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Intake of Fiber and Nuts during Adolescence and Incidence of Proliferative Benign Breast Disease

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Abstract

Objective—We examined the association between adolescent fiber intake and proliferative BBD, a marker of increased breast cancer risk, in the Nurses' Health Study II.

Methods—Among 29,480 women who completed a high school diet questionnaire in 1998, 682 proliferative BBD cases were identified and confirmed by centralized pathology review between 1991 and 2001. Multivariate-adjusted Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results—Women in the highest quintile of adolescent fiber intake had a 25% lower risk of proliferative BBD (multivariate HR (95% CI): 0.75 (0.59, 0.96), p-trend = 0.01) than women in the lowest quintile. High school intake of nuts and apples was also related to significantly reduced BBD risk. Women consuming ≥2 servings of nuts/week had a 36% lower risk (multivariate HR (95% CI): 0.64 (0.48, 0.85), p-trend < 0.01) than women consuming <1 serving/month. Results were essentially the same when the analysis was restricted to prospective cases (n = 142) diagnosed after return of the high school diet questionnaire.

Conclusions—These findings support the hypothesis that dietary intake of fiber and nuts during adolescence influence subsequent risk of breast disease and may suggest a viable means for breast cancer prevention.

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Keywords

adolescent intake; fiber; nuts; proliferative BBD

Introduction

Large international variation in breast cancer risk has been observed, with the highest disease incidence in more-developed western countries and lower rates in less-developed eastern countries (1). This remarkable variation may not be attributable to genetic factors alone. Migrant studies have found that incidence for Asian American women who moved from traditionally low-risk countries approached the higher rates in their host country after immigration (2,3), suggesting that potentially modifiable environmental factors, such as diet, may play an important role in breast cancer development. Because intake of fruits and vegetables is higher in countries with low incidence of breast cancer than in those with higher incidence, fiber has been hypothesized as a candidate nutrient to explain these differences. Supporting this hypothesis, animal studies have shown that high fiber intake reduces mammary tumor incidence (4). Numerous epidemiologic studies have examined the association between adult fiber intake and breast cancer risk, with inconsistent results. In general, inverse associations have been reported in case-control studies (5–9) and some recent cohort studies (10,11), while no association was observed in other large prospective studies (12–25).

Benign breast disease (BBD) is a marker of increased breast cancer risk. Women whose biopsies show proliferative changes without atypia have a 1.3–1.9 fold greater risk of subsequent breast cancer than women with nonproliferative lesions, and women with atypical hyperplasia (AH) have a 3.9- to 13-fold greater risk (26). Studies on diet and BBD may provide insights regarding the role of diet in the earlier stages of breast carcinogenesis.

The association between adult intake of fiber and BBD has been inconsistent, with no association observed in some (27–29) and inverse associations reported in other case-control studies (30,31). Adult fiber intake was not associated with risk of BBD overall or with the proliferative subtypes in the only prospective study conducted in the Nurses' Health Study II (NHSII) cohort (32). One potential explanation for the lack of association is that these studies did not focus on an etiologically relevant exposure period.

Evidence from both animal (33) and human studies (2,3,34–36) suggests that exposures during childhood and adolescence may be important in breast carcinogenesis, because breast tissues may be most vulnerable to carcinogens due to rapid proliferation of cells and lack of terminal differentiation during this time period. In the few studies that have examined the relation between adolescent diet and breast cancer risk (37–41), suggestive inverse associations were observed for fiber intake in the Nurses' Health Study (NHS) (38) and NHSII (37). While adolescent total fiber intake was associated with an elevated risk of breast cancer in postmenopausal women, fiber from grains was associated with a reduced risk in both premenopausal and postmenopausal women in a study in Utah (41). In an analysis conducted in the NHSII cohort, Baer et al. (42) found a significant inverse association between adolescent fiber intake and risk of proliferative BBD. However, one potential limitation of this study was the retrospective assessment of adolescent diet intake, in which women reported their high school diet after diagnosis of BBD. Hence, the disease diagnosis could have influenced the report of dietary intake during adolescence, and possible differential recall for BBD cases and non-cases cannot be completely ruled out.

The current analysis expanded upon this previous study (42), with the addition of more than 200 new cases (n = 682 total). In addition, to the best of our knowledge, this is the first study to prospectively assess the relations of adolescent intake of fiber and sources of fiber with the incidence of proliferative BBD.

Materials and methods

Study design and population

The NHSII is an ongoing cohort study of 116,671 U.S. female registered nurses who completed a mailed, self-administered questionnaire asking about a variety of health-related exposures and conditions in 1989, when their age range was between 25 and 42 years. Information on risk factors and medical events, including diagnosis of BBD, has been updated biennially by questionnaire since study initiation. The response rate in the NHSII cohort has been high (~ 90%) during each 2-year period (43). On the 1997 questionnaire, women were asked whether they would be willing to fill out a supplemental high school diet questionnaire. In 1998, a semi-quantitative food-frequency questionnaire (FFQ) was sent to those who indicated their willingness to participate to assess their usual dietary intake during adolescence, further defined as ages 13–18 years.

High school food-frequency questionnaire (HS-FFQ)

The 131-item HS-FFQ used in the NHSII was modified from the well-validated adult diet FFQ used in the Nurses' Health Study (NHS) and NHSII cohorts. Participants were asked how often, on average, they had consumed a specified unit or portion size of each food or beverage item when they were in high school. Nine possible response categories were provided ranging from 'never or less than once per month' to 'six or more times per day'. Nutrient intake was calculated for each participant as the sum of the contributions from all foods, using an extensive food composition database maintained by a team of research dieticians. Because the composition of some foods has changed over time, to provide the best approximation of intake during adolescence, food composition data from the relevant time period (1960s and 1970s) were used, whenever available.

A reproducibility study conducted among a random sample of women who returned the 1998 HS-FFQ showed moderately high correlations between the same two HS-FFQs administered approximately four years apart (Intraclass correlation coefficients (ICC) for dietary fiber: 0.67) (44). The recalled adolescent diet was only moderately correlated with current adult diet in 1995 (the last adult dietary assessment prior to the 1998 HS-FFQ) (Pearson correlation for fiber: 0.38), suggesting that current diet did not strongly affect recall of adolescent diet. When comparing the nurses' recall with their mothers' reports on the nurses' high school dietary intake (44), the Pearson correlation was 0.35 for fiber. These results suggest that the HS-FFQ used in the NHSII cohort provides a reasonable record of adolescent diet.

Identification of BBD cases

On the 1989 questionnaire, all women were asked whether they had ever received a physician diagnosis of fibrocystic or other BBD. Each subsequent biennial questionnaire asked women whether they had received a BBD diagnosis from a physician since the previous questionnaire and whether the diagnosis had been confirmed by biopsy and/or aspiration. Women who reported a first diagnosis of biopsy-confirmed BBD on the 1993, 1995, 1997, 1999, or 2001 questionnaires were contacted to seek confirmation of the diagnosis and to ask permission to obtain their biopsy specimens.

The biopsy slides collected from hospital pathology departments were coded and submitted to the study pathologists (LCC, SJS, JLC) for independent review. The pathologists were blinded to participants' exposure information and classified benign breast lesions as nonproliferative, proliferative disease without atypia, and atypical hyperplasia (ductal and lobular), according to the criteria of Dupont and Page (45). Any biopsy specimens that showed atypia or questionable atypia were jointly reviewed by two pathologists, and a consensus diagnosis was reached. Specimens with intraductal papilloma, radial scar, sclerosing adenosis, fibroadenoma, fibroadenomatous change, or moderate to florid ductal hyperplasia in the absence of AH were classified as proliferative without atypia. Because proliferative BBD, in contrast to other subtypes, is associated with increased risk of breast cancer, proliferative BBD with or without atypia confirmed by pathology review was the outcome of interest in the current analysis.

A total of 3,273 participants reported a first diagnosis of biopsy-confirmed BBD on the 1993 through 2001 questionnaires. Among these, 1,662 (50.8%) responded to the HS-FFQ, and 1,333 (80.2%) of the HS-FFQ respondents confirmed the BBD diagnosis and granted permission for review of their biopsy records and pathology slides. Pathology materials were obtained and reviewed for 1,160 women (87.0% of those who had given permission); and valid biopsy information was obtained for 1,149 women (99.1% of those for whom biopsy specimens were received). The main reasons for exclusion were that the pathology specimen did not contain breast tissue or that the biopsy date was before 1989. Of these 1,149 BBD cases, 717 (62.4%) were classified as proliferative (with or without atypia) by the study pathologists. We further excluded women whose biopsy date was before the return date of the 1991 questionnaire (n = 7), after the return date of the 2001 questionnaire (n = 5), or after the date they reported BBD (n = 19), and those who reported a prior diagnosis of cancer other than non-melanoma skin cancer (n = 4) from the analysis. After these exclusions, the total number of proliferative BBD cases was 682, and 142 of them were diagnosed after completion of the HS-FFQ. Because of the small number of atypical hyperplasia cases (ductal and lobular, n = 61, among which 14 were diagnosed after return of the HS-FFQ), this was not examined as a separate outcome.

Statistical analysis

Participants eligible for inclusion in the current study included 45,948 women who returned the high-school diet questionnaire in 1998 and had plausible values for total energy intake (between 600 and 5000 kcal/day). High school diet questionnaire respondents had slightly larger childhood body size and were more likely to be nulliparous and have an older age at first birth than the non-respondents, but respondents and non-respondents were very similar in terms of other characteristics. To assess the possibility of recall bias, we conducted an analysis restricting to incident proliferative BBD cases diagnosed after completion of the HS-FFQ (described hereafter as prospective analysis). We also conducted the analysis combining all proliferative BBD cases diagnosed before and after return of the HS-FFQ (described hereafter as combined analysis) and presented results from both analyses, as the combined analysis results supported those of the prospective analysis and had greater power. In the combined analysis, each participant contributed person-time of follow-up from the return date of the 1991 questionnaire until the return date of the 2001 questionnaire, death from any cause, BBD diagnosis, report of cancer other than non-melanoma skin cancer, or loss to follow-up, whichever came first. In the prospective analysis, person-time accumulation was counted from the return date of the 1998 high school diet questionnaire. At 1991 baseline, we excluded women who had a previous self-reported diagnosis of BBD (n = 16,038), who reported a prior diagnosis of cancer other than non-melanoma skin cancer (n = 396), and whose biopsy date was before the return date of the 1991 questionnaire from the analysis (n = 17). The number of participants included in the combined analysis was

29,480 women. At 1998 baseline, we further excluded women who had a self-reported (n = 4,253) or histologically confirmed diagnosis of BBD (n = 319) and those who reported a prior diagnosis of cancer other than non-melanoma skin cancer (n = 430) between the return date of the 1991 questionnaire and the return date of the high school diet questionnaire and included 23,950 women in the prospective analysis. The study was approved by human research committees at the Harvard School of Public Health and Brigham and Women's Hospital.

Dietary fiber was the main exposure of interest. Energy-adjusted intake of fiber and sources of fiber, including fiber from fruits, vegetables, cruciferous vegetables, legume, and cereal, was calculated using the residual method, in which energy-adjusted values were the residuals from a regression model with total calorie intake as the independent variable and absolute fiber intake as the dependent variable (46). Energy-adjusted residuals of fiber and sources of fiber were divided into quintiles based on the distributions of intake for all eligible women. Further analyses examined individual food items or food groups of potential sources of fiber, including total nuts, separate and combined peanuts and peanut butter, separate and combined fruits and vegetables, apples, oranges/grapefruit, bananas, beans/lentils, peas or lima beans, and cold breakfast cereal. Categories for servings of these food items or food groups were determined on the basis of their distributions among all eligible women; those with small numbers of participants were combined to improve stability of the estimates.

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs), with the lowest quintile or category as the reference group. This method allows for the updating of time-varying covariates every two years. The multivariate Cox models were adjusted for age in months, total energy intake, and other potential confounders including age at menarche, menopausal status, average body size between ages 5 and 10 years, family history of breast cancer in mother or sister(s), alcohol intake between ages 18 and 22 years, multivitamin use between ages 13 and 18 years, recency and duration of oral contraceptive (OC) use, and parity and age at first birth. Age, menopausal status, OC use, and parity and age at first birth were updated in each questionnaire cycle. Family history of breast cancer was initially assessed in 1989 and updated in 1997. SAS PROC PHREG was used for all analyses, and the Anderson-Gill data structure (47) was used to handle time-varying covariates efficiently, with a new data record created for every questionnaire cycle at which a participant was at risk and covariates set to the values at the time the questionnaire was returned. Tests for trend were performed by calculating the Wald statistics, using the median values of each quintile or category as a continuous variable in the model. All tests of statistical significance were two-sided.

Results

Table 1 presents the baseline distributions in 1991 of selected characteristics of participants, according to their high school intake of fiber and total nuts. Women with high adolescent intake of fiber and nuts were more likely to be nulliparous, be older at first birth, and to have used multivitamins in high school and less likely to have ever used OCs than women with low intake.

A significant inverse association was observed between high school fiber intake and proliferative BBD risk (Table 2). Women in the highest quintile had a 25% lower risk of proliferative BBD (multivariate HR (95% CI): 0.75 (0.59, 0.96), p-trend = 0.01) than women in the lowest quintile of fiber intake. The same inverse association was also observed in the prospective analysis (multivariate highest vs. lowest quintile HR (95% CI): 0.61 (0.36, 1.03), p-trend = 0.05). Additional adjustment for adult fiber intake did not change the

estimates (multivariate highest vs. lowest quintile HR (95% CI): 0.72 (0.55, 0.93), p-trend < 0.01 in the combined analysis). Although no statistically significant trends were observed (p-trend > 0.05), inverse associations were observed for fiber from different sources, particularly for the fourth and fifth quintiles.

Higher intake of peanuts was also associated with significantly reduced risk of proliferative BBD (Table 3). Women who consumed ≥1 serving of peanuts/week during high school had 34% lower risk of proliferative BBD (multivariate HR (95% CI): 0.66 (0.51, 0.86), p-trend = 0.01) than women with the lowest intake (<1 serving/month). Total nut (peanuts and other nuts) consumption was also inversely associated with proliferative BBD (multivariate HR (95% CI) ≥2 servings/week vs. <1 serving/month: 0.64 (0.48, 0.85), p-trend < 0.01). The relations were essentially the same after additional adjustment for fiber intake. Results for fiber were slightly attenuated (highest vs. lowest quintile HR (95% CI): 0.80 (0.62, 1.02), p-trend = 0.05) after additional adjustment for total nut intake. Significant inverse associations were also observed for other nuts (multivariate HR (95% CI) ≥2 servings/week vs. <1 serving/month: 0.62 (0.44, 0.88), p-trend < 0.01) and total nuts with peanut butter (multivariate HR (95% CI) ≥4 servings/week vs. <1 serving/month: 0.70 (0.51, 0.95), p-trend = 0.04). The inverse associations between high school nut intake and proliferative BBD remained when analyses were restricted to prospective cases only.

Table 4 present the results for high school intake of separate and combined fruits and vegetables, apples, oranges/grapefruit, bananas, beans/lentils, peas or lima beans, and cold breakfast cereal. These food groups or items were chosen because they made up large percentage of fiber. Adolescent intake of fruits or vegetables, separately or combined, was not associated with risk of proliferative BBD. Although no significant trend was observed in the combined analysis (p-trend = 0.17), intake levels of one or more apples per month during adolescence were associated with lower proliferative BBD risk than the intake of less than one per month. This association was significant in the prospective analysis (multivariate HR (95% CI) ≥5 servings/week vs. <1 serving/month: 0.18 (0.07, 0.45), p-trend < 0.01).

Discussion

In this study, with a larger number of proliferative BBD cases (n = 682) than the previous retrospective analysis in the same cohort (42), we confirmed the originally observed significant inverse association between adolescent intake of fiber and nuts and risk of proliferative BBD. The unique feature of the current study is the addition of new prospective cases diagnosed after completion of the high school diet questionnaire. The results of the prospective only analysis were consistent with those of the larger combined analysis, suggesting that recall bias is not a plausible explanation of the inverse associations observed. Consistent with the original analysis (42), with the addition of over 200 incident cases, no association was observed for fruit or vegetable consumption and proliferative BBD.

Our results suggest that fiber intake during adolescence is protective in the early breast carcinogenic process. Previous studies observed increased adolescent fiber intake to be associated with a reduced risk of breast cancer (37,38,41), suggesting again the potential role of dietary intake in early life in breast cancer development. Inconsistent results, however, were reported in studies that have examined the relations of adult fiber intake with BBD (27–31) or breast cancer (5–25). No associations were observed between adult fiber intake and BBD risk overall or the proliferative subtypes in the only prospective analysis of adult diet and BBD in the same NHSII cohort (32). In the current study, the results were unchanged after additional adjustment for adult fiber intake, suggesting that the observed association was independent of recent intake.

Dietary fiber intake has been hypothesized to be protective in mammary tumorigenesis through several biological mechanisms. Dietary fiber may increase excretion of estrogen by inhibiting deconjugation and reabsorption of estrogen from the gastrointestinal tract (4,48–53). In addition, the protective effect may also be partly due to the anti-estrogenic effects of lignans and isoflavonoid compounds, which occur naturally in fiber-rich foods or arise as a result of bacterial action on such foods (54–57). Dietary lignans were postulated to have an inhibitory effect on cell proliferation in breast tumors through decreased levels of circulating estrogens either by inhibiting the aromatase enzyme in biosynthesis of estrogen (58) or by stimulating the synthesis of sex-hormone binding globulin (SHBG) (56). Diet intervention studies have shown that the combination of low dietary fat and high dietary fiber was associated with reduced serum estrogen levels among premenopausal women (59–61). Our results provide further support to the hypothesis that exposures during a susceptible period in women's life play important roles in breast cancer development. It is possible that fiber intake during adolescence may set steroid hormone levels and endocrine profiles in adulthood and reduce risk of proliferative BBD and/or breast cancer. Future studies are needed to examine the associations between adolescent dietary fiber intake and adolescent and/or adult serum estrogen levels to confirm the hypothesized biological mechanisms.

Previous studies have shown that soluble and insoluble fiber may have different effects possibly through different biological mechanisms (22). We do not have data on soluble or insoluble fiber, limiting our ability to assess their relations with proliferative BBD risk. We did, however, observe that, in general, higher intake levels of fiber from different sources were associated with lower risk of proliferative BBD. No statistically significant trends were observed for fiber from different sources possibly due to the relatively narrower range and lower variability of the intake levels for specific sources of fiber, compared to total fiber. The significant inverse association observed between total fiber and proliferative BBD could be due to the total amount of fiber with each source of fiber contributing a little, suggesting that dietary fiber itself, rather than a specific source of fiber, is important. Alternatively, results for fiber became somewhat attenuated when we additionally adjusted for nuts, suggesting that nut intake accounts for some of the fiber BBD association and a combination of nutrients including dietary fiber found in certain whole foods such as nuts act synergistically to produce the effect instead of just dietary fiber. Additional studies are warranted to further clarify the effects of different sources and types of fiber throughout the life course on breast proliferation and breast carcinogenesis.

High school intake of nuts was also related to a significantly reduced risk of proliferative BBD. Results were fairly consistent across the different types of nuts examined in this study. Results for nuts were essentially the same with additional adjustment for fiber, suggesting that in addition to fiber, the inverse associations between nut intake and proliferative BBD risk may also be attributable to nutrients other than fiber in nuts. A significant inverse association was observed between adolescent nut intake and proliferative BBD in the previous retrospective study by Baer et al. (42), whereas no association was found between adult nut intake and breast cancer in the Malmo Diet and Cancer cohort (21) Nuts are rich sources of unsaturated fat as well as a variety of other bioactive compounds (62). Nut intake has consistently been reported to reduce the incidence of cardiovascular disease (63). Given the scarce literature on nut intake and cancer risk, more experimental and epidemiological research is clearly needed to better understand whether the intake of this food group provides health benefits with respect to cancer and to elucidate the possible mechanisms of action.

We observed no association between adolescent intake of fruits and vegetables and proliferative BBD, although these food groups are also sources of fiber. Further examination of individual food items making up large percentages of fiber revealed an inverse

association between apple intake and proliferative BBD, particularly in the prospective analysis. The associations between high school intake of fruits and vegetables and proliferative BBD have not been evaluated in previous studies except the original analysis in NHSII (42). Some studies, however, have reported inverse associations between adult intake of fruits and vegetables and proliferative BBD risk (27,29,64–66). Recently, a case-control study in China found inverse associations between adult intake of fruits and vegetables and risk of both proliferative fibrocystic breast conditions alone and with concurrent breast cancer (27) and the risk of all three types of fibrocystic breast conditions (nonproliferative, proliferative, and atypia) (29). Further, no significant association was observed for total crude fiber after adjustment for total fruit and vegetable intake (27,29). One possible explanation of the inconsistent findings between the current study and the previous studies is that dietary intake during different periods in a woman's lifetime may have different relations with BBD risk. Different study design may also partly account for the discrepant results, as our study is the only cohort study, while all the previous studies being case-control studies. Other factors may include different study populations and consequently different dietary patterns in these populations. For instance, an overall dietary pattern rich in fruits and vegetables in China could be quite different from those of western countries. Future large prospective studies are needed to clarify the role of fiber and fruit and vegetable intake during adolescence and adulthood in breast cancer development.

There are several major strengths in our study. The combined analysis included a large number of proliferative BBD cases, and this was the first prospective analysis to evaluate the relations between adolescent dietary intake and proliferative BBD risk. The centralized pathology review of BBD cases reduces the likelihood of misclassification, and we focused on a specific histological subtype of proliferative BBD, a marker of increased breast cancer risk. The similar results of the combined and prospective analyses suggest that any possible bias due to BBD diagnosis or changes in diet after BBD diagnosis on the recall of adolescent dietary intake should be minimal. We collected detailed information on potential confounding factors and adjusted for these factors in our analyses. Although the possibility of residual confounding cannot be completely ruled out, the almost identical results observed in the age-adjusted and multivariate-adjusted analyses suggest that it is unlikely that uncontrolled confounding could entirely account for the observed associations.

The study does have limitations. Although the HS-FFQ has been shown to be moderately reproducible and not strongly correlated with current diet as an adult (44) and comparison with maternal report provided some form of validity, recall of adolescent diet in our study exceeded an average of 25 years (44), and the validity of recall 15–35 years later has not been established. The estimates of the prospective analysis are less stable than those of the combined analysis due to the small number of prospective cases, and results need to be confirmed with longer follow-up and more cases. In addition, studies are needed to confirm our findings and to identify the biological mechanisms of action, particularly for nut intake. Furthermore, given the multiple comparisons of many foods tested in this study, the observed inverse association between adolescent apple intake and proliferative BBD in the prospective analysis could be a chance finding. Finally, the results of this study may not be readily generalizable to the general population of U.S. women, given that the reported intake levels of fiber in our study participants is higher than the intake levels for most Americans. In addition, the adolescent diets assessed in this study are from over 20 years ago. The diets of adolescent girls today may contain higher levels of fiber due to the addition of fiber to certain foods and increases in the consumption of whole grains in general. However, if adolescent fiber intake is associated with reduced risk of proliferative BBD through hormonal mechanisms as hypothesized, it is unlikely that the biological effects of fiber would have different effects in other populations of women.

In summary, our study observed significant inverse associations between adolescent dietary intake of fiber and nuts and risk of proliferative benign breast disease. Our results provide supportive evidence of the important role of dietary exposures during a unique period in a woman's life in the earlier stage of breast carcinogenesis. These findings, if corroborated, may suggest a viable means for breast cancer prevention.

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Table 1

Age and age-standardized characteristics of participants according to fiber and nut intake during adolescence among 29,480 women in the Nurses' Health Study II[a]

	Categories				
	Fiber			Total nuts	
	Q1 (low)	Q3	Q5 (high)	<1/mo	≥2/wk
No. of women	5898	5901	5895	12551	3597
Percentage (%)					
Family history of breast cancer in mother or sister(s)[b]	4.4	4.6	5.0	4.6	4.7
Age at menarche <12 yrs	23.5	23.4	25.6	24.2	24.7
Premenopausal[c]	97.8	97.7	98.1	97.8	98.1
Average body size between ages 5 and 10 somatotype pictogram >3	27.6	27.8	27.3	28.2	26.4
Nulliparous[c]	25.7	26.3	31.8	26.5	28.7
Age at first birth ≥30 yrs[c,d]	14.7	17.3	20.4	15.8	20.4
Ever oral contraceptive use[c]	85.4	84.6	81.8	84.0	83.7
Multivitamin use in high school	11.7	15.5	19.6	13.8	20.4
Mean					
Age[c] (yrs)	36.3	35.6	35.0	35.6	35.7
Alcohol intake between ages 18 and 22 (g/day)	5.5	5.5	4.4	4.9	5.8
Average body size between ages 5 and 10	2.6	2.7	2.7	2.7	2.6
Parity[c,d]	2.2	2.1	2.1	2.1	2.1
Age at first birth (yrs)[c,d]	25.6	25.9	26.2	25.7	26.2
Adolescent fiber intake (g/day, energy-adjusted)	14.7	20.3	29.0	20.3	22.8

[a] Except for the data on mean age, all data shown are standardized to the age distribution of the cohort in 1991.

[b] Family history of breast cancer in mother or sister(s) in 1989.

[c] Variables are 1991 values.

[d] Among parous women.

Table 2

Intake of fiber and sources of fiber during adolescence and relative risk (95% confidence interval) of proliferative BBD in NHSII

Exposures	Quintile of energy-adjusted fiber intake					P trend
	1 (low)	2	3	4	5 (high)	
Fiber						
Intake (g/day)[a]	15.1	18.0	20.3	22.8	27.5	
No. of combined BBD cases[b]/pys[c]	157/51815	147/51610	139/52007	127/51951	112/52444	
Age-adjusted HR (95% CI)	1.00 (ref)	0.96 (0.76, 1.20)	0.91 (0.72, 1.14)	0.83 (0.66, 1.06)	0.73 (0.57, 0.93)	**<0.01**
Multivariate HR (95% CI)[d]	1.00 (ref)	0.96 (0.76, 1.20)	0.91 (0.73, 1.15)	0.85 (0.67, 1.07)	0.75 (0.59, 0.96)	**0.01**
Additional adjustment for total nuts[d]	1.00 (ref)	0.98 (0.78, 1.22)	0.94 (0.74, 1.18)	0.88 (0.69, 1.12)	0.80 (0.62, 1.02)	**0.05**
No. of prospective BBD cases[e]/pys[c]	37/13824	29/13817	28/13752	23/13744	25/13879	
Age-adjusted HR (95% CI)	1.00 (ref)	0.78 (0.48, 1.28)	0.75 (0.46, 1.24)	0.61 (0.36, 1.03)	0.61 (0.37, 1.03)	**0.05**
Multivariate HR (95% CI)[f]	1.00 (ref)	0.77 (0.47, 1.27)	0.77 (0.47, 1.26)	0.62 (0.36, 1.05)	0.61 (0.36, 1.03)	**0.05**
Additional adjustment for total nuts[f]	1.00 (ref)	0.80 (0.49, 1.32)	0.81 (0.49, 1.34)	0.67 (0.39, 1.14)	0.66 (0.39, 1.13)	0.11
Fiber from fruits						
Intake (g/day)[a]	1.7	2.9	4.0	5.3	7.6	
No. of combined BBD cases[b]/pys[c]	154/53746	139/53143	138/52007	125/49759	126/51173	
Age-adjusted HR (95% CI)	1.00 (ref)	0.90 (0.71, 1.13)	0.90 (0.72, 1.14)	0.87 (0.68, 1.10)	0.85 (0.67, 1.08)	0.20
Multivariate HR (95% CI)[d]	1.00 (ref)	0.91 (0.72, 1.14)	0.92 (0.73, 1.16)	0.90 (0.71, 1.14)	0.89 (0.70, 1.13)	0.38
No. of prospective BBD cases[e]/pys[c]	33/14270	26/14078	28/13746	29/13191	26/13731	
Age-adjusted HR (95% CI)	1.00 (ref)	0.82 (0.49, 1.38)	0.83 (0.50, 1.38)	0.91 (0.55, 1.51)	0.76 (0.45, 1.28)	0.42
Multivariate HR (95% CI)[f]	1.00 (ref)	0.83 (0.49, 1.39)	0.84 (0.50, 1.40)	0.95 (0.57, 1.59)	0.77 (0.45, 1.30)	0.47
Fiber from vegetables						
Intake (g/day)[a]	3.3	4.8	6.0	7.5	10.5	
No. of combined BBD cases[b]/pys[c]	158/55760	136/50795	136/50163	123/52946	129/50163	
Age-adjusted HR (95% CI)	1.00 (ref)	0.94 (0.74, 1.18)	0.93 (0.74, 1.17)	0.79 (0.62, 1.00)	0.88 (0.69, 1.11)	0.16
Multivariate HR (95% CI)[d]	1.00 (ref)	0.95 (0.76, 1.20)	0.94 (0.75, 1.19)	0.81 (0.64, 1.02)	0.91 (0.72, 1.15)	0.28
No. of prospective BBD cases[e]/pys[c]	38/13912	29/14411	23/13206	25/14135	27/13353	
Age-adjusted HR (95% CI)	1.00 (ref)	0.75 (0.46, 1.22)	0.64 (0.38, 1.08)	0.63 (0.38, 1.05)	0.73 (0.44, 1.20)	0.21
Multivariate HR (95% CI)[f]	1.00 (ref)	0.76 (0.46, 1.24)	0.62 (0.37, 1.05)	0.64 (0.38, 1.07)	0.73 (0.44, 1.21)	0.22
Fiber from cruciferous vegetables						
Intake (g/day)[a]	0.1	0.3	0.6	0.8	1.3	
No. of combined BBD cases[b]/pys[c]	168/62316	114/43807	151/51617	127/52170	122/49918	
Age-adjusted HR (95% CI)	1.00 (ref)	0.95 (0.75, 1.21)	1.08 (0.86, 1.34)	0.90 (0.71, 1.13)	0.90 (0.71, 1.14)	0.34
Multivariate HR (95% CI)[d]	1.00 (ref)	0.96 (0.75, 1.21)	1.09 (0.87, 1.37)	0.91 (0.72, 1.15)	0.91 (0.72, 1.15)	0.42

Exposures	Quintile of energy-adjusted fiber intake					P trend
	1 (low)	2	3	4	5 (high)	
No. of prospective BBD cases[e]/pys[c]	39/16518	20/11630	30/13644	21/13831	32/13394	
Age-adjusted HR (95% CI)	1.00 (ref)	0.70 (0.41, 1.21)	0.92 (0.57, 1.49)	0.62 (0.36, 1.05)	0.98 (0.61, 1.58)	0.98
Multivariate HR (95% CI)[f]	1.00 (ref)	0.68 (0.40, 1.18)	0.94 (0.58, 1.53)	0.60 (0.35, 1.04)	0.98 (0.61, 1.59)	0.97
Fiber from legumes						
Intake (g/day)[a]	1.1	1.8	2.3	3.1	4.6	
No. of combined BBD cases[b]/pys[c]	147/53247	151/53585	130/50295	124/52415	130/50286	
Age-adjusted HR (95% CI)	1.00 (ref)	0.99 (0.79, 1.24)	0.90 (0.71, 1.14)	0.81 (0.63, 1.03)	0.90 (0.71, 1.14)	0.19
Multivariate HR (95% CI)[d]	1.00 (ref)	0.99 (0.79, 1.24)	0.91 (0.72, 1.16)	0.81 (0.64, 1.03)	0.91 (0.72, 1.16)	0.26
No. of prospective BBD cases[e]/pys[c]	33/14197	35/14162	24/13329	23/13967	27/13361	
Age-adjusted HR (95% CI)	1.00 (ref)	1.03 (0.64, 1.66)	0.76 (0.45, 1.30)	0.66 (0.39, 1.14)	0.83 (0.49, 1.40)	0.27
Multivariate HR (95% CI)[f]	1.00 (ref)	1.00 (0.62, 1.62)	0.75 (0.44, 1.28)	0.64 (0.37, 1.10)	0.81 (0.48, 1.37)	0.24
Fiber from cereal						
Intake (g/day)[a]	3.6	4.7	5.5	6.4	8.4	
No. of combined BBD cases[b]/pys[c]	158/55068	158/54091	123/47585	126/51659	117/51425	
Age-adjusted HR (95% CI)	1.00 (ref)	1.06 (0.85, 1.32)	0.95 (0.75, 1.20)	0.89 (0.70, 1.13)	0.85 (0.67, 1.09)	0.09
Multivariate HR (95% CI)[d]	1.00 (ref)	1.07 (0.86, 1.34)	0.97 (0.76, 1.23)	0.91 (0.72, 1.15)	0.88 (0.69, 1.12)	0.14
No. of prospective BBD cases[e]/pys[c]	27/14667	32/14278	33/12676	28/13681	22/13715	
Age-adjusted HR (95% CI)	1.00 (ref)	1.19 (0.71, 1.99)	1.36 (0.81, 2.28)	1.08 (0.63, 1.84)	0.84 (0.47, 1.49)	0.38
Multivariate HR (95% CI)[f]	1.00 (ref)	1.17 (0.69, 1.97)	1.35 (0.80, 2.27)	1.06 (0.62, 1.81)	0.85 (0.48, 1.51)	0.41

[a] Median fiber intake of each quintile, adjusted for total energy intake using the residual method.

[b] 682 cases of proliferative BBD (with or without atypia) were diagnosed during the follow-up period 1991–2001.

[c] pys: person-years.

[d] The multivariate models are adjusted for age in months, time period (5 periods), total energy intake (quintiles), age at menarche (<12, 12, 13, or ≥14 years), menopausal status (premenopausal, postmenopausal, or uncertain), average body size between ages 5 and 10 (somatotype pictogram 1, 1.5–2, 2.5–3, 3.5–4.5, or ≥5), family history of breast cancer in mother or sister(s) (yes vs. no), alcohol intake between ages 18 and 22 years (0, <5, 5–14, or ≥15 grams/day), multivitamin use between ages 13 and 18 years (yes vs. no), recency and duration of OC use (never, past <4 years, past ≥4 years, current <4 years, or current ≥4 years), and parity and age at first birth (nulliparous; 1–2 pregnancies, age at first birth <25 years; 1–2 pregnancies, age at first birth 25–29 years; 1–2 pregnancies, age at first birth ≥30 years; ≥3 pregnancies, age at first birth <25 years; ≥3 pregnancies, age at first birth 25–29 years; or ≥3 pregnancies, age at first birth ≥30 years).

[e] 142 cases of proliferative BBD (with or without atypia) were diagnosed during the follow-up period 1998–2001.

[f] The multivariate models are adjusted for age in months, time period (2 periods), total energy intake (quintiles), age at menarche (<12, 12, 13, or ≥ 14 years), menopausal status (premenopausal, postmenopausal, or uncertain), average body size between ages 5 and 10 (somatotype pictogram 1, 1.5–2, 2.5–3, 3.5–4.5, ≥5), history of breast cancer in mother or sister(s) (yes vs. no), alcohol intake between ages 18 and 22 (0, <5, 5–14, or ≥15 grams/day), multivitamin use between ages 13 and 18 (yes vs. no), recency and duration of OC use (never, past <4 years, past ≥4 years, or current), and parity and age at first birth (nulliparous; 1–2 pregnancies, age at first birth <25 years; 1–2 pregnancies, age at first birth 25–29 years; 1–2 pregnancies, age at first birth ≥30 years; ≥3 pregnancies, age at first birth <25 years; or ≥3 pregnancies, age at first birth ≥25 years).

Table 3

Intake of nuts during adolescence and relative risk (95% confidence interval) of proliferative BBD in NHSII

Exposures	Level of intake					P trend	Per 1 serving/week
Peanuts							
Intake (sm. bag or 1 oz)	<1/month	1–3/month	≥1/week				
No. of combined BBD cases[a]/pys[b]	333/122462	278/98816	71/38550				
Age-adjusted HR (95% CI)	1.00 (ref)	1.02 (0.87, 1.20)	0.68 (0.52, 0.88)			**0.02**	0.86 (0.75, 0.99)
Multivariate HR (95% CI)[c]	1.00 (ref)	1.01 (0.86, 1.19)	0.66 (0.51, 0.86)			**0.01**	0.85 (0.74, 0.98)
Additional adjustment for fiber[c]	1.00 (ref)	1.03 (0.87, 1.21)	0.68 (0.52, 0.89)			**0.03**	0.87 (0.75, 1.00)
No. of prospective BBD cases[d]/pys[b]	73/32514	56/26183	13/10320				
Age-adjusted HR (95% CI)	1.00 (ref)	0.92 (0.65, 1.31)	0.57 (0.31, 1.03)			0.08	0.80 (0.58, 1.11)
Multivariate HR (95% CI)[e]	1.00 (ref)	0.90 (0.63, 1.29)	0.54 (0.29, 0.99)			0.06	0.78 (0.56, 1.09)
Additional adjustment for fiber[e]	1.00 (ref)	0.94 (0.65, 1.35)	0.58 (0.31, 1.08)			0.13	0.82 (0.59, 1.14)
Peanut butter							
Intake (1 teaspoon)	<1/month	1–3/month	1/week	2–4/week	≥5/week		
No. of combined BBD cases[a]/pys[b]	91/26965	64/29900	159/57369	251/95140	117/50454		
Age-adjusted HR (95% CI)	1.00 (ref)	0.64 (0.46, 0.88)	0.82 (0.63, 1.06)	0.79 (0.62, 1.01)	0.69 (0.53, 0.91)	0.12	0.99 (0.96, 1.01)
Multivariate HR (95% CI)[c]	1.00 (ref)	0.64 (0.46, 0.88)	0.82 (0.63, 1.07)	0.79 (0.62, 1.01)	0.68 (0.51, 0.90)	0.09	0.98 (0.95, 1.01)
No. of prospective BBD cases[d]/pys[b]	21/7229	13/8029	32/15242	51/25132	25/13385		
Age-adjusted HR (95% CI)	1.00 (ref)	0.54 (0.27, 1.09)	0.72 (0.41, 1.25)	0.69 (0.41, 1.15)	0.63 (0.35, 1.13)	0.42	0.98 (0.92, 1.05)
Multivariate HR (95% CI)[e]	1.00 (ref)	0.55 (0.27, 1.10)	0.71 (0.40, 1.24)	0.68 (0.40, 1.14)	0.61 (0.34, 1.12)	0.38	0.98 (0.91, 1.05)
Peanuts and peanut butter							
Intake (servings)	<1/month	1–3/month	1/week	2–3/week	≥4/week		
No. of combined BBD cases[a]/pys[b]	56/17463	62/24094	119/40691	183/70257	262/107323		
Age-adjusted HR (95% CI)	1.00 (ref)	0.80 (0.56, 1.15)	0.88 (0.64, 1.21)	0.83 (0.61, 1.12)	0.76 (0.57, 1.01)	0.08	0.98 (0.95, 1.01)
Multivariate HR (95% CI)[c]	1.00 (ref)	0.80 (0.56, 1.15)	0.88 (0.64, 1.21)	0.83 (0.61, 1.12)	0.74 (0.55, 1.00)	0.06	0.98 (0.95, 1.01)

Exposures	Level of intake					P trend	Per 1 serving/week
No. of prospective BBD cases[d]/pys[b]	13/4690	12/6424	25/10844	35/18590	57/28469		
Age-adjusted HR (95% CI)	1.00 (ref)	0.69 (0.31, 1.52)	0.85 (0.43, 1.68)	0.70 (0.37, 1.34)	0.73 (0.40, 1.34)	0.48	0.97 (0.91, 1.04)
Multivariate HR (95% CI)[e]	1.00 (ref)	0.70 (0.31, 1.54)	0.86 (0.43, 1.69)	0.71 (0.37, 1.35)	0.71 (0.38, 1.33)	0.40	0.97 (0.90, 1.04)
Total nuts (peanuts & other nuts)							
Intake (sm. bag or 1 oz)	<1/month	1–3/month	1/week	≥2/week			
No. of combined BBD cases[a]/pys[b]	309/110678	164/58447	149/58577	60/32126			
Age-adjusted HR (95% CI)	1.00 (ref)	1.00 (0.83, 1.21)	0.89 (0.73, 1.09)	0.66 (0.50, 0.87)		**<0.01**	0.88 (0.80, 0.97)
Multivariate HR (95% CI)[c]	1.00 (ref)	1.00 (0.82, 1.21)	0.88 (0.72, 1.08)	0.64 (0.48, 0.85)		**<0.01**	0.87 (0.79, 0.96)
Additional adjustment for fiber[c]	1.00 (ref)	1.00 (0.83, 1.22)	0.90 (0.74, 1.11)	0.67 (0.50, 0.89)		**<0.01**	0.88 (0.80, 0.98)
No. of prospective BBD cases[d]/pys[b]	69/29379	32/15504	29/15523	12/8611			
Age-adjusted HR (95% CI)	1.00 (ref)	0.88 (0.57, 1.34)	0.75 (0.48, 1.16)	0.61 (0.33, 1.12)		0.06	0.83 (0.67, 1.04)
Multivariate HR (95% CI)[e]	1.00 (ref)	0.86 (0.56, 1.31)	0.71 (0.46, 1.12)	0.56 (0.29, 1.06)		**0.04**	0.81 (0.64, 1.02)
Additional adjustment for fiber[e]	1.00 (ref)	0.87 (0.57, 1.34)	0.76 (0.48, 1.20)	0.61 (0.32, 1.18)		0.10	0.84 (0.66, 1.06)

[a] 682 cases of proliferative BBD (with or without atypia) were diagnosed during the follow-up period 1991–2001.

[b] pys: person-years.

[c] The multivariate models are adjusted the same way as in Table 2.

[d] 142 cases of proliferative BBD (with or without atypia) were diagnosed during the follow-up period 1998–2001.

[e] The multivariate models are adjusted the same way as in Table 2.

Table 4

Intake of fruits, vegetables, and foods contributing to fiber during adolescence and relative risk (95% confidence interval) of proliferative BBD in NHSII

Exposures	Level of Intake					P trend	Per 1 serving/day
Fruits							
Intake (servings/day)	<1.5	1.5-<2.5	2.5-<3.5	≥3.5			
No. of combined BBD cases[a]/pys[b]	229/86391	213/80620	156/52307	84/40510			
Multivariate HR (95% CI)[c]	1.00 (ref)	1.00 (0.83, 1.21)	1.14 (0.92, 1.42)	0.79 (0.60, 1.04)		0.32	0.97 (0.92, 1.03)
Vegetables							
Intake (servings/day)	<1.5	1.5-<2.5	2.5-<3.5	≥3.5			
No. of combined BBD cases[a]/pys[b]	124/47946	217/82769	176/63164	165/65949			
Multivariate HR (95% CI)[c]	1.00 (ref)	1.03 (0.82, 1.29)	1.09 (0.86, 1.39)	0.97 (0.76, 1.26)		0.80	0.99 (0.94, 1.04)
Fruits and vegetables							
Intake (servings/day)	<3	3-<4	4-<5	5-<6	≥6		
No. of combined BBD cases[a]/pys[b]	142/55326	124/46723	126/45914	109/37068	181/74797		
Multivariate HR (95% CI)[c]	1.00 (ref)	1.04 (0.81, 1.33)	1.09 (0.85, 1.40)	1.16 (0.89, 1.50)	0.96 (0.75, 1.23)	0.67	0.99 (0.95, 1.02)
Apples							
Intake (one)	<1/month	1–3/month	1/week	2–4/week	≥5/week		
No. of combined BBD cases[a]/pys[b]	51/12065	140/52186	181/73287	254/96149	56/26140		
Multivariate HR (95% CI)[c]	1.00 (ref)	0.62 (0.45, 0.86)	0.57 (0.42, 0.79)	0.63 (0.46, 0.85)	0.52 (0.35, 0.77)	0.17	0.77 (0.57, 1.05)
Oranges/grapefruit							
Intake (one/1/2)	<1/month	1–3/month	1/week	≥2/week			
No. of combined BBD cases[a]/pys[b]	76/28210	217/79267	206/74602	183/77749			
Multivariate HR (95% CI)[c]	1.00 (ref)	1.01 (0.78, 1.32)	1.04 (0.79, 1.35)	0.89 (0.68, 1.17)		0.17	0.93 (0.67, 1.27)
Bananas							
Intake (one)	<1/month	1–3/month	1/week	≥2/week			
No. of combined BBD cases[a]/pys[b]	53/19870	178/65213	219/82705	232/92039			
Multivariate HR (95% CI)[c]	1.00 (ref)	1.05 (0.77, 1.42)	1.02 (0.75, 1.38)	0.98 (0.72, 1.33)		0.57	0.95 (0.67, 1.35)
Beans/lentils							
Intake (1/2 cup)	<1/month	1–3/month	1/week	≥2/week			

Exposures	Level of Intake					P trend	Per 1 serving/day
No. of combined BBD cases[a]/pys[b]	214/74602	210/80636	187/74081	71/30509			
Multivariate HR (95% CI)[c]	1.00 (ref)	0.92 (0.76, 1.12)	0.87 (0.72, 1.07)	0.81 (0.62, 1.07)		0.13	0.65 (0.39, 1.06)
Peas or lima beans							
Intake (1/2 cup)	<1/month	1–3/month	1/week	≥2/week			
No. of combined BBD cases[a]/pys[b]	103/41683	131/46564	281/111269	167/60312			
Multivariate HR (95% CI)[c]	1.00 (ref)	1.09 (0.84, 1.41)	0.96 (0.77, 1.21)	1.08 (0.84, 1.39)		0.57	1.05 (0.66, 1.67)
Cold breakfast cereal							
Intake (1 bowl)	<1/month	1/month-1/week	2–4/week	5–6/week	≥1/day		
No. of combined BBD cases[a]/pys[b]	109/37632	118/49711	251/94868	117/45671	87/31947		
Multivariate HR (95% CI)[c]	1.00 (ref)	0.85 (0.65, 1.10)	0.94 (0.75, 1.19)	0.94 (0.72, 1.22)	1.04 (0.78, 1.39)	0.46	1.08 (0.90, 1.30)

[a] 682 cases of proliferative BBD (with or without atypia) were diagnosed during the follow-up period 1991–2001.

[b] pys: person-years.

[c] The multivariate models are adjusted the same way as in Table 2.