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Award Number: DAMD17-00-1-0165

TITLE: Training Grant in Epidemiology and Prevention of Breast Cancer

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REPORT DATE: July 2003

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	July 2003	Annual (1 Jul 2002 - 30 Jun 2003)

4. TITLE AND SUBTITLE

Training Grant in Epidemiology and Prevention of Breast Cancer

5. FUNDING NUMBERS

DAMD17-00-1-0165

6. AUTHOR(S)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

We propose a training grant to recruit and train two postdoctoral students and three physicians. These trainees will acquire skills in the epidemiology and prevention of breast cancer. They will work closely with mentors who have a long track record of training epidemiologists. The funding will allow our research group to focus specific training opportunities on breast cancer. The ongoing epidemiologic studies and prevention trials offer a unique resource in which trainees can participate in cutting edge research and acquire skills that will establish them as future leaders. We have to date enrolled three doctoral students: Heather Baer, Heather Eliassen and Jeanne Marie Gaare-Eby; and three physicians: Ann Partridge, M.D. received her M.P.H. and is working as a clinician and a breast cancer researcher; Larissa Nekhlyadov, M.D., M.P.H., this past year, has been pursuing several research projects in breast cancer prevention and early detection; and Candice Aitken, M.D., a resident in radiation oncology will pursue her M.P.H., and has an interest in cancer prevention, and identification of risk factors for educational models. As a result of this award, we have also established the Advanced Cancer Epidemiology Seminar in Breast Cancer each spring in which all trainees participate.

14. SUBJECT TERMS

Breast Cancer, Training Grant, Epidemiology

15. NUMBER OF PAGES

46

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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INTRODUCTION

We have proposed a training grant to recruit and train two doctoral students and three physicians. As a result of our analysis of the budget so far, we have funds to train an additional doctoral student. These trainees will acquire skills in the epidemiology and prevention of breast cancer. They will work closely with mentors who have a long track record of training epidemiologists. The funding will allow our research group to focus specific training opportunities on breast cancer. The ongoing epidemiologic studies and prevention trials offer a unique resource in which trainees can participate in cutting edge research and acquire skills that will establish them as future leaders.

BODY

(Approved Statement of Work is italicized)

*We will advertise and recruit **one pre-doctoral candidate** for the first year of this proposed training program.* We did not recruit in the first year (year one was expected to begin 7/1/00) due to funding not being received until September 2000 we were delayed in starting the recruitment process.

*We will advertise and recruit **one physician for a two-year training** opportunity that includes course work in the first year and research on one of the ongoing studies in the second year.* We have recruited Dr. Ann Partridge, MD whose research focuses on the assessment, perception and communication of breast cancer risk as well as other aspects of provider-patient communication in oncology. Other projects she is involved in include breast cancer prevention and adherence with oral antineoplastic agents. In the first year of the grant, she was involved in starting a breast cancer chemoprevention study in conjunction with the Cancer Risk and Prevention Clinic at Dana-Farber and the Nurses' Health Study. This study, a randomized placebo controlled trial, will assess the safety and feasibility of utilizing an aromatase inhibitor for breast cancer prevention in women who are at high risk for breast cancer based on an elevated estradiol level. In March 2002 she received her MPH from Harvard School of Public Health and this year she will continue working in the second year of the breast cancer chemoprevention study in conjunction with the Cancer Risk and Prevention Clinic at Dana-Farber Cancer Institute and the Nurses' Health Study. This study, a randomized placebo-controlled trial, is assessing the safety and feasibility of utilizing an aromatase inhibitor for breast cancer prevention in women who are at high risk for breast cancer based on an elevated estradiol level. She also developed a research plan to study adherence with oral antineoplastic agents. She published a review on this subject in the Journal of the National Cancer Institute[1] and recently submitted a manuscript evaluating non-adherence with adjuvant tamoxifen in patients with early stage breast cancer in a large population.[2] As part a planned NIH Career Development Award application, she plans to evaluate the relationship between non-adherence and survival in this same database. In conjunction with this, she plans to study adherence with oral antineoplastic agents in breast cancer patients in several breast cancer clinics to better understand adherence from a biopsychosocial perspective. Dr. Partridge is also currently piloting questionnaires among breast cancer patients on oral investigational agents in her clinic. In addition, in the past year, she was selected as Adherence Co-Chair of a large national NIH-funded randomized study conducted by CALGB comparing oral chemotherapy to standard chemotherapy in older breast cancer patients. She will be measuring adherence among a subset of patients on the oral medication in association with reported side effects, quality of life, health beliefs, and other variables.

Another research plan she is pursuing entails understanding the issues surrounding sharing clinical trial results with participants. She recently published a commentary on this subject in the Journal of the American Medical Association[3] and she presented an abstract at this year's ASCO describing a study she performed on patient preferences and attitudes about this issue.[4] This manuscript is in preparation. She is currently conducting a national survey of over 2000 oncology physicians and nurses through the CALGB evaluating their attitudes about this issue. This study is funded by an ASCO Young Investigator's Award and results will be presented at next year's ASCO.

Her other ongoing projects include a study assessing risk perceptions of women with DCIS as well as assessing physician perceptions of DCIS risk as part of the Dana-Farber breast cancer SPORE, and she is co-investigator on an R-01 to evaluate and improve risk communication among women with DCIS and early stage breast cancer.

*We will recruit **a second pre-doctoral candidate** to begin training in the second year.* We have recruited two pre-doctoral students, Heather Baer and Heather Eliassen, to make up for the first year. We are now entering the last year of the grant and after a budget analysis resulting in an extension, we have recruited a third doctoral student trainee to start this July, Jeanne Marie Gaare-Eby. Ms. Gaare-Eby's major area of interest is cancer and women's health, especially breast cancer. She currently has a manuscript in preparation looking at the comparitive ability of dual x-ray absorptiometry (DXA) and quantitative computed tomography (QCT) to predict fractures in the elderly. Both Ms. Baer and Ms. Eliassen have completed the first and second years of training which involved course work, including advanced

epidemiologic methods, cancer cell biology, biostatistics, nutritional epidemiology, research synthesis and the use of biomarkers in epidemiology, and have begun analyses for their dissertations. Ms. Baer and Ms. Eliassen also successfully passed the departmental qualifying exam and more currently, the the oral qualifying exam. These accomplishments are definitive steps towards attaining a doctorate degree.

Last summer Ms. Eliassen was working on data analysis in the Nurses' Health Study, exploring possible dissertation topics such as adult weight loss and breast cancer risk and tubal ligation and breast cancer risk. This year, Ms. Eliassen has elected that her dissertation topic address potential lifestyle factors that may lower risk of breast cancer. Her first paper addresses the association between use of the statin family of lipid-lowering drugs and breast cancer. She submitted an abstract on this topic to the annual Society for Epidemiologic Research Meeting, entitled "Use of Lipid Lowering Drugs in Relation to Breast Cancer Risk"[5]. At the meeting in Atlanta in June 2003, she submitted a poster on this topic. She plans to also address the association between weight gain and loss in adult life and incidence of breast cancer. Her dissertation proposal addressed the background for each of these topics, as well as the planned methods and analyses. She presented her proposal to her oral examination committee, and successfully completed the oral examination in June 2003. Her goals for this summer and the upcoming academic year are to continue to work on each of my dissertation papers, and to gain more experience throughout the process.

Ms. Baer has begun to develop her own research in the field of breast cancer etiology and prevention. Areas of interest are early life and adolescent risk factors for breast cancer, predictors of benign breast disease and conditions associated with future breast cancer risk. She has submitted a manuscript on Adolescent Diet and Benign Breast Disease utilizing the resources of the Nurses' Health Study II. This was presented at the Era of Hope DOD Breast Cancer Research Program Meeting in September 2002. She began her doctoral thesis this year and wrote a proposal entitled "Early Life Predictors of Breast Disease and Reproductive Outcomes". The goals of this research are to identify specific factors during early life, childhood, and adolescence that influence subsequent risk of breast cancer and benign breast disease, as well as to examine the effects of childhood socioeconomic status on age of menarche, onset of natural menopause, and breast cancer risk. She is using Nurses' Health Study and Nurses' Health Study II to conduct this research. After writing this proposal, she passed her oral qualifying examination in April to continue toward her doctorate. She has actually begun her research, first focusing on body size and the timing of growth during early life in relation to breast cancer incidence. She has preliminary findings that support her hypothesis, which she hopes to finish and submit as a publication this fall. Outside of her dissertation work, she has worked with Dr. Colditz on several projects. In particular, she is assisting with the collection and analysis of data for a nested case-control study of benign breast lesions as markers of breast cancer risk, which involves collaboration with several breast pathologists at Beth Israel Deaconess Medical Center. She has also worked on the preparation of a chapter about breast cancer for a cancer epidemiology textbook. This past June, she presented an abstract at the Society of Epidemiologic Research Meeting, entitled "Adolescent Diet and Incidence of Benign Breast Disease"[6]. She also recently completed a manuscript entitled "Adolescent Diet and Incidence of Proliferative Benign Breast Disease" [7] which has been accepted for publication in Cancer Epidemiology, Biomarkers & Prevention.

*During the second year we will advertise for **two physicians** to begin training in the third year.*
We successfully recruited two more physicians for a final total of three. Dr. Larissa Nekhlyadov, a third year research fellow, began last summer and has pursued several clinical research projects addressing the issues that shape women's decisions in the areas of breast cancer prevention and early detection. This fellowship specifically supports her work studying quality of life among women with ductal carcinoma in situ (DCIS). Our hypothesis is that a woman with the DCIS diagnosis will experience detrimental effects on her quality of life, particularly vitality, emotional and social functioning, as well as mental health. Dr. Nekhlyadov is currently analyzing the data and plans to submit the manuscript for publication in December 2003. The fellowship is also supporting her effort in developing a research proposal for a career development award, which she plans to submit in the fall of 2003. The goal of the proposal is to develop effective means to communicate breast cancer preventive and screening strategies to women in low literacy populations. In addition, she is either pricipal or co-investigator on studies addressing screening mammography among women in their 40's, predictors of DCIS recurrence, and patient-oriented outcomes of prophylactic mastectomy.

The second physician recruited to begin this year is Dr. Candice Aitken, a resident in radiation oncology, will pursue her M.P.H. She has an interest in cancer prevention, and identification of risk factors for educational models.

During the first ***year we will develop and implement an advanced seminar in breast cancer.*** *This will bring new depth to course work not previously available at the Harvard School of Public Health. This seminar will cover topics in detail and will span from basic biology of the breast, to early lesions, epidemiologic risk factors, statistical models of breast cancer incidence and issues in risk stratification and counseling for prevention.* The Breast Cancer Program of Dana Farber/Harvard Cancer Center has run a monthly seminar in unsolved research issues for breast cancer. Last year this seminar was attended by the first physician trainee, Ann Partridge. Two years ago, an eight-week seminar was developed and implemented specifically for breast cancer epidemiology, covering such topics as modeling breast cancer risk, postmenopausal hormones and breast cancer, gene environment interactions and benign breast disease. It was attended by Heather Baer, Heather Eliassen and Dr. Partridge along with other breast cancer researchers. This past spring Dr. Colditz again organized and led this course. Topics covered included mathematical models of breast carcinogenesis, associations between endogenous and exogenous hormones and breast cancer, histopathology of benign and malignant breast conditions, estrogen receptivity of tumors, breast morphology (mammographic density), mechanisms of chemoprevention and public health implications of such a strategy, lifestyle factors, (diet and physical activity) and breast cancer, mammographich screening and risk communication.

KEY RESEARCH ACCOMPLISHMENTS IN REFERENCE TO STATEMENT OF WORK

- We have successfully recruited two pre-doctoral fellows. They both have completed required coursework with commendation. Both have passed the departmental exam and oral exam progressing towards the doctorate degree. In their third year of this fellowship, they both continue with analyses utilizing the training opportunities in the Nurses' Health Study group and will continue coursework in the fall and begin analyses for their dissertation.
- We have successfully recruited two post-doctoral, physician trainees. The first, Dr. Ann Partridge received her MPH this past March is continuing on many research projects. Our second recruit, Dr. Larissa Nekhlyodov is entering a second year of the fellowship and as a result of this fellowship award, is successfully contributing to the field breast cancer research.
- The Advanced Cancer Epidemiology Seminar in Breast Cancer was established.
- We have successfully recruited our third physician trainee, Candice Aitken, a resident in radiation oncology to begin this July.
- After an analysis of the budget and extension, we have recruited a third doctoral student, Jeanne Marie Gaare-Eby to begin this July.

REPORTABLE OUTCOMES

- Dr. Ann Partridge now has four peer reviewed journal articles; three of which she is first author and involve clinical and epidemiologic issues. Last year she presented the attached abstract at the American Society of Clinical Oncology.
- Heather Baer has written an abstract which was presented at the Era of Hope DOD Breast Cancer Research Program Meeting.
- Dr. Ann Partridge was awarded her MPH from Harvard School of Public Health.
- Both predoctoral trainees, Heather Eliassen and Heather Baer passed the Harvard School of Public Health's epidemiology departmental exam.
- Ms. Baer has a published abstract entitled " Adolescent Diet and Incidence fo Benign Breast Disease in the *Proceedings of the Annual Meeting of the Society for Epidemiologic Research*, June 2003.
- Ms. Baer has a manuscript in press entitled "Adolescent Diet and Incidence of Proliferative Benign Breast Disease" in *Cancer Epidemiology, Biomarkers and Prevention*.
- Ms. Baer wrote a proposal for her dissertation on the topic of "Early Life Predictors of Breast Disease and Reproductive Outcomes" and passed the oral examination and becomes a doctoral candidate.
- Ms. Baer has also begun research on body size and growth during early life in relation to breast cancer incidence and has preliminary findings.
- Ms. Baer served as Teaching Assistant for graduate-level, intermediate course in Epidemiologic Methods.
- Ms. Eliassen wrote her dissertation proposal addressing potential lifestyle factors that may lower risk of breast cancer. She specifically addressed the back ground, planned methods and analyses for the association between use of the statin family of lipid lowering drugs and breast cancer, as well as the relation of tubal ligation with breast cancer incidence. She passed the oral exam and is officially a doctoral candidate.
- Ms. Eliassen has a published abstract entitled "Use of Lipid-Lowering Drugs in Relation to Breast Cancer Risk" in the *Proceedings of the Annual Meeting of the Society for Epidemiologic Research*, June 2003.

CONCLUSIONS

Our trainees in breast cancer epidemiology and prevention are proving to be exceptional researchers. As a result of this award, trainees graduate with advanced degrees in epidemiology from HSPH and the resources of the on-going epidemiologic research at the Brigham and Women's Hospital are providing excellent training opportunities for more in depth breast cancer epidemiology and prevention. As we progress, we are achieving our goals of training professionals in translational research.

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Adolescent Diet and Incidence of Benign Breast Disease

Objective: Studies of adult diet and risk of breast cancer have yielded inconsistent results, but this does not rule out the possible impact of childhood and adolescent diet. This study examined associations between components of adolescent diet and incidence of benign breast disease (BBD), which may be a precursor marker of breast cancer.

Methods: The study population consisted of 29,378 women in the Nurses' Health Study II who completed a questionnaire on adolescent diet. Between 1991 and 1997, 4994 of these women reported a first diagnosis of BBD, and 997 of these cases (20%) were reported as biopsy-confirmed. Valid tissue samples were obtained for 753 cases of biopsy-confirmed BBD. Incidence rate ratios and 95% confidence intervals (CI) for self-reported BBD and histologically-confirmed BBD were calculated for quartiles of energy-adjusted fat and nutrient intakes.

Results: We observed no consistent associations between incidence of self-reported BBD or histologically-confirmed BBD and intake of total fat or any subtypes of fat during adolescence. Fiber and vitamin E intake during adolescence were inversely associated with incidence of self-reported BBD and proliferative BBD. Compared to women in the lowest quartile of vitamin E intake, the age-adjusted rate ratios for proliferative BBD were 0.92 (95% CI: 0.72-1.17) for women in the second quartile, 0.82 (95% CI: 0.63-1.06) for women in the third quartile, and 0.72 (95% CI: 0.55-0.94) for women in the highest quartile (p for trend = 0.01). Compared to women in the lowest quartile of fiber intake, the age-adjusted incidence rate ratios for proliferative BBD were 0.96 (95% CI: 0.75-1.22) for women in the second quartile, 0.92 (95% CI: 0.72-1.18) for women in the third quartile, and 0.68 (95% CI: 0.52-0.89) for women in the highest quartile (p for trend = 0.01). Further adjustment for age at menarche, body mass index at age 18, family history of breast cancer, and alcohol intake did not substantially change the incidence rate ratios.

Conclusions: Fiber and vitamin E intake during adolescence may be inversely associated with risk of BBD. Confirmation of these associations may offer a means for prevention of breast cancer if BBD is a plausible precursor marker of breast cancer development.

Heather Baer

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USE OF LIPID-LOWERING DRUGS IN RELATION TO BREAST CANCER RISK.

*AH Eliassen, SE Hankinson, WC Willett, and GA Colditz for the Nurses' Health Study Research Group (Harvard University, Boston, MA 02115)

Experimental evidence suggests that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins), the class of lipid-lowering drugs responsible for more than two-thirds of market share since the early 1990s, may protect against carcinogenesis. Statins appear to interfere with insulin-like growth factor I receptor expression and promote apoptosis. We conducted a prospective analysis within the Nurses' Health Study cohort to assess the relation of lipid-lowering drug use to breast cancer risk. A total of 95,598 women, aged 41 to 75 and free of cancer, were followed prospectively from 1988 to June 2000. Lipid-lowering drug data were collected in 1988 and updated biennially from 1994. Of these women, 15,587 reported ever using lipid-lowering drugs and 3,653 reported a diagnosis of invasive breast cancer during follow-up. Cox proportional hazards models, adjusting for age, body mass index, and postmenopausal hormone use and duration, provided the estimated rate ratios (RRs) with 95% confidence intervals (CIs). Compared to never users, women who used lipid-lowering drugs experienced similar risk of breast cancer, with RRs (95% CIs) of 0.96 (0.84, 1.10) for current use and 0.97 (0.70, 1.33) for past use. Long-term statin use also appeared unrelated to risk of breast cancer. Compared to women who never used lipid-lowering drugs, current and past users of statins who began use in 1988 experienced no change in risk, with adjusted RRs (95% CIs) of 1.08 (0.72, 1.62) for current use and 1.02 (0.38, 2.72) for past use. Overall, these data suggest that lipid-lowering drugs, and long-term use of statins in particular, are not associated with breast cancer risk.

APPENDIX 3

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ADOLESCENT DIET AND INCIDENCE OF BENIGN BREAST DISEASE. *H. J. Baer, S. J. Schnitt, J. L. Connolly, C. Byrne, E. Cho, W. C. Willett, and G. A. Colditz (Harvard University, Boston, MA 02115)

Studies of adult diet and risk of breast cancer have yielded inconsistent results, but this does not rule out a possible impact of adolescent diet. We examined associations between components of adolescent diet and incidence of proliferative benign breast disease (BBD), a marker for increased breast cancer risk. The study population consisted of 29,494 women in the Nurses' Health Study II who completed a questionnaire on adolescent diet in 1998 and who were 33 to 53 years of age at that time. 470 cases of proliferative BBD were identified between 1991 and 1997 through a centralized pathology review. Cox proportional hazards regression was used to estimate incidence rate ratios (RRs) and 95% confidence intervals (CIs) for quartiles of energy-adjusted intakes, using the lowest quartile of each as the reference group. Total fat intake during adolescence was unrelated to incidence of proliferative BBD; however, there were positive associations for animal and monounsaturated fat intakes and inverse associations for vegetable and polyunsaturated fat intakes. Significant inverse associations were observed for intakes of vitamin E and fiber. The multivariate RRs for vitamin E intake were 1.13 (95% CI = 0.89, 1.44), 0.88 (95% CI = 0.68, 1.14) and 0.79 (95% CI = 0.61, 1.04), for women in the second, third, and highest quartiles, respectively (p for trend = 0.05). For fiber intake, the multivariate RRs for women in the second, third, and highest quartiles were 0.94 (95% CI = 0.73–1.21), 0.99 (95% CI = 0.78, 1.27), and 0.75 (95% CI = 0.57, 0.98), respectively (p for trend = 0.05). Confirmation of these associations may suggest a means for prevention of breast cancer.

Adolescent Diet and Incidence of Proliferative Benign Breast Disease[1]

Heather J. Baer,[2] Stuart J. Schnitt, James L. Connolly, Celia Byrne, Eunyoung Cho, Walter C. Willett, Graham A. Colditz

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Key words: Diet, adolescence, benign breast disease, breast cancer

The abbreviations used are: BBD, benign breast disease; FFQ, food frequency questionnaire; RR, rate ratio; CI, confidence interval

[1] Supported by NIH Grant CA50385 and U.S. Department of Defense Grant DAMD17-00-1-0165
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Abstract

Studies of adult diet and risk of breast cancer have yielded mainly null results, but this does not rule out a possible impact of adolescent diet. This study examined associations between components of adolescent diet and risk of proliferative benign breast disease (BBD), a marker for breast cancer. The study population consisted of 29,494 women in the Nurses' Health Study II who completed a questionnaire on adolescent diet in 1998 and who were 33 to 53 years of age at that time. 470 new cases of proliferative BBD were identified between 1991 and 1997. Incidence rate ratios and 95% confidence intervals were calculated for quartiles of energy-adjusted intakes, using the lowest quartile of each as the reference group. Total fat intake during adolescence was unrelated to risk of proliferative BBD, although there were positive associations for intakes of animal fat and monounsaturated fat and an inverse association for intake of vegetable fat. For vitamin E intake, the multivariate rate ratios were 1.13, 0.88, and 0.79 (95% CI = 0.61-1.04) for women in the second, third, and highest quartiles, respectively (*P* for trend = 0.05). The multivariate rate ratios were 0.94, 0.99, and 0.75 (95% CI = 0.57-0.98) for women in increasing quartiles of fiber intake (*P* for trend = 0.05). Vegetable fat, vitamin E, and fiber intakes during adolescence were inversely associated with risk of proliferative BBD in this population. Confirmation of these associations may suggest a means for prevention of breast cancer.

Introduction

Benign breast disease (BBD) is a heterogeneous group of lesions including a variety of tissue abnormalities. Certain subtypes of BBD are associated with increased breast cancer risk. Compared to women with nonproliferative lesions, women whose biopsies show proliferative changes without atypia have a 1.5 to 2-fold greater risk of developing breast cancer in the future, and women with atypical hyperplasia have a 3.5 to 5-fold greater risk (1). These findings suggest that proliferative BBD may be a marker for breast cancer.

The relation of diet to breast cancer risk has been investigated in numerous epidemiologic studies. Although ecologic studies and some case-control studies originally suggested that adult intakes of total and saturated fat might be positively associated with breast cancer risk (2, 3), more recent prospective studies have not supported these earlier findings (4-6). Carotenoids and vitamins C and E have antioxidant properties that may contribute to reduced breast cancer risk (7, 8), and vitamin A also may confer some protection by regulating cell differentiation (9, 10). Results from epidemiologic studies of these micronutrients have been inconclusive (2), although a recent prospective study showed decreasing risk of breast cancer with increasing serum carotenoid levels (11). Similarly, studies of adult diet and benign breast disease have not identified any clear and consistent associations (12-15).

The lack of evidence supporting the role of adult diet in relation to risk of breast cancer does not rule out a possible impact of childhood and adolescent diet. Reviewing the epidemiologic evidence on the potential role of early life factors, Colditz and Frazier concluded that exposures between menarche and first birth may exert important effects on future risk (16). Furthermore, studies of mammary gland development in rats have shown that breast tissue may be most vulnerable to carcinogens during this time period, due to rapid proliferation of cells and

lack of terminal differentiation (17). Hence, previous studies may have focused on the wrong time period, because adolescent diet may have a stronger influence on risk than adult diet.

To date, only a few studies have examined the role of adolescent diet in the etiology of breast cancer (18-21). In a population-based case-control study that included 172 cases and 190 controls, a nonsignificant inverse association between adolescent fat intake and premenopausal breast cancer risk was seen (19). Total fiber intake during adolescence was associated with increased breast cancer risk in postmenopausal women (odds ratio for highest versus lowest quartile = 6.6, 95% confidence interval = 1.5-29.6), but fiber from grains was associated with decreased risk in both premenopausal and postmenopausal women. In a larger population-based case-control study including 1647 incident breast cancer cases and 1501 controls, there was a nonsignificant inverse association between fruit and vegetable consumption during adolescence and breast cancer risk (odds ratio for highest versus lowest quartile = 0.9, 95% confidence interval = 0.7-1.1), while adolescent intakes of animal fat, high-fat foods, high-fat snacks and desserts, and dairy products had no clear relation to risk (20). Neither of these studies examined associations between intakes of specific micronutrients during adolescence and breast cancer risk. In a recent retrospective analysis in the Nurses' Health Study that included 843 incident cases of breast cancer, higher consumption of eggs, vegetable fat, and fiber during adolescence were associated with decreased breast cancer risk (21). The 24-item food frequency questionnaire used in this study, however, did not allow complete assessment of total energy intake or specific nutrients, due to the restricted list of foods.

If dietary factors are involved in the early stages of breast cancer development, important associations may exist between components of adolescent diet and marker lesions such as benign breast disease. To examine this hypothesis, we studied intakes of total fat and specific types of

fat, micronutrients, fiber, and foods during adolescence in relation to risk of proliferative benign breast disease within the Nurses' Health Study II.

Materials and Methods

Study Design and Population. The Nurses' Health Study II is a prospective cohort study that began in 1989, when 116,671 female nurses between the ages of 25 and 44 completed a mailed, self-administered questionnaire including information on a variety of health behaviors and conditions. Since 1989, questionnaires have been sent to these women every two years to obtain updated information on lifestyle factors and recent medical events. The response rate during each two-year period has been 90% or greater.

The present study was a retrospective analysis within the Nurses' Health Study II. The study population included 45,947 women who completed a questionnaire on adolescent diet (described below) in 1998 and had plausible values for total energy intake (between 600 and 5000 kilocalories per day). We excluded 16,057 women who had a self-reported or histologically-confirmed diagnosis of benign breast disease prior to return of the 1991 questionnaire, because pathology specimens were only collected for incident cases diagnosed after the 1991 cycle. 396 women were excluded because of a prior diagnosis of cancer other than non-melanoma skin cancer. The final study population consisted of 29,494 women. This investigation was approved by human research committees at the Harvard School of Public Health and Brigham and Women's Hospital.

Adolescent Diet Questionnaire. In 1998, a semi-quantitative food frequency questionnaire (FFQ) with 131 items on adolescent diet was completed by 45,947 women who had previously indicated that they would be willing to participate. This self-administered questionnaire was a

modified version of the validated FFQ used to assess adult diet in the Nurses' Health Study and several other cohorts. Participants were asked to report how often they consumed a specified quantity of 122 foods and beverages during high school, further defined as ages 13 to 18.

A reproducibility study conducted among a random sample of women in a separate cohort showed moderately high correlations between two separate recalls, eight years apart, of consumption of 24 food items during high school (22). The average Spearman correlation coefficient for the first and second recall was 0.57, although values ranged from 0.38 to 0.74. The mean correlation between reported high school diet and current diet was only 0.25, which may indicate that current diet did not strongly affect recall of remote diet. Although data on the validity of the adolescent diet questionnaire are not yet available, research in survey methodology shows that provision of a clear definition of the reference time period – high school, in this case – enhances recall on self-administered questionnaires (23).

Energy, fat, and micronutrient intakes were derived from participants' responses on the FFQ using an extensive food composition database maintained by a team of research dietitians. Because the composition of some foods has changed over time, food composition data from the relevant time period (1960's and 1970's) were used, when available, to provide the best approximation of intakes during adolescence.

Identification of Cases of Benign Breast Disease. On the 1989 baseline questionnaire, all women were asked if they had ever received a diagnosis of fibrocystic or other benign breast disease from a physician. On each of the subsequent biennial questionnaires in 1991, 1993, 1995, and 1997, women were asked if they had received a diagnosis of BBD since the previous questionnaire and if the diagnosis had been confirmed by biopsy and/or aspiration. A total of 2454 participants reported a first diagnosis of biopsy-confirmed BBD between 1991 and 1997.

Of these cases, 1022 (42%) contributed information on diet during adolescence. This is similar to the overall proportion of women in the entire Nurses' Health Study II cohort with adolescent dietary data (45,947 out of 116,671, or 39%).

Because proliferative BBD, in contrast with other subtypes, is associated with increased risk of breast cancer, proliferative BBD with or without atypia was the primary outcome of interest. Women who reported a first diagnosis of biopsy-confirmed BBD on the 1993, 1995, or 1997 questionnaires were contacted to confirm the diagnosis and to acquire permission to review their pathology specimens. Among the 987 women with adolescent diet information who were initially contacted, 89% (883) confirmed the BBD diagnosis and granted permission for review of their biopsy records and pathology slides. Adequate pathology material was obtained and reviewed for 800 women (91% of those who had given their permission). 754 (94%) of these were confirmed to be eligible cases and a valid diagnosis was obtained. The main reasons for exclusion were that the pathology specimen did not contain breast tissue or that the biopsy date was before June of 1991. Women were also excluded if their biopsy date was after the date they reported benign breast disease or if they had a prior cancer, a diagnosis of breast cancer within the same questionnaire cycle, or a diagnosis of breast carcinoma *in situ*. Included cases were slightly older and reported greater alcohol consumption between ages 18 and 22 than cases not included in the analysis, but included and excluded cases were similar in terms of other characteristics (data not shown).

Biopsy materials were reviewed by one of four pathologists (SJS, JLC, TJ, or GP) who had no knowledge of participants' exposure information. All slides from the breast biopsies were classified as normal or nonproliferative, proliferative without atypia, or atypical hyperplasia, according to the criteria of Dupont and Page (24). Any biopsies that showed atypia

or questionable atypia were jointly reviewed by two pathologists (SJS and JLC) with one of the other pathologists (TJ or GP) and a consensus diagnosis was reached. Biopsy tissue with intraductal papilloma, radial scar, sclerosing adenosis, fibroadenoma, fibroadenomatous change or moderate to florid ductal hyperplasia in the absence of atypical hyperplasia was classified as proliferative without atypia.

Of the 754 cases identified among eligible participants, 470 (62%) were classified as proliferative (with or without atypia) by the study pathologists. Because there were only 39 cases of atypical hyperplasia, this was not examined as a separate outcome in the main analyses. Consistent with a previous report from this cohort, proliferative cases were less likely to report a family history of breast cancer and more likely to have had menarche before age 12 compared to nonproliferative cases (25).

Statistical Analysis. Cohort analyses were conducted among the 29,494 women who completed the adolescent diet questionnaire and met the other eligibility criteria, using proliferative disease with or without atypia as the primary outcome. Secondary analyses were also performed using all self-reported benign breast disease and self-reported BBD confirmed by biopsy as outcomes. Eligible participants contributed person-time of follow-up from the time they returned the 1991 questionnaire until the return date of the 1997 questionnaire, death from any cause, report of BBD or cancer other than non-melanoma skin cancer, or loss to follow-up. This method allows for the updating of time-varying covariates every two years.

Total fat, types of fat, and specific micronutrients were the main exposures of interest. To adjust for total energy intake (26), total fat and types of fat were examined as nutrient densities, computed as percentages of total caloric intake. For micronutrients, energy-adjusted intakes were calculated using the residual method, in which energy-adjusted values are the

residuals from a regression model with total caloric intake as the independent variable and absolute nutrient intake as the dependent variable (26). Fat densities and energy-adjusted micronutrient residuals were then divided into quartiles based on the distributions of values for all women who completed the adolescent diet questionnaire.

Age-adjusted incidence rate ratios for proliferative BBD were calculated for quartiles of energy-adjusted fat and micronutrient intakes, using the lowest quartile of each as the reference group, and two-sided tests for trend were also conducted. Cox proportional hazards regression was used to estimate rate ratios and 95% confidence intervals for quartiles of fat and micronutrient intakes while controlling for relevant covariates simultaneously. The multivariate Cox models adjusted for the following variables: age in months, time period (3 periods), age at menarche (<12, 12, 13, $\geq$ 14), menopausal status (premenopausal, postmenopausal, or uncertain), body mass index at age 18 (<19, 19-20.4, 20.5-21.9, 22-24.9, $\geq$ 25 kg/m^2), history of breast cancer in mother or sister (yes/no), alcohol intake between ages 18 and 22 (0, <5, 5-14, $\geq$ 15 gm/day), and multivitamin use between ages 13 and 18 (yes/no). These variables were selected based on their established or hypothesized associations with breast cancer, BBD, or adolescent diet. Terms for quartiles of total energy intake were also included in multivariate models to adjust fully for potential confounding, and types of fat were also mutually adjusted for one another.

Further analyses of associations between individual foods and proliferative BBD were also conducted. The original frequency categories for a serving of each food – ranging from "never or less than once per month" to "6 or more per day" – were used first, and then categories with small numbers of participants were combined to improve the stability of the estimates. Foods were selected according to their contributions to macro- and micronutrients that appeared

most important in the previous set of analyses. In addition, three major food groups – fruits and vegetables, meats, and dairy foods – were examined in relation to risk of proliferative BBD. Categories for servings of these food groups were determined based on their distributions among women who completed the adolescent diet questionnaire, and total energy intake was included in the multivariate models.

Results

Between 1991 and 1997, 29,494 women in the study contributed 165,141 person-years of follow-up. The baseline distributions of selected characteristics of participants are presented in Table 1, according to their intakes of fat and vitamins A, E, and C during adolescence. Age, family history of breast cancer, age at menarche, menopausal status, alcohol intake between ages 18 and 22, and body mass index at age 18 did not vary substantially across quartiles of intake.

We observed no association between total fat intake during adolescence and incidence of proliferative BBD (Table 2). There was some suggestion of a positive association for animal fat intake and an inverse association for vegetable fat intake, however. Compared to women in the lowest quartile of animal fat intake, the multivariate rate ratios for proliferative BBD were 1.24 (95% CI = 0.94-1.63) for women in the second quartile, 1.16 (95% CI = 0.87-1.54) for women in the third quartile, and 1.33 (95% CI = 1.00-1.78) for women in the highest quartile (*P* for trend = 0.08). For vegetable fat intake, the multivariate rate ratios were 0.89 (95% CI = 0.70-1.14), 0.92 (95% CI = 0.71-1.18), and 0.73 (95% CI = 0.55-0.96) for women in the second, third, and highest quartiles, respectively (*P* for trend = 0.04). Because animal fat and vegetable fat intake are negatively correlated, we also included both animal fat and vegetable fat in the same multivariate model to mutually adjust for one another. Although the rate ratios were somewhat

attenuated and the trends were no longer statistically significant, the directions of both associations remained the same.

In addition, monounsaturated fat was positively associated with risk of proliferative BBD. The multivariate rate ratios were 1.21 (95% CI = 0.90-1.64), 1.33 (95% CI = 0.95-1.85), and 1.52 (95% CI = 1.05-2.21) for women in the second, third, and fourth quartiles of monounsaturated fat intake, respectively, after adjustment for other types of fat (*P* for trend = 0.03). Polyunsaturated fat intake showed a nonsignificant inverse association with risk, while saturated fat and trans unsaturated fat intakes were unrelated to risk.

Of the micronutrients that were examined, only vitamin E and total vitamin A intakes were inversely associated with risk of proliferative BBD (Table 3). Intakes of vitamin C, retinol, carotenoids, and folate were not related to risk. The weak inverse association for vitamin E was most apparent in the two quartiles with highest intake. Compared to women in the lowest quartile of vitamin E intake, the multivariate rate ratios for proliferative BBD were 0.88 (95% CI = 0.68-1.14) for women in the third quartile and 0.79 (95% CI = 0.61-1.04) for women in the highest quartile (*P* for trend = 0.05). The inverse association for vitamin A was slightly weaker and the trend was nonsignificant. The multivariate rate ratio was 0.84 (95% CI = 0.64-1.11) for women in the highest versus the lowest quartile of total vitamin A intake (*P* for trend = 0.07). These associations were still apparent when only vitamins from food sources, as opposed to supplements, were included.

Because vegetable fat was inversely associated with risk of proliferative BBD and vegetable fat is a major source of dietary vitamin E, we included both vitamin E and vegetable fat in the same multivariate model. The inverse association for vegetable fat was somewhat attenuated after adjustment for animal fat and vitamin E; the rate ratio for women in the highest

quartile versus the lowest quartile was 0.87 (95% CI = 0.59-1.28, *P* for trend = 0.59). The inverse association for vitamin E was also attenuated after adjustment for vegetable fat, with a rate ratio of 0.88 (95% CI = 0.63-1.22, *P* for trend = 0.38) for women in the highest quartile versus the lowest quartile. The directions of both associations, however, remained the same.

In addition, we observed a significant inverse association between fiber intake and proliferative BBD (Table 4). The multivariate rate ratio was 0.75 (95% CI = 0.57-0.98) for women in the highest versus the lowest quartile of fiber intake (*P* for trend = 0.05). Neither fruit nor vegetable intakes, separately or combined, were significantly associated with risk of proliferative BBD.

Both total meat intake and red meat intake were positively associated with risk of proliferative BBD (data not shown). For total meat intake, the multivariate rate ratio for women who ate three or more servings per day compared to those who ate less than one and a half servings per day was 1.50 (95% CI = 1.01-2.22, *P* for trend = 0.03), while for red meat intake, the multivariate rate ratio for women who ate two or more servings per day compared to those who ate less than one serving per day was 1.33 (95% CI = 0.97-1.84, *P* for trend = 0.03). These rate ratios were somewhat attenuated after adjustment for animal fat, but the directions of both associations remained unchanged. No associations were observed for intakes of milk or total, high-fat, or low-fat dairy foods.

We also calculated age-adjusted and multivariate ratios for associations between intakes of individual foods and proliferative BBD. We examined foods that contributed substantially to intakes of animal fat, vegetable fat, vitamin E, vitamin A, and fiber during adolescence. Consumption of nuts and raw carrots were inversely associated with risk of proliferative BBD. For nuts, the multivariate rate ratios for women who ate two to three servings per month, one

serving per week, and greater than one serving per week were 1.03 (95% CI = 0.82-1.29), 0.93 (95% CI = 0.73-1.18), and 0.64 (95% CI = 0.45-0.91), respectively, compared to women who ate one serving per month or less (*P* for trend = 0.02). The multivariate rate ratios for intake of raw carrots were 0.87 (95% CI = 0.68-1.11) for women who ate one to three servings per month, 0.74 (95% CI = 0.57-0.96) for women who ate one serving per week, and 0.70 (95% CI = 0.52-0.92) for women who ate two servings per week or more, compared to those who ate less than one serving per month (*P* for trend = 0.02). This inverse association was not observed for intake of cooked carrots. Nonsignificant inverse associations were also observed for intakes of grapes, strawberries, oranges, and fruit juice. Consumption of hot dogs was positively associated with risk of proliferative BBD; multivariate rate ratios for women who ate one to three servings per month, one serving per week, and two servings per week or more were 1.02 (95% CI = 0.76-1.38), 1.11 (95% CI = 0.81-1.50), and 1.49 (95% CI = 1.04-2.13), respectively (*P* for trend = 0.01). This association remained significant even after adjustment for animal fat. There were also nonsignificant positive associations between intakes of processed meats (e.g., cold cuts), bacon, and pork and proliferative BBD.

Finally, in the secondary analyses using all self-reported benign breast disease as the outcome (5012 cases), we observed no consistent associations for intakes of total fat or any types of fat. Restricting the outcome to cases that participants reported as confirmed by biopsy (998 cases), we observed a weak inverse association for vegetable fat intake; however, the trend was not statistically significant (*P* = 0.18) and was no longer apparent after adjustment for vitamin E. Animal fat intake was not associated with risk of biopsy-confirmed benign breast disease. There was a nonsignificant positive association for monounsaturated fat intake, while saturated, polyunsaturated, and trans unsaturated fat intakes were unrelated to risk. There were significant

inverse associations for intakes of vitamin C, vitamin E, vitamin A, beta cryptoxanthin, fiber, and fruits and self-reported BBD; however, the actual risk reduction in the highest quartile of each of these was small, approximately 10% or less. For self-reported BBD confirmed by biopsy, some of the same inverse associations were apparent, but the inverse association for vitamin E was the only one that was statistically significant; the multivariate rate ratios were 0.94 (95% CI = 0.79-1.11), 0.88 (95% CI = 0.74-1.05), and 0.84 (95% CI = 0.70-1.00) for women in increasing quartiles of vitamin E intake (*P* for trend = 0.04).

Discussion

In this study, we observed that vitamin E and fiber intake during adolescence were inversely related to the incidence of proliferative benign breast disease. Women in the highest quartiles of vitamin E and fiber intake had approximately 20% and 25% lower risk of proliferative benign breast disease compared to women in the lowest quartiles, respectively. Polyunsaturated fat and vegetable fat intake (which are highly correlated with each other) were also inversely associated with risk of proliferative BBD. However, the associations between vitamin E and vegetable fat in relation to proliferative BBD were greatly attenuated after mutual adjustment for one another, making it difficult to determine which factor is responsible for the observed inverse associations. Monounsaturated fat intake during adolescence (derived mainly from animal sources such as beef, milk, and pork in this population) was positively associated with risk of proliferative benign breast disease, while total fat, saturated fat, and trans unsaturated fat intake were unrelated to risk. The patterns for vitamin E, vegetable fat, monounsaturated fat, and fiber were still apparent when the study population was restricted to participants who reported having a mammogram or clinical breast exam within the previous two

years (data not shown), suggesting that selective referral for biopsy and subsequent diagnosis of BBD based on adolescent diet is not a viable explanation for these results.

An important limitation of this study is the retrospective assessment of adolescent diet and the potential for recall bias: a diagnosis of benign breast disease between 1991 and 1997 could have influenced participants' recall or reporting of adolescent diet in 1998. If women diagnosed with BBD systematically over- or under-reported their consumption of certain foods during adolescence in comparison with women who did not develop benign breast disease, this could bias our results. A nested case-control study in a similar but older population (27) examined the impact of recall bias by comparing observed associations between fat intake and breast cancer risk using prospective and retrospective diet assessments; the investigators found some differences in the direction and magnitude of observed associations based on the timing of the diet assessment. In this study, however, both diet assessments referred to a time period only a few years prior to the breast cancer diagnosis. A disease diagnosis may have a greater effect on recall of recent diet than on recall of diet in the remote past. Other studies have shown little or no difference between cancer cases and controls in the reliability of long-term recall (28-30). Furthermore, whereas the relationship between fat and breast cancer has been the focus of numerous epidemiologic studies and has received substantial attention in the popular press, increasing the chance that participants would be aware of hypothesized associations, there has been little information about the association of diet with benign breast disease in the scientific literature or popular press, making it less likely that recall bias could explain the findings of the present study.

A related issue is the influence of adult diet on recall of adolescent diet. If current diet is strongly correlated with recall of past diet and is related to risk of benign breast disease, then

current diet could confound observed associations between adolescent intake and BBD. However, as mentioned earlier, the average correlation between two separate recalls of foods consumed during high school in a similar population was much higher than the correlation between current consumption of those foods and the first recall of high school diet (22). Furthermore, women participating in the present study were younger than the women in the previous reproducibility study when they completed the high school diet questionnaire, which should lead to more accurate recall.

Recall bias and the influence of current diet on recall of adolescent diet may be particularly relevant to the findings for vitamin E. Although their clinical efficacy has not been proven, vitamin E supplements have been used to treat symptoms of benign breast disease for a number of years (31, 32). Therefore, a greater proportion of women with a confirmed diagnosis or symptoms of benign breast disease may be taking vitamin E supplements compared to women with no diagnosis or symptoms. If women with benign breast disease who are currently taking vitamin supplements have a tendency to over-report their use of vitamin supplements in high school, this could bias the estimate of the association between adolescent vitamin E intake and proliferative BBD, making vitamin E look less protective. However, since the reported prevalence of multivitamin use during high school (15.7%) among women in the study was fairly low, and the correlation between adolescent vitamin E intake and adult vitamin E intake reported in 1991 ($r = 0.12$) was small, it is unlikely that this bias had an important impact on our results. Alternatively, if study participants were aware of a potential inverse association between vitamin E intake and benign breast disease, it is possible that women with benign breast disease may have under-reported their use of vitamin supplements during adolescence compared to noncases, which could induce a spurious inverse association between vitamin E and benign breast disease.

This type of biased recall is also unlikely, however, given that the hypothesized association between vitamin E intake and benign breast disease has not been widely publicized and that supplements accounted for only slightly more than 1% of total vitamin E intake during adolescence among participants.

Another limitation of the study pertains to the comparability between actual and recalled adolescent diet. The validity of recall of adolescent diet 20 to 40 years later has not been established, and nondifferential misclassification of participants' true consumption of foods and nutrients could bias associations toward the null. A study is currently being conducted to examine the reproducibility and validity of recall of adolescent diet in this cohort. The reproducibility study conducted in a similar cohort showed moderately high correlations between two separate recalls, eight years apart, of consumption of 24 food items during adolescence (22). Studies that have examined the validity of recall of diet from the distant past in other populations have had mixed results (20, 28). Given the exploratory nature of this analysis and the absence of dietary data actually recorded during adolescence, however, recall of adolescent diet currently provides the best available information on diet during this time period. Future studies that collect data on childhood and adolescent diet prospectively are needed in order to confirm these findings.

Uncontrolled confounding is always a possibility in observational research. Although it is unlikely that adolescent diet is strongly correlated with adult risk factors for benign breast disease, it may be associated with other early life and adolescent lifestyle exposures that affect risk of BBD and breast cancer (although few such exposures have been identified to date). To address this concern, we have presented age-adjusted results as well as results adjusted for age and time period, age at menarche, body mass index at age 18, alcohol intake between 18 and 22,

multivitamin use during adolescence, family history of breast cancer, and menopausal status. The age-adjusted and multivariate rate ratios were very similar, suggesting that there is minimal confounding by these known risk factors for breast cancer. Although there may be some degree of confounding by other factors, it is unlikely that uncontrolled confounding could entirely account for our findings.

Many dietary factors were considered in this study, which may increase the probability of observing a falsely significant result simply due to chance. Because the comparisons of interest were specified before the data were examined, it was not necessary to make a uniform adjustment to the critical level of the p-value (33). Readers should exercise caution, however, in the interpretation of the results, paying close attention to internal consistency, findings from other studies, and biologic plausibility.

The similar findings for vegetable fat and vitamin E provide evidence for internal consistency; both vegetable fat and vitamin E intakes during adolescence were inversely associated with incidence of benign breast disease, and vegetable oils are a major source of vitamin E. Other evidence for internal consistency comes from the analyses of food sources of nutrients. Although foods were not the primary focus of this study, the findings for the individual foods and food groups that were examined were generally consistent with the results from the nutrient analyses. For example, nuts contain vegetable fat, and nut consumption was inversely associated with incidence of proliferative BBD. Higher consumption of all meat and red meat were associated with increased risk of proliferative BBD, which is consistent with the positive associations for animal fat and monounsaturated fat. In addition to demonstrating internal consistency, the findings are compatible with those from a recent retrospective study in a similar cohort, in which higher consumption of vegetable fat and fiber during adolescence were

related to lower breast cancer risk (21), and with those from a retrospective case-control study in British Columbia, in which consumption of vegetable oils in childhood was associated with reduced risk of premenopausal breast cancer (18).

Biologic plausibility of the observed associations should also be considered in the interpretation of these findings. Fiber has been hypothesized to be related to lower breast cancer risk by decreasing circulating levels of estrogens, which stimulate proliferation of mammary cells. Fiber inhibits reabsorption of estrogens in the gastrointestinal tract (34) and has been associated with increased levels of sex-hormone binding globulin, which binds to estrogen and thereby reduces its bioavailability (35). Vitamin E has long been believed to be protective against the development of some cancers, including breast cancer, through its function as an antioxidant, neutralizing free radicals that can cause DNA damage and thereby inhibiting mutagenesis and cell transformation (7, 8). More recently, vitamin E has also been shown to induce apoptosis *in vitro* and to inhibit the growth of breast cancer cells *in vitro* and *in vivo* (36). The effects of these and other nutrients may be particularly important during adolescence, as cells of the mammary gland are undergoing rapid development between menarche and first birth and, thus, may be vulnerable to malignant transformation (16, 17). Data from epidemiological studies on the relationship between intakes of vitamin E and fiber and breast cancer have yielded weak and inconsistent results (9, 37-41). Our results suggest that previous studies may have had null findings because they were focusing on diet during adulthood, which may not be the most relevant time period.

An important strength of this study is our definition of proliferative benign breast disease. There is likely to be some misclassification in the reporting of benign breast disease, as BBD is a heterogeneous group of lesions and may be confused with other breast disorders. This

misclassification could result in attenuation of the effect estimates. Restricting the outcome definition to cases for whom tissue samples were available and using a uniform, centralized pathology review to classify the cases as proliferative or nonproliferative reduces the likelihood of misclassification. A small study that was conducted to examine inter-rater reliability showed that the pathologists' classification of the confirmed cases as proliferative or nonproliferative was highly reproducible (unpublished data). The decision to focus only on proliferative cases was based on evidence from a number of studies showing that proliferative lesions are associated with increased risk of breast cancer, whereas nonproliferative lesions do not confer any increase in risk (1). These findings suggest that proliferative benign breast disease is the most etiologically relevant indicator of breast cancer risk.

In summary, this study examined the relationship between intakes of fats and micronutrients during adolescence and incidence of proliferative benign breast disease. These results suggest that monounsaturated fat intake is positively associated with risk of proliferative BBD, while vegetable fat, vitamin E and fiber intakes are inversely associated with risk. Confirmation of these associations may suggest a means for prevention of breast cancer.

Table 1 Age-standardized percentages and means for characteristics of participants according to fat and vitamin intake during adolescence [a]

	Total fat quartile [b]		Total vitamin A quartile [c]		Total vitamin E quartile [c]		Total vitamin C quartile [c]	
	1 (low)	4 (high)	1 (low)	4 (high)	1 (low)	4 (high)	1 (low)	4 (high)
Number of women	7658	7140	7474	7313	7340	7519	7358	7371
Percent of group								
Family history of breast cancer in mother or sister(s)	8	9	8	8	8	9	8	9
Age at menarche < 12 yr	25	25	24	25	23	26	24	25
Premenopausal in 1991	98	98	98	98	98	98	98	98
Mean								
Age in 1991 (yr)	34	37	35	36	37	35	36	35
Alcohol intake between ages 18 and 22 (gm/day)	5	6	6	5	5	6	5	5
BMI at age 18 (kg/m^2)	21	22	21	21	21	22	22	21
Adolescent fat intake (% of energy)	35	46	42	39	40	42	43	38
Adolescent fiber intake (gm/day, energy-adjusted)	25	18	18	25	19	23	18	25

[a] Except for the data on mean age, all data shown are standardized to the age distribution of the cohort in 1991.
[b] Quartile of percent calories from fat
[c] Quartile of energy-adjusted nutrient residuals

Table 2 Rate ratios (RRs) and 95% confidence intervals (CIs) of proliferative benign breast disease (BBD) among 29,494 women followed from 1991 to 1997, according to percent calories from total fat and types of fat during adolescence

	Quartile of percent calories from fat				
	1 (low)	2	3	4 (high)	*P* for trend
Total fat					
Intake (% of energy) [a]	35.6	39.4	42.1	45.5	
Cases of BBD [b]	106	122	109	133	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.15 (0.89-1.49)	1.01 (0.77-1.33)	1.24 (0.95-1.61)	0.22
Multivariate [c]	1.00 (referent)	1.10 (0.85-1.43)	0.98 (0.75-1.29)	1.17 (0.90-1.52)	0.37
Animal fat					
Intake (% of energy) [a]	19.5	24.0	27.6	32.4	
Cases of BBD [b]	94	121	119	136	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.26 (0.96-1.67)	1.24 (0.92-1.67)	1.55 (1.15-2.09)	0.03
Multivariate [c]	1.00 (referent)	1.24 (0.94-1.63)	1.16 (0.87-1.54)	1.33 (1.00-1.78)	0.08
Additional adjustment for vegetable fat	1.00 (referent)	1.18 (0.89-1.57)	1.07 (0.79-1.45)	1.19 (0.86-1.65)	0.40
Vegetable fat					
Intake (% of energy) [a]	10.2	13.3	15.8	19.3	
Cases of BBD [b]	136	120	121	93	
RR (95% CI)					
Age-adjusted	1.00 (referent)	0.88 (0.69-1.13)	0.94 (0.74-1.21)	0.69 (0.52-0.92)	0.02
Multivariate [c]	1.00 (referent)	0.89 (0.70-1.14)	0.92 (0.71-1.18)	0.73 (0.55-0.96)	0.04
Additional adjustment for animal fat	1.00 (referent)	0.91 (0.70-1.18)	0.95 (0.72-1.25)	0.77 (0.56-1.06)	0.15
Saturated fat					
Intake (% of energy) [a]	13.3	15.2	16.8	18.9	
Cases of BBD [b]	100	121	118	131	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.23 (0.94-1.60)	1.12 (0.85-1.49)	1.30 (0.98-1.72)	0.12
Multivariate [c]	1.00 (referent)	1.15 (0.88-1.51)	1.09 (0.83-1.44)	1.19 (0.90-1.56)	0.30
Additional adjustment for monounsaturated, polyunsaturated, and trans unsaturated fats	1.00 (referent)	1.02 (0.76-1.37)	0.88 (0.63-1.23)	0.87 (0.59-1.27)	0.36
Monounsaturated fat					
Intake (% of energy) [a]	12.6	14.1	15.1	16.5	
Cases of BBD [b]	101	117	120	132	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.18 (0.90-1.54)	1.23 (0.94-1.60)	1.32 (1.01-1.72)	0.04
Multivariate [c]	1.00 (referent)	1.15 (0.88-1.50)	1.19 (0.91-1.56)	1.28 (0.99-1.67)	0.06
Additional adjustment for saturated, polyunsaturated, and trans unsaturated fats	1.00 (referent)	1.21 (0.90-1.64)	1.33 (0.95-1.85)	1.52 (1.05-2.21)	0.03
Polyunsaturated fat					
Intake (% of energy) [a]	5.2	6.1	6.9	8.1	
Cases of BBD [b]	124	121	126	99	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.02 (0.79-1.30)	1.04 (0.81-1.34)	0.81 (0.62-1.06)	0.22
Multivariate [c]	1.00 (referent)	1.00 (0.78-1.29)	1.07 (0.83-1.38)	0.81 (0.62-1.06)	0.17
Additional adjustment for saturated, monounsaturated, and trans unsaturated fats	1.00 (referent)	0.97 (0.75-1.25)	1.00 (0.77-1.31)	0.74 (0.55-1.00)	0.06
Trans unsaturated fat					
Intake (% of energy) [a]	1.6	2.0	2.5	3.2	
Cases of BBD [b]	115	128	126	101	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.17 (0.90-1.50)	1.13 (0.87-1.47)	0.89 (0.67-1.67)	0.48
Multivariate [c]	1.00 (referent)	1.18 (0.91-1.52)	1.16 (0.90-1.51)	0.92 (0.70-1.21)	0.39
Additional adjustment for saturated, monounsaturated, and polyunsaturated fats	1.00 (referent)	1.17 (0.90-1.51)	1.14 (0.87-1.50)	0.91 (0.68-1.21)	0.33

[a] Values for % of energy are medians of each quartile.

[b] A total of 470 cases of proliferative benign breast disease (with or without atypia) were diagnosed during the follow-up period.

[c] The multivariate models are adjusted for the following: age in months, time period (3 periods), total energy intake (quartiles), age at menarche (< 12, 12, 13, ≥14), menopausal status (premenopausal, postmenopausal, or uncertain), body mass index at age 18 (<19, 19-20.4, 20.5-21.9, 22-24.9, ≥25), history of breast cancer in mother or sister (yes/no), alcohol intake between ages 18 and 22 (0, <5, 5-14, ≥15 gm/day), and multivitamin use between ages 13 and 18 (yes/no).

Table 3 Rate ratios (RRs) and 95% confidence intervals (CIs) of proliferative benign breast disease (BBD) among 29,494 women followed from 1991 to 1997, according to energy-adjusted micronutrient intakes during adolescence

	Quartile of energy-adjusted micronutrient intake				
	1 (low)	2	3	4 (high)	*P* for trend
Vitamin C (including supplements)					
Intake (mg/day) [a]	81	120	158	228	
Cases of BBD [b]	126	131	104	109	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.03 (0.81-1.32)	0.81 (0.53-1.05)	0.87 (0.67-1.12)	0.11
Multivariate [c]	1.00 (referent)	1.05 (0.82-1.34)	0.82 (0.63-1.07)	0.90 (0.68-1.18)	0.24
Vitamin E (including supplements)					
Intake (mg/day) [a]	11	12	13	15	
Cases of BBD [b]	128	137	108	97	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.11 (0.88-1.42)	0.86 (0.66-1.11)	0.76 (0.58-1.00)	0.02
Multivariate [c]	1.00 (referent)	1.13 (0.89-1.44)	0.88 (0.68-1.14)	0.79 (0.61-1.04)	0.05
Vitamin A (including supplements)					
Intake (IU/day) [a]	6316	9399	12771	19634	
Cases of BBD [b]	121	142	108	99	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.18 (0.92-1.50)	0.91 (0.70-1.18)	0.81 (0.62-1.06)	0.04
Multivariate [c]	1.00 (referent)	1.17 (0.91-1.49)	0.92 (0.71-1.20)	0.84 (0.64-1.11)	0.07
Retinol					
Intake (IU/day) [a]	1486	2023	2697	5145	
Cases of BBD [b]	112	129	128	101	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.19 (0.92-1.53)	1.17 (0.91-1.51)	0.94 (0.72-1.23)	0.72
Multivariate [c]	1.00 (referent)	1.21 (0.93-1.56)	1.21 (0.94-1.57)	0.99 (0.72-1.38)	0.71
Total carotenoids					
Intake (IU/day) [a]	4012	6622	9466	16228	
Cases of BBD [b]	120	129	117	104	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.08 (0.84-1.38)	0.98 (0.76-1.26)	0.85 (0.65-1.10)	0.17
Multivariate [c]	1.00 (referent)	1.07 (0.83-1.37)	0.96 (0.74-1.25)	0.87 (0.67-1.14)	0.19
α-Carotene					
Intake (mcg/day) [a]	353	694	1074	2105	
Cases of BBD [b]	114	123	127	106	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.08 (0.84-1.40)	1.11 (0.86-1.43)	0.91 (0.70-1.19)	0.58
Multivariate [c]	1.00 (referent)	1.07 (0.83-1.39)	1.09 (0.85-1.41)	0.93 (0.71-1.22)	0.44
β-Carotene					
Intake (mcg/day) [a]	1753	2814	3952	6252	
Cases of BBD [b]	123	127	113	107	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.04 (0.81-1.33)	0.92 (0.72-1.19)	0.87 (0.67-1.12)	0.18
Multivariate [c]	1.00 (referent)	1.04 (0.81-1.33)	0.92 (0.71-1.19)	0.88 (0.68-1.15)	0.24
β-Cryptoxanthin					
Intake (mcg/day) [a]	63	122	189	287	
Cases of BBD [b]	111	130	114	115	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.15 (0.89-1.48)	1.01 (0.78-1.31)	1.02 (0.79-1.33)	0.87
Multivariate [c]	1.00 (referent)	1.17 (0.90-1.51)	1.02 (0.78-1.33)	1.04 (0.80-1.36)	0.92
Lycopene					
Intake (mcg/day) [a]	3604	5190	7152	12119	
Cases of BBD [b]	110	124	136	100	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.15 (0.89-1.48)	1.26 (0.98-1.62)	0.95 (0.73-1.25)	0.98
Multivariate [c]	1.00 (referent)	1.16 (0.90-1.51)	1.31 (1.01-1.69)	0.97 (0.74-1.27)	0.56
Lutein & zeaxanthin					
Intake (mcg/day) [a]	1022	1674	2387	3841	
Cases of BBD [b]	125	108	130	107	
RR (95% CI)					
Age-adjusted	1.00 (referent)	0.88 (0.68-1.13)	1.05 (0.82-1.34)	0.88 (0.68-1.14)	0.58
Multivariate [c]	1.00 (referent)	0.86 (0.66-1.11)	1.04 (0.82-1.33)	0.88 (0.68-1.14)	0.57
Folate					
Intake (mcg/day) [a]	233	286	333	421	
Cases of BBD [b]	122	127	114	107	
RR (95% CI)					
Age-adjusted	1.00 (referent)	1.05 (0.82-1.35)	0.95 (0.74-1.22)	0.95 (0.73-1.23)	0.43
Multivariate [c]	1.00 (referent)	1.07 (0.83-1.38)	0.97 (0.75-1.26)	1.00 (0.76-1.31)	0.84

[a] Values for intake are medians of each quartile, adjusted for total energy intake using the residual method.

[b] A total of 470 cases of histologically-confirmed proliferative benign breast disease occurred during the follow-up period.

[c] The multivariate models are adjusted for the following: age in months, time period (3 periods), total energy intake (quartiles), age at menarche (< 12, 12, 13, ≥14), menopausal status (premenopausal, postmenopausal, or uncertain), body mass index at age 18 (<19, 19-20.4, 20.5-21.9, 22-24.9, ≥25), history of breast cancer in mother or sister (yes/no), alcohol intake between ages 18 and 22 (0, <5, 5-14, ≥15 gm/day), and multivitamin use between ages 13 and 18 (yes/no).

Table 4 Rate ratios (RRs) and 95% confidence intervals (CIs) of proliferative benign breast disease (BBD) among 29,494 women followed from 1991 to 1997, according to intakes of fiber, fruits, and vegetables during adolescence

	Cases of BBD [a]	Age-adjusted RR	Multivariate RR [b]
Fiber (gm/day, energy-adjusted)			
Quartile 1 (lowest)	133	1.00 (referent)	1.00 (referent)
Quartile 2	118	0.91 (0.71-1.17)	0.94 (0.73-1.21)
Quartile 3	127	0.96 (0.75-1.22)	0.99 (0.78-1.27)
Quartile 4 (highest)	92	0.71 (0.54-0.92)	0.75 (0.57-0.98)
P for trend		0.03	0.05
Fruits (servings/day)			
< 1	92	1.00 (referent)	1.00 (referent)
1.0-1.9	150	0.97 (0.74-1.25)	0.95 (0.73-1.23)
2.0-2.9	128	0.97 (0.74-1.27)	0.96 (0.73-1.27)
≥ 3	100	0.84 (0.64-1.12)	0.85 (0.63-1.16)
P for trend		0.25	0.34
Vegetables (servings/day)			
< 2	157	1.00 (referent)	1.00 (referent)
2.0-2.9	138	1.02 (0.81-1.28)	1.02 (0.81-1.29)
3.0-3.9	99	1.15 (0.89-1.48)	1.17 (0.90-1.52)
≥ 4	76	0.93 (0.71-1.23)	0.97 (0.72-1.30)
P for trend		0.96	0.91
Fruits and vegetables combined (servings/day)			
< 3	93	1.00 (referent)	1.00 (referent)
3.0-3.9	88	1.11 (0.83-1.48)	1.10 (0.82-1.48)
4.0-4.9	96	1.23 (0.92-1.63)	1.23 (0.92-1.65)
5.0-5.9	70	1.11 (0.82-1.52)	1.12 (0.81-1.55)
≥ 6	123	0.97 (0.74-1.27)	1.00 (0.74-1.35)
P for trend		0.66	0.77

[a] A total of 470 cases of histologically-confirmed proliferative benign breast disease occurred during the follow-up period.

[b] A total of 470 cases of histologically-confirmed proliferative benign breast disease occurred during the follow-up period.

The multivariate models are adjusted for the following: age in months, time period (3 periods), total energy intake (quartiles), age at menarche (< 12, 12, 13, ≥14), menopausal status (premenopausal, postmenopausal, or uncertain), body mass index at age 18 (<19, 19-20.4, 20.5-21.9, 22-24.9, ≥25), history of breast cancer in mother or sister (yes/no), alcohol intake between ages 18 and 22 (0, <5, 5-14, ≥15 gm/day), and multivitamin use between ages 13 and 18 (yes/no).

Acknowledgments

We thank the participants of the Nurses' Health Study II for their dedication to this study, Drs. Timothy Jacobs and Gloria Peiro for their assistance with classifying the biopsies for the benign breast disease cases, and Sue Malspeis for her technical support.

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