Published in final edited form as:

Breast Cancer Res Treat. 2012 April ; 132(2): 683–691. doi:10.1007/s10549-011-1885-4.

Vitamin D intake, vitamin D receptor polymorphisms, and breast cancer risk among women living in the southwestern U.S.

Dana E. Rollison,

Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

Ashley L. Cole,

Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

Ko-Hui Tung,

Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

Martha L. Slattery,

Health Research Center, University of Utah, Salt Lake City, UT, USA

Kathy B. Baumgartner,

Department of Epidemiology and Population Health, School of Public Health and Information Sciences, University of Louisville, Louisville, KY, USA

Tim Byers,

University of Colorado School of Medicine, Denver, CO, USA

Roger K. Wolff, and

Health Research Center, University of Utah, Salt Lake City, UT, USA

Anna R. Giuliano

Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

Dana E. Rollison: dana.rollison@moffitt.org

Abstract

No studies of dietary vitamin D intake and vitamin D receptor (VDR) have been conducted comparing breast risk among Hispanic women and non-Hispanic white (NHW) women. We investigated the association between vitamin D intake and breast cancer in a population-based case–control study of 1,527 NHW and 791 Hispanic breast cancer cases diagnosed in 1999–2004 in Arizona, New Mexico, Utah, and Colorado, and 1,599 NHW and 922 Hispanic age-matched controls. Vitamin D intake was assessed using food frequency questionnaires, and associations with breast cancer were adjusted for age, ethnicity, state, education, body mass index, smoking, age at menarche, age at first birth, parity, hormone exposure, height, and physical activity using logistic regression. *BsmI*, *Poly A* and *FokI* vitamin D receptor (VDR) genotypes were also measured. Dietary vitamin D intake was positively associated with breast cancer (highest vs. lowest quartile (Q_4 vs. Q_1): odds ratio (OR) = 1.35, 95% confidence interval (CI) = 1.15–1.60; $P_{\text{trend}} = 0.003$), whereas vitamin D supplement use was inversely associated with breast cancer (10+ $\mu\text{g/day}$ vs. none: OR = 0.79, 95% CI = 0.65–0.96, $P_{\text{trend}} = 0.01$). Similar patterns in risk were

observed by ethnicity and menopausal status. Positive associations with dietary vitamin D intake and inverse associations with supplement use were observed for ER+/PR+ and ER-/PR- breast cancers, but not for ER+/PR-disease. *BsmI* genotype significantly modified the association between dietary vitamin D and breast cancer overall. Future research is needed to better understand potential differences in breast cancer risk by vitamin D source and hormone receptor status.

Keywords

Breast cancer; Vitamin D; Vitamin D receptor; Hispanics; Diet

Introduction

Higher levels of circulating vitamin D metabolites have been consistently associated with decreased risk of breast cancer in several epidemiologic studies [1–5]. In contrast, epidemiologic studies of dietary vitamin D intake and breast cancer have been mostly null [6–13], perhaps due in part to the relatively minor contribution of dietary intake to circulating 25-hydroxyvitamin D [25(OH)D] level. However, most of the women in the previous studies were white, and the relative contribution of diet and sunlight exposure to circulating vitamin D metabolites may differ by ethnicity.

For example, some subgroups of Hispanic women in the U.S. are more likely to eat native Mexican foods than non-Hispanic white (NHW) women, including Mexican cheeses and other foods containing vitamin D [14]. Conversely, Hispanic women on average have darker constitutive skin pigmentation, which may reduce their biologically effective dose of UV radiation, in turn resulting on reduced vitamin D synthesis from sun exposure [15, 16]. Therefore, the impact of dietary vitamin D intake on circulating levels of [25(OH)D] may be higher among Hispanic than NHW women [14]. Furthermore, these ethnic differences in dietary vitamin D intake may partially explain the reduced incidence of breast cancer among Hispanic women compared with NHW women in the U.S. However, no previous studies of dietary vitamin D intake and breast cancer have been conducted among Hispanic women.

To investigate the association between dietary intake of vitamin D and breast cancer among Hispanic and non-Hispanic white women, we conducted a population-based case-control study among women living in the U.S. Southwest using a standardized food frequency questionnaire modified to include foods typically consumed in the Mexican diet. Genotyping of the vitamin D receptor (*VDR*) gene also was conducted to examine ethnic differences in *VDR*-associated breast cancer risk.

Materials and methods

Study population

The study design and methods of the 4-Corners Breast Cancer Study have been previously described in detail [17, 18]. Briefly, a population-based case-control study of breast cancer was conducted to investigate differences in the breast cancer risk profiles of Hispanic and non-Hispanic women living in Colorado, New Mexico, Utah and selected counties of Arizona. Sampling was stratified by race/ethnicity, and women who self-reported their race as NHW, Hispanic, or American Indian not living on reservations were eligible. Histologically confirmed first primary breast cancer cases (in situ or invasive) were identified between October 1999 and May 2004 (ICDO sites C50.0–C50.6 and C50.8–C50.9) through population-based cancer registries in each state. Information on estrogen

receptor (ER) and progesterone receptor (PR) status of tumors was available through the cancer registries for approximately 70 percent of cases.

Population-based controls were frequency-matched to cases in 5-year age groups. Control participants under 65 were randomly selected from driver's license lists in New Mexico and Utah, and from commercial mailing lists in Colorado and Arizona. In all states, women 65 years and older were randomly selected from the Center for Medicare Services (Social Security lists). Of all women contacted, 2,325 cases (68%) and 2,525 (42%) controls participated in the study [18], with participants and nonparticipants having similar community socioeconomic characteristics [19]. Ages ranged from 24 to 79 years, and 65% of women were postmenopausal. All participants signed informed written consent. The study protocol was approved by the Institutional Review Board at each institution.

Data collection

A computerized questionnaire was administered in-person by trained and certified interviewers to obtain information on medical and reproductive histories, lifestyle factors, and family history of cancer. Study participants were given the option of having the interview administered in either English or Spanish. For several questions, women were asked to provide information for a reference period defined as 1 year prior to diagnosis for the cases or selection for the controls. Dietary intake information during the referent period was obtained through a questionnaire modeled after the Coronary Artery Risk Development in Young Adults (CARDIA) study and adapted to include ethnic and other foods commonly consumed in the study region [20, 21]. Major dietary sources of vitamin D included fatty fish, eggs, milk, yogurt, and cheese. Dietary history included specific foods consumed, the frequency of consumption (times per day, week, year), as well as portion sizes. Vitamin intake was also assessed, including the type of vitamin/mineral taken, frequency of intake and dose. Daily vitamin D ($\mu\text{g}/\text{day}$) was calculated from the questionnaire using the Nutritional Data System for Research (NDS-R) Database Version, 4.02_30 (©Regents of the University of Minnesota). Information on vitamin D intake was available for 2,318 cases and 2,521 controls. One woman who reported a dietary vitamin D intake of 3,886 μg per day was excluded from the analysis of vitamin D intake.

Blood samples for genotyping were available for 1,740 (75.1%) cases and 2,051 (81.4%) controls. Three *VDR* genotypes, including two single nucleotide polymorphisms (*BsmI*, *FokI*) and a polyadenosine (*Poly A*) repeat variant were assessed using PCR and restriction fragment length polymorphism (RFLP) methods with modifications [22–24]. As is the convention, a lower case letter was used to denote the presence of the restriction or start site (“*b*” for *BsmI*[rs 154410] and “*f*” for *FokI*[2228570 (previously known as rs10735810)]), while an upper case letter was used to denote the absence of the restriction or start site (“*B*” and “*F*” for *BsmI* and *FokI*, respectively). The length of *Poly A* variants were designated as long (*L*) (18–22 repeats) or short (*S*) (14–17 repeats).

Statistical methods

Quartiles of dietary vitamin D intake were defined based on the distributions in controls. Quartile ranges are presented in both micrograms (μg) and international units (IU) in Table 1. A clear bimodal distribution of vitamin D supplementation was observed in the controls, resulting in a natural cutoff of <10 versus 10+ $\mu\text{g}/\text{day}$ among users. Associations between vitamin D intake, *VDR*, and breast cancer were estimated by calculating odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression, adjusting for age, ethnicity, study center, education, body mass index (BMI (<25, 25–29.9, and 30+ kg/m^2), smoking, age at menarche, age at first birth, parity, height, lifetime physical activity, and recent hormone exposure. (Recent hormone exposure was defined as “positive” for women who

reported having taken hormone replacement therapy (HRT) in the past 2 years; and “negative” for postmenopausal women who did not take HRT within the past 2 years.) Main effects of vitamin D intake were also adjusted for total calorie intake, total dietary fat and total calcium intake, and no appreciable differences in ORs were observed. Therefore, subsequent analyses did not include adjustment for these factors. Trends between vitamin D intake and breast cancer were assessed using a variable set to equal the median value of the respective category of vitamin D intake for each woman.

Departures from Hardy–Weinberg equilibrium were assessed for *VDR* genotypes among controls using the Chisquare test. Associations between *VDR* genotypes and breast cancer were modeled for each individual genotype, using women who were homozygous for the more common allele as the reference category (*GG* (*bb*) for *BsmI*, *CC* (*FF*) for *FokI*, and *LL* (long/long) for *Poly A*. Main effects for vitamin D intake, *VDR* genotypes and breast cancer were stratified by ethnicity (NHW and Hispanics) and menopausal status (pre/perimenopausal and postmenopausal). Interactions between *VDR* genotypes and vitamin D intake in relation to breast cancer were assessed through simultaneous stratification of results by both factors, and statistical significance of the interactions were determined using the Wald test for the interaction terms in the logistic regression models. Associations between vitamin D intake and breast cancer were also investigated by hormone receptor status of the tumors (ER+/PR+, ER+/PR–, and ER–/PR–). (There were too few numbers of ER–/PR+ cases for a separate group.) All tests used a significance level of $P = 0.05$. All data were analyzed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Among controls, dietary vitamin D intake ranged from 0.174 to 34.1 µg/day (7–1,363 IU) (Table 1). A statistically significant age-adjusted positive association was observed between higher dietary vitamin D intake and breast cancer (odds ratio (OR) for the highest quartile (Q_4) versus lowest quartile (Q_1) = 1.28, 95% CI = 1.09–1.50, P for trend = 0.02). A similar association was observed after adjustment for age, race, study center, BMI, smoking, age at menarche, age at first birth, parity, recent hormone exposure, height, and lifetime physical activity (OR = 1.35, 95% CI = 1.15–1.60; P for trend = 0.003). Additional adjustment for total calorie intake, total fat intake and total calcium intake did not appreciably change the risk estimates (Q_4 vs. Q_1 : OR = 1.43, 95% CI = 1.15–1.79, P for trend = 0.008). Vitamin D supplementation was inversely associated with breast cancer, with a statistically significant decreased risk of breast cancer observed for 10+ µg of vitamin D supplement intake per day (OR = 0.79, 95% CI = 0.65–0.96; P for trend = 0.01). Similar associations were observed when analyses were restricted to the 83% of breast cancer cases that were invasive (data not shown).

Positive associations between dietary vitamin D intake and breast cancer risk were observed in both NHW women and Hispanic women (P for trend = 0.04 for both groups), with statistically significant increased risks observed for Q_4 vs. Q_1 (OR = 1.29, 95% CI = 1.05–1.60 in NHW; OR = 1.46, 95% CI = 1.10–1.94 in Hispanics) (Table 2). Vitamin D supplementation was not clearly associated with breast cancer among NHW women, while a statistically significant decreased risk of breast cancer was observed for 10+ µg/day among Hispanic women (OR = 0.68, 95% CI = 0.47–0.97). However, the interaction between vitamin D supplement use, ethnicity, and breast cancer was not statistically significant ($P = 0.62$). None of the *VDR* genes were associated with breast cancer among NHW or Hispanic women. No departures from Hardy–Weinberg equilibrium were observed among controls for the single nucleotide polymorphisms.

Associations between vitamin D intake and breast cancer did not vary by menopausal status (data not shown). Higher levels of dietary vitamin D intake were associated with increased risks of both premenopausal breast cancer (Q_4 vs. Q_1 : OR = 1.37, 95% CI = 1.03–1.83) and postmenopausal breast cancer (Q_4 vs. Q_1 : OR = 1.37, 95% CI = 1.12–1.68), with a statistically significant trend observed only for postmenopausal women ($P = 0.005$), most likely due to the larger sample size. Vitamin D supplementation of 10+ $\mu\text{g/day}$ was associated inversely with both pre- and postmenopausal breast cancer, although none of the individual ORs were statistically significant. No statistically significant associations of either pre- or postmenopausal breast cancer were observed with the *VDR* genotypes.

Higher dietary vitamin D intake was statistically significantly associated with increased breast cancer risk among women with at least one *BsmI* A allele (*Bb* + *BB*) *VDR* genotype (Q_4 vs. Q_1 : OR = 1.48, 95% CI = 1.16–1.89; P for trend = 0.006), while no associations were observed among those women with the *GG* (*bb*) genotype (P for interaction = 0.04) (Table 3). A similar pattern was observed for the *Poly A* *VDR* genotype, with increased risks of breast cancer associated with higher dietary vitamin D intake among women with long/short (*LS*) or short/short (*SS*) *Poly A* genotypes (Q_4 vs. Q_1 : OR = 1.41, 95% CI = 1.10–1.81; P for trend = 0.02) but not among those with the long/long (*LL*) *Poly A* genotype (P for interaction = 0.09). Dietary vitamin D intake also was positively associated with breast cancer among women with the *FokI* CC (*FF*) genotype (Q_4 vs. Q_1 : OR = 1.43, 95% CI = 1.04–1.96; P for trend = 0.05), whereas no pattern of association was observed among women with *CT* and *TT* (*Ff* and *ff*) *FokI* genotypes (P for interaction = 0.07). In contrast to the interactions observed for dietary vitamin D intake, none of the three *VDR* genotypes significantly modified the inverse associations observed between vitamin D supplementation and breast cancer risk. When the interactions between vitamin D and *VDR* genotypes were examined by ethnicity, there were no substantive differences between NHW and Hispanic women (data not shown).

Higher dietary vitamin D intake was significantly associated with breast cancers of ER+/PR+ (Q_4 vs. Q_1 : OR = 1.35, 95% CI = 1.08–1.68, P for trend = 0.05) and ER–/PR– (Q_4 vs. Q_1 : OR = 1.63, 95% CI = 1.14–2.34, P for trend = 0.01), but not with ER+/PR– cancer (Table 4). Similarly, statistically significant inverse associations were observed between vitamin D supplementation and ER+/PR+ breast cancer (10+ vs. 0 μg : OR = 0.74, 95% CI = 0.57–0.96, P for trend = 0.008) and ER–/PR– disease (10+ vs. 0 μg : OR = 0.44, 95% CI = 0.26–0.75, P for trend = 0.002), but not for ER+/PR– cancers (10+ vs. 0 μg : OR = 0.98, 95% CI = 0.57–1.70, P for trend = 0.70).

Discussion

Overall, dietary vitamin D was positively associated with breast cancer, while vitamin D supplement was inversely associated with breast cancer. The positive associations with dietary vitamin D intake were observed for both pre- and postmenopausal breast cancer, and among both NHW and Hispanic women. Our findings of a positive association between dietary vitamin D intake and breast cancer are inconsistent with previous epidemiologic studies of mostly white women, which observed either an inverse association [13, 25, 26] or no association [6–13]. Previous studies of vitamin D supplementation and breast cancer also have been mostly null [8, 10, 12]. Similar to our findings, a recent case–control study reported a significant inverse relationship of vitamin D supplement intake >10 $\mu\text{g/day}$ with premenopausal breast cancer risk [27].

Several possible explanations exist for the positive association observed between dietary vitamin D intake and breast cancer in the current study, the first of which is chance. Although all analyses were adjusted for conventional breast cancer risk factors, and

additional adjustment for dietary fats, calcium and total calories did not attenuate the observed positive associations, there may have been residual confounding. For example, women who consume higher levels of dietary vitamin D may be more likely to consume foods comprising a “Western diet” pattern, which has been shown to be associated with increased breast cancer risk [14]. However, adjustment for dietary patterns did not diminish the observed positive association between dietary vitamin D and breast cancer (data not shown). Furthermore, no specific source of dietary vitamin D was associated with breast cancer more than any other, based on analyses of specific foods (milk, cheeses, yogurts, etc.). We also considered possible effect modification of the association between dietary vitamin D and breast cancer by several factors including body mass index, total calories, total fat intake, and total calcium intake, and observed no statistically significant differences between groups. However, residual confounding and/or effect modification by unmeasured factors cannot be ruled out. Furthermore, although study participants did not differ from non-participants with respect to socioeconomic factors [19], no information on vitamin D intake, supplement use, or other potential confounding factors was available for non-participants. If participants differed from non-participants with respect to these factors, it is possible the observed results could have been biased.

The contrast between the positive associations of dietary vitamin D intake and the inverse associations of vitamin D supplementation with breast cancer may be due to differences in misclassification of exposures. Dietary vitamin D intake is based on dietary recall of the consumption of specific foods, coupled with estimation of the vitamin D content of those foods using a validated database. There may be measurement errors in both steps. Although vitamin D supplementation also was based on self-report, one’s ability to recall supplement use may be more precise than the ability to recall consumption of specific foods, both with respect to frequency of intake and amount or dose. However, if the magnitude of exposure misclassification was similar among breast cancer cases and controls, then the observed positive association between dietary vitamin D intake and breast cancer would represent an underestimation.

Lower circulating vitamin D [25(OH)D] levels have been previously associated with increased breast cancer mortality [28]. To investigate the effect of survival time after cancer diagnosis on study results, we stratified the associations between dietary and supplement intake of vitamin D and breast cancer by the length of time between breast cancer diagnosis and study interview. The positive association between high levels of dietary vitamin D intake and breast cancer was consistently observed across women interviewed less than 1 year, 1–2 years or more than 2 years after diagnosis, suggesting survival time did not bias the dietary vitamin D results. Regarding supplement use, those cases who were interviewed more than 2 years after diagnosis were *less* likely to report having taken 10+ µg of vitamin D per day during the reference period (one year prior to diagnosis) as compared with those who were interviewed within one year of diagnosis ($P = 0.01$). Although this observation is not consistent with the reported association between vitamin D intake and breast cancer survival, it is possible that cases in the current study were less likely to recall their supplement use the further out the interview was from the reference period.

Although there were no statistically significant differences in the inverse associations observed between vitamin D supplement use and breast cancer among NHW versus Hispanic women, the inverse association for 10+ µg/day was greater in magnitude and statistically significant among Hispanic women despite the substantially smaller sample size. There may be ethnic differences in the relative contribution of oral vitamin D intake versus vitamin D synthesis from sunlight exposure to circulating vitamin D levels. Dietary vitamin D intake is thought to be a minor source of circulating 25(OH)D concentrations, as compared with vitamin D derived from sun exposure [29]. However, some [15, 16] but not

all [30, 31] studies suggest that increased skin pigmentation reduces the dose of UV exposure, resulting in less vitamin D synthesis. Thus, if Hispanic women in the current study experienced lower circulating vitamin D levels compared with white women under the same amount of sun exposure, then vitamin D supplementation would have had a greater relative impact on circulating vitamin D levels in Hispanic women.

Both the positive association with dietary vitamin D intake and the inverse association with vitamin D supplementation were of greater magnitude for ER-/PR- breast cancer than for ER+/PR+ breast cancer, despite the smaller sample size of this subgroup. In contrast, neither dietary vitamin D nor supplement use was associated with ER+/PR- breast cancer. Two previous studies have investigated vitamin D in the context of combined ER and PR status, one of which observed inverse associations between vitamin D supplementation in adolescence and ER+/PR+, ER+/PR-, and ER-/PR- breast cancers, with the association reaching statistical significance for only the ER+/PR+ group [32]. Another study observed statistically significant inverse associations between plasma 25(OH)D and breast cancers defined as "ER+ and/or PR+" as well as ER-/PR- cancers [3]. An inverse association between vitamin D supplementation and reduced risk of both ER+ and ER- cancers is consistent with experimental data that Gemini vitamin D analogues have inhibitory effects on both ER+ and ER- mammary tumorigenesis [33]. Overall, emerging evidence suggests that vitamin D supplementation may be potentially important for reducing risk of ER-/PR- breast cancer, a subtype for which few modifiable risk factors have been established.

No statistically significant main effects were observed for *BsmI*, *Poly A*, or *FokI VDR* genotypes among NHW or Hispanic women in the current study. The null findings for both *BsmI* and *Poly A* are consistent with the fact that these polymorphisms have been reported to be in linkage disequilibrium [34]. Two recent meta-analyses [35, 36] also observed no association between *BsmI* genotype and breast cancer. The same two meta-analyses reported a statistically significant but modest increased risk of breast cancer associated with the *FokI ff* genotype (OR = 1.14 for *ff* vs. *FF* [35]), while the another study reported a inverse association [37]. The only *VDR* results published from Hispanic women are from the multiethnic cohort (MEC) study, in which neither *FokI* nor *BsmI* genotypes were associated with statistically significant risk of breast cancer [38], and from a population-based case-control study in which ethnicity-specific risk estimates were not presented [39]. To the best of our knowledge, only two case-control studies have examined the interaction between *VDR* genotype and dietary vitamin D intake, but neither observed significant interactions between total vitamin D intake and *FokI*, *BsmI* or *Poly A VDR* genotypes in relation to breast cancer [37, 40]. Thus, the statistically significant interaction observed between dietary intake and *BsmI* genotype in the current study may be due to chance.

This is the first study to investigate the associations between dietary vitamin D, supplementation and breast cancer among Hispanic women. No differences in the directions of these associations were observed between NHW and Hispanic women, although the sample size was too limited to evaluate ethnic differences in the magnitude of these associations and the interactions between dietary vitamin D intake and *VDR* genotype. Future studies of vitamin D and breast cancer among Hispanic women should include measures of vitamin D dietary intake and supplement use in addition to measures of UV exposure, circulating vitamin D metabolites and hormone receptor status of the tumor to further characterize the role of vitamin D in etiology and, ultimately, the potential for breast cancer prevention.

Acknowledgments

Financial support was provided by the National Institutes of Health (CA078682, CA078762, CA078552, CA078802, CA40002). The Utah Cancer Registry is funded by the National Cancer Institute (Contract # N01-PC-67000) with additional support from the State of Utah Department Health. The New Mexico Tumor Registry and Arizona and Colorado cancer registries are funded by the Centers for Disease Control and Prevention National Program of Cancer Registries.

References

1. Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, Flesch-Janys D, Chang-Claude J. Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer—results of a large case–control study. *Carcinogenesis*. 2008; 29:93–99. [PubMed: 17974532]
2. Bertone-Johnson ER, Chen WY, Holick MF, Hollis BW, Colditz GA, Willett WC, Hankinson SE. Plasma 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:1991–1997. [PubMed: 16103450]
3. Crew KD, Gammon MD, Steck SE, Hershman DL, Cremers S, Dworakowski E, Shane E, Terry MB, Desai M, Teitelbaum SL, Neugut AI, Santella RM. Association between plasma 25-hydroxyvitamin D and breast cancer risk. *Cancer Prev Res (Phila Pa)*. 2009; 2:598–604.
4. Janowsky EC, Lester GE, Weinberg CR, Millikan RC, Schild-kraut JM, Garrett PA, Hulka BS. Association between low levels of 1,25-dihydroxyvitamin D and breast cancer risk. *Public Health Nutr*. 1999; 2:283–291. [PubMed: 10512563]
5. Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, Wilson RG, Colston KW. Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. *Eur J Cancer*. 2005; 41:1164–1169. [PubMed: 15911240]
6. Frazier AL, Ryan CT, Rockett H, Willett WC, Colditz GA. Adolescent diet and risk of breast cancer. *Breast Cancer Res*. 2003; 5:R59–R64. [PubMed: 12631400]
7. Frazier AL, Li L, Cho E, Willett WC, Colditz GA. Adolescent diet and risk of breast cancer. *Cancer Causes Control*. 2004; 15:73–82. [PubMed: 14970737]
8. John EM, Schwartz GG, Dreon DM, Koo J. Vitamin D and breast cancer risk: the NHANES I epidemiologic follow-up study, 1971–1975 to 1992. *National Health and Nutrition Examination Survey*. *Cancer Epidemiol Biomarkers Prev*. 1999; 8:399–406. [PubMed: 10350434]
9. Levi F, Pasche C, Lucchini F, La VC. Dietary intake of selected micronutrients and breast-cancer risk. *Int J Cancer*. 2001; 91:260–263. [PubMed: 11146455]
10. Lin J, Manson JE, Lee IM, Cook NR, Buring JE, Zhang SM. Intakes of calcium and vitamin D and breast cancer risk in women. *Arch Intern Med*. 2007; 167:1050–1059. [PubMed: 17533208]
11. McCullough ML, Rodriguez C, Diver WR, Feigelson HS, Stevens VL, Thun MJ, Calle EE. Dairy, calcium, and vitamin D intake and postmenopausal breast cancer risk in the Cancer Prevention Study II Nutrition Cohort. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:2898–2904. [PubMed: 16365007]
12. Robien K, Cutler GJ, Lazovich D. Vitamin D intake and breast cancer risk in postmenopausal women: the Iowa Women's Health Study. *Cancer Causes Control*. 2007; 18:775–782. [PubMed: 17549593]
13. Shin MH, Holmes MD, Hankinson SE, Wu K, Colditz GA, Willett WC. Intake of dairy products, calcium, and vitamin D and risk of breast cancer. *J Natl Cancer Inst*. 2002; 94:1301–1311. [PubMed: 12208895]
14. Murtaugh MA, Sweeney C, Giuliano AR, Herrick JS, Hines L, Byers T, Baumgartner KB, Slattery ML. Diet patterns and breast cancer risk in Hispanic and non-Hispanic white women: the Four-Corners Breast Cancer Study. *Am J Clin Nutr*. 2008; 87:978–984. [PubMed: 18400722]
15. Armas LA, Dowell S, Akhter M, Duthuluru S, Huerter C, Hollis BW, Lund R, Heaney RP. Ultraviolet-B radiation increases serum 25-hydroxyvitamin D levels: the effect of UVB dose and skin color. *J Am Acad Dermatol*. 2007; 57:588–593. [PubMed: 17637484]
16. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. *Lancet*. 1982; 1:74–76. [PubMed: 6119494]

17. Slattery ML, Sweeney C, Edwards S, Herrick J, Baumgartner K, Wolff R, Murtaugh M, Baumgartner R, Giuliano A, Byers T. Body size, weight change, fat distribution and breast cancer risk in Hispanic and non-Hispanic white women. *Breast Cancer Res Treat.* 2006; 102(1):85–101. [PubMed: 17080310]
18. Slattery ML, Sweeney C, Wolff R, Herrick J, Baumgartner K, Giuliano A, Byers T. Genetic variation in IGF1, IGFBP3, IRS1, IRS2 and risk of breast cancer in women living in Southwestern United States. *Breast Cancer Res Treat.* 2006; 104(2):197–209. [PubMed: 17051426]
19. Sweeney C, Edwards SL, Baumgartner KB, Herrick JS, Palmer LE, Murtaugh MA, Stroup A, Slattery ML. Recruiting Hispanic women for a population-based study: validity of surname search and characteristics of nonparticipants. *Am J Epidemiol.* 2007; 166:1210–1219. [PubMed: 17827445]
20. Liu K, Slattery M, Jacobs D Jr, Cutter G, McDonald A, Van HL, Hilner JE, Caan B, Bragg C, Dyer A. A study of the reliability and comparative validity of the cardia dietary history. *Ethn Dis.* 1994; 4:15–27. [PubMed: 7742729]
21. Slattery ML, Caan BJ, Duncan D, Berry TD, Coates A, Kerber R. A computerized diet history questionnaire for epidemiologic studies. *J Am Diet Assoc.* 1994; 94:761–766. [PubMed: 8021418]
22. Harris SS, Eccleshall TR, Gross C, wson-Hughes B, Feldman D. The vitamin D receptor start codon polymorphism (FokI) and bone mineral density in premenopausal American black and white women. *J Bone Miner Res.* 1997; 12:1043–1048. [PubMed: 9200003]
23. McClure L, Eccleshall TR, Gross C, Villa ML, Lin N, Ramaswamy V, Kohlmeier L, Kelsey JL, Marcus R, Feldman D. Vitamin D receptor polymorphisms, bone mineral density, and bone metabolism in postmenopausal Mexican-American women. *J Bone Miner Res.* 1997; 12:234–240. [PubMed: 9041055]
24. Slatter ML, Yakumo K, Hoffman M, Neuhausen S. Variants of the VDR gene and risk of colon cancer (United States). *Cancer Causes Control.* 2001; 12:359–364. [PubMed: 11456232]
25. Knight JA, Lesosky M, Barnett H, Raboud JM, Vieth R. Vitamin D and reduced risk of breast cancer: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:422–429. [PubMed: 17372236]
26. Rossi M, McLaughlin JK, Lagiou P, Bosetti C, Talamini R, Lipworth L, Giacosa A, Montella M, Franceschi S, Negri E, La VC. Vitamin D intake and breast cancer risk: a case-control study in Italy. *Ann Oncol.* 2009; 20:374–378. [PubMed: 18711029]
27. Anderson LN, Cotterchio M, Vieth R, Knight JA. Vitamin D and calcium intakes and breast cancer risk in pre- and post-menopausal women. *Am J Clin Nutr.* 2010; 91:1699–1707. [PubMed: 20392891]
28. Goodwin PJ, Ennis M, Pritchard KI, Koo J, Hood N. Prognostic effects of 25-hydroxyvitamin D levels in early breast cancer. *J Clin Oncol.* 2009; 27:3757–3763. [PubMed: 19451439]
29. Colston KW. Vitamin D and breast cancer risk. *Best Pract Res Clin Endocrinol Metab.* 2008; 22:587–599. [PubMed: 18971120]
30. Bogh MK, Schmedes AV, Philipsen PA, Thieden E, Wulf HC. Vitamin D production after UVB exposure depends on baseline vitamin D and total cholesterol but not on skin pigmentation. *J Invest Dermatol.* 2010; 130:546–553. [PubMed: 19812604]
31. Brazierol WF, McPhee AJ, Mimouni F, Specker BL, Tsang RC. Serial ultraviolet B exposure and serum 25 hydroxyvitamin D response in young adult American blacks and whites: no racial differences. *J Am Coll Nutr.* 1988; 7:111–118. [PubMed: 3361035]
32. Blackmore KM, Lesosky M, Barnett H, Raboud JM, Vieth R, Knight JA. Vitamin D from dietary intake and sunlight exposure and the risk of hormone-receptor-defined breast cancer. *Am J Epidemiol.* 2008; 168:915–924. [PubMed: 18756015]
33. Lee HJ, Paul S, Atalla N, Thomas PE, Lin X, Yang I, Buckley B, Lu G, Zheng X, Lou YR, Conney AH, Maehr H, Adorini L, Uskokovic M, Suh N. Gemini vitamin D analogues inhibit estrogen receptor-positive and estrogen receptor-negative mammary tumorigenesis without hypercalcemic toxicity. *Cancer Prev Res (Phila Pa).* 2008; 1:476–484.
34. Bretherton-Watt D, Given-Wilson R, Mansi JL, Thomas V, Carter N, Colston KW. Vitamin D receptor gene polymorphisms are associated with breast cancer risk in a UK Caucasian population. *Br J Cancer.* 2001; 85:171–175. [PubMed: 11461072]

35. Raimondi S, Johansson H, Maisonneuve P, Gandini S. Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. *Carcinogenesis*. 2009; 30:1170–1180. [PubMed: 19403841]
36. Tang C, Chen N, Wu M, Yuan H, Du Y. FokI polymorphism of vitamin D receptor gene contributes to breast cancer susceptibility: a meta-analysis. *Breast Cancer Res Treat*. 2009; 117:391–399. [PubMed: 19145484]
37. Anderson LN, Cotterchio M, Cole DE, Knight JA. Vitamin D-related genetic variants, interactions with vitamin D exposure, and breast cancer risk among Caucasian women in Ontario. *Cancer Epidemiol Biomarkers Prev*. 2011; 20(8):1708–1717. [PubMed: 21693626]
38. McKay JD, McCullough ML, Ziegler RG, Kraft P, Saltzman BS, Riboli E, Barricarte A, Berg CD, Bergland G, Bingham S, Brustad M, Bueno-de-Mesquita HB, Burdette L, Buring J, Calle EE, Chanock SJ, Clavel-Chapelon F, Cox DG, Dossus L, Feigelson HS, Haiman CA, Hankinson SE, Hoover RN, Hunter DJ, Husing A, Kaaks R, Kolonel LN, Le ML, Linseisen J, McCarty CA, Overvad K, Panico S, Purdue MP, Stram DO, Stevens VL, Trichopoulos D, Willett WC, Yuenger J, Thun MJ. Vitamin D receptor polymorphisms and breast cancer risk: results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. *Cancer Epidemiol Biomarkers Prev*. 2009; 18:297–305. [PubMed: 19124512]
39. John EM, Schwartz GG, Koo J, Wang W, Ingles SA. Sun exposure, vitamin D receptor gene polymorphisms, and breast cancer risk in a multiethnic population. *Am J Epidemiol*. 2007; 166:1409–1419. [PubMed: 17934201]
40. McCullough ML, Stevens VL, Diver WR, Feigelson HS, Rodriguez C, Bostick RM, Thun MJ, Calle EE. Vitamin D pathway gene polymorphisms, diet, and risk of postmenopausal breast cancer: a nested case-control study. *Breast Cancer Res*. 2007; 9:R9. [PubMed: 17244366]

Dietary vitamin D intake, supplement use, vitamin D receptor genotype, and breast cancer among women living in the U.S. Southwest, 1999–2004

Table 1

	Cases (<i>n</i> = 2,318)		Controls (<i>n</i> = 2,521)		Age-adjusted		Full model ^a	
	<i>n</i>	%	<i>n</i>	%	OR	95% CI	OR	95% CI
Vitamin D intake (cases <i>n</i> = 2,317)								
Dietary intake ^b								
Quartile 1	483	20.8	630	25.0	1.00	Reference	1.00	Reference
Quartile 2	614	26.5	631	25.0	1.26	1.07–1.49	1.28	1.08–1.51
Quartile 3	586	25.3	629	25.0	1.20	1.02–1.41	1.23	1.04–1.45
Quartile 4	634	27.4	631	25.0	1.28	1.09–1.50	1.35	1.15–1.60
					<i>P</i> _{trend} = 0.02		<i>P</i> _{trend} = 0.003	
Supplements								
None	951	41.0	959	38.0	1.00	Reference	1.00	Reference
<10 µg (<400 IU)	1,134	49.0	1,261	50.0	0.93	0.83–1.05	0.90	0.79–1.02
10+ µg (400+ IU)	232	10.0	301	11.9	0.82	0.67–1.00	0.79	0.65–0.96
					<i>P</i> _{trend} = 0.05		<i>P</i> _{trend} = 0.01	
Vitamin D receptor (VDR)								
<i>BsmI</i> genotype								
<i>GG</i> (<i>bb</i>)	684	39.3	864	42.2	1.00	Reference	1.00	Reference
<i>GA</i> (<i>Bb</i>)	809	46.5	905	44.2	1.14	0.99–1.30	1.12	0.97–1.29
<i>AA</i> (<i>BB</i>)	247	14.2	278	13.6	1.13	0.93–1.38	1.10	0.90–1.34
<i>Poly A</i> genotype ^c								
<i>LL</i>	699	40.7	888	43.6	1.00	Reference	1.00	Reference
<i>LS</i>	773	45.1	875	43.0	1.13	0.98–1.30	1.11	0.96–1.28
<i>SS</i>	244	14.2	274	13.5	1.14	0.94–1.39	1.11	0.90–1.36
<i>FokI</i> genotype								
<i>CC</i> (<i>FF</i>)	662	38.1	752	36.7	1.00	Reference	1.00	Reference
<i>CT</i> (<i>Ff</i>)	807	46.5	983	47.9	0.93	0.81–1.07	0.94	0.82–1.08
<i>TT</i> (<i>ff</i>)	268	15.4	316	15.4	0.96	0.79–1.16	0.99	0.81–1.20

^a Adjusted for age, ethnicity, study center, education, body mass index, smoking, age at menarche, age at first birth, parity, recent hormone exposure, height, and lifetime physical activity

^bQuartiles (*Q*) 1–4 of dietary vitamin D intake corresponded to the following ranges expressed in micrograms (*Q*₁: 0.174–3.063, *Q*₂: 3.064–5.065, *Q*₃: 5.066–7.712; *Q*₄: 7.713–34.067) and international units (IU) (*Q*₁: 7.0–122.5; *Q*₂: 122.6–202.6; *Q*₃: 202.7–308.5; *Q*₄: 308.6–1362.7)

^clong; *S* short

Table 2

Vitamin D intake, *VDR* genotypes and breast cancer among non-Hispanic White and Hispanic women

	Non-Hispanic White women						Hispanic women						<i>P</i> for interaction
	Cases			Controls			Cases			Controls			
	<i>n</i>	%		<i>n</i>	%		<i>n</i>	%		<i>n</i>	%		
Vitamin D intake													
Dietary intake													
Quartile 1	314	20.6	383	24.0	1.00	Reference	169	21.4	247	26.8	1.00	Reference	
Quartile 2	401	26.3	402	25.1	1.22	1.00–1.50	213	26.9	229	24.8	1.41	1.07–1.87	
Quartile 3	396	25.9	411	25.7	1.21	0.98–1.49	190	24.0	218	23.6	1.26	0.94–1.67	
Quartile 4	415	27.2	403	25.2	1.29	1.05–1.59	219	27.7	228	24.7	1.46	1.10–1.94	0.57
						<i>P</i> _{trend} = 0.04						<i>P</i> _{trend} = 0.04	
Supplements													
None	539	35.3	507	31.7	1.00	Reference	412	52.1	452	49.0	1.00	Reference	
<10 mcg	814	53.4	888	55.5	0.86	0.74–1.01	320	40.5	373	40.5	0.96	0.78–1.19	
10+ mcg	173	11.3	204	12.8	0.82	0.64–1.05	59	7.5	97	10.5	0.68	0.47–0.97	0.62
						<i>P</i> _{trend} = 0.05						<i>P</i> _{trend} = 0.09	
VDR													
<i>BsmI</i> genotype													
<i>GG (bb)</i>	399	34.1	478	36.0	1.00	Reference	285	49.9	386	53.7	1.00	Reference	
<i>GA (Bb)</i>	579	49.5	631	47.5	1.11	0.93–1.33	230	40.3	274	38.1	1.13	0.89–1.43	
<i>AA (BB)</i>	191	16.3	219	16.5	1.05	0.83–1.33	56	9.8	59	8.2	1.24	0.83–1.86	0.33
<i>Poly A</i> genotype ^b													
<i>LL</i>	411	35.7	491	37.3	1.00	Reference	288	51.1	397	55.2	1.00	Reference	
<i>LS</i>	548	47.6	616	46.7	1.08	0.90–1.29	225	39.9	259	36.0	1.19	0.94–1.51	
<i>SS</i>	193	16.8	211	16.0	1.09	0.86–1.39	51	9.0	63	8.8	1.11	0.74–1.67	0.50
<i>FokI</i> genotype													
<i>CC (FF)</i>	461	39.6	508	38.3	1.00	Reference	201	35.1	244	33.7	1.00	Reference	
<i>CT (Ff)</i>	533	45.8	631	47.6	0.93	0.79–1.11	274	47.9	352	48.6	0.93	0.72–1.20	
<i>TT (ff)</i>	171	14.7	188	14.2	1.04	0.81–1.33	97	17.0	128	17.7	0.91	0.66–1.27	0.64

^a Adjusted for age, study center, education, body mass index, smoking, age at menarche, age at first birth, parity, recent hormone exposure, height, and lifetime physical activity

^b *L* long; *S* short

Table 3

Dietary vitamin D, supplement use and breast cancer by *VDR* genotypes

Vitamin D intake	Cases		Controls		OR ^a	95% CI ^a	Cases		Controls		OR ^a	95% CI ^a	P for interaction
	n	%	n	%			n	%	n	%			
BsmI genotype (rs1544410): GG (bb)													
Dietary intake													
Quartile 1	148	21.6	197	22.8	1.00	Reference	224	21.2	301	25.4	1.00	Reference	
Quartile 2	182	26.6	211	24.4	1.13	0.84–1.53	286	27.1	303	25.6	1.29	1.02–1.64	
Quartile 3	177	25.9	220	25.5	1.06	0.78–1.42	247	23.4	299	25.3	1.14	0.89–1.46	
Quartile 4	177	25.9	236	27.3	1.01	0.75–1.36	298	28.3	280	23.7	1.48	1.16–1.89	
					P _{trend} = 0.77						P _{trend} = 0.006	P _{int} = 0.04	
Supplements													
None	299	43.7	324	37.5	1.00	Reference	401	38.0	429	36.3	1.00	Reference	
<10 mcg	314	45.9	445	51.5	0.79	0.63–1.99	547	51.9	614	51.9	0.94	0.78–1.14	
10+ mcg	71	10.4	95	11.0	0.87	0.61–1.25	107	10.1	140	11.8	0.80	0.59–1.07	
					P _{trend} = 0.14						P _{trend} = 0.16	P _{int} = 0.41	
Poly A genotype: LL (long/long)													
LS (long/short) + SS (short/short)													
Dietary intake													
Quartile 1	144	20.6	203	22.9	1.00	Reference	221	21.7	289	25.2	1.00	Reference	
Quartile 2	195	27.9	219	24.7	1.24	0.92–1.66	272	26.8	296	25.8	1.22	0.96–1.56	
Quartile 3	179	25.6	226	25.5	1.10	0.81–1.48	239	23.5	290	25.2	1.11	0.86–1.42	
Quartile 4	181	25.9	240	27.0	1.06	0.79–1.43	284	28.0	274	23.9	1.41	1.10–1.81	
					P _{trend} = 0.89						P _{trend} = 0.02	P _{int} = 0.09	
Supplements													
None	302	43.2	334	37.6	1.00	Reference	389	38.3	417	36.3	1.00	Reference	
<10 mcg	325	46.5	458	51.6	0.81	0.65–1.01	524	51.6	594	51.7	0.94	0.78–1.14	
10+ mcg	72	10.3	96	10.8	0.91	0.64–1.30	103	10.1	138	12.0	0.79	0.58–1.07	
					P _{trend} = 0.22						P _{trend} = 0.15	P _{int} = 0.59	
FokI genotype (rs2228570): CC (ff)													
CT + TT (Ff + ff)													
Dietary intake													
Quartile 1	127	19.2	178	23.7	1.00	Reference	242	22.5	321	24.7	1.00	Reference	

Vitamin D intake	Cases		Controls		OR ^a	95% CI ^a		OR ^a	95% CI ^a		P for interaction
	n	%	n	%		n	%		n	%	
Quartile 2	188	28.4	207	27.5	1.28	281	26.2	1.22	309	23.8	0.96–1.54
Quartile 3	170	25.7	187	24.9	1.31	255	23.7	1.01	332	25.6	0.80–1.29
Quartile 4	177	26.7	180	23.9	1.43	296	27.6	1.22	337	25.9	0.96–1.54
					$P_{\text{trend}} = 0.05$			$P_{\text{trend}} = 0.25$			$P_{\text{int}} = 0.07$
Supplements											
None	253	38.2	255	33.9	1.00	445	41.4	1.00	501	38.6	Reference
<10 mcg	342	51.7	416	55.3	0.80	518	48.2	0.91	643	49.5	0.76–1.09
10+ mcg	67	10.1	81	10.8	0.80	111	10.4	0.83	155	11.9	0.62–1.10
					$P_{\text{trend}} = 0.10$			$P_{\text{trend}} = 0.16$			$P_{\text{int}} = 0.73$

^a Adjusted for age, ethnicity, study center, education, body mass index, smoking, age at menarche, age at first birth, parity, recent hormone exposure, height, and lifetime physical activity

Table 4

Dietary vitamin D, supplement use and breast cancer by ER/PR status

Vitamin D intake	Controls		ER+/PR+ cases				ER+/PR- cases				ER-/PR- cases			
	n	%	n	%	OR ^a	95% CI ^a	n	%	OR ^a	95% CI ^a	n	%	OR ^a	95% CI ^a
Dietary intake														
Quartile 1	630	25.0	206	20.7	1.00	Reference	52	29.6	1.00	Reference	54	18.0	1.00	Reference
Quartile 2	631	25.0	277	27.8	1.34	1.08–1.66	35	19.9	0.67	0.43–1.04	74	24.7	1.35	0.93–1.96
Quartile 3	629	25.0	239	24.0	1.17	0.94–1.46	42	23.9	0.84	0.55–1.28	77	25.7	1.38	0.95–2.00
Quartile 4	631	25.0	274	27.5	1.35	1.08–1.68	47	26.7	0.92	0.61–1.40	95	31.7	1.63	1.14–2.34
					$P_{\text{trend}} = 0.05$				$P_{\text{trend}} = 0.91$				$P_{\text{trend}} = 0.01$	
Supplements														
None	959	38.0	420	42.2	1.00	Reference	61	34.7	1.00	Reference	145	48.3	1.00	Reference
<10 mcg	1,261	50.0	478	48.0	0.84	0.71–0.99	96	54.6	1.21	0.85–1.70	138	46.0	0.80	0.61–1.03
10+ mcg	301	11.9	98	9.8	0.74	0.57–0.96	19	10.8	0.98	0.57–1.70	17	5.7	0.44	0.26–0.75
					$P_{\text{trend}} = 0.008$				$P_{\text{trend}} = 0.70$				$P_{\text{trend}} = 0.002$	

^a Adjusted for age, ethnicity, study center, education, body mass index, smoking, age at menarche, age at first birth, parity, recent hormone exposure, height, and lifetime physical activity