Associations Between Polymorphisms in the Vitamin D Receptor and Breast Cancer Risk

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Abstract

Biological and epidemiologic data suggest that vitamin D levels may influence breast cancer development. The vitamin D receptor (VDR) is a crucial mediator for the cellular effects of vitamin D and additionally interacts with other cell-signaling pathways that influence cancer development. Because functional data exist on *FOK1* and previous studies have suggested a relation between *BSM1* and breast cancer risk, we evaluated the associations of the *FOK1* and *BSM1* VDR polymorphisms and breast cancer risk. In a case-control study nested within the Nurses' Health Study, we genotyped 1,234 incident cases (diagnosed between return of a blood sample in 1989-1990 and June 1, 2000) and 1,676 controls for *FOK1*, and 1,180 cases and 1,547 controls for *BSM1*. We observed a significantly increased risk of breast cancer among carriers of the *ff* genotype of *FOK1* (multivariate odds ratio, 1.34; 95% confidence intervals, 1.06-1.69) compared with those with *FF*. We did not observe an association between polymorphisms in *BSM1* and breast cancer risk (multivariate odds ratio, 0.93; 95% confidence intervals, 0.72-1.20) for *BB* versus *bb*). The *FOK1* association did not vary significantly by menopausal status, estrogen, and progesterone receptor status of the tumors, or plasma levels of 25 hydroxyvitamin D or 1,25 dihydroxyvitamin D. Our results suggest that the VDR may be a mediator of breast cancer risk and could represent a target for cancer prevention efforts. (Cancer Epidemiol Biomarkers Prev 2005;14(10):2335–9)

Introduction

In observational studies, vitamin D plasma levels (1) and intake (2, 3) have been associated with decreased breast cancer risk. Vitamin D_3 from dietary and skin sources is hydroxylated in the liver into 25-hydroxyvitamin D (25(OH)D), which is the vitamin D metabolite circulating in the greatest concentration. 25(OH)D is then further hydroxylated in the kidneys and other tissues to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), the most biologically active metabolite and the natural ligand for the vitamin D receptor (VDR; ref. 4). $1,25(OH)_2D$ and its analogues can inhibit breast cancer cell proliferation *in vitro* and *in vivo* (5-8). In addition to its role in skeletal metabolism and calcium/phosphate balance, the VDR interacts with many other pathways, including p21 (5), fibronectin (6), and retinoid signaling (7). Therefore, the VDR is a crucial mediator for the cellular growth and differentiation effects of vitamin D and polymorphisms in the VDR may influence breast cancer risk. Most tissues in the body, as well as both normal breast and breast cancer cells, express VDR (8, 9).

The gene encoding VDR is known to have several polymorphisms. The *FOK1* restriction enzyme identifies a polymorphic site (T→C transition) in exon 2 at the 5′-end of the *VDR* gene. The presence of this site (''*f*'') allows protein translation to begin from the first initiation codon rather than from the second (''*F*''), resulting in a protein that is three amino acids longer. The longer protein (*f* allele) is a less active transcriptional activator (10, 11), and the *ff* genotype has been associated with decreased bone mineral density in multiple ethnic groups (12-17). The *BSM1* restriction enzyme identifies a polymorphic site at an intron at the 3′-end which is in linkage disequilibrium with several other polymorphisms, including *APA1*, *TAQ1*, and the variable-length poly(A) (ref. 18). Although functional data have been inconclusive for *BSM1*, several small studies evaluating *BSM1* have reported significant associations with breast cancer risk (19-21), suggesting the need to replicate these results in larger populations. For this analysis, we examined the association between the *FOK1* and *BSM1* VDR polymorphisms and breast cancer risk in a case-control study nested within the Nurses' Health Study. In addition, we assessed whether the relation varied by vitamin D intake or plasma vitamin D levels.

Materials and Methods

Study Population. The Nurses' Health Study began in 1976, when 121,700 female registered nurses ages 30 to 55 living in the U.S. completed a questionnaire on risk factors for cancer and cardiovascular disease. Every 2 years, follow-up questionnaires have been sent to update risk factor information and disease development. The study population was mainly Caucasian. In 1989 to 1990, 32,826 study participants ages 43 to 69 provided blood samples, as described previously (22). As of 2000, follow-up of the cohort who provided a blood sample was 99%. The protocol for this study was approved by the Institutional Review Board of the Brigham and Women's Hospital.

Nested Case-Control Study. Eligible cases included women who provided blood samples and did not have a prior history of cancer (excluding non–melanoma skin cancer) at the time of blood draw and were subsequently diagnosed with breast cancer between the date of the return of the blood sample and June 1, 2000. We asked women for permission to obtain medical records to confirm the diagnosis of cancer. Medical records were obtained for 98% of these participants. Because the confirmation rate was >99%, we included all reported

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incident breast cancer cases. Estrogen receptor (ER) and progesterone receptor (PR) status was abstracted from medical records. Both invasive and *in situ* cancers were included.

Controls were chosen from among women who provided a blood sample but did not report a diagnosis of any type of cancer up to and including the 2-year interval during which the case was diagnosed. One control was matched to each breast cancer case on the basis of age (±1 year), menopausal status (pre- versus post- versus unknown), recent use of postmenopausal hormones (yes versus no), month and time of day (±2 hours) of blood collection, and fasting status (<10 hours or unknown versus ≥10 hours since last meal). For postmenopausal women who did not use postmenopausal hormones at blood draw, a second control was also selected. In some instances, samples were available only for one member of a case-control pair, and these were still included in the analysis.

VDR Genotyping. All samples were genotyped using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA), in 384-well format. The 5′ nuclease assay (TaqMan) was used to distinguish the alleles of the *VDR* gene at the restriction enzyme sites Fok1 and Bsm1, involving a T→C (Fok1) and a C→T (Bsm1) transition. The PCR amplifications were carried out on 5 to 20 ng DNA using 1× TaqMan universal PCR master mix (no Amp-erase UNG). Additional details of the TaqMan primers, probes, and conditions for genotyping assays are available on request. Genotyping was done by laboratory personnel blinded to case-control status, and blinded quality control samples were inserted to validate genotyping procedures. Concordance for blinded samples was 100% (64 of 64) for *BSM1* and was 97% (64 of 66) for *FOK1*.

Plasma Vitamin D Levels. Plasma vitamin D levels were available on a subset of the cases diagnosed between 1990 and 1996 and their matched controls. 25 hydroxyvitamin D (25(OH)D) was analyzed in three batches: batches 1 and 2 by Dr. Michael Holick (Boston University School of Medicine, Boston, MA) and batch 3 by Dr. Bruce W. Hollis (Medical University of South Carolina, Charleston, SC). Assay methods have been discussed in detail previously (23). Briefly, plasma samples in batches 1 and 2 were extracted with absolute ethanol, and the extract was then treated with a protein-binding assay with a high affinity for 25(OH)D. Plasma samples in batch 3 were done by RIA. Mean coefficients of variation for 25(OH)D were 17.6% (batch 1), 16.4% (batch 2), and 8.7% (batch 3). $1,25(OH)_2D$ was analyzed by Dr. Hollis in a single batch using RIA with radioiodinated tracers (24). The mean coefficient of variation for $1,25(OH)_2D$ was 7.3%.

Statistical Analyses. Women were divided into three groups on the basis of genotype, *ff*, *Ff*, and *FF* or *bb*, *Bb*, *BB*. Simple conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals. Multivariate conditional regression was used to control for other breast cancer risk factors, which were determined from the Nurses' Health Study questionnaires prior to the blood draw, including age at menopause (<45, 45-49, 50-55, >55), age at menarche (<12, 12, 13, >13), parity/age at first birth [nulliparous, age at first birth <25 (1-3 children), age at first birth 25-29 (1-3 children), age at first birth >29 (1-3 children), age at first birth <25 (4 or more children), age at first birth ≥25 (4 or more children)], average daily alcohol consumption (0, 0-9.9, 10-19.9, ≥20 g/d), body mass index (quartiles), family history of breast cancer in a first-degree relative (yes or no), and history of benign breast disease (yes or no). Menopausal status and postmenopausal hormone use were determined by questionnaires at the time of blood draw. Cumulative average vitamin D intake, including vitamin D from dietary sources and supplements, was calculated from the semiquantitative food-frequency questionnaire administered in 1980, 1984, 1986, and 1990 to all Nurses' Health Study participants (3). Variables included in the multivariate models were ones that were associated with breast cancer risk in the Nurses' Health Study and could confound the VDR and breast cancer association, as well as commonly accepted breast cancer risk factors. Several risk factors such as oral contraceptive use, physical activity, and smoking status were evaluated but were not included because they did not show strong associations within our cohort nor did they influence the associations under study. Unconditional logistic regression yielded results similar to those of conditional analyses; therefore, unconditional regression was used for the analyses by ER/PR status to increase power with the inclusion of unmatched cases and controls.

Analyses were done stratifying cases and controls by menopausal status, vitamin D intake, and 25(OH)D and $1,25(OH)_2D$ plasma levels and stratifying cases by ER/PR status. We also cross-classified *BSM1* by *FOK1* genotypes. For analyses by $1,25(OH)_2D$, women were stratified by the median level. For 25(OH)D, we used batch-specific medians to account for batch-to-batch variation. Interactions were evaluated with a Wald test for the cross-product interaction term. A two-sided P value of <0.05 was used to determine statistical significance. All analyses were done in SAS version 8.0.

Results

Our study included 1,234 cases and 1,676 controls with *FOK1* genotype data and 1,180 cases and 1,547 controls with *BSM1* genotype data. Table 1 shows the demographic characteristics for the women included in the *FOK1* analysis. As expected, cases were more likely than controls to have a family history of breast cancer and a personal history of benign breast disease.

Table 1. Characteristics of study population

	Cases (n = 1,234)	Controls (n = 1,676)	P value for case-control comparison*
Mean age at blood draw (y)	57.1	57.9	†
Mean age at menarche (y)	12.4	12.5	0.11
Mean body mass index (kg/m^2)	25.2	25.3	0.69
Nulliparous (%)	7.5	6.8	0.45
Mean parity (among parous women)	3.2	3.3	0.05
Mean age at first birth (among parous women)	25.1	24.9	0.06
Premenopausal at blood draw (%)	21.2	18.5	†
Benign breast disease (%)	34.9	23.8	<0.0001
Family history of breast cancer (%)	16.3	10.6	<0.0001
Median average alcohol use (g/d)	2.0	1.8	0.28
FOK1 (n = 2,910)	(n = 1,234)	(n = 1,676)	
FF	440 (36%)	661 (39%)	
Ff	587 (48%)	777 (46%)	0.05
ff	207 (17%)	238 (14%)	
BSM1 (n = 2,728)	(n = 1,180)	(n = 1,547)	
bb	431 (37%)	565 (37%)	0.30
Bb	586 (50%)	737 (48%)	
BB	163 (14%)	245 (16%)	

*P value by t test for body mass index, alcohol, and ages at blood draw and menarche; by Wilcoxon rank-sum test for parity and age at first birth; by χ^2 for all other covariates and genotype.

† Matching factors (1:1 match for premenopausal women and 1:2 match for postmenopausal women).

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Table 2. Breast cancer risk with *FOK1* and *BSM1* polymorphism

FOK1 polymorphism (cases/controls)	*FF*	*Ff*	*ff*
All women (1,234 cases/1,676 controls)			
Simple	1.0 (ref)	1.14 (0.97-1.34)	1.36 (1.08-1.71)
Multivariate	1.0 (ref)	1.13 (0.95-1.33)	1.34 (1.06-1.69)
Menopausal status at blood draw*			
Postmenopausal (842/1,218)	1.0 (ref)	1.04 (0.85-1.27)	1.25 (0.94-1.66)
Premenopausal (261/310)	1.0 (ref)	1.52 (0.96-2.41)	2.18 (1.18-4.00)
Invasive cancer only (1,018/1,676)	1.0 (ref)	1.11 (0.93-1.32)	1.23 (0.97-1.57)
ER/PR status of cancers			
ER+/PR+ (601/1,676)	1.0 (ref)	1.07 (0.87-1.32)	1.30 (0.98-1.73)
ER−/PR− (158/1,676)	1.0 (ref)	1.17 (0.80-1.71)	1.54 (0.96-2.49)
BSM1 polymorphism (cases/controls)	*bb*	*Bb*	*BB*
All women (1,180/1,547)			
Simple	1.0 (ref)	1.04 (0.87-1.24)	0.92 (0.72-1.18)
Multivariate	1.0 (ref)	1.05 (0.88-1.26)	0.93 (0.72-1.20)
Menopausal status at blood draw*			
Postmenopausal (821/1,115)	1.0 (ref)	1.05 (0.85-1.29)	0.94 (0.69-1.26)
Premenopausal (239/298)	1.0 (ref)	1.01 (0.65-1.58)	0.92 (0.46-1.85)
Invasive cancer only (970/1,547)	1.0 (ref)	1.07 (0.89-1.28)	0.87 (0.68-1.13)
ER/PR status of cancers			
ER+/PR+ (574/1,547)	1.0 (ref)	1.04 (0.84-1.29)	0.94 (0.69-1.27)
ER−/PR− (153/1,547)	1.0 (ref)	1.11 (0.77-1.61)	0.72 (0.40-1.28)

NOTE: All OR's presented in this table are multivariate (adjusted for matching factors and body mass index, parity/age at first birth, family history of breast cancer in first-degree relative, benign breast disease, alcohol consumption, age at menarche, age at menopause), except those marked ''Simple'' which were adjusted only for matching factors (age, menopausal status, postmenopausal hormone use, fasting status, and month, day, and time of blood draw).
*Women with an unknown menopausal status were excluded from the subanalysis by menopausal status.

There was no significant difference between cases and controls according to *BSM1* genotype ($P = 0.30$). For *FOK1*, cases were more likely then controls to have the *ff* genotype ($P = 0.05$). For the controls, both *BSM1* and *FOK1* genotype frequencies did not differ significantly from the expected frequencies under Hardy-Weinberg equilibrium ($P > 0.98$ for χ^2 test). The genotype frequencies for *FOK1* and *BSM1* were comparable to those reported in other breast cancer studies with predominantly Caucasian populations (19, 21, 25).

We did not observe an association between polymorphisms in *BSM1* and breast cancer risk (Table 2). However, for *FOK1*, women who were homozygous *ff* had an elevated breast cancer risk [multivariate OR, 1.34 (1.06-1.69)] compared with women with the *FF* genotype. Results were similar when limited to cases with invasive cancers, stratified by menopausal status, or classified by ER/PR status. The OR for premenopausal breast cancer seemed to be higher than that for postmenopausal breast cancer and the difference approached statistical significance (P for interaction = 0.08). Although risk seemed highest for women who were *ff* and also carried the *B* allele, no statistically significant interaction was found between *BSM1* and *FOK1* genotypes ($P = 0.15$; Table 3). Results were unchanged in analyses excluding the small number of African-American, Asian, and Hispanic women (16 cases/27 controls).

Previously, we have shown that higher levels of 25(OH)D and $1,25(OH)_2D$ (26) and vitamin D intake (3) might be associated with a modestly reduced risk of breast cancer. Therefore, we examined the *FOK1* breast cancer association stratified by 25(OH)D and $1,25(OH)_2D$ levels and cumulative vitamin D intake (Table 4). Although we did not find significant variations in the *FOK1* association by plasma vitamin D levels, the risk seemed strongest in women with the *ff* genotype and higher vitamin D intake ($P = 0.05$).

Discussion

Within the Nurses' Health Study, we observed an increased risk of breast cancer in women with the *ff* genotype of the *FOK1* polymorphism. No association was observed between *BSM1* polymorphisms and cancer risk. The *FOK1* polymorphism is a compelling candidate for associations with cancer risk given its lack of linkage disequilibrium with other VDR polymorphisms and the functional data demonstrating that the *ff* genotype results in a longer protein that is a less potent transcriptional activator (10, 11). Vitamin D is also known to have antiproliferative effects (27, 28) and to interact with many other systems besides calcium metabolism, including immune modulation and regulation of cell growth and differentiation (29). In addition, the *ff* genotype has been associated with decreased bone mineral density in a number of studies across multiple ethnic groups (12-17).

Bone mineral density has been positively associated with breast cancer risk in epidemiologic studies (30, 31), and it would seem paradoxical that the *ff* genotype could be associated with both decreased bone density and increased breast cancer risk. Bone density has been considered a surrogate for a woman's lifetime estrogen exposure, such that women with lower bone mineral density have less estrogen exposure and therefore lower breast cancer risk. However, the association between bone mineral density and the *ff* genotype would not be based upon a sex steroid hormonal mechanism. Vitamin D deficiency or other factors decreasing the effectiveness of the VDR system can upset the calcium/phosphate balance and lead to ostemalacia and osteoporosis (4). Our

Table 3. Multivariate OR (cases/controls) for breast cancer risk by *FOK1* and *BSM1* genotypes ($n = 2,624$)

	bb	*Bb*	*BB*
ff	1.09 (0.71-1.68) 65/86	1.63 (1.10-2.40) 99/89	1.37 (0.75-2.48) 28/29
Ff	1.09 (0.80-1.49) 209/256	1.09 (0.81-1.47) 261/320	0.99 (0.67-1.47) 77/115
FF	1.0 (ref) 144/196	0.92 (0.68-1.25) 206/302	0.77 (0.49-1.22) 50/92

NOTE: Adjusted for the same factors as multivariate models in Table 2. P for interaction = 0.15.

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Table 4. Multivariate breast cancer risk and *FOK1* polymorphism by 25(OH)D, 1,25(OH)$_2$D and vitamin D intake

	FF	*Ff*	*FF*
25(OH)D* (671 cases/658 controls)			
≤Median	1.0 (referent)	1.12 (0.77-1.61)	1.44 (0.86-2.41)
>Median	0.84 (0.56-1.25)	0.88 (0.60-1.30)	1.27 (0.76-2.13)
		P for interaction = 0.95	
1,25(OH)$_2$D† (607 cases/576 controls)			
≤Median	1.0 (referent)	1.16 (0.79-1.71)	1.65 (1.00-2.72)
>Median	0.87 (0.57-1.34)	0.97 (0.66-1.42)	1.45 (0.82-2.57)
		P for interaction = 0.94	
Vitamin D intake‡ (1,218 cases/1,663 controls)			
≤Median	1.0 (referent)	1.03 (0.80-1.34)	0.99 (0.69-1.42)
>Median	0.84 (0.65-1.10)	0.98 (0.76-1.25)	1.39 (0.99-1.94)
		P for interaction = 0.05	

NOTE: Adjusted for the same factors as multivariate OR in Table 2.
*Batch-specific medians: batch 1, 30; batch 2, 37; batch 3, 27.5 ng/mL.
†Median, 33.1 ng/mL.
‡Median, 292 IU/d.

findings support the hypothesis that the antiproliferative effects of vitamin D could decrease breast cancer risk, because women with the *ff* genotype have the less active form of the VDR and would thus be expected to derive less benefit from vitamin D and have higher breast cancer risk and lower bone mineral density.

In several previous studies, polymorphisms in *FOK1* have not been associated with breast cancer risk (19, 21, 25), but two (19, 25) of the three studies had <150 cases each. Because the *ff* genotype occurs in <20% of the population and the *Ff* heterozygote was not associated with increased risk, larger sample sizes would be necessary to detect a moderate association of the *ff* polymorphism with cancer risk. To improve power, the Curran et al. study (25) evaluated allele frequencies, rather than genotype frequencies, which may dilute the ability to detect an effect because we observed an association primarily among carriers of *ff*. We had more than twice the number of cases and controls than previous studies and thus greater power to detect an association. We did not find a significant interaction between *BSM1* and *FOK1* genotypes. If anything, the *FOK1* association was apparent primarily among carriers of a *B* allele. In the study by Guy et al. (21), the *F* allele of *FOK1* seemed to augment the risk they observed with the *bb* genotype, although this would be contrary to the functional data on the *F* allele.

Studies on the association between the *BSM1* polymorphism and breast cancer risk have not been consistent. Two studies showed an increased risk of breast cancer with the *B* allele (19, 20), whereas other studies found no difference (32) or a decreased risk (21). The two largest studies observed no association (Newcomb et al., 32: 420 cases/402 controls) or decreased risk (Guy et al. 21: 398 cases/427 controls). *BSM1* genotype frequencies vary considerably across ethnic groups, making results difficult to compare across studies. For example, 43% of 241 controls were *bb* in a British case-control series, whereas 91% of 169 controls were *bb* in a Taiwanese hospital-based case-control series (20). Functional studies have not conclusively shown an effect of *BSM1* polymorphisms on VDR function or coding sequence, mRNA stability, osteocalcin levels or changes in bone mineral density in response to treatment (17, 29, 33, 34). Several other polymorphisms at the 3′-end of VDR that are closely linked with *BSM1* have been implicated in breast cancer risk, including *APA1* (20, 25) and *TAQ1* (25). Given that none of these are known to be functional polymorphisms, it is hypothesized that these nonfunctional ''marker'' alleles are in linkage disequilibrium with the truly functional allele. The varying degree of linkage disequilibrium between these marker alleles and the functional allele might explain the variations in the strengths of associations seen across studies (29). Given the large area of linkage disequilibrium at the 3′-end and the absence of consistent functional data, it is difficult to interpret the body of data relating *BSM1* to breast cancer risk, although our data do not support an important association in a primarily Caucasian population.

Although 1,25(OH)$_2$D is considered to be the more biologically active metabolite and functions as the ligand for VDR, 25(OH)D may be hydroxylated to 1,25(OH)$_2$D at various target tissues, including the breast, and therefore may be more representative of intracellular levels (35, 36). Nevertheless, we did not find that the disease/genotype relation varied significantly by 25 or 1,25(OH)$_2$D or vitamin D intake. We did control for batch-to-batch variations in 25(OH)D levels, but assay variability and seasonal and geographic variations may have interfered with our ability to detect an association. Contrary to our a priori hypothesis, the breast cancer risk associated with the *ff* genotype was higher among women with higher cumulative vitamin D intake. This may be due to chance, but should be investigated in other studies. We did not have detailed data on routine sunlight exposure.

The strengths of our study include its prospective nature, large size, and our ability to control for most of the important breast cancer risk factors. Our population was mainly Caucasian; thus, we were unable to evaluate these relationships in other racial groups. Power was limited to evaluate interaction effects by subgroups of plasma vitamin D levels and genotype.

In conclusion, we found an increased risk of breast cancer among women with the *ff* genotype. This relationship did not seem to be modified by menopausal status, ER/PR status, *BSM1* genotype, or plasma vitamin D levels, although power was limited for several of these subanalyses. Our findings on *FOK1* and the increasing evidence demonstrating a protective effect of higher vitamin D levels on breast cancer risk suggest that the vitamin D pathway is a potentially important mediator of breast cancer risk. The VDR may represent an important target for breast cancer prevention outside of the known hormonal mechanisms.

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