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Adolescent Intakes of Vitamin D and Calcium and Incidence of Proliferative Benign Breast Disease

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Abstract

Vitamin D and calcium have been shown to have protective effects against breast cancer development in animal studies. Vitamin D and calcium play important anticarcinogenic roles in animal studies. Exposures between menarche and first birth may be important in breast development and future breast cancer risk. However, the relations between adolescent vitamin D and calcium intake and the risk of proliferative benign breast disease (BBD), a marker of increased breast cancer risk, have not yet been evaluated. We examined these associations in the Nurses' Health Study II. Among the 29,480 women who completed an adolescent diet questionnaire in 1998, 682 proliferative BBD cases were identified and confirmed by centralized pathology review between 1991 and 2001. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression and adjusted for potential confounders. A suggestive inverse association was observed between adolescent total vitamin D intake and proliferative BBD. Women in the highest quintile of vitamin D intake during adolescence had a 21% lower risk (multivariate HR (95% CI): 0.79 (0.61, 1.01), p-trend = 0.07) of proliferative BBD than women in the lowest quintile. Results were essentially the same when the analysis was restricted to prospective cases (n = 142) diagnosed after return of the adolescent diet questionnaire and independent of adult vitamin D intake. Adolescent total milk intake was

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Ethical standards

The experiment complies with the current laws of the United States of America.

Conflicts of interest

The authors declare that they have no conflict of interest.

positively associated with proliferative BBD (≥3 servings/day vs. <1 serving/day HR (95% CI): 1.41 (0.91, 2.17), p-trend = 0.03), after additional adjustment for total vitamin D. Calcium intake during adolescence was not associated with proliferative BBD (p-trend = 0.91). Vitamin D intake during adolescence may be important in the earlier stage of breast carcinogenesis. These findings, if corroborated, may suggest new pathways and strategies for breast cancer prevention.

Keywords

Adolescent Diet; Vitamin D; Calcium; Proliferative BBD

Introduction

Vitamin D and calcium play important anticarcinogenic roles in cell proliferation, differentiation, and apoptosis in animal studies [1, 2]. A meta-analysis of epidemiological studies reported significant inverse associations between intakes of vitamin D and calcium and breast cancer among premenopausal but not postmenopausal women [3]. Exposures during childhood and adolescence can be more important than adult exposures in breast cancer development [4–8] due to rapid proliferation of cells and lack of terminal differentiation. Whereas adolescent vitamin D intake was not associated with breast cancer risk in the Nurses' Health Study (NHS) [9] or Nurses' Health Study II (NHSII) [10], inverse associations were observed in a case-control study [11].

Benign breast disease (BBD) includes various histologic subtypes, among which proliferative BBD is a marker of subsequent breast cancer risk [12]. Studies of diet and BBD could provide insights into the role of diet in the earlier stage of breast carcinogenesis. A non-significant inverse association was found between adult calcium and BBD [13, 14]. Calcium plus vitamin D supplementation was not associated with breast cancer [15] or BBD in the Women's Health Initiative (WHI) [16].

To our knowledge, the associations between adolescent intakes of vitamin D and calcium and proliferative BBD have not been examined in previous studies. We evaluated these associations and dairy consumption in relation to proliferative BBD in the NHSII, because dairy products are the main sources of dietary calcium and vitamin D. We further conducted analysis prospectively by restricting to cases diagnosed after the return of the adolescent diet questionnaire.

Methods

Study Design and Population

The NHSII cohort was established in 1989 when 116,671 U.S. female registered nurses aged 25 to 42 years returned a self-administered questionnaire on health-related exposures and diseases. Biennial follow-up has been conducted since 1989. The current study included 45,948 women who completed a supplemental food-frequency questionnaire (FFQ) in 1998 with plausible energy intake values (600~5000 kcal/day).

High School Food-Frequency Questionnaire (HS-FFQ)

The semi-quantitative 124-item HS-FFQ asked about the nurses' usual dietary intake during adolescence, further defined as ages 13–18 years. The development of the HS-FFQ has been described in detail in another report [17]. Briefly, it was modified from the well-validated adult diet FFQ of the NHS and NHSII and specifically designed to include commonly consumed food items (e.g. milkshakes, peanut butter, French fries, and other snack foods) when this cohort of women would have been in high school, i.e., from 1960 to 1982. There

were eight categories including main dishes, bread/cereal/grains, fruits, vegetables, condiments, snack foods/desserts, dairy products, and beverages. Participants were asked how often, on average, they had consumed a specified portion size of each item during adolescence.

Historical trends in the food supply enrichment with certain key vitamins, for instance, the vitamin D fortification of milk were incorporated in nutrient intake derivation. We used each participant's year of birth and food composition data from the relevant time period (1960s and 1970s), whenever available, to assign different nutrient profiles for specific foods.

In a reproducibility study among randomly selected 333 women who completed the HS-FFQ, the intraclass correlation coefficient (ICC) between two HS-FFQs administered in 1998 and 2002 was 0.71 for total vitamin D, 0.68 for vitamin D without supplements, and 0.73 for calcium, and the Spearman correlation for dairy foods was 0.64 [17]. The recalled adolescent diet was weakly correlated with the 1995 diet, the last adult dietary assessment before the 1998 HS-FFQ (total vitamin D: 0.16; vitamin D without supplements: 0.22; calcium: 0.13). Correlations remained low using diet reported in 1999 [17].

A validation study using data collected during adolescence from the participants who returned the HS-FFQ in 1998 is not possible because these women were 34 to 51 years at the time of HS-FFQ completion. However, 272 nurses' mothers reported their daughters' adolescent diet and adequate validity was found. The Pearson correlation was 0.48 for total vitamin D, 0.46 for vitamin D without supplements, and 0.47 for calcium [17]. These findings indicate that the HS-FFQ provides a reasonable record of adolescent dietary intake.

Identification of BBD Cases

Details about BBD case identification, confirmation, and exclusion criteria have been published previously [18]. Briefly, women who reported a biopsy-confirmed BBD diagnosis between the 1993 through 2001 questionnaires were contacted for permission to obtain pathology specimens. Three pathologists (LCC, SJS, JLC) blinded to participants' adolescent diet information independently classified benign breast lesions as nonproliferative, proliferative without atypia, and atypical hyperplasia (AH, ductal and lobular) following Dupont and Page's criteria [19]. The same three pathologists reviewed all benign biopsy slides throughout the study, and any biopsy specimens that showed atypia or questionable atypia were jointly reviewed by two pathologists. Pathology-confirmed proliferative BBD with or without atypia was the outcome of interest, because this histological subtype is associated with increased breast cancer risk. The total number of proliferative BBD cases included was 682, among which 142 were prospective cases whose biopsy date was after their return of the HS-FFQ. Atypical hyperplasia (AH, ductal and lobular) was not examined as a separate outcome due to the small numbers of cases (n = 61 total AH cases; n = 14 prospective AH cases).

Statistical Analysis

We conducted two main analyses: combined analysis including all proliferative BBD cases diagnosed before and after the return of the HS-FFQ and prospective analysis to assess the possibility of recall bias by restricting to cases diagnosed after completion of the HS-FFQ. The combined analysis is the primary analysis, because these results are consistent with those of the prospective analysis and have increased study power. Details of the two analyses have been published previously [18]. The combined analysis included 29,480 participants with 259,828 person-years of follow-up and the prospective analysis had 23,946 women (69,008 person-years). The study was approved by human research committees at the Harvard School of Public Health and Brigham and Women's Hospital, Boston, MA.

The main exposures were adolescent total vitamin D (percent making-up: dairy vitamin D: 59.8%, non-dairy vitamin D: 28.2%, and vitamin D from supplements: 12.1%) and calcium (81.4% dairy calcium and 18.6% non-dairy calcium). Nutrients were energy-adjusted using the residuals from the linear regression of nutrient intake on total caloric intake [20]. We also evaluated sources of vitamin D and calcium, including vitamin D without supplements, vitamin D supplements, dairy and non-dairy vitamin D, dairy and non-dairy calcium, and dairy protein. Raw nutrient values were derived for vitamin D supplements by subtracting vitamin D without supplements from total vitamin D and total energy included in the model for adjustment, due to very little correlation between vitamin D supplementation and total energy (Spearman correlation coefficient: 0.06). Non-dairy vitamin D (calcium) was derived by subtracting dairy vitamin D (calcium) from vitamin D without supplements (total calcium) and energy-adjusted nutrient residuals calculated. Because milk was the major contributing food to vitamin D (making-up 41.6% of total vitamin D, 47.3% of vitamin D without supplements, and 72.9% of dairy vitamin D) and calcium (making-up 40.6% of total calcium and 56.1% of dairy calcium) and dark fish the major contributing food to non-dairy vitamin D (total vitamin D: 8.7%; vitamin D without supplements: 9.9%), we further examined the associations between consumption of these foods and proliferative BBD. Quintiles of energy-adjusted nutrient residuals and categories of food servings were determined by the distributions among all eligible women.

Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs), with the lowest quintile or category as the reference group and follow-up time as the time variable. The multivariate Cox models were adjusted for age, total energy, age at menarche, menopausal status, childhood body size, family history of breast cancer, alcohol intake between ages 18 and 22, adolescent multivitamin use, recency and duration of oral contraceptive (OC) use, and parity and age at first birth. Models with total vitamin D, vitamin D supplements and calcium as exposures were not adjusted for multivitamin use due to the consideration of colinearity. Adolescent multivitamin use was asked and energy intake calculated from the HS-FFQ. Age at menarche, alcohol intake between ages 18 and 22, and childhood body size were assessed in 1989. The body size measurement asked women to choose one of nine pictorial diagrams (somatotypes) that best depicted their body outline at ages 5 and 10, where level 1 represents the most lean and level 9 represents the most overweight [21]. The childhood body size was obtained by averaging the figures at ages 5 and 10. Age, menopausal status, OC use, and parity and age at first birth were updated every two years. Family history of breast cancer was initially assessed in 1989 and updated in 1997. To test for trend, the Wald statistic was calculated by including the median value of each quintile or category as a continuous variable. All statistical tests were two-sided.

Results

Women with high intake of total vitamin D and calcium were more likely to be older at first birth, have smaller childhood body size and have used multivitamins during adolescence, but less likely to have ever used OC than women with lower intake (Table 1). The Spearman correlation coefficient was 0.69 for vitamin D and calcium, 0.95 for dairy vitamin D and dairy calcium, and 0.25 for non-dairy vitamin D and non-dairy calcium (all $p < 0.0001$).

A suggestive inverse association was observed between adolescent total vitamin D intake and proliferative BBD (Table 2). Women in the highest quintile had a 21% lower risk of proliferative BBD (multivariate HR (95% CI): 0.79 (0.61, 1.01), p-trend = 0.07) than women in the lowest quintile. Adjustment for adult vitamin D intake did not change the estimates (multivariate highest vs. lowest quintile HR (95% CI): 0.78 (0.60, 1.00), p-trend = 0.06). The vitamin D-BBD association became statistically significant after additional adjustment

for calcium intake (p-trend = 0.03). The inverse association remained, though not significant, in the prospective analysis (multivariate highest vs. lowest quintile HR (95% CI): 0.81 (0.46, 1.41), p-trend = 0.46). Higher intake of vitamin D without supplements and from supplements was also associated with lower proliferative BBD risk, although no significant trend was observed. No association was observed for dairy vitamin D (p-trend = 0.67). For non-dairy vitamin D, reduction of proliferative BBD risk was observed in the highest intake level in the combined (multivariate highest vs. lowest quintile HR (95% CI): 0.82 (0.64, 1.06), p-trend = 0.06) and prospective analysis (multivariate highest vs. lowest quintile HR (95% CI): 0.52 (0.29, 0.94), p-trend = 0.05). Intake of dark fish was marginally significant in the combined analysis (≥ 1 serving/week vs. never or <1 serving/month HR (95% CI): 0.74 (0.47, 1.16, p-trend = 0.06) and became significant in the prospective analysis (HR (95% CI): 0.45 (0.14, 1.44), p-trend = 0.04).

No association was observed for calcium intake (p-trend = 0.91), dairy calcium (p-trend = 0.71) or non-dairy calcium (p-trend = 0.47) (Table 3).

Adolescent dairy product consumption was not associated with proliferative BBD risk (Table 4). Total milk intake was associated with an increased BBD risk after additional adjustment for total vitamin D (≥ 3 servings/day vs. <1 serving/day HR (95% CI) = 1.41 (0.91, 2.17), p-trend = 0.03).

Discussion

To our knowledge, this is the first study to comprehensively examine the associations between adolescent intakes of various sources of vitamin D and calcium and the risk of proliferative BBD. We observed a suggestive inverse association between adolescent intake of total vitamin D and proliferative BBD. Total milk intake was associated with an increased risk of proliferative BBD, after additional adjustment for total vitamin D. The highest intake level of non-dairy vitamin D was associated with a reduced risk, whereas no association was found between dairy vitamin D and proliferative BBD.

Our study may have limited power to detect a significant association for vitamin D from supplements, because only 16% of women used multivitamin during adolescence. Dark fish, the major source of adolescent non-dairy vitamin D in our study, was marginally associated with proliferative BBD. One possible explanation could be that the inverse association attributed to vitamin D is due to dark fish. Alternatively, this difference could be an artifact of differential recall for different foods and the recall of fish intake may be better than that of other foods and hence less measurement error. Nonetheless, recall of milk was highly reproducible and in general dairy foods had higher correlations between the first and second administration than main dishes [17]. Finally, it may be not differences in the vitamin D in dairy and non-dairy products that affect BBD risk, but that other nutrients in milk or dairy products might be linked to increased risk and mask the effect of vitamin D in these products. More research on adolescent diet and breast disease may provide further insights into these issues. The reduction in risk for non-dairy vitamin D was only found in the 5th quintile. Future studies need to ascertain the optimal vitamin D intake from different sources during adolescence.

It is hypothesized that Vitamin D exerts protective effects on breast carcinogenesis mainly through its metabolites. Animal studies have shown that 1,25$(OH)_2$D, the biologically active vitamin D metabolite, can inhibit cellular proliferation and angiogenesis and induce differentiation and apoptosis [1]. Higher levels of circulating 25(OH)D, the precursor of 1,25$(OH)_2$D and best indicator of endogenous vitamin D status, have been related to lower breast cancer risk [3]. A statistically significant inverse association between vitamin D

intake and breast cancer has been observed among premenopausal but not postmenopausal women [3]. A possible explanation to the difference by menopausal status could be due to biologic interactions between vitamin D metabolites, the vitamin D receptor, and the higher circulating estrogen and insulin-like growth factor-I (IGF-I)[1] among premenopausal than postmenopausal women [22, 23]. Vitamin D could suppress 17β-estradiol and IGF-I-stimulated cellular growth, inhibit the antiapoptotic effect of IGF-I, and decrease expression levels of receptors of estrogen and IGF-I [1]. Meanwhile, the expression of VDR can be up-regulated by estrogen and IGF-I in breast cancer cells [1]. Because a majority of participants (>95%) in our study were premenopausal at the time of their benign breast disease, it is possible that vitamin D may interact with other hormones to reduce proliferative BBD risk. Adolescent vitamin D intake was, however, not associated with breast cancer risk in the NHS or NHSII cohorts [9, 10]. One possible explanation is that vitamin D may be more important in the earlier breast carcinogenic process. Conversely, inverse associations were observed between adolescent vitamin D exposures and breast cancer in a case-control study [11]. Future studies, particularly studies focusing on the late stage from benign breast disease to breast cancer development, will further illuminate the role of vitamin D in breast carcinogenesis.

No association has been observed between adolescent [24] or adult dairy intake and BBD [25–27]. Results on the associations between adolescent [11, 28, 29]or adult dairy intake and breast cancer[30] have been inconsistent. Few studies, however, had taken vitamin D or calcium into account when examining dairy consumption and breast disease risk. Previous studies have linked higher milk intake with more rapid child growth [31, 32]. Childhood and adolescent vitamin D and dairy intake may influence hormone levels and/or growth during this critical period and set endocrine profiles in adulthood, thus affecting subsequent breast disease and/or cancer risk. Considering the varying practices of vitamin D fortification in different countries and the high correlation between various nutrients in dairy products, it will be important to understand the relation between milk and dairy consumption, circulating hormone levels, and breast disease risk across the life course.

Adolescent calcium intake was not associated with proliferative BBD in our study. Adjustment for calcium intake, however, strengthened the vitamin D-BBD association. Given the much stronger correlation between dairy vitamin D and dairy calcium (0.95) than that between vitamin D and calcium from non-dairy sources (0.25), one possible explanation could be that the adjustment for calcium is basically adjusting for dairy intake, leaving mostly the non-dairy vitamin D. Alternatively, these results may suggest that the association observed for vitamin D is independent of calcium.

This is the first study to comprehensively assess the associations between adolescent intakes of various sources of vitamin D and calcium and the subsequent BBD. The centralized pathology review and confirmation minimized misclassification of BBD cases. We included a large number of cases and had sufficient power to detect significant associations. The consistent results obtained from the combined and prospective analyses, suggesting that any possible recall bias due to BBD diagnosis or changes in diet after diagnosis should be minimal. The essentially equivalent results of the age- and multivariate-adjusted analyses suggest that uncontrolled confounding is unlikely to entirely account for the observed associations.

One limitation of this study is the measurement of adolescent diet. In our study, women recalled their adolescent dietary intake 16 to 38 years later. Although comparison with maternal reports provides some reassurance, the validity of recall after so many years has not been established. However, the observed association was independent of current intake. Another limitation for vitamin D is the assessment of diet only. Since a high percentage of

vitamin D exposure comes from ultraviolet B radiation via sunlight to skin, the measurement of vitamin D dietary intake is only a weak indicator of vitamin D status. Nonetheless, information on adolescent sunlight exposure or geographical residential region as a proxy of sunlight exposure was not available in NHSII. In the absence of dietary data actually collected during adolescence and given that collecting blood samples and measuring adolescent circulating 25(OH)D would not be feasible in this sort of cohort study, our results provide the best estimate currently available of relationships between adolescent vitamin D intake and proliferative BBD.

In summary, we observed suggestive inverse associations between adolescent intake of total vitamin D and non-dairy vitamin D and proliferative BBD. Our results support the hypothesis that early life exposures are important in breast carcinogenesis. As diet is a modifiable risk factor, these findings, if substantiated, may open new pathways and strategies for breast cancer prevention.

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Abbreviations used

AH	Atypical hyperplasia
BBD	Benign breast disease
CI	Confidence interval
FFQ	Food-frequency questionnaire
HR	Hazard ratio
HS-FFQ	High school food-frequency questionnaire
ICC	Intraclass correlation coefficients
NHS	Nurses' Health Study
NHSII	Nurses' Health Study II
OC	Oral contraceptive

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Table 1

Age and age-standardized percentages and means for characteristics of participants according to total vitamin D and calcium intake during adolescence among 29,480 women in the Nurses' Health Study II[a]

	Quintiles[b]					
	Total vitamin D			Calcium		
	1 (low)	3	5 (high)	1 (low)	3	5 (high)
No. of women	5,896	5,894	5,895	5,914	5,892	5,888
Percentage (%)						
Family history of breast cancer in mother or sister(s)[c]	4.8	4.9	4.6	4.7	4.6	4.6
Age at menarche <12 yrs[c]	25.4	23.4	23.4	25.2	24.4	22.6
Premenopausal[d]	97.8	97.9	97.8	97.7	98.2	97.9
Average body size between ages 5 and 10 yrs somatotype pictogram >3[c]	29.6	27.0	24.6	28.4	28.5	25.3
Nulliparous[d]	28.2	26.7	28.8	29.6	27.7	24.2
Age at first birth ≥ 30 yrs[d,e]	15.2	17.7	18.8	15.5	17.7	18.0
Ever oc use[d,f]	85.5	84.8	81.9	85.2	84.1	82.3
Multivitamin use between ages 13 and 18 yrs[g]	1.0	6.1	54.4	10.8	16.7	19.2
Mean						
Age[d] (yrs)	35.5	35.8	35.7	36.1	35.5	35.5
Alcohol intake between ages 18 and 22 yrs (g/day)[c]	5.3	5.5	4.7	4.8	5.6	4.8
Average body size between ages 5 and 10 yrs[c]	2.7	2.6	2.6	2.7	2.7	2.6
Parity[d,e]	2.1	2.1	2.1	2.1	2.1	2.2
Age at first birth (yrs)[d,e]	25.5	26.0	26.1	25.5	26.0	26.1

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

[b] Quintile of energy-adjusted nutrient residuals.

[c] Variables are obtained from 1989 questionnaire.

[d] Variables are obtained from 1991 questionnaire.

[e] Among parous women.

[f] oc: oral contraceptive.

[g] Variable is obtained from the High School Food-Frequency Questionnaire.

Table 2

Intakes of vitamin D and sources of vitamin D during adolescence and relative risk (95% confidence interval) of proliferative BBD in NHSII

Exposures	Quintile of vitamin D intake					P trend
	1	2	3	4	5	
Vitamin D (including supplements)						
Intake (IU/day)*	148	227	315	403	586	
No. of BBD cases§/pys¶	148/51,664	145/52,181	128/51,734	145/52,003	116/52,245	
Multivariate RR (95% CI)†	1.00 (ref)	0.98 (0.78, 1.24)	0.88 (0.69, 1.12)	1.00 (0.79, 1.26)	0.79 (0.61, 1.01)	0.07
Additional adjustment for calcium†	1.00 (ref)	0.94 (0.73, 1.21)	0.82 (0.62, 1.09)	0.90 (0.67, 1.22)	0.70 (0.51, 0.96)	**0.03**
Vitamin D (without supplements)						
Intake (IU/day)*	143	214	289	363	478	
No. of BBD cases§/pys¶	150/51,758	126/52,006	146/51,861	135/51,858	125/52,345	
Multivariate RR (95% CI)†	1.00 (ref)	0.86 (0.67, 1.09)	0.98 (0.78, 1.24)	0.92 (0.72, 1.17)	0.84 (0.66, 1.07)	0.28
Additional adjustment for calcium†	1.00 (ref)	0.81 (0.62, 1.05)	0.94 (0.71, 1.24)	0.85 (0.62, 1.16)	0.74 (0.52, 1.04)	0.15
Vitamin D from supplements						
Intake (IU/day)*	0	56	228	400		
No. of BBD cases§/pys¶	579/219,185	32/7,953	37/17,779	34/14,911		
Multivariate RR (95% CI)†	1.00 (ref)	1.61 (1.12, 2.31)	0.78 (0.56, 1.09)	0.88 (0.62, 1.25)		0.23
Additional adjustment for calcium†	1.00 (ref)	1.61 (1.13, 2.31)	0.78 (0.56, 1.09)	0.88 (0.62, 1.25)		0.23
Dairy vitamin D						
Intake (IU/day)*	57	117	175	255	361	
No. of BBD cases§/pys¶	127/52,052	149/51,765	128/51,883	129/52,188	149/51,941	
Multivariate RR (95% CI)†	1.00 (ref)	1.18 (0.93, 1.50)	0.98 (0.76, 1.26)	0.99 (0.77, 1.28)	1.14 (0.90, 1.46)	0.67
Additional adjustment for non-dairy vitamin D†	1.00 (ref)	1.18 (0.93, 1.50)	0.98 (0.76, 1.25)	0.99 (0.76, 1.27)	1.14 (0.89, 1.46)	0.70
Non-dairy vitamin D						
Intake (IU/day)*	48	62	76	107	209	

Exposures	Quintile of vitamin D intake					P trend
	1	2	3	4	5	
No. of BBD cases[§]/pys[¶]	147/51,552	149/51,535	146/51,586	128/52,935	112/52,220	
Multivariate RR (95% CI)[†]	1.00 (ref)	1.02 (0.81, 1.28)	1.06 (0.84, 1.34)	1.06 (0.82, 1.36)	0.82 (0.64, 1.06)	0.06
Additional adjustment for dairy vitamin D[†]	1.00 (ref)	1.02 (0.81, 1.29)	1.07 (0.84, 1.35)	1.06 (0.82, 1.37)	0.83 (0.64, 1.06)	**0.05**

[*] Values for vitamin D with and without supplements, and dairy vitamin D, are medians of nutrient intakes in each quintile, adjusted for total energy intake using the residual method. Values for vitamin D supplements and non-dairy vitamin D are medians of raw nutrient values in each quintile.

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

[†] 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 years (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 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). The age-adjusted results are essentially the same, and only multivariate adjusted results are presented. Models with total vitamin D and vitamin D supplements as exposure variables are not adjusted for multivitamin use.

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Table 3

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

Exposures	Quintile of calcium intake					P trend
	1	2	3	4	5	
Calcium						
Intake (mg/day) *	675	863	1038	1251	1542	
No. of BBD cases§/pys¶	138/51,869	148/51,790	127/51,996	133/51,903	136/52,270	
Multivariate RR (95% CI)†	1.00 (ref)	1.12 (0.89, 1.42)	0.97 (0.76, 1.24)	1.00 (0.78, 1.27)	1.04 (0.82, 1.32)	0.91
Additional adjustment for vitamin D†	1.00 (ref)	1.17 (0.91, 1.50)	1.06 (0.81, 1.40)	1.14 (0.85, 1.54)	1.25 (0.91, 1.72)	0.24
Dairy calcium						
Intake (mg/day) *	350	544	729	957	1275	
No. of BBD cases§/pys¶	130/52,066	145/51,801	133/51,926	133/51,939	141/52,096	
Multivariate RR (95% CI)†	1.00 (ref)	1.15 (0.91, 1.46)	1.05 (0.82, 1.34)	1.03 (0.81, 1.32)	1.11 (0.87, 1.42)	0.71
Additional adjustment for non-dairy calcium†	1.00 (ref)	1.15 (0.90, 1.46)	1.04 (0.81, 1.33)	1.02 (0.79, 1.31)	1.08 (0.84, 1.39)	0.90
Non-dairy calcium						
Intake (mg/day) *	229	267	297	330	386	
No. of BBD cases§/pys¶	163/51,562	127/51,800	143/51,759	131/51,839	118/52,869	
Multivariate RR (95% CI)†	1.00 (ref)	0.80 (0.63, 1.01)	0.96 (0.76, 1.20)	0.91 (0.72, 1.15)	0.86 (0.67, 1.11)	0.47
Additional adjustment for dairy calcium†	1.00 (ref)	0.80 (0.63, 1.01)	0.96 (0.76, 1.21)	0.91 (0.71, 1.16)	0.86 (0.66, 1.12)	0.51

*Values for calcium, dairy calcium, and dairy protein are medians of nutrient intakes in each quintile, adjusted for total energy intake using the residual method. Values for non-dairy calcium are medians of raw nutrient values in each quintile.

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

†The multivariate models are adjusted the same way as in Table 2. The age-adjusted results are essentially the same, and only multivariate adjusted results are presented. Models with calcium as the exposure variable are not adjusted for multivitamin use.

Table 4

Intakes of dairy protein, total dairy and milk during adolescence and relative risk (95% confidence interval) of proliferative BBD in NHSII

Exposures	Level of intake					P trend	Per 1 serving/week
Dairy protein							
Intake (g/day) *	13	19	24	31	40		
No. of BBD cases§/pys¶	137/51,792	137/52,144	123/51,833	152/51,869	133/52,190		
Multivariate RR (95% CI) †	1.00 (ref)	1.01 (0.80, 1.29)	0.92 (0.72, 1.17)	1.13 (0.89, 1.43)	0.99 (0.78, 1.27)	0.77	
Total dairy [a]							
Intake (servings/day)	<1	1–<2	2–<3	3–<4	≥ 4		
No. of BBD cases§/pys¶	75/27,810	172/67,998	150/52,146	166/64,101	119/47,773		
Multivariate RR (95% CI) †	1.00 (ref)	0.98 (0.74, 1.30)	1.12 (0.83, 1.50)	0.99 (0.74, 1.33)	0.99 (0.71, 1.37)	0.87	1.00 (0.94, 1.06)
Total milk [b]							
Intake (servings/day)	<1	1–<2	2–<3	≥ 3			
No. of BBD cases§/pys¶	258/96,333	126/54,651	256/92,765	42/16,079			
Multivariate RR (95% CI) †	1.00 (ref)	0.87 (0.70, 1.08)	1.02 (0.85, 1.23)	0.95 (0.67, 1.33)		0.78	1.00 (0.94, 1.07)
Additional adjustment for vitamin D †	1.00 (ref)	0.93 (0.74, 1.18)	1.33 (1.01, 1.73)	1.41 (0.91, 2.17)		**0.03**	1.11 (1.01, 1.23)

* Values for calcium, dairy calcium, and dairy protein are medians of nutrient intakes in each quintile, adjusted for total energy intake using the residual method. Values for non-dairy calcium are medians of raw nutrient values in each quintile.

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

† The multivariate models are adjusted the same way as in Table 2. The age-adjusted results are essentially the same, and only multivariate adjusted results are presented.

[a] Includes milk, yogurt, instant breakfast drink, yogurt, cottage or ricotta cheese, cream cheese, other cheese (including grilled cheese sandwich, cheeseburgers, etc.), sherbet, ice cream, and milkshake or frappe. Butter is not included.

[b] Includes chocolate milk and regular milk.