Published in final edited form as:

Cancer Causes Control. 2015 August ; 26(8): 1181–1187. doi:10.1007/s10552-015-0612-6.

Adolescent Dietary Vitamin D and Sun Exposure in Relation to Benign Breast Disease

Caroline E. Boeke, ScD^{1,2}, Rulla M. Tamimi, ScD^{1,2,3}, Catherine S. Berkey, PhD^{2,3}, Graham A. Colditz, MD DrPH⁴, Edward Giovannucci, MD ScD^{1,2,3,5}, Susan Malspeis, MS², Walter C. Willett, MD MPH DrPH^{1,2,3,5}, and A. Lindsay Frazier, MD⁶

¹Department of Epidemiology, Harvard School of Public Health, Boston, MA

²Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA

³Department of Medicine, Harvard Medical School, Boston, MA

⁴Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO

⁵Department of Nutrition, Harvard School of Public Health, Boston, MA

⁶Division of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA

Abstract

Purpose—Vitamin D may reduce cell proliferation and tumor growth in breast tissue, and exposure may be most important during adolescence when breast tissue is developing. In the Nurses' Health Study II, higher recalled adolescent vitamin D intake was associated with a lower risk of benign breast disease (BBD). Our study aim was to assess adolescent vitamin D exposure in relation to BBD in young women.

Methods—Vitamin D was assessed in 6,593 adolescent girls (9 to 15 years of age at baseline) in the prospective Growing Up Today Study cohort using the mean energy-adjusted intakes from food frequency questionnaires in 1996, 1997, and 1998. In 1999, 5286 girls reported skin color, sunscreen use, tanning bed use, and number of sunburns in the past year, and we used state of residence to assess low vs. high ultraviolet (UV) index. Biopsy-confirmed BBD was reported on questionnaires in 2005, 2007, and 2010 (n=122).

Results—Dietary vitamin D, tanning behaviors, and other sun exposure variables were not significantly associated with BBD in logistic regression models adjusted for age, family history of breast cancer or BBD, age at menarche, nulliparity, alcohol intake, body mass index, and physical activity. The relative risk for the top (>467 IU/day) vs. bottom (<243 IU/day) quartile of vitamin D intake was 0.76 (95% CI: 0.47, 1.23).

Address correspondence to: Caroline Boeke, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115. caroline.boeke@mail.harvard.edu.

The authors have no conflicts of interest to disclose.

Conclusions—Sun exposure was not significantly associated with BBD in this prospective cohort study. However, a suggestive inverse association between dietary vitamin D and BBD was observed that merits further study.

Keywords

vitamin D; sun; cancer; adolescent health; diet; breast

INTRODUCTION

Vitamin D deficiency/insufficiency is highly prevalent worldwide; an estimated 1 billion people have 25-hydroxyvitamin D levels below 30 ng/mL. [1] Experimental evidence suggests that vitamin D may be important for breast cancer prevention given its pro-apoptotic and cell differentiation properties, [2] although prospective studies of adult vitamin D exposure and breast cancer risk have been inconsistent.[3] Because adolescence is a period of heightened breast tissue sensitivity to environmental exposures,[4, 5] adolescent vitamin D insufficiency may be related to higher risk of benign breast disease (BBD), a group of breast lesions that develop during young adulthood and are associated with a higher risk of breast cancer.[6] Among 29,480 women in the Nurses' Health Study II, women in the top quartile of adolescent dietary vitamin D intake had a 21% lower risk of proliferative BBD compared to those in the bottom quartile (HR=0.79; 95% Confidence Interval [CI]: 0.61, 1.01; p-trend = 0.07).[7] Although this study included prospectively reported cases, adult women recalled their adolescent diet, which is subject to measurement error. Also, this study did not include sun exposure, which is the main contributor to serum vitamin D concentrations in most individuals. To our knowledge, no previous prospective study has assessed current vitamin D intake or sun exposure in adolescent girls in relation to BBD risk.

We examined adolescent dietary vitamin D intake/sun exposure and BBD in young women in the Growing Up Today Study, a large prospective cohort study based in the US. We hypothesized that high vitamin D intake and high sun exposure would be associated with lower risk of BBD.

METHODS

Study Population

The Growing Up Today Study (GUTS) was initiated in 1996 and included 16,882 girls and boys ages 9 to 15 years living throughout the United States, as described previously.[8] The participants are all children of the Nurses' Health Study II, a prospective cohort of adult women.

Of the 9033 females participating in the study, 8999 reported dietary intake in 1996. Eight girls with a history of childhood cancer were excluded, as well as participants who did not fill out at least one questionnaire in 2005, 2007, and 2010 (n=1782), those who reported BBD that was not confirmed by biopsy (n=139), and those missing data on covariates (n=477), leaving 6,593 participants in the analytic data set for the dietary vitamin D analysis.

The number of girls who completed questionnaires in subsequent years is as follows: 1997, 7296; 1998, 7862; 1999, 7120; 2003, 6575. Given the lower questionnaire return rates over time, for the other analyses (using exposure data collected in 1999), the final sample size was smaller (UV index: n=6590; sunscreen use: n=5301; sunburns in past year: n=5304; tanning bed use: n=5298; skin color: n=5264).

Exposures

Participants reported their habitual dietary intake in 1996, 1997, and 1998 using the Youth/Adolescent Food Frequency Questionnaire (YAQ), a modification of the validated adult Nurses' Health Study semi-quantitative food frequency questionnaire; the YAQ includes more foods commonly consumed by children and a format better suited for youth. Participants described how often in the past year they ate specified quantities of foods, choosing among 5 categories ranging from never/less than once per month to one or more times per day, depending on the food. Nutrient intakes were calculated using the nutrient values in foods, including foods routinely fortified with vitamin D, from the US Department of Agriculture database.[8] Participants also reported vitamin D and multivitamin supplement use; total vitamin D intake from supplements plus foods was calculated. Although in this cohort no validation studies have been conducted specifically of vitamin D intake assessment, among 261 children of the NHSII, the average de-attenuated correlation coefficient (for several different macro- and micronutrients) between the means of three 24-hour recalls and two YAQs was 0.54, after correction for within-person error.[9] For calcium, which is highly correlated with vitamin D, the de-attenuated correlation coefficient was 0.64.[9] The reproducibility of the YAQ for milk, a major source of dietary vitamin D, was 0.60 in 101 girls and the reproducibility for calcium was 0.67.[10]

Based upon state of residence in 1999, participants were grouped into high (13 states) and low (37 states) mean UV index states as described previously.[11, 12] We also queried participant state of residence in 1997 and assessed state UV index in 1997 as a secondary analysis.

Sun exposure and skin tone were assessed using questionnaires in 1999. While the specific questions used were not individually validated against adolescent plasma 25(OH)D, previous studies have suggested a positive association between plasma vitamin D and lighter skin, [13] less frequent sunscreen use, [14] [15] and tanning bed use [16] and we hypothesize that girls with more frequent sunburns are likely to have greater vitamin D exposure. We asked participants about the color of their untanned skin (very fair, fair, olive, or dark). To assess sunscreen use, we asked: "When you were outside on a sunny day this past summer for >15 minutes, how often did you use sunscreen or sunblock with a Sun Protection Factor (SPF) of 15 or more?" We collapsed the responses into 3 categories (never/seldom, sometimes, often/always). To estimate sunburn frequency, we asked: "How many times did you get a sunburn this past summer (that is, how many times did exposed parts of your skin stay red for several hours after you had been out in the sun)?" Response categories were collapsed into: No sunburn, 1 to 2 times, 3 or more times. Finally, to assess tanning bed use, we asked: "During the past year, how many times did you use a tanning booth or tanning salon?" We collapsed response categories into 3 categories: never, 1 to 2

times, 3+ times. Sunscreen use, tanning bed use, and sun exposure were also assessed in 2003, but fewer participants answered the 2003 questionnaire. We examined exposures in 2003 as secondary analyses.

Ascertainment of BBD

In 2005, 2007, and 2010, participants reported whether they ever had been diagnosed with BBD by a health care provider, and whether the BBD was confirmed by biopsy. The questionnaires did not query exact date of diagnosis. The primary outcome was defined as biopsy-confirmed BBD; we included all BBD cases (confirmed and unconfirmed) in secondary sensitivity analyses. Most BBD cases were likely diagnosed because participants (or their physicians) found a clinically palpable mass which was then biopsied, as participants were too young to be undergoing routine screening mammography. The most common type of BBD occurring in adolescents and young women is fibroadenoma, which accounts for nearly 70% of benign breast lesions.[17] The remaining types are primarily cysts and fibrocystic changes.[17] In a validation study in 730 women reporting BBD in the NHSII, 95% of those with biopsy pathology material available for review were confirmed as valid BBD cases.[18]

Covariate Assessment

Participant age at baseline was calculated using date of baseline questionnaire return and date of birth. At baseline and on subsequent questionnaires, participants reported weight and height. BMI was calculated as weight in kilograms/(height in meters)². Participants reported time per week spent engaging in 18 different moderate and vigorous activities (e.g. basketball, biking, and swimming) in six categories ranging from zero to 10 or more hours/week in 1996, 1997, and 1998. We filled in missing data on BMI and physical activity by carrying forward the value from the previous questionnaire and adding the median change between the two questionnaires. Mean BMI and hours per week of physical activity were calculated using data from 1996, 1997, and 1998. Total mean energy intake in 1996 through 1998 was assessed using the YAQ. Girls reported beer, wine, and liquor intake (drinks per week) in 1996, 1997, 1998, and 2001, and mean alcohol intake during this time period was calculated. Smoking was reported annually through 2001. Participants reported age at menarche through 2003, by which time 99.9% had undergone menarche, and whether they had ever been pregnant. The participants' mothers (in the NHSII cohort) reported personal history of biopsy-confirmed BBD and personal and family history of breast cancer.[19] Pregnancies and family history of BBD and breast cancer were included through report of BBD diagnosis or end of follow-up because these factors could lead to increased BBD detection as well as be related to risk.

Statistical Analysis

Multivariable-adjusted logistic regression was utilized to assess vitamin D intake in relation to BBD using generalized estimating equations to adjust for non-independence among sisters. Logistic regression was used instead of Cox proportional hazards regression because data on date of BBD diagnosis were not available. Vitamin D intake was categorized into quartiles to allow for non-linear associations and to minimize the influence of outliers. Adjusting for family income, region of the country, multivitamin use, height, total caloric

intake, beta carotene intake, calcium intake, and smoking did not change the magnitude of the associations, so these variables were not included in the final models. The final multivariable model adjusted for age, family history of breast cancer (in mother or aunt), mother's history of BBD, age at menarche (continuous), average BMI (continuous), nulliparity, average hours of moderate to vigorous physical activity (continuous), and alcohol intake (continuous). Tests for trend were assessed by including the median value within each category as a continuous variable in the model and calculating the Wald statistic. In exploratory secondary analyses, we stratified by UV index in state of residence and skin color.

All analyses were conducted with SAS version 9.3 (SAS, Cary, USA). All statistical tests were two sided, and p -values < 0.05 were considered statistically significant. This protocol was approved by the Human Subjects Committees of the Harvard School of Public Health and the Brigham and Women's Hospital.

RESULTS

Girls were mean age 12.0 (SD=1.6) years at baseline. On average, girls with higher vitamin D intake were slightly younger and tanning bed users were older (Table 1). Girls with higher vitamin D intake, more sunscreen use, and more sunburns in the past year were less likely to have olive/dark skin, while girls who used tanning beds and lived in states with higher UV residence were more likely to have olive/dark skin. Girls with high vitamin D intake and frequent sunscreen use were less likely to ever have been pregnant, while girls who used tanning beds were more likely to have been pregnant. There were 122 cases of BBD in the analyses of dietary vitamin D and UV index. There were 101 cases of BBD in all other analyses.

Higher vitamin D intake appeared to be suggestively associated with lower BBD risk, although the associations for top vs. bottom quartile were not statistically significant (Table 2). In an age-adjusted model, the odds ratio (OR) comparing the top (>467 IU/day) vs. bottom (<243 IU/day) quartile of vitamin D intake was 0.77 (95% CI: 0.48, 1.25; p -trend=0.47). After adjusting for other potential confounders, the OR was 0.76 (95% CI: 0.47, 1.23; p -trend=0.42). However, the association did not appear to be linear; those in the top three quartiles had a lower odds of BBD compared to the bottom quartile. The U-shaped association between dietary vitamin D and BBD may have been driven by the association in darker skinned women; in analyses stratified by skin color, there was an inverse linear trend in very fair/fair women. When we collapsed the top three quartiles of vitamin D intake in the main analysis among all women, the OR of BBD was 0.67 (95% CI: 0.46, 0.98) compared to the bottom quartile, suggesting that insufficient vitamin D levels (lowest quartile) are harmful. The results were similar for total reported, rather than only biopsy-confirmed, BBD cases (top vs. bottom quartile: OR=0.75, 95% CI: 0.53, 1.04; p -trend=0.13). Sun exposure behaviors were not significantly associated with biopsy-confirmed or total BBD, nor were skin color or UV index in state of residence.

Secondary analyses using variables assessed later (UV index based on residence in 1997, sun exposure variables assessed in 2003) were also null, and some associations that

appeared borderline significant using the earlier sun exposure variables were in the opposite direction when later exposure variables were used. For example, the OR comparing always/often sunscreen use to never/rarely sunscreen use when assessed in 1999 was 1.47 (95% CI: 0.92, 2.34); when assessed in 2003 the OR was 0.84 (95% CI: 0.52, 1.37). The OR comparing tanning bed users to nonusers was 1.45 (95% CI: 0.86, 2.44) in 1999 but 0.97 (95% CI: 0.64, 1.48) in 2003.

Analyses stratified by UV index in state of residence were consistent with the overall findings.

DISCUSSION

Sun exposure behaviors, skin color, and UV index in state of residence were not strongly related to BBD risk in this prospective cohort study of adolescent females. Dietary vitamin D intake was not significantly associated with BBD, but a suggestive inverse association was observed. Girls in the top three quartiles of vitamin D intake had a significantly lower odds of BBD than those in the lowest quartile.

The strength of the association in the highest vs. lowest quartile of vitamin D intake with BBD (OR=0.76) was similar to that in a study on adolescent vitamin D intake that used recalled diet (HR comparing highest to lowest quartile=0.79);[7] however our association was not statistically significant and was not supported by the sun exposure variables. Previous studies of adult vitamin D intake and breast cancer risk have been inconsistent. A meta-analysis of vitamin D intake and blood concentrations found a weak inverse association with breast cancer risk (e.g., highest vs. lowest blood 25(OH)D concentrations HR=0.92 (95% CI: 0.83, 1.02) and a strong inverse association with breast cancer survival (e.g., highest vs. lowest blood 25(OH)D concentrations HR=0.61 (95% CI: 0.48, 0.79).[3] A randomized controlled trial of vitamin D plus calcium in 36,282 postmenopausal women in the Women's Health Initiative with a mean follow-up of 6.8 years did not observe an association with proliferative BBD (HR=0.99; 95% CI: 0.86, 1.13).[20] A meta-analysis of all randomized controlled trials of vitamin D supplementation and breast cancer risk found no association, although only two studies were included and the authors concluded that the current literature is limited.[21] However, adult breast tissue may be less sensitive to nutritional factors than breast tissue prior to first pregnancy,[4, 5] and limited studies have assessed adolescent vitamin D as an exposure. The results of our study are consistent with a weak protective association between dietary vitamin D intake and breast cancer outcomes. The suggestive association observed with BBD in our study may be due to chance but is worth exploring in the future with more cases.

We did not observe consistent associations of sun exposure, assessed using tanning behaviors, UV index, and state of residence, with BBD. In a recent systematic review on the topic, van der Rhee et al. described consistent inverse associations between sun exposure variables and breast cancer in all case-control studies, but mixed results in prospective analyses.[22] Admittedly, these studies used different methods to assess sun exposure, many of which likely had a large amount of measurement error which could obscure a true underlying association. Also, the sun exposure variables have some caveats. For example,

tanning booths sometimes use UV-A radiation only, which does not increase vitamin D exposure. However, if there were truly a strong causal relationship between vitamin D and breast cancer, one would expect to see at least a modest association with variables assessing exposure to the sun, which is the primary source of vitamin D in humans.

This study is limited by measurement error in the exposure variables, as questionnaire measures of dietary intake and sun exposure do not provide a perfect measure of vitamin D exposure. The sun exposure variables (sunscreen use, sunburns, UV index) do not fully assess how much time the participants spent in the sun; to our knowledge, no widely accepted method of combining sun exposure behaviors exists. However, any measurement error in the exposure is unlikely to be differentially related to BBD status. We had a relatively small number of BBD cases, meaning that the study had limited statistical power. As with any observational study, residual confounding is possible, but we carefully adjusted for potential confounders and other risk factors for BBD and the effect estimates changed very little, suggesting very little confounding. Strengths of this study include the prospectively collected, detailed data from multiple time points on diet and sun exposure practices and careful adjustment for a large number of potential confounders.

Adolescent sun exposure was not related to BBD risk in this prospective cohort study of young women, but a suggestive inverse association of dietary vitamin D intake and BBD was observed. This study underlines that there are many factors occurring simultaneously that contribute to vitamin D, and that considerations such as tanning bed use, sun behaviors, and skin color all interact to determine vitamin D exposure. Ultimately, measuring blood 25(OH)D concentration is likely to provide more meaningful information than examining each individual contributor of vitamin D exposure separately. Prospective studies with repeated direct measures of blood 25(OH)D and more BBD cases are needed.

ACKNOWLEDGEMENTS

We would like to thank the female participants of the Growing Up Today Study, their mothers from the Nurses' Health Study II, and our colleagues working on both cohort studies. We would also like to acknowledge the Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School. This work was funded by NIH grants R01 DK084001, UM1 CA176726 and R01 CA 050385 as well as the Breast Cancer Research Foundation. Caroline Boeke was funded by T32 CA 09001. Lindsay Frazier was supported by an award from the American Institute for Cancer Research.

REFERENCES

1. Holick MF. Vitamin D deficiency. *The New England journal of medicine*. 2007; 357:266–81. [PubMed: 17634462]
2. Lopes N, Paredes J, Costa JL, Ylstra B, Schmitt F. Vitamin D and the mammary gland: a review on its role in normal development and breast cancer. *Breast cancer research : BCR*. 2012; 14:211. [PubMed: 22676419]
3. Kim Y, Je Y. Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: a meta-analysis. *British journal of cancer*. 2014; 110:2772–84. [PubMed: 24714744]
4. Colditz GA, Frazier AL. Models of breast cancer show that risk is set by events of early life: prevention efforts must shift focus. *Cancer Epidemiol. Biomark. Prev.* 1995; 4:567–571.
5. Pike MC, Krailo MD, Henderson BE, Casagrande JT, Hoel DG. 'Hormonal' risk factors, 'breast tissue age' and the age-incidence of breast cancer. *Nature*. 1983; 303:767–70. [PubMed: 6866078]

6. Schnitt, SJ.; Collins, LC., editors. Pathology of benign breast disorders. Lippincott Williams & Wilkins; Philadelphia: 2010.
7. Su X, Colditz GA, Collins LC, Baer HJ, Sampson LA, Willett WC, Berkey CS, Schnitt SJ, Connolly JL, Rosner BA, Tamimi RM. Adolescent intakes of vitamin D and calcium and incidence of proliferative benign breast disease. *Breast cancer research and treatment*. 2012; 134:783–91. [PubMed: 22622809]
8. Rockett HR, Berkey CS, Field AE, Colditz GA. Cross-sectional measurement of nutrient intake among adolescents in 1996. *Preventive medicine*. 2001; 33:27–37. [PubMed: 11482993]
9. Rockett HR, Breitenbach M, Frazier AL, Witschi J, Wolf AM, Field AE, Colditz GA. Validation of a youth/adolescent food frequency questionnaire. *Preventive medicine*. 1997; 26:808–16. [PubMed: 9388792]
10. Rockett HR, Wolf AM, Colditz GA. Development and reproducibility of a food frequency questionnaire to assess diets of older children and adolescents. *Journal of the American Dietetic Association*. 1995; 95:336–40. [PubMed: 7860946]
11. Geller AC, Colditz G, Oliveria S, Emmons K, Jorgensen C, Aweh GN, Frazier AL. Use of sunscreen, sunburning rates, and tanning bed use among more than 10 000 US children and adolescents. *Pediatrics*. 2002; 109:1009–14. [PubMed: 12042536]
12. C.S.M. Long AJ, Lee HT, Wild JD, Przywarty RC, Hufford D. Ultraviolet index forecasts issued by the National Weather Service. *Bull Am Meteorological Soc*. 1996; 77:729–748.
13. Bertrand KA, Giovannucci E, Liu Y, Malspeis S, Eliassen AH, Wu K, Holmes MD, Laden F, Feskanich D. Determinants of plasma 25-hydroxyvitamin D and development of prediction models in three US cohorts. *Br J Nutr*. 2012; 108:1889–96. [PubMed: 22264926]
14. Nakamura K, Kitamura K, Takachi R, Saito T, Kobayashi R, Oshiki R, Watanabe Y, Tsugane S, Sasaki A, Yamazaki O. Impact of demographic, environmental, and lifestyle factors on vitamin D sufficiency in 9084 Japanese adults. *Bone*. 2015; 74:10–7. [PubMed: 25576673]
15. Munoz-Ortego J, Torrente-Segarra V, Prieto-Alhambra D, Salman-Monte TC, Carbonell-Abello J. Prevalence and predictors of vitamin D deficiency in non-supplemented women with systemic lupus erythematosus in the Mediterranean region: a cohort study. *Scand J Rheumatol*. 2012; 41:472–5. [PubMed: 22830580]
16. de Gruijl FR, Pavel S. The effects of a mid-winter 8-week course of sub-sunburn sunbed exposures on tanning, vitamin D status and colds. *Photochem Photobiol Sci*. 2012; 11:1848–54. [PubMed: 23104230]
17. Neinstein LS. Breast disease in adolescents and young women. *Pediatric clinics of North America*. 1999; 46:607–29. [PubMed: 10384810]
18. Su X, Colditz GA, Willett WC, Collins LC, Schnitt SJ, Connolly JL, Pollak MN, Rosner B, Tamimi RM. Genetic variation and circulating levels of IGF-I and IGFBP-3 in relation to risk of proliferative benign breast disease, *International journal of cancer*. *Journal international du cancer*. 2010; 126:180–90. [PubMed: 19551864]
19. Colditz GA, Hankinson SE. The Nurses' Health Study: lifestyle and health among women. *Nature reviews. Cancer*. 2005; 5:388–96.
20. Rohan TE, Negassa A, Chlebowski RT, Ceria-Ulep CD, Cochrane BB, Lane DS, Ginsberg M, Wassertheil-Smoller S, Page DL. A randomized controlled trial of calcium plus vitamin D supplementation and risk of benign proliferative breast disease. *Breast cancer research and treatment*. 2009; 116:339–50. [PubMed: 18853250]
21. Sperati F, Vici P, Maugeri-Sacca M, Stranges S, Santesso N, Mariani L, Giordano A, Sergi D, Pizzuti L, Di Lauro L, Montella M, Crispo A, Mottolese M, Barba M. Vitamin D supplementation and breast cancer prevention: a systematic review and meta-analysis of randomized clinical trials. *PLoS one*. 2013; 8:e69269. [PubMed: 23894438]
22. van der Rhee H, Coebergh JW, de Vries E. Is prevention of cancer by sun exposure more than just the effect of vitamin D? A systematic review of epidemiological studies. *European journal of cancer*. 2013; 49:1422–36. [PubMed: 23237739]

COMPLIANCE WITH ETHICAL STANDARDS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the mothers of the children included in this study, and the children assented by completing baseline questionnaires.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Age-adjusted characteristics [mean (standard deviation)/percent] of girls in the Growing Up Today Study, by vitamin D intake and tanning behaviors.¹

Table 1

Variable	Vitamin D Intake, ^{1,2}		Sunscreen Use ³		Sunburns in past year ³		Tanning bed use ³		UV Index in state of residence ³	
	Quartile 1	Quartile 4	Never/Rarely	Often/Always	None	3+	No	Yes	Low	High
N	1648	1648	1834	2137	789	2042	4611	681	3976	1325
Vitamin D intake, International Units/day ¹	181 (44)	602 (127)	359 (167)	384 (171)	367 (179)	373 (174)	376 (172)	361 (170)	375 (168)	372 (179)
Age at baseline questionnaire, years	12.3 (1.6)	11.8 (1.6)	12.1 (1.6)	11.8 (1.6)	11.7 (1.6)	12.0 (1.6)	11.7 (1.5)	13.1 (1.4)	11.9 (1.6)	11.9 (1.6)
BMI, kilograms/(meter ²) ²	20.0 (3.6)	19.6 (3.3)	20.0 (3.7)	19.6 (3.2)	19.4 (3.4)	19.8 (3.4)	19.7 (3.5)	19.9 (3.2)	19.8 (3.5)	19.5 (3.5)
Age at menarche, years	12.3 (1.2)	12.4 (1.2)	12.3 (1.2)	12.3 (1.2)	12.4 (1.2)	12.3 (1.2)	12.3 (1.2)	12.2 (1.2)	12.3 (1.2)	12.3 (1.2)
Alcohol intake, drinks/week ⁴	0.6 (1.7)	0.4 (1.2)	0.7 (1.9)	0.5 (1.5)	0.5 (1.5)	0.6 (1.8)	0.5 (1.4)	0.8 (2.1)	0.6 (1.7)	0.5 (1.5)
Total energy intake, calories/day ²	1942 (543)	1880 (494)	1952 (547)	1995 (512)	1945 (545)	2013 (534)	1981 (524)	1986 (536)	2014 (532)	1899 (504)
Moderate to vigorous physical activity, hours/week ²	11.7 (6.5)	12.0 (6.6)	11.8 (6.5)	11.4 (6.0)	11.4 (6.4)	12.1 (6.3)	11.3 (6.1)	14.0 (6.5)	11.7 (6.3)	11.3 (6.1)
Olive, dark, or very dark skin color	32%	24%	35%	22%	46%	18%	26%	33%	26%	32%
Ever pregnant ⁵	17%	14%	20%	12%	15%	15%	14%	22%	15%	14%
Mother or aunt with breast cancer ⁵	9%	9%	9%	9%	10%	9%	9%	9%	9%	11%
Mother with benign breast disease ⁵	24%	26%	25%	25%	27%	25%	26%	24%	25%	25%

¹Vitamin D intake was assessed on the Youth/Adolescent Food Frequency Questionnaire and adjusted for total energy intake using the residual method.

²Derived as a mean of participant values reported in 1996, 1997, and 1998.

³Assessed in 1999.

⁴Derived as a mean of participant values reported in 1997, 1998, 1999, and 2001.

⁵Through year of benign breast disease report or end of follow-up (2010), whichever came first.

Vitamin D intake (mean intake from 1996, 1997, and 1998) and sun exposure variables (1999) in relation to benign breast disease in the Growing Up Today Study.

Table 2

	N	Cases	Age-Adjusted OR (95% CI)	Multivariable OR (95% CI)
Vitamin D intake				
Q1(<243 IU/day)	1648	41	1.00 (ref)	1.00 (ref)
Q2 (243 to 350 IU/day)	1648	23	0.57 (0.34, 0.96)	0.57 (0.34, 0.95)
Q3 (350 to 467 IU/day)	1649	28	0.71 (0.44, 1.16)	0.69 (0.42, 1.12)
Q4 (>467 IU/day)	1648	30	0.77 (0.48, 1.25)	0.76 (0.47, 1.23)
			p-trend=0.47	p-trend=0.42
Sunscreen use				
Never/Rarely	1834	30	1.00 (ref)	1.00 (ref)
Sometimes	1330	24	1.13 (0.66, 1.95)	1.13 (0.65, 1.94)
Always/Often	2137	47	1.44 (0.91, 2.28)	1.47 (0.92, 2.34)
			p-trend=0.12	p-trend=0.10
Sunburns in the past year				
None	790	15	1.00 (ref)	1.00 (ref)
1 to 2	2469	44	0.90 (0.50, 1.62)	0.92 (0.51, 1.67)
3+	2045	42	1.04 (0.57, 1.88)	1.04 (0.57, 1.88)
			p-trend=0.74	p-trend=0.78
Tanning bed use				
No	4617	78	1.00 (ref)	1.00 (ref)
Yes	681	23	1.69 (1.03, 2.77)	1.45 (0.86, 2.44)
Skin Color				
Very fair or fair	3836	70	1.00 (ref)	1.00 (ref)
Olive, dark, or very dark	1428	31	1.20 (0.78, 1.84)	1.18 (0.76, 1.84)
UV index in state of residence				
Low	4942	90	1.00 (ref)	1.00 (ref)
High	1648	32	1.07 (0.71, 1.60)	1.07 (0.71, 1.60)

IU, International Units.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Logistic regression using generalized estimating equation regression models to control for siblings. Multivariable models adjusted for age, family history of breast cancer (in mother or aunt), mother's history of BBD, age at menarche (continuous), BMI (continuous), nulliparity, average hours per week of moderate to vigorous physical activity (continuous), and alcohol intake (continuous). P-trend based on median values within each category where possible.