteristics may be less likely to be diagnosed with disease, not because of the lifestyle but because of their access to care. This factor could then substantially distort relations, giving biased results. Women from ethnic groups other than Caucasian are not well represented in this cohort. Thus, when findings are expected to vary due to some underlying biologic difference among ethnic groups, which will be rare, those women will need to be specifically studied.

The Nurses' Health Study, the largest and longest ongoing cohort study of lifestyle and health that is focused on women, is a tribute to the commitment of its participants over the 20 years of the study to date and the foresight of Frank Speizer, M.D., who initiated pilot studies for the cohort >24 years ago. Components of the study, such as the collection of blood samples, have been possible only because of the education and professional experience of its participants, in addition to their willingness to give of their time to the research effort. (As a token of appreciation and in recognition of their excellent record of participation, Harvard Medical School and the Brigham and Women's Hospital jointly awarded to each participant a 20th Anniversary Certificate of Appreciation in June 1996.)

Long-term follow-up with high participation, as exemplified by the Nurses' Health Study, is essential to providing valid estimates of the relations between lifestyle and risk of chronic diseases. For cancer, behaviors may act

as initiators (cigarette smoking and colon cancer risk),<sup>42</sup> promoters (red meat for colon cancer), or proliferators (estrogens for breast cancer). Repeated measures and long-term follow-up permit a detailed understanding of these relations. The detailed history of use of vitamin supplements, at different doses and over varying durations, adds a richness to the data that cannot be obtained through a randomized study in which the dose and duration are predetermined (and are perhaps more or less than ideal). This unique feature will allow the identification of the dietary and other lifestyle factors that are most beneficial to women in terms of morbidity, mortality, and quality of life as the study continues through the coming years.

Through the Nurses' Health Study, many important advances have been made in understanding the etiology and prevention of major illnesses among women. Before the Women's Health Initiative began, the Nurses' Health Study study was the largest and most comprehensive study of health among women. It remains the most detailed study of diet and major illnesses, providing details on many components of lifestyle updated over the years. This unique study will continue to shed light on the causes and prevention of disease and the features of healthy aging over the coming years. Needless to say, this all reflects the enormous contribution made by over 120,000 registered nurses who entered the study 20 years ago.

#### ACKNOWLEDGMENTS

The continuing commitment of the study participants is gratefully acknowledged. The investigators on the Nurses' Health Study have made major contributions over the years. Current members of the study team include Catherine Berkey, Celia Byrne, Carlos Camargo, Vincent Carey, Gary Chase, Graham Colditz, Karen Corsano, Gary Curhan, Barbara Egan, Diane Feskanich, Lindsay Frazier, Charles Fuchs, Edward Giovannucci, Francine Grodstein, Susan Hankinson, Charles Hennekens, David Hunter, JoAnn Manson, Stefanie Parker, Cathy Rexrode, Janet Rich-Edwards, Bernard Rosner, Caren Solomon, Meir Stampfer, Harry Taplin,

Walter Willett, and Frank E. Speizer (principal investigator).

#### REFERENCES

1. Barton J, Bain C, Hennekens CH, et al. Characteristics of respondents and non-respondents to a mailed questionnaire. *Am J Public Health* 1980;70:823.
2. Stampfer MJ, Willett WC, FE, et al. Test of the National Death Index. *Am J Epidemiol* 1984;119:837.
3. Rimm EB, Stampfer MJ, Colditz G, Giovannucci E, Willett WC. Effectiveness of various mailing strategies among nonrespondents in a prospective cohort study. *Am J Epidemiol* 1990;131:1068.
4. Rose GA, Blackburn H. Cardiovascular survey methods. WHO Monograph Series No. 58. Geneva: World Health Organization, 1982.
5. Walker AE, Robins M, Weinfeld FD. The National Survey of Stroke. Clinical findings. *Stroke* 1981;12(2 Part 2 Suppl 1):I13.
6. Doll R, Hill A. Lung cancer and other causes of death in relation to smoking. A second report on the mortality of British doctors. *Br Med J* 1956 (November 10):1071.
7. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 1986;123:894.
8. Giovannucci E, Tosteson T, Speizer F, Vessey M, Colditz G. A long-term study of mortality in men who have undergone vasectomy. *N Engl J Med* 1992;326:1392.
9. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 1985;122:51.
10. Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Variability in portion sizes of commonly consumed foods among a population of women in the United States. *Am J Epidemiol* 1988;127:1240.
11. Salvini S, Hunter DJ, Sampson L, et al. Food-based validation of a dietary questionnaire: The effects of week-to-week variation in food consumption. *Int J Epidemiol* 1989;18:858.
12. Willett WC, Stampfer MJ, Underwood BA, Speizer FE, Rosner B, Hennekens CH. Validation of a dietary questionnaire with plasma carotenoid and alpha-to-copherol levels. *Am J Clin Nutr* 1983;38:631.
13. Willett WC. Nutritional epidemiology. New York: Oxford University Press, 1990.
14. Colditz GA, Willett WC, Stampfer MJ, et al. The influence of age, relative weight, smoking, and alcohol intake on the reproducibility of a dietary questionnaire. *Int J Epidemiol* 1987;16:392.
15. Ullrey DE. Selenium in the soil-plant-food chain. In: Spallholz JE, et al., eds. *Selenium in biology and medicine*. Westport, CT: AVI Publishing, 1981:176.

16. Morris JS, Stampfer MJ, Willett WC. Dietary selenium in humans: Toenails as an indicator. *Boil Trace Element Res* 1983;5:529.
17. Hankinson S, Manson J, Speigelman D, Willett W, Longcope C, Speizer F. Reproducibility of plasma hormone levels in postmenopausal women over a 2-3 year period. *Cancer Epidemiol Biol Prev* 1995;4:649.
18. Hankinson SE, Willett WC, Manson JE, et al. Alcohol, height, and adiposity in relation to estrogen and prolactin levels in postmenopausal women. *J Natl Cancer Inst* 1995;1297.
19. Ware J, Snow K, Kosinski M, Gandek B. SF-36. Manual and interpretation guide. Boston: The Health Institute, New England Medical Center, 1993.
20. Karasek R, Theorell T. Health work: Stress, productivity, and the reconstruction of working life. New York: Basic Books, 1990.
21. Berkman LF, Syme SL. Social networks, host resistance and mortality: A nine-year follow-up study of Alameda County residents. *Am J Epidemiol* 1979;109:186.
22. Thalji L, Haggerty CC, Rubin R, Berckmans TR, Pardee BL. National survey of junctional health status: Final report. Chicago: National Opinion Research Center, 1991.
23. Colditz GA. The Nurses' Health Study: Findings during 10 years of follow-up of a cohort of US women. *Curr Probl Obstet Gynecol Fertil* 1990;13:129.
24. Martinez M, Giovannucci E, Colditz G, et al. Calcium, vitamin D, and the occurrence of colorectal cancer among women. *J Natl Cancer Inst* 1996;88:1375.
25. Fuchs C, Colditz G, Stampfer M, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. *Arch Intern Med* 1996;156:2255.
26. Hankinson S, Colditz G, Hunter D, et al. A prospective study of reproductive factors and risk of epithelial ovarian cancer. *Cancer* 1995;76:284.
27. Willett WC, Manson JE, Stampfer MJ, et al. Weight, weight change, and coronary heart disease in women: Risk within the "normal" weight range. *JAMA* 1995;273:461.
28. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes in women. *Ann Intern Med* 1995;122:481.
29. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *N Engl J Med* 1995;333:677.
30. U.S. Department of Agriculture. Report of the dietary guidelines advisory committee on the dietary guidelines for Americans, 1995. To the Secretary of Health and Human Services and the Secretary of Agriculture. Washington, DC: U.S. Department of Agriculture, 1995.
31. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med* 1995;332:1589.
32. Grodstein F, Stampfer M, Manson J, et al. Postmenopausal estrogen and progestin use and the risk of cardiovascular disease. *N Engl J Med* 1996;335:453.
33. Giovannucci E, Egan KM, Hunter DJ, et al. Aspirin and the risk of colorectal cancer in women. *N Engl J Med* 1995;333:609.
34. Willett W, Stampfer M, Manson J, et al. Coffee consumption and coronary heart disease in women: A ten-year follow-up. *JAMA* 1996;275:458.
35. Kawachi I, Willett W, Colditz G, Stampfer M, Speizer F. A prospective study of coffee drinking and suicide in women. *Arch Intern Med* 1996;156:521.
36. Colditz G, for the NHS Research Group. Oral contraceptive use and mortality during twelve years of follow-up: The Nurses' Health Study. *Ann Intern Med* 1994;120:821.
37. Kawachi I, Colditz GA, Stampfer MJ, et al. Smoking cessation in relation to total mortality rates in women: A prospective cohort study. *Ann Intern Med* 1993;119:992.
38. Fuchs CS, Stampfer MJ, Colditz GA, et al. Alcohol consumption and mortality among women. *N Engl J Med* 1995;332:1245.
39. King M-C, Rowell S, Love SM. Inherited breast and ovarian cancer. What are the risks? What are the choices? *JAMA* 1993;269:1975.
40. Rosner B, Colditz G. Extended mathematical model of breast cancer incidence in the Nurses' Health Study. *J Natl Cancer Inst* 1996;88:359.
41. Roth A, Graham D, Schmittling G. National sample survey of registered nurses (1977). A report on the nurse population and factors affecting their supply. Hyattsville: Public Health Service, 1977.
42. Giovannucci E, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and risk of colorectal adenoma and colorectal cancer in U.S. women. *J Natl Cancer Inst* 1994;86:192.
43. London SJ, Colditz GA, Stampfer MJ, Willett WC, Rosner BA, Speizer FE. Prospective study of smoking and the risk of breast cancer. *J Natl Cancer Inst* 1989;81:1625.
44. Willett WC, Green A, Stampfer MJ, et al. Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. *N Engl J Med* 1987;317:1303.
45. Kawachi I, Colditz G, Stampfer M, et al. Smoking cessation and time course of decreased risk of coronary heart disease in women. *Arch Intern Med* 1993;154:169.
46. Colditz GA, Bonita R, Stampfer MJ, et al. Cigarette smoking and risk of stroke in middle-aged women. *N Engl J Med* 1988;318:937.
47. Kawachi I, Colditz G, Stampfer M, et al. Smoking cessation and decreased risk of stroke in women. *JAMA* 1993;269:232.
48. Rimm EB, Manson JE, Stampfer MJ, et al. Cigarette smoking and the risk of diabetes in women. *Am J Public Health* 1993;83:211.
49. Hemenway D, Sondick S, Colditz G. Smoking, suicide, and nurses. *Am J Public Health* 1993;83:249.
50. Hankinson SE, Willett WC, Colditz GA, et al. A prospective study of smoking and risk of cataract surgery in women. *JAMA* 1992;268:994.

51. Kawachi I, Troisi R, Rotnitzky A, Coakley E, Speizer F, Colditz G. A prospective study of smoking cessation and weight change in women. *J Smoking Rel Dis* 1994;5(Suppl 1):91.
52. Romieu I, Willett WC, Colditz GA, et al. A prospective study of oral contraceptive use and the risk of breast cancer in women. *J Natl Cancer Inst* 1989;81: 1313.
53. Stampfer MJ, Willett WC, Colditz GA, Speizer FE, Hennekens CH. A prospective study of past use of oral contraceptive agents and risk of cardiovascular diseases. *N Engl J Med* 1988;319:1313.
54. Chute CG, Willett WC, Colditz GA, Stampfer MJ, Rosner B, Speizer FE. A prospective study of reproductive history and exogenous estrogens on the risk of colorectal cancer in women. *Epidemiology* 1991;2: 201.
55. Rimm E, Manson J, Stampfer M, et al. Oral contraceptive use and the risk of non-insulin-dependent diabetes mellitus in a large prospective study of women. *Diabetologia* 1992;35:967.
56. Hernandez-Avila M, Liang MH, Willett WC, et al. Exogenous sex hormones and the risk of rheumatoid arthritis. *Arthritis Rheum* 1990;33:947.
57. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. *N Engl J Med* 1991;325:756.
58. Manson J, Rimm E, Colditz G, et al. A prospective study of postmenopausal estrogen therapy and subsequent incidence of noninsulin-dependent diabetes mellitus. *Ann Epidemiol* 1992;2:665.
59. Sanchez-Guerrero J, Liang M, Karlson E, Hunter D, Colditz G. Postmenopausal estrogen therapy and risk of developing systemic lupus erythematosus. *Ann Intern Med* 1995;122:430.
60. Grodstein F, Colditz G, Stampfer M. Postmenopausal hormone use and cholecystectomy in a large prospective study. *Obstet Gynecol* 1994;83:5.
61. London SJ, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Speizer FE. Prospective study of relative weight, height and the risk of breast cancer. *JAMA* 1989;262:2853.
62. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of obesity and risk of coronary heart disease in women. *N Engl J Med* 1990;332:882.
63. Chute C, Willett W, Colditz G, et al. A prospective study of body mass, height, and smoking on the risk of colorectal cancer in women. *Cancer Causes Control* 1991;2:117.
64. Colditz GA, Willett WC, Stampfer MJ, et al. Weight as a risk factor for clinical diabetes in women. *Am J Epidemiol* 1990;132:501.
65. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet and risk of symptomatic gallstones in middle-aged women. *N Engl J Med* 1989;321:563.
66. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Hennekens CH, Speizer FE. Moderate alcohol consumption and the risk of breast cancer. *N Engl J Med* 1987;316:1174.
67. Stampfer MJ, Colditz GA, Willett WC, et al. A prospective study of moderate alcohol drinking and risk of diabetes in women. *Am J Epidemiol* 1988; 128:549.
68. Giovannucci E, Stampfer MJ, Colditz GA, et al. Folate, methionine and alcohol intake and risk of colorectal adenoma. *J Natl Cancer Inst* 1993;85:875.
69. Hernandez-Avila M, Colditz GA, Stampfer MJ, Rosner B, Speizer FE, Willett WC. Caffeine, moderate alcohol intake and risk of fractures of the hip and forearm among middle-aged women. *Am J Clin Nutr* 1991;54:157.
70. Hunter DJ, Manson JE, Colditz GA, et al. A prospective study of intake of vitamins C, E and A and risk of breast cancer. *N Engl J Med* 1993;329:234.
71. Willett WC, Hunter DJ, Stampfer MJ, et al. Dietary fat and fiber in relation to risk of breast cancer. An eight-year follow-up. *JAMA* 1992;268:2037.
72. Hunter DJ, Morris JS, Stampfer MJ, Colditz GA, Speizer FE, Willett WC. A prospective study of selenium status and breast cancer risk. *JAMA* 1990; 264:1128.
73. Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. A prospective study of vitamin E consumption and risk of coronary disease in women. *N Engl J Med* 1993;328:1444.
74. Willett WC, Stampfer MJ, Manson JE, et al. Trans-fatty acid intake in relation to risk of coronary heart disease among women. *Lancet* 1993;341:581.
75. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat and fiber intake to colon cancer risk in a prospective study among women. *N Engl J Med* 1990;323:1664.
76. Kampman E, Giovannucci E, van't Veer P, et al. Calcium, vitamin D, dairy foods and the occurrence of colorectal adenomas among men and women in two prospective studies. *Am J Epidemiol* 1994;139:16.
77. Feskanich D, Colditz G, Stampfer M, Willett W. Dietary calcium and bone fractures in middle-aged women. [Abstract] *Am J Epidemiol* 1994;139:S35.
78. Feskanich D, Willett W, Stampfer M, Colditz G. Protein consumption and bone fractures in women. *Am J Epidemiol* 1996;143:472.
79. Colditz G, Manson J, Stampfer M, Rosner B, Willett W, Speizer F. Diet and risk of clinical diabetes in women. *Am J Clin Nutr* 1992;55:1018.
80. Hankinson SE, Stampfer MJ, Seddon JM, et al. Nutrient intake and cataract extraction in women: A prospective study. *Br Med J* 1992;305:335.
81. Troisi R, Willett W, Weiss S, Trichopoulos D, Rosner B, Speizer F. A prospective study of diet and adult-onset asthma. *Am J Respir Crit Care Med* 1995;151: 1401.
82. London SJ, Connolly JL, Schnitt SJ, Colditz GA. A prospective study of benign breast disease and the risk of breast cancer. *JAMA* 1992;267:91.
83. Colditz GA, Willett WC, Hunter DJ, et al. Family history, age and risk of breast cancer: Prospective data from the Nurses' Health Study. *JAMA* 1993;270:338.
84. Green A, Willett WC, Colditz GA, et al. Use of per-

- manent hair dyes and risk of breast cancer. *J Natl Cancer Inst* 1987;79:253.
85. Rosner B, Colditz GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: The Nurses' Health Study. *Am J Epidemiol* 1994;139:819.
  86. Manson J, Stampfer M, Colditz G, et al. A prospective study of aspirin use and primary prevention of cardiovascular disease in women. *JAMA* 1991;266:521.
  87. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. *Arch Intern Med* 1991;151:1141.
  88. Rich-Edwards J, Manson J, Stampfer M, et al. Height and the risk of cardiovascular disease in women. *Am J Epidemiol* 1995;142:909.
  89. Kawachi I, Colditz G, Stampfer M, et al. Prospective study of shift work and risk of coronary heart disease in women. *Circulation* 1995;92:3178.
  90. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history, age, and diet and colorectal cancer. *N Engl J Med* 1994;331:1669.
  91. Martinez ME, Giovannucci E, Spiegelman D, et al. Physical activity, body size, and colorectal cancer in women. *Am J Epidemiol* 1996;143:S73.
  92. Hemenway D, Feskanich D, Colditz G. Body height and hip fracture: A cohort of 90,000 women. *Int J Epidemiol* 1995;24:783.
  93. Manson JE, Rimm EB, Stampfer MJ, et al. A prospective study of physical activity and the incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 1991;338:774.
  94. Hankinson SE, Hunter DJ, Colditz GA, et al. Tubal ligation, hysterectomy and risk of ovarian cancer: A prospective study. *JAMA* 1993;270:2813.
  95. Weinstock MA, Colditz GA, Willett WC, et al. Non-familial cutaneous melanoma incidence in women is associated with sun exposure before 20 years of age. *Pediatrics* 1989;84:199.

Address reprint requests to:  
Graham A. Colditz, M.D.  
*Nurses' Health Study*  
*Channing Laboratory*  
*181 Longwood Avenue*  
*Boston, MA 02115*