

Intakes of fat and micronutrients between ages 13 and 18 years and the incidence of proliferative benign breast disease

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Abstract

Purpose Dietary exposures during adolescence may exert important effects on breast development and future breast cancer risk. This study evaluated the associations between high school intakes of fat and micronutrients and the incidence of proliferative benign breast disease (BBD), a marker of increased breast cancer risk.

Methods 29,480 women (mean age 43.3 years, range 33.6–52.9) completed a high school food frequency questionnaire in 1998 in the Nurses' Health Study II. Between

1991 and 2001, 682 women (follow-up time: 259,828 person-years) were diagnosed with proliferative BBD whose biopsy slides were reviewed and confirmed by the study pathologists.

Results In multivariate Cox proportional hazards models, high school intakes of total fat and types of fat were not associated with proliferative BBD. Women in the highest quintile of total retinol activity equivalents (RAEs), which incorporate retinol, α - and β -carotene, and β -cryptoxanthin intakes, had a 17 % lower risk of proliferative BBD than those in the lowest quintile [multivariate hazard ratio (HR) 95 % CI 0.83 (0.64, 1.07), p trend = 0.01]; however, additional adjustment for high school dietary factors (vitamin D, nuts, and fiber) rendered the association

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nonsignificant [0.99 (0.73, 1.34), p trend = 0.32]. Results were similar with additional adjustment for adult RAE intake. Intakes of vitamin E and individual carotenoids were not associated with proliferative BBD, although an inverse association cannot be ruled out.

Conclusions In this study, adolescent fat and micronutrient intakes were not associated with risk of proliferative BBD.

Keywords Fat · Micronutrients · High school · Dietary intake · Proliferative benign breast disease

Introduction

Since the 1970s, when national breast cancer incidence rates were found to be strongly correlated with per capita fat consumption in each country [1], dietary fat intake has been suggested as a possible risk factor for breast cancer. Numerous studies conducted subsequently [2–5], particularly large cohort studies [4, 5] and clinical trials [6, 7], did not confirm the role of adult dietary fat in breast carcinogenesis. More recently, certain micronutrients, such as vitamin A and vitamin E, have been hypothesized to be associated with a reduced risk of breast cancer due to their anti-oxidative properties [8, 9] and roles in cell proliferation, differentiation, apoptosis [10], and host immunology [11]. Results regarding the associations between these dietary factors and breast cancer risk, however, have been largely inconsistent [4, 12]. For carotenoids, the data are more convincing; recent meta-analyses and pooled analyses have noted an inverse association of both dietary [13, 14] and circulating [15, 16] carotenoids with breast cancer risk [e.g., for β -carotene in a pooled analysis of eight prospective cohort studies, women in the highest (vs. lowest) quintile of plasma/serum concentration for β -carotene had a relative risk (RR) = 0.83 (95 % CI 0.70, 1.01, p trend = 0.05)] [15].

Benign breast disease (BBD) is a heterogeneous group of lesions that can develop during adolescence and young adulthood and includes a variety of histologic subtypes, among which proliferative BBD is a marker of subsequent breast cancer and may even be in the pathway for a subset of breast cancers [17]. Women whose biopsies show proliferative changes without atypia have a 1.3- to 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 [17]. Studies on diet and BBD could provide insights regarding the role of diet in the early stages of breast cancer development. Adult intakes of total fat [18], animal fat [19], saturated fat, and polyunsaturated fat [20] were positively associated with BBD in some case–control studies. Vegetable fats, but not

other fats, were inversely associated with BBD in the only prospective study, conducted in the Nurses' Health Study II (NHSII) cohort [21]. No association was found between adult fat intake and BBD in a case-cohort study in Canada [22]. One potential reason for the inconsistency across studies could be that a majority of the previous studies which observed an association between fat intake and BBD were case–control studies and retrospective in nature; thus, recall bias or selection bias was not completely avoidable, and the observed association could be spurious. In addition, the lack of standard classification of BBD subtypes may result in misclassification and attenuate the associations. Furthermore, dietary intake during adulthood may not be an etiologically relevant exposure period.

Evidence from both animal [23] and human studies [24–26] suggests that exposures during childhood and adolescence may be important in breast cancer development, because breast tissue may be most vulnerable to carcinogens due to rapid proliferation of cells and lack of terminal differentiation during this time period. Higher vitamin E intake during adolescence was inversely associated with breast cancer risk in the Nurses' Health Study (NHS) [27] and NHSII cohorts [28]. In a retrospective analysis in the NHSII in which women reported adolescent dietary intake after their diagnosis of BBD, high school intake of monounsaturated fat was positively associated with proliferative BBD risk, while vegetable fat and vitamin E had borderline significant inverse associations [29]. However, the retrospective nature of the study cannot completely rule out the possibility of differential recall for BBD cases and non-cases, and the small numbers of cases meant that power was limited to detect statistically significant associations.

We expanded upon the previous study [29] with the addition of more than 200 new cases ($n = 682$ total) and assessed the association between recalled high school diet and proliferative BBD. To the best of our knowledge, this is the first study to prospectively assess the associations between reported adolescent intakes of fats, carotenoids, and vitamins A and E and the incidence of proliferative BBD.

Materials and methods

Study design and population

The NHSII cohort was established in 1989 when 116,671 US female registered nurses aged between 25 and 42 years responded to a mailed, self-administered questionnaire asking about information on a variety of health-related exposures and conditions. The cohort has been followed up every 2 years by questionnaire since study initiation to

obtain updated information on risk factors and disease outcomes, including diagnosis of BBD. The response rate in the NHSII cohort has been very high ($\geq 90\%$) during each 2-year questionnaire cycle period [30]. In 1998, 45,948 women completed a semi-quantitative 131-item food frequency questionnaire (FFQ) asking about their usual dietary intake during adolescence, further defined as ages 13–18 years. 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 nonrespondents, but respondents and nonrespondents were very similar in terms of other characteristics [31].

The current study included 45,948 women who returned the high school FFQ in 1998 and had plausible values for total energy intake (between 600 and 5,000 kcal/day). Women who had a previous self-reported or histologically confirmed 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 ($n = 17$), were excluded at 1991 baseline, leaving a total of 29,480 women.

High school food frequency questionnaire

The high school food frequency questionnaire (HS-FFQ) used in NHSII was a modified version of the well-validated adult diet FFQ used in the NHS and NHSII cohorts. However, it was designed to include commonly consumed food items when this cohort of women would have been in high school, i.e., from 1960 to 1982. Foods that were not prevalent during that period of time were not included. Foods that account for major sources of fat, antioxidant vitamins, and carotenoids were included. The questionnaire asked participants how often, on average, they had consumed a specified unit or portion size of each food or beverage item during high school. Nine possible responses were provided ranging from ‘never or less than once per month’ to ‘six or more times per day’.

Nutrient intakes were computed for each participant by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portions and then summing the contributions from all foods. Food contributions were based on an extensive food composition database derived using information from different sources and maintained by a team of research dietitians. Food composition data from the relevant time period (1960s and 1970s) were used, whenever available, as the composition of some foods has changed over time, to provide the best approximation of adolescent dietary intakes. Retinol activity equivalent (RAE) was calculated to represent vitamin A activity based on bioconversion from provitamin

A carotenoids [32] using the formula: $\text{RAE (mcg)} = (\text{retinol, mcg}) + (\beta\text{-carotene from food, mcg}/12) + (\beta\text{-carotene from vitamins and supplemented foods, mcg}/2) + (\alpha\text{-carotene, mcg}/24) + (\beta\text{-cryptoxanthin, mcg}/24)$. This formula is based on the biochemical structures of provitamin A carotenoids and the number of provitamin A units needed for a given number of active vitamin A units.

The HS-FFQ is moderately reproducible [33], with intraclass correlations ranging from 0.58 for polyunsaturated fat to 0.66 for animal and saturated fats, and from 0.61 for vitamin E without supplements to 0.72 for β -carotene. Recall of adolescent diet was not strongly affected by current diet, as the recalled adolescent diet was only weakly correlated with adult diet in 1995, the last adult dietary assessment prior to the 1998 HS-FFQ (for fat intakes, range = 0.07 for polyunsaturated fat to 0.24 for saturated fat; for micronutrients, range = -0.11 for vitamin E to 0.32 for vitamin A (RAE) and β -carotene). When comparing the high school dietary data reported by the nurses themselves with reports of their high school diets by their mothers, Pearson correlations ranged from 0.30 for monounsaturated fat to 0.51 for animal and vegetable fats and from 0.33 for β -carotene to 0.42 for vitamin A (RAE) with or without supplements, suggesting that the HS-FFQ had modest validity.

Identification of BBD cases

Incident BBD cases were initially identified from the biennial follow-up questionnaires. Women who reported a first diagnosis of biopsy-confirmed BBD between the 1993 and 2001 questionnaire cycles were contacted to seek diagnosis confirmation and to request permission to obtain their pathology specimens.

Between 1991 and 2001, a total of 3,273 women reported a first diagnosis of biopsy-confirmed BBD. Of these, 1,663 (50.8 %) completed the HS-FFQ. Among the 1,662 women with adolescent diet information who were initially contacted (one woman was deleted due to missing all covariate information), 1,333 (80.2 %) confirmed the BBD diagnosis and gave permission to review their biopsy records and pathology slides. Pathology material was obtained and reviewed for 1,160 women (87.0 % of those who had given their permission); 1,149 women (99.1 % of those for whom biopsy specimens were received) had valid biopsy information. The main reasons for exclusion included that the pathology specimen did not contain breast tissue or that the biopsy date was before 1989.

Three pathologists (LCC, SJS, JLC) without knowledge of participants’ adolescent diet information reviewed the collected benign breast biopsy slides independently and classified benign breast lesions into three broad categories

of histology: nonproliferative, proliferative disease without atypia, and atypical hyperplasia (AH; ductal and lobular), using the criteria of Dupont and Page [34]. Any biopsy specimens that showed atypia or questionable atypia were jointly reviewed by two pathologists to reach a consensus diagnosis. 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. Proliferative BBD with or without atypia confirmed by pathology review was the outcome of interest in the current analysis, because proliferative BBD, in contrast with other histological subtypes, is associated with increased risk of breast cancer. Of the 1,149 women who had valid biopsy information, 717 (62.4 %) were classified as proliferative (with or without atypia) by the study pathologists.

Statistical analysis

Our main analysis assessed high school diet in relation to all cases of proliferative BBD from 1991 to 2001 diagnosed before or after the return of the HS-FFQ (referred to as the combined analysis). To assess the possibility of recall bias, we conducted the analysis considering only proliferative BBD cases diagnosed after completion of the HS-FFQ (described hereafter as the prospective analysis; Fig. 1). Because results from the prospective analysis and the combined analysis were very similar and to increase study power, the combined analysis was considered the primary analysis. In the combined analysis, each participant was followed 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, follow-up started from the return date of the 1998 high school diet questionnaire. A total of 23,946 women were included in the prospective analysis. After the baseline exclusions in 1991 or 1998, the total numbers of cases in the final combined and prospective analyses were 682 and 142, respectively. Atypical hyperplasia was not examined as a separate outcome due to the small numbers of cases ($n = 61$ and 14 , respectively).

Total fat, types of fat, and a variety of micronutrients were the main exposures of interest in the current study. To adjust for total energy intake [35], we used nutrient densities, computed as percentages of total caloric intake, for total fat and types of fat. For micronutrients, the residual method was used, in which energy-adjusted values are the residuals from a regression model with total caloric intake as the independent variable and absolute micronutrient intake as the dependent variable [35]. We divided fat

densities and energy-adjusted nutrient residuals into quintiles based on the distribution of intakes for all eligible women.

To estimate the associations between nutrient intakes and the risk of proliferative BBD, multivariable-adjusted Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95 % CIs, using the lowest quintile as the reference group and follow-up time as the time variable. The final 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 use, and parity and age at first birth. The time-varying covariates of age, menopausal status, oral contraceptive use, and parity and age at first birth were updated every 2 years in each questionnaire cycle. Family history of breast cancer was initially assessed in 1989 and updated in 1997. In our final model, we additionally adjusted for adolescent intakes of vitamin D, fiber, and nuts, dietary variables associated with BBD in this cohort [31, 36]. In the models where type of fat was the exposure variable, we also adjusted for the other types of fat in the final model. For instance, when saturated fat was the exposure of interest, we additionally adjusted for monounsaturated, polyunsaturated, and trans-unsaturated fats.

SAS PROC PHREG was used for all analyses, and the Anderson–Gill data structure [37] 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 their values at the time of return of questionnaire. To test for trend, the Wald statistic was calculated by including the median value of each quintile as a continuous variable in the model.

The study was approved by human research committees at the Harvard School of Public Health and Brigham and Women's Hospital.

Results

Table 1 presents the baseline distributions in 1991 of selected characteristics of participants, according to their intakes of total fat, RAE, and vitamin E during adolescence. Compared with women with low dietary fat intake during adolescence, women with high intake of total fat were more likely to have a larger body size between ages 5 and 10 and higher alcohol consumption between ages 18 and 22, and to have ever used oral contraceptives, but less likely to have used multivitamins in high school. Women with high intakes of micronutrients were more likely to be

Table 1 Age-standardized characteristics of participants according to total fat, retinol activity equivalents (RAE), and vitamin E intake during adolescence among 29,480 women in the Nurses' Health Study II

	Total fat ^a		Total retinol activity equivalents (mcg/day) ^b		Total vitamin E (mg/day) ^b	
	Quintile 1 (low)	Quintile 5 (high)	Quintile 1 (low)	Quintile 5 (high)	Quintile 1 (low)	Quintile 5 (high)
Number of women	5,896	5,896	5,897	5,891	5,927	5,889
Percentage (%)						
Family history of breast cancer in mother or sister(s)	5	5	5	5	4	5
Age at menarche <12 years	25	25	23	25	22	26
Pre-menopausal	98	98	98	98	98	98
Average body size between ages 5 and 10 years, somatotype pictogram category >3 ^c	25	31	27	26	24	31
Nulliparous	29	27	25	31	26	30
Ever oral contraceptive use	82	87	87	83	84	85
Multivitamin use between ages 13 and 18	21	10	0	60	11	24
Mean						
Age (years)	34.3	37.2	35.8	35.7	36.7	34.6
Alcohol intake between ages 18 and 22 (g/day)	4.4	5.7	5.3	4.8	4.9	5.4
Parity ^d	2.1	2.1	2.2	2.1	2.2	2.1
Age at first birth ^d (years)	26.1	25.7	25.4	26.2	25.7	26.1

Except for the data on mean age, all data shown are standardized to the age distribution of the cohort in 1991. Except for multivitamin use between ages 13 and 18, all data shown are 1991 baseline values

^a Quintile of percent calories from fat

^b Quintile of energy-adjusted nutrient residuals

^c Based on a 9-point pictogram scale. (Stunkard et al.)

^d Among parous women

nulliparous, have an older age at first birth, and much more likely to have used multivitamins in high school.

No association was observed between adolescent total fat intake and proliferative BBD risk (Table 2). Similarly, we found no associations for high school intakes of different types of fat: animal fat, vegetable fat, saturated fat, mono-unsaturated fat, polyunsaturated fat, and trans-unsaturated fat. Additionally, total fat and types of fat were not associated with proliferative BBD in the prospective analysis.

Overall, adolescent intakes of the micronutrients examined were not associated with BBD risk in the combined analysis or the prospective analysis (Table 3). Women in the highest quintile of RAE had a slightly lower risk of proliferative BBD than those in the lowest quintile [multivariate hazard ratio (HR) 95 % CI 0.83 (0.64, 1.07), *p* trend = 0.01]. Results were similar with additional adjustment for adult RAE intake. However, additional adjustment for high school dietary factors (vitamin D, nuts, and fiber) rendered the association nonsignificant [0.99 (0.73, 1.34), *p* trend = 0.32]. In sum, intakes of vitamin E and individual carotenoids were not associated with proliferative BBD, although an inverse association cannot be ruled out.

Discussion

In this large cohort study, we did not observe associations of adolescent intake of dietary fats with proliferative BBD. There was a suggestive inverse association between adolescent RAE and proliferative BBD risk, but this association became null when further adjusted for other adolescent dietary risk factors for BBD. Adolescent intakes of carotenoids and vitamin E were not associated with proliferative BBD in the combined analysis or the prospective analysis, although an inverse association cannot be ruled out.

Our null results are inconsistent with some of the results of our previous retrospective study of adolescent diet and proliferative BBD risk in this population [29], findings on adolescent diet and BBD in the Growing Up Today Study [38, 39], as well as results of adolescent diet and breast cancer in the NHS and NHSII [27, 28]. In these previous studies, adolescent vegetable fat, carotenoids, and vitamin E intakes were associated with a reduced risk of BBD and breast cancer [27–29, 38, 39]. However, the previous associations with BBD were only borderline significant [e.g., highest vs. lowest quartile of vegetable fat: RR = 0.77

Table 2 Percentage of calories from total fat and types of fat during adolescence and relative risks (95 % CI) of proliferative benign breast disease in NHSII

Exposures	Quintiles of percentage of calories from fat					<i>p</i> trend
	1	2	3	4	5	
Total fat						
Median intake (% of energy)	34.8	38.4	40.7	42.8	46.0	
No. of combined BBD cases ^a	126	144	120	138	154	
Multivariate RR (95 % CI) ^b	1.00 (ref)	1.08 (0.85, 1.38)	0.88 (0.69, 1.14)	0.98 (0.77, 1.26)	1.09 (0.85, 1.39)	0.72
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.04 (0.81, 1.32)	0.82 (0.63, 1.06)	0.89 (0.68, 1.15)	0.96 (0.73, 1.25)	0.50
No. of incident BBD cases ^c	25	31	28	29	29	
Multivariate RR (95 % CI) ^d	1.00 (ref)	1.25 (0.73, 2.14)	1.13 (0.65, 1.96)	1.21 (0.70, 2.10)	1.26 (0.72, 2.19)	0.49
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.18 (0.69, 2.04)	1.02 (0.57, 1.81)	1.04 (0.58, 1.87)	0.99 (0.54, 1.83)	0.86
Animal fat						
Median intake (% of energy)	18.6	22.6	25.4	28.5	32.9	
No. of combined BBD cases ^a	112	121	141	151	157	
Multivariate RR (95 % CI) ^b	1.00 (ref)	1.02 (0.78, 1.32)	1.10 (0.84, 1.42)	1.15 (0.89, 1.50)	1.15 (0.88, 1.51)	0.20
Additional adjustment for vegetable fat ^b and fiber, nuts, and vitamin D	1.00 (ref)	0.96 (0.73, 1.25)	0.98 (0.74, 1.30)	0.99 (0.73, 1.33)	0.95 (0.68, 1.32)	0.82
No. of incident BBD cases ^c	26	29	34	25	28	
Multivariate RR (95 % CI) ^d	1.00 (ref)	1.25 (0.72, 2.16)	1.47 (0.85, 2.53)	1.01 (0.56, 1.83)	1.19 (0.66, 2.17)	0.83
Additional adjustment for vegetable fat ^d and fiber, nuts, and vitamin D	1.00 (ref)	1.17 (0.67, 2.05)	1.28 (0.71, 2.32)	0.79 (0.40, 1.55)	0.87 (0.41, 1.85)	0.48
Vegetable fat						
Median intake (% of energy)	9.8	12.6	14.7	16.8	20.0	
No. of combined BBD cases ^a	158	140	147	126	111	
Multivariate RR (95 % CI) ^b	1.00 (ref)	0.93 (0.74, 1.17)	1.01 (0.80, 1.28)	0.88 (0.69, 1.13)	0.82 (0.63, 1.07)	0.15
Additional adjustment for animal fat ^b and fiber, nuts, and vitamin D	1.00 (ref)	0.92 (0.72, 1.17)	0.99 (0.77, 1.28)	0.86 (0.66, 1.13)	0.80 (0.59, 1.09)	0.15
No. of incident BBD cases ^c	30	26	35	22	29	
Multivariate RR (95 % CI) ^d	1.00 (ref)	0.92 (0.54, 1.56)	1.31 (0.78, 2.17)	0.80 (0.45, 1.42)	1.03 (0.59, 1.81)	0.95
Additional adjustment for animal fat ^d and fiber, nuts, and vitamin D	1.00 (ref)	0.86 (0.49, 1.50)	1.18 (0.67, 2.07)	0.69 (0.36, 1.32)	0.94 (0.48, 1.82)	0.69
Saturated fat						
Median intake (% of energy)	12.9	14.6	15.9	17.2	19.2	
No. of combined BBD cases ^a	115	141	132	138	156	
Multivariate RR (95 % CI) ^b	1.00 (ref)	1.18 (0.92, 1.51)	1.04 (0.81, 1.35)	1.04 (0.80, 1.35)	1.13 (0.87, 1.46)	0.62
Additional adjustment for other types of fat ^b and fiber, nuts, and vitamin D	1.00 (ref)	1.13 (0.86, 1.48)	0.95 (0.70, 1.28)	0.91 (0.65, 1.27)	0.93 (0.64, 1.36)	0.48
No. of incident BBD cases ^c	28	27	30	28	29	
Multivariate RR (95 % CI) ^d	1.00 (ref)	1.00 (0.58, 1.72)	1.13 (0.66, 1.93)	1.04 (0.60, 1.81)	1.10 (0.62, 1.92)	0.74
Additional adjustment for other types of fat ^d and fiber, nuts, and vitamin D	1.00 (ref)	0.94 (0.52, 1.68)	1.03 (0.54, 1.94)	0.90 (0.44, 1.81)	0.94 (0.41, 2.15)	0.87
Monounsaturated fat						
Median intake (% of energy)	12.3	13.7	14.6	15.4	16.7	
No. of combined BBD cases ^a	129	129	147	127	150	

Table 2 continued

Exposures	Quintiles of percentage of calories from fat					<i>p</i> trend
	1	2	3	4	5	
Multivariate RR (95 % CI) ^b	1.00 (ref)	0.97 (0.75, 1.23)	1.12 (0.88, 1.42)	0.94 (0.73, 1.20)	1.10 (0.86, 1.39)	0.55
Additional adjustment for other types of fat ^b and fiber, nuts, and vitamin D	1.00 (ref)	0.95 (0.72, 1.25)	1.12 (0.83, 1.50)	0.93 (0.67, 1.29)	1.09 (0.76, 1.57)	0.67
No. of incident BBD cases ^c	26	32	31	25	28	
Multivariate RR (95 % CI) ^d	1.00 (ref)	1.24 (0.73, 2.10)	1.26 (0.74, 2.14)	1.00 (0.57, 1.74)	1.13 (0.66, 1.96)	0.90
Additional adjustment for other types of fat ^d and fiber, nuts, and vitamin D	1.00 (ref)	1.20 (0.67, 2.15)	1.16 (0.61, 2.23)	0.88 (0.43, 1.79)	0.90 (0.41, 1.99)	0.56
Polyunsaturated fat						
Median intake (% of energy)	5.0	5.9	6.5	7.2	8.3	
No. of combined BBD cases ^a	152	135	145	134	116	
Multivariate RR (95 % CI) ^b	1.00 (ref)	0.91 (0.72, 1.15)	1.01 (0.80, 1.27)	0.94 (0.74, 1.19)	0.82 (0.64, 1.05)	0.16
Additional adjustment for other types of fat ^b and fiber, nuts, and vitamin D	1.00 (ref)	0.90 (0.71, 1.14)	0.99 (0.78, 1.27)	0.92 (0.71, 1.20)	0.81 (0.61, 1.07)	0.19
No. of incident BBD cases ^c	30	29	32	22	29	
Multivariate RR (95 % CI) ^d	1.00 (ref)	0.98 (0.58, 1.65)	1.04 (0.63, 1.73)	0.77 (0.44, 1.35)	1.04 (0.61, 1.75)	0.88
Additional adjustment for other types of fat ^d and fiber, nuts, and vitamin D	1.00 (ref)	1.02 (0.60, 1.73)	1.12 (0.65, 1.92)	0.87 (0.47, 1.59)	1.20 (0.66, 2.19)	0.69
Trans-unsaturated fat						
Median intake (% of energy)	1.5	1.9	2.3	2.7	3.3	
No. of combined BBD cases ^a	139	147	130	142	124	
Multivariate RR (95 % CI) ^b	1.00 (ref)	1.15 (0.91, 1.46)	1.07 (0.84, 1.36)	1.16 (0.91, 1.48)	0.98 (0.77, 1.26)	0.84
Additional adjustment for other types of fat ^b and fiber, nuts, and vitamin D	1.00 (ref)	1.13 (0.89, 1.44)	1.03 (0.80, 1.33)	1.11 (0.86, 1.43)	0.92 (0.70, 1.20)	0.43
No. of incident BBD cases ^c	34	27	22	33	26	
Multivariate RR (95 % CI) ^d	1.00 (ref)	0.84 (0.50, 1.40)	0.70 (0.40, 1.23)	1.11 (0.67, 1.83)	0.84 (0.49, 1.42)	0.85
Additional adjustment for other types of fat ^d and fiber, nuts, and vitamin D	1.00 (ref)	0.77 (0.46, 1.30)	0.61 (0.34, 1.09)	0.94 (0.55, 1.62)	0.67 (0.38, 1.21)	0.37

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

^b The multivariate models are adjusted for age in months, time period (five 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 (yes vs. no), alcohol intake between ages 18 and 22 years (0, <5, 5–14, or ≥15 g/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 and age at first birth <25 years, 1–2 pregnancies and age at first birth 25–29 years, 1–2 pregnancies and age at first birth ≥30 years, ≥3 pregnancies and age at first birth <25 years, ≥3 pregnancies and age at first birth 25–29 years, or ≥3 pregnancies and age at first birth ≥30 years). Age-adjusted results were similar

^c 142 cases of proliferative BBD (with or without atypia) were diagnosed during the follow-up period 1998–2001

^d The multivariate models are adjusted for variables categorized as above, except for time period (two periods), 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 and age at first birth <25 years, 1–2 pregnancies and age at first birth 25–29 years, 1–2 pregnancies and age at first birth ≥30 years, ≥3 pregnancies and age at first birth <25 years, ≥3 pregnancies and age at first birth ≥25 years). Age-adjusted results were similar

(95 % CI 0.56, 1.06, *p* trend = 0.15); vitamin E: RR = 0.79 (95 % CI 0.61, 1.04, *p* trend = 0.05) in final models [29], and in the breast cancer analysis by Frazier et al. [28], the association with vegetable fat was no longer significant after

adjusting for vitamin E, suggesting that the observed associations in those analyses may have been attributable to vitamin E or other dietary factors. Monounsaturated fat was positively associated with BBD in the previous study

Table 3 Energy-adjusted micronutrient intake during adolescence and relative risk (95 % CI) of proliferative benign breast disease in NHSII

Exposures	Quintile of energy-adjusted micronutrient intake					<i>p</i> trend
	1	2	3	4	5	
Retinol activity equivalents (RAE)						
Median intake (mcg/day)	710	913	1,100	1,370	2,179	
No. of combined BBD cases ^a	133	155	164	124	106	
Multivariate RR (95 % CI)	1.00 (ref)	1.19 (0.94, 1.50)	1.27 (1.01, 1.60)	0.98 (0.76, 1.25)	0.83 (0.64, 1.07)	0.01
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.24 (0.98, 1.58)	1.37 (1.08, 1.75)	1.09 (0.84, 1.43)	0.99 (0.73, 1.34)	0.32
No. of incident BBD cases ^b	31	33	31	25	22	
Multivariate RR (95 % CI)	1.00 (ref)	1.06 (0.65, 1.75)	1.01 (0.61, 1.68)	0.77 (0.45, 1.32)	0.73 (0.42, 1.28)	0.14
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.11 (0.67, 1.86)	1.11 (0.65, 1.89)	0.88 (0.49, 1.58)	0.93 (0.48, 1.81)	0.63
RAE from food only						
Median intake (mcg/day)	699	884	1,041	1,236	1,638	
No. of combined BBD cases ^a	135	142	155	130	120	
Multivariate RR (95 % CI)	1.00 (ref)	1.08 (0.85, 1.37)	1.20 (0.95, 1.51)	1.02 (0.80, 1.30)	0.94 (0.73, 1.20)	0.37
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.15 (0.90, 1.46)	1.31 (1.03, 1.67)	1.17 (0.90, 1.51)	1.12 (0.86, 1.47)	0.60
No. of incident BBD cases ^b	29	34	31	26	22	
Multivariate RR (95 % CI)	1.00 (ref)	1.16 (0.70, 1.91)	1.11 (0.66, 1.85)	0.88 (0.51, 1.51)	0.70 (0.39, 1.24)	0.10
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.24 (0.74, 2.07)	1.26 (0.74, 2.15)	1.06 (0.60, 1.87)	0.88 (0.47, 1.63)	0.46
Vitamin E						
Median intake (mg/day)	9.8	11.3	12.4	13.6	15.7	
No. of combined BBD cases ^a	147	160	140	112	123	
Multivariate RR (95 % CI)	1.00 (ref)	1.14 (0.91, 1.43)	1.00 (0.79, 1.27)	0.82 (0.64, 1.05)	0.90 (0.70, 1.15)	0.08
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.16 (0.93, 1.46)	1.04 (0.82, 1.32)	0.86 (0.67, 1.11)	0.97 (0.76, 1.25)	0.30
No. of incident BBD cases ^b	36	28	29	19	30	
Multivariate RR (95 % CI)	1.00 (ref)	0.80 (0.49, 1.32)	0.86 (0.52, 1.43)	0.54 (0.31, 0.95)	0.87 (0.52, 1.43)	0.37
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	0.83 (0.50, 1.38)	0.94 (0.56, 1.56)	0.61 (0.34, 1.08)	1.02 (0.60, 1.72)	0.83
Vitamin E from food only						
Median intake (mg/day)	9.8	11.3	12.3	13.4	15.3	
No. of combined BBD cases ^a	145	159	145	110	123	
Multivariate RR (95 % CI)	1.00 (ref)	1.15 (0.91, 1.44)	1.05 (0.83, 1.33)	0.81 (0.63, 1.04)	0.87 (0.68, 1.12)	0.04
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.16 (0.92, 1.46)	1.08 (0.85, 1.37)	0.84 (0.65, 1.09)	0.92 (0.71, 1.18)	0.13
No. of incident BBD cases ^b	36	32	28	19	27	
Multivariate RR (95 % CI)	1.00 (ref)	0.91 (0.56, 1.47)	0.78 (0.47, 1.29)	0.55 (0.31, 0.96)	0.77 (0.46, 1.28)	0.13
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	0.94 (0.58, 1.53)	0.84 (0.50, 1.40)	0.60 (0.33, 1.07)	0.84 (0.49, 1.43)	0.28
α-Carotene						
Median intake (mcg/day)	310	598	856	1,283	2,295	
No. of combined BBD cases ^a	139	146	129	142	126	
Multivariate RR (95 % CI)	1.00 (ref)	1.02 (0.81, 1.29)	0.92 (0.72, 1.17)	1.00 (0.79, 1.26)	0.90 (0.71, 1.15)	0.39
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.07 (0.84, 1.35)	1.01 (0.78, 1.29)	1.13 (0.87, 1.45)	1.08 (0.82, 1.43)	0.56
No. of incident BBD cases ^b	32	30	25	30	25	
Multivariate RR (95 % CI)	1.00 (ref)	0.96 (0.58, 1.58)	0.76 (0.44, 1.30)	0.94 (0.56, 1.56)	0.78 (0.46, 1.33)	0.42

Table 3 continued

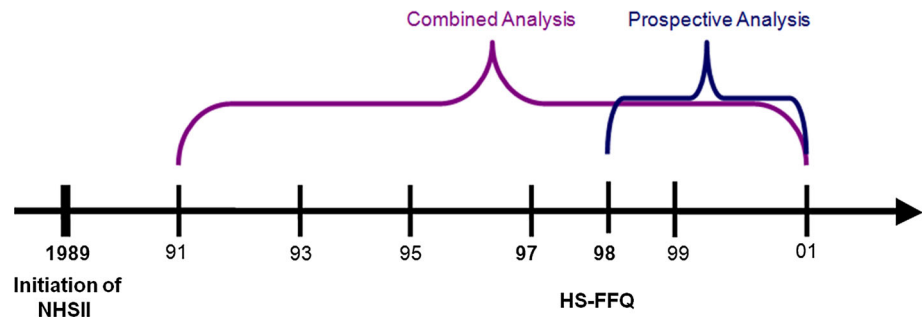
Exposures	Quintile of energy-adjusted micronutrient intake					<i>p</i> trend
	1	2	3	4	5	
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.03 (0.62, 1.73)	0.90 (0.51, 1.57)	1.14 (0.66, 1.96)	1.02 (0.55, 1.88)	0.85
β-Carotene						
Median intake (mcg/day)	1,599	2,509	3,319	4,411	6,713	
No. of combined BBD cases ^a	146	123	147	144	122	
Multivariate RR (95 % CI)	1.00 (ref)	0.85 (0.67, 1.08)	1.01 (0.80, 1.27)	0.98 (0.78, 1.24)	0.85 (0.66, 1.08)	0.35
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	0.90 (0.70, 1.15)	1.13 (0.88, 1.44)	1.16 (0.89, 1.51)	1.09 (0.81, 1.47)	0.33
No. of incident BBD cases ^b	30	27	38	25	22	
Multivariate RR (95 % CI)	1.00 (ref)	0.91 (0.54, 1.54)	1.27 (0.78, 2.07)	0.82 (0.48, 1.42)	0.72 (0.41, 1.26)	0.17
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.01 (0.59, 1.72)	1.52 (0.90, 2.57)	1.07 (0.58, 1.95)	0.97 (0.49, 1.93)	0.85
β-Cryptoxanthin						
Median intake (mcg/day)	57	103	154	212	304	
No. of combined BBD cases ^a	135	119	159	127	142	
Multivariate RR (95 % CI)	1.00 (ref)	0.88 (0.69, 1.13)	1.19 (0.95, 1.51)	0.93 (0.73, 1.19)	1.06 (0.83, 1.34)	0.57
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	0.92 (0.72, 1.19)	1.29 (1.01, 1.63)	1.04 (0.81, 1.34)	1.22 (0.94, 1.57)	0.09
No. of incident BBD cases ^b	31	16	35	31	29	
Multivariate RR (95 % CI)	1.00 (ref)	0.53 (0.29, 0.97)	1.13 (0.69, 1.84)	0.98 (0.59, 1.64)	0.88 (0.53, 1.48)	0.74
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	0.58 (0.31, 1.07)	1.32 (0.79, 2.18)	1.19 (0.70, 2.02)	1.12 (0.64, 1.95)	0.26
Lycopene						
Median intake (mcg/day)	3,374	4,770	5,975	8,359	12,803	
No. of combined BBD cases ^a	135	138	149	141	119	
Multivariate RR (95 % CI)	1.00 (ref)	1.08 (0.85, 1.38)	1.16 (0.91, 1.47)	1.09 (0.86, 1.38)	0.95 (0.74, 1.22)	0.46
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.09 (0.86, 1.39)	1.18 (0.93, 1.50)	1.12 (0.88, 1.43)	0.99 (0.77, 1.29)	0.71
No. of incident BBD cases ^b	29	32	29	24	28	
Multivariate RR (95 % CI)	1.00 (ref)	1.10 (0.66, 1.83)	1.01 (0.60, 1.71)	0.82 (0.47, 1.43)	1.00 (0.59, 1.70)	0.74
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.11 (0.67, 1.86)	1.06 (0.62, 1.81)	0.88 (0.50, 1.53)	1.11 (0.64, 1.93)	0.93
Lutein and zeaxanthin						
Median intake (mcg/day)	938	1,473	1,997	2,658	4,144	
No. of combined BBD cases ^a	140	139	132	145	126	
Multivariate RR (95 % CI)	1.00 (ref)	0.99 (0.78, 1.25)	0.95 (0.75, 1.21)	1.02 (0.81, 1.30)	0.90 (0.71, 1.15)	0.46
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.05 (0.82, 1.34)	1.05 (0.81, 1.36)	1.19 (0.92, 1.54)	1.12 (0.84, 1.49)	0.37
No. of incident BBD cases ^b	28	29	30	31	24	
Multivariate RR (95 % CI)	1.00 (ref)	1.04 (0.62, 1.76)	1.07 (0.64, 1.80)	1.08 (0.64, 1.82)	0.79 (0.45, 1.38)	0.37
Additional adjustment for fiber, nuts, and vitamin D	1.00 (ref)	1.19 (0.69, 2.04)	1.31 (0.75, 2.29)	1.42 (0.80, 2.53)	1.13 (0.59, 2.17)	0.77

The multivariate models were adjusted for the same variables as in the combined and incident BBD analyses in Table 2. Age-adjusted results were similar. Models of total micronutrient intake (including supplements) not adjusted for multivitamin intake. Variables represent total intake unless otherwise stated

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

^b 142 cases of proliferative BBD (with or without atypia) were diagnosed during the follow-up period 1998–2001

Fig. 1 Timeline for completion of high school food frequency questionnaire and benign breast disease selection in NHSII



[highest vs. lowest quartile RR = 1.52 (95 % CI 1.06, 2.21, p trend = 0.03)] [29], whereas we did not observe an association in this larger study.

More recently in meta-analyses and pooled analyses, data from prospective studies show a more consistent and inverse association of both dietary [13, 14] and circulating [15, 16] carotenoids and breast cancer risk. In addition, the associations between antioxidants and breast cancer may be potentially modified by oxidative stress. For instance, high intake of vitamin C or β -carotene was associated with a reduced breast cancer risk in postmenopausal women taking exogenous hormones and for β -carotene consuming moderate to high amounts of alcohol in the EPIC studies [40].

The discrepancies in our findings in this analysis from previous studies in this cohort could be due to several factors. First, the previous BBD analysis in NHSII had a small number of cases and suggestive associations, but with a larger sample size, the associations did not hold up; perhaps, the suggestive associations observed earlier occurred by chance and do not represent true associations. The previous study could have been affected by recall bias, whereas in this study, the additional cases were prospective. The previous analysis did not adjust for vitamin D, nuts, or fiber, variables more recently found to be associated with BBD risk [31, 36] that may be confounders; in our study, we observed an association for RAE that no longer was significant after adjusting for these factors. Finally, adolescent dietary factors could be related to breast cancer but not BBD, due to differences in etiology and/or screening practices.

The current study is limited in that the recall of high school diet ranged from 16 to 38 years later in our study [33]. Although the HS-FFQ has been shown to be moderately reproducible and not strongly correlated with current adult diet, and the modest correlations between the nurses' and their mothers' recall of the nurses' high school dietary intake provided some reassurance [33], the validity of recall many years later has not been established. However, the participants in the NHSII cohort were registered nurses, a population with high levels of health awareness and consciousness, who may be able to recall diet with greater

accuracy than the general population. The differences in adolescent dietary recall in our study, particularly in the prospective analysis, should be most likely non-differential and unrelated to BBD diagnosis. Non-differential measurement error in recalled diet would most likely attenuate associations toward the null; thus, we cannot rule out modest true associations. Recently, inverse associations were observed between intakes of vegetable protein, vegetable fat, and carotenoids actually collected during adolescence, and BBD in the prospective Growing Up Today Study [38, 39]. In addition, we previously observed associations of vitamin D, nuts, and fiber with BBD risk, indicating that our questionnaire assessed these foods/nutrients adequately enough to allow for a detectable association [31, 36]. Findings from NHSII may not be directly generalizable to the general population, given that participants are not a random sample of US women. However, we believe epidemiological relations and the underlying biological mechanisms among women in the NHSII are unlikely to differ from women in general. Generalization of the study results to women in other countries is further limited, considering that the dietary pattern of participants in NHSII mainly reflect the North American diet and large difference in dietary patterns across different populations. For instance, an overall dietary pattern rich in fruits and vegetables and carotenoids in China could be quite different from those of western countries [31].

This study has a number of strengths. BBD cases were centrally reviewed by our team of pathologists, which reduced the likelihood of misclassification. We focused on a specific histological subtype of proliferative BBD, a marker of increased breast cancer risk. The results, however, may not be generalizable to other histological subgroups, given the heterogeneity of BBD. The combined analysis includes a large number of proliferative BBD cases. This is the first prospective analysis to evaluate the relation of adolescent dietary intakes of fat, carotenoids, RAE, and vitamin E with proliferative BBD risk. Careful control for confounding allowed us to assess the exposures of interest independent of dietary and other BBD risk factors.

In summary, we did not observe associations between high school intakes of fats, carotenoids, or vitamin E with risk of proliferative benign breast disease, even with a large number of cases. Prospectively collected adolescent dietary data and long-term follow-up of BBD are needed to confirm these findings.

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Conflict of interest The authors declare that they have no conflict of interest.

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