Vitamin D Receptor Gene Polymorphisms and Epithelial Ovarian Cancer Risk

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Abstract

Epidemiologic and laboratory studies support a role for the vitamin D endocrine system in ovarian carcinogenesis. The association of ovarian cancer risk with polymorphisms in the *vitamin D receptor* (*VDR*) gene, including rs10735810 (*Fok*I), rs11568820 (*Cdx*-2), rs1544410 (*Bsm*I), rs7975232 (*Apa*I), rs731236 (*Taq*I), and *Bsm*I-*Apa*I-*Taq*I combined genotypes, was examined among 313 women with epithelial ovarian carcinoma and 574 controls. Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using unconditional logistic regression. The associations of *VDR* polymorphisms with risk were generally inconsistent across ethnic groups. Among Caucasian women (72 cases, 148 controls), heterozygous and homozygous *Apa*I *A* allele carriers were at increased ovarian carcinoma risk compared with homozygous carriers of the *Apa*I *a* allele (OR 2.8, 95% CI 1.2-7.0 and OR 3.4, 95% CI 1.3-9.1; P_{trend} = 0.02). Caucasian heterozygous carriers of *Fok*I *f* allele were also at increased risk of ovarian carcinoma compared with homozygous carriers of the common allele (OR 2.5, 95% CI 1.3-4.8; P_{trend} = 0.04). Among Japanese women (94 cases, 173 controls), ovarian cancer risk was significantly decreased (OR 0.5, 95% CI 0.3-0.9) among *Cdx*-2 *A* allele heterozygotes compared with homozygote *G* allele carriers (P_{trend} = 0.03). Compared with the *bbaaTT Bsm*I-*Apa*I-*Taq*I genotype, *bbaATT* and *BBAAtt* genotypes were associated with increased ovarian cancer risk in Caucasian women (OR 4.2, 95% CI 1.3-13.1 and OR 5.2, 95% CI 1.6-17.5), but not in Japanese women (OR 1.1, 95% CI 0.6-1.9 and OR 2.3, 95% CI:0.4-12.3). This investigation provides some evidence that polymorphisms in the *VDR* gene might influence ovarian cancer susceptibility. (Cancer Epidemiol Biomarkers Prev 2007;16(12):2566–71)

Introduction

Evidence from epidemiologic and laboratory studies supports a role for the vitamin D endocrine system in ovarian carcinogenesis. Several ecologic investigations have reported an inverse association between sunlight exposure and age-specific ovarian cancer incidence (1) and mortality (2) rates. Because the major source of vitamin D in humans is sunlight synthesis in the skin, these investigations suggest that vitamin D exposure may reduce the risk for ovarian cancer. In addition, an inverse association of dietary vitamin D and ovarian cancer has been shown in one study (3), although not in other studies (4, 5). The observations that vitamin D and its synthetic analogues inhibit growth and induce apoptosis in ovarian cells in culture and in animal models of ovarian cancer (6-9) provide further plausibility to this hypothesis.

The vitamin D receptor (VDR) is a nuclear transcription factor that belongs to the steroid hormone receptor family (10) and mediates most of the actions of vitamin D (11). The presence of VDR in the normal ovarian epithelium, in human ovarian tumors, and in human ovarian cancer cell lines has been shown (6, 12, 13). A proposed mechanism for the role of vitamin D in carcinogenesis involves regulation of differentiation and proliferation of cancer cells possibly by influencing cell cycle regulatory proteins (14). Down-regulation of telomerase activity by vitamin D might be another component of the ovarian cancer cells growth suppression (7). Vitamin D might influence ovarian carcinogenesis indirectly through an endocrine pathway. VDR is necessary for full ovarian function through direct effects on estrogen biosynthesis and regulation of aromatase gene expression. *VDR*-null mice exhibit gonadal insufficiency, reduced aromatase gene expression, low aromatase activity, and elevated serum levels of luteinizing and follicle-stimulating hormones (15). The concept of ovarian cancer as a result of hypergonadotropic hypogonadism was first suggested by Cramer et al. (16, 17).

We hypothesize that common genetic variants in the *VDR* gene might be associated with ovarian cancer risk. In this study, we selected single-nucleotide polymorphisms (SNP) that have been found to have some functional significance *in vitro* (reviewed by ref. 18). Each of the candidate SNPs were previously found associated with the risk of breast (19-21), colon (22, 23), or prostate cancers (24-26) that are malignancies with possible etiologic similarities to ovarian cancer (27). The rs10735810 (*Fok*I) is a coding nonsynonymous SNP in the translational initiation codon that has been reported to

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have functional significance in several *in vitro* studies with C (often called ''*F*'' allele) more effective than the T (or ''*f*'') allele in transactivation of the vitamin D signal (28-30). The *Fok*I polymorphism was considered an independent marker of the *VDR* gene as it has not been reported to be in linkage disequilibrium with any of the other *VDR* polymorphisms (18). The *Cdx*-2 (rs11568820) SNP is within a functional binding site of the intestinal specific transcription factor Cdx-2 in the promoter region of the *VDR* gene and is thought to modulate the transcription of the *VDR* gene (18, 30-32). *Bsm*I (rs1544410), *Apa*I (rs7975232) in intron 8, and a silent *Taq*I (rs731236) in exon 9 SNPs, located near the 3′ end of the *VDR* gene, have been reported to be in strong linkage disequilibrium. These 3′ SNPs do not change the amino acid sequence of the encoded protein; however, they may affect gene expression through regulation of mRNA stability (33).

Materials and Methods

Study Design and Population. This population-based case-control study included 313 cases 18 years of age or older diagnosed with primary histologically confirmed epithelial ovarian carcinoma in 1993 to 2006 and identified through the rapid reporting system of the Hawaii Tumor Registry, which is part of the Surveillance, Epidemiology, and End-Results Program of the National Cancer Institute (34). Control subjects (n = 574) were randomly selected from participants in an annual survey of representative households in Hawaii (35) and supplemented with women 65 years of age or older through random sampling from lists obtained from the Health Care Finance Administration and were frequency-matched to cases based on ethnicity and 5-year age groups in an approximate 1:1.5 ratio. Eligibility criteria for controls included age 18 years or older, residency in Hawaii for a minimum of 1 year, no prior history of ovarian cancer, and having at least one intact ovary. The response rate was 64% for cases and 67% for controls. The study protocol was approved by the Institutional Review Board of the University of Hawaii. All study participants signed detailed consent forms before participation.

Data Collection. Study participants were interviewed using a structured pretested questionnaire that included sociodemographic and health-related information, menstrual, reproductive and gynecologic histories, and exogenous hormone use (36). Interviewers were uniformly trained and supervised to standardize interviewing and coding techniques. Quality control and performance of the interviewers was monitored by the project coordinator through a repeat interview of a random sample of 15% of subjects on a random 5% of the interview questions.

Genetic Analysis. DNA was purified from whole blood using Qiagen midi kits (Qiagen). The DNA samples were analyzed by PCR/RFLP using TaqMan (Applied Biosystems). Samples from cases and controls were intermixed on each plate. We included 144 (7.4%) randomly placed blinded samples on each plate to evaluate accuracy and reproducibility. In addition, each 384-well plate included eight non-DNA controls. The concordance rates among duplicates were 98% for *Bsm*I and 100% for all other SNPs. Call rates were 98% to 100% for all polymorphisms.

Statistical Analysis. Unconditional multiple logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for the association of genotype with ovarian carcinoma. The genotype for each SNP was treated as a nonordered categorical variable to test for heterogeneity and as an ordered categorical variable with three levels (0, 1, and 2) assigned to each genotype to test for a gene-dose effect. Pair-wise linkage disequilibrium (D') and correlation coefficients (r^2) were estimated using the HAPLOVIEW program (37). We also created a variable reflecting all possible combinations of *Bsm*I-*Apa*I-*Taq*I genotypes for each SNP. All genotypes were included into the model, and homozygous carriers of *bbaaTT* genotype (including common alleles of all three SNPs among our study participants) were used as a reference group. The distribution of the following variables was examined by genotype for each SNP among Caucasians and Japanese control subjects separately: age (continuous), education (≤12 years for ''high school or less,'' 13-14 years for ''post-high school training other than academic college or partial academic college,'' and ≥15 years for ''college or professional school''); family history of ovarian cancer among first-degree relatives (yes, no); gravidity (0, 1, 2-3, 4, or more); history of a tubal ligation procedure (yes, no); hysterectomy (yes, no); use of contraceptive steroids (yes, no); menopausal status (premenopausal versus postmenopausal); use of menopausal hormones (estrogen alone, progesterone alone, combination of estrogen and progesterone). There was no difference in the distribution of any of these variables by *Fok*I and *Cdx*-2 genotypes. The distributions of age, education, gravidity, use of contraceptive, and menopausal hormones were different by *Apa*I, *Bsm*I, and *Taq*I genotypes in Caucasian women. Education and use of menopausal hormones were distributed differently by genotypes of several of the 3′untranslated region SNPs in Japanese women. Variables that were associated with ovarian cancer risk and which were distributed nonrandomly by VDR genotypes in control subjects were included into the statistical models (38). Including all of the covariates did not change associations of VDR SNPs with risk. All P values were based on two-tailed tests.

Results

The mean age of the study participants was 55.0 years (SD 13.8, range 18-88). Participant characteristics are presented in Table 1. Participant with a family history of ovarian cancer in first-degree relatives had a higher ovarian cancer risk. Education, gravidity, tubal ligation, use of contraceptive steroids, premenopausal status, and the use of menopausal estrogen in combination with progesterone were inversely associated with ovarian cancer risk.

The distributions of the alleles among control subjects within each ethnic group were consistent with Hardy-Weinberg equilibrium, except for the *Bsm*I SNP in Japanese and other Asian women (P = 0.001) in whom *BB* genotype frequency was very low. The minor allele frequency distributions differed significantly by ethnicity

Table 1. Participant characteristics

Characteristics	No. participants (%)	
	Cases (n = 313)	Controls (n = 574)
Age (y)		
<45	70 (22)	117 (21)
45-54	90 (29)	173 (30)
55-64	75 (24)	146 (25)
>64	78 (25)	138 (24)
Ethnicity		
Caucasian	72 (23)	148 (26)
Japanese	94 (30)	173 (30)
Filipino	36 (12)	79 (14)
Hawaiian	69 (22)	106 (18)
Other Asian	17 (5)	27 (5)
Mixed	25 (8)	41 (7)
Education (y)		
≤12	128 (41)	169 (29)
13-14	98 (31)	190 (33)
≥15	87 (28)	215 (38)
Family history of ovarian cancer		
Yes	16 (5)	9 (2)
No	297 (95)	565 (98)
Gravidity		
Nulligravid	74 (24)	56 (10)
1	42 (13)	67 (12)
2-3	121 (39)	246 (43)
≥4	76 (24)	205 (36)
Used oral contraceptives		
Yes	144 (46)	394 (69)
No	169 (54)	180 (31)
Had tubal ligation		
Yes	48 (15)	181 (32)
No	265 (85)	393 (68)
Menopausal status		
Premenopausal	111 (35)	215 (37)
Postmenopausal	202 (65)	359 (63)
Type of menopause		
Hysterectomy	32 (16)	47 (13)
Natural menopause	170 (84)	312 (87)
Use of menopausal hormones		
Never used	106 (52)	149 (42)
Estrogen only	32 (16)	50 (14)
Progesterone only	12 (6)	19 (5)
Combined estrogen and progesterone	52 (26)	141 (39)

for all polymorphisms under study (Table 2). Strong linkage disequilibrium ($D' > 0.90$; $r^2 > 0.90$) was observed between *Bsm*I, *ApaI*, and *Taq*I among Japanese and Caucasian women and was weaker among other ethnic groups. *Fok*I and *Cdx*-2 SNPs were not in linkage disequilibrium with other SNPs.

Caucasian carriers of the *Apa*I *A* allele were at increased risk of ovarian cancer (P_{trend} = 0.02; Table 3). A nonsignificant increased risk associated with this allele was also observed among Japanese women. Although *Bsm*I *B* and *Taq*I *t* allele carriers among Caucasian and Japanese women were at higher ovarian cancer risk, these associations were not statistically significant. Among Caucasians, carriers of the *Fok*I *f* allele were at significantly increased risk of ovarian carcinoma compared with women who were homozygous for the common allele (P_{trend} = 0.04). The *Cdx*-2 *A* allele was associated with a decreased ovarian cancer risk in Japanese women: carriers of the *GA* genotype had a significantly reduced risk of ovarian cancer (OR 0.5, 95% CI 0.3-0.9; P_{trend} = 0.03). When all three SNPs in the 3′ region were studied simultaneously, five common *Bsm*I-*Apa*I-*Taq*I genotypes were observed. Homozygous carriers of the *bbaaTT* genotype, including all common alleles of all three polymorphisms, represented a majority of our population (74%). Among Caucasian women, significantly higher risk was observed for carriers of the *bbaATT* and *BBAAtt* genotypes when compared with homozygous *bbaaTT* carriers.

Discussion

In this multiethnic study, we explored the association of several common *VDR* gene polymorphisms with ovarian cancer risk. Frequency distributions of the minor alleles for all five SNPs varied significantly by ethnicity and were similar to the data in the National Center for Biotechnology Information data base and in the published literature (18, 32, 39, 40). The association of *VDR* polymorphisms with ovarian cancer risk was generally inconsistent among ethnic groups. In Caucasian women, the *Apa*I *A* allele was associated with an increased risk of ovarian carcinoma, as were two of the 3′ area genotypes, *bbaATT* and *BBAAtt*. Although Japanese women who were carriers of the *Apa*I *A* allele and *bbaATT* and *BBAAtt* genotypes were at increased risk, the results were not statistically significant. The *Fok*I *f* allele was associated with increased ovarian cancer risk in Caucasian women, but not in other ethnic groups. In contrast, the *Cdx*-2 *GA* genotype was associated with a decreased risk of ovarian cancer only in Japanese women.

An association of the *Fok*I *f* allele with increased risk of ovarian cancer was consistent with our hypothesis. The *f* variant was found to have lower transcriptional activation in laboratory studies (29, 30, 41, 42) and has been associated with an increased breast cancer risk in Caucasian women when studied in combination with the poly(A) polymorphism in the 3′ region of *VDR* (43).

Table 2. Frequency distributions of minor alleles among control subjects by ethnic group

SNPs*	Minor allele*	Restriction site present	Caucasians (n = 148)	Japanese (n = 173)	Other Asian (n = 27)	Filipino (n = 79)	Hawaiians (n = 106)	Mixed (n = 41)	P, χ^2 test
rs10735810 (*Fok*I)	T (*f*)	Yes	0.38	0.25	0.48	0.30	0.36	0.40	0.04
rs11568820 (*Cdx-2*)	A		0.18	0.44	0.44	0.46	0.45	0.35	<0.0001
rs731236 (*Taq*I)	C (*t*)	Yes	0.41	0.11	0.06	0.03	0.22	0.28	<0.0001
rs7975232 (*Apa*I)	C (*a*)	Yes	0.50	0.68	0.80	0.78	0.49	0.65	<0.0001
rs1544410 (*Bsm*I)	A (*B*)	No	0.42	0.12	0.02	0.08	0.28	0.30	<0.0001

*Minor allele in Caucasians. Nomenclature is based on the National Center of Biotechnology Information. In brackets, variant allele designations often used in publications.

Table 3. *VDR* SNP and 3′ area *BsmI-ApaI-TaqI* combined genotype associations with epithelial ovarian cancer risk

Genotype	Caucasian			Japanese		
	Cases *n* (%)	Controls *n* (%)	OR (95% CI)*	Cases *n* (%)	Controls *n* (%)	OR (95% CI)†
rs7975232 (*Apa*I)						
aa	11 (16)	33 (24)	1.0 reference	38 (41)	75 (45)	1.0 (reference)
aA	37 (53)	72 (52)	2.8 (1.2-7.0)	47 (50)	79 (47)	1.2 (0.7-2.1)
AA	22 (31)	34 (24)	3.4 (1.3-9.1)	8 (9)	14 (8)	1.2 (0.5-3.1)
P_{trend}			0.02			0.56
rs1544410 (*Bsm*I)						
bb	26 (27)	48 (33)	1.0 (reference)	72 (77)	137 (80)	1.0 (reference)
bB	30 (42)	70 (49)	1.2 (0.6-2.4)	19 (20)	28 (16)	1.4 (0.7-2.8)
BB	15 (21)	26 (18)	1.3 (0.5-3.3)	3 (3)	6 (4)	0.9 (0.2-4.0)
P_{trend}			*0.53*			*0.49*
rs731236 (*Taq*I)						
TT	26 (36)	48 (33)	1.0 reference	73 (79)	138 (80)	1.0 (reference)
Tt	30 (42)	77 (53)	1.1 (0.5-2.1)	17 (18)	31 (18)	1.1 (0.6-2.2)
tt	16 (22)	21 (14)	1.8 (0.7-4.4)	3 (3)	4 (2)	1.7 (0.4-7.9)
P_{trend}			0.28			0.53
rs10735810 (*Fok*I)						
FF	16 (23)	58 (40)	1.0 reference	37 (40)	74 (43)	1.0 (reference)
Ff	44 (62)	64 (44)	2.5 (1.3-4.8)	48 (52)	80 (47)	1.2 (0.7-2.0)
ff	11 (15)	22 (15)	2.1 (0.8-5.2)	8 (9)	18 (10)	0.9 (0.4-2.2)
P_{trend}			0.04			0.87
rs11568820 (*Cdx-2*)						
GG	44 (63)	95 (66)	1.0 reference	36 (39)	45 (26)	1.0 (reference)
GA	21 (30)	44 (30)	1.0 (0.6-1.8)	41 (45)	99 (58)	0.5 (0.3-0.9)
AA	5 (7)	6 (4)	1.5 (0.4-5.2)	15 (16)	27 (16)	0.9 (0.4-1.8)
P_{trend}			0.96			0.03
*Bsm*I-*Apa*I-*Taq*I						
bb/aa/TT	11 (16)	33 (24)	1.0 reference	75 (45)	38 (41)	1.0 reference
bb/aA/TT	13 (19)	12 (9)	4.2 (1.3-13.1)	31 (33)	55 (33)	1.1 (0.6-1.9)
bB/aA/Tt	24 (35)	54 (40)	2.3 (0.9-5.9)	15 (16)	19 (11)	1.8 (0.8-4.0)
bB/AA/Tt	5 (7)	12 (9)	2.4 (0.6-9.7)	2 (2)	8 (5)	0.5 (0.1-2.4)
BB/AA/tt	15 (22)	16 (12)	5.2 (1.6-17.5)	3 (3)	1 (2)	2.3 (0.4-12.3)

*For 3′ area SNPs (*Apa*I, *Bsm*I, and *Taq*I) and combined genotypes, adjusted for education, gravidity, use of oral contraceptives, and menopausal hormones.
†For 3′ area SNPs and combined genotypes, adjusted for education and use of menopausal hormones.

*Apa*I and two other SNPs in the 3′ region of the gene do not affect the structure of the *VDR* protein but have been shown to affect VDR mRNA stability or may be in linkage disequilibrium with some other functional SNP (33). The association of the *Cdx-2 A* allele with decreased ovarian cancer risk may result from more efficient Cdx-2 binding and higher VDR activity associated with this variant (31).

Ethnic differences in the association of VDR polymorphisms with ovarian cancer risk might be partially explained by differences in variant allele frequencies. Frequencies of the *Apa*I *A* allele, *Taq*I *t*, and *Bsm*I *B* alleles were very low in Japanese and other Asian women. In addition, the distribution of *Bsm*I in Japanese women was not consistent with Hardy-Weinberg equilibrium, which might influence its association with risk. Substantial racial/ethnic variation is observed in the incidence of ovarian cancer with the highest rates in Caucasian women and the lowest rates among Asian women (44). Lower ovarian cancer incidence in Japanese women, who have significantly lower prevalence of the *Apa*I *A* allele and *BBAAtt Apa*I-*Bsm*I-*Taq*I, is consistent with our findings. On the other hand, the *Cdx-2* variant allele, which was associated with decreased ovarian cancer risk in Japanese women only, was much more common in Asian women than in Caucasians. Increased bone mineral density in Japanese postmenopausal women (31, 32), but not in Caucasian women (39), with the *Cdx-2 A* allele has been reported. At present, the reason for this difference is not known and might be related to environmental factors, such as calcium intake (45).

VDR and its ligand vitamin D regulate fundamental processes of cellular proliferation, differentiation, and apoptosis that have the potential to influence ovarian cancer development. Specific mechanisms for the antiproliferative effect of VDR have yet to be determined. This effect in neoplastic cells may be related to ability of liganded VDR to interacts with cell cycle regulatory proteins p21 and p27 leading to G_1 arrest, as well as to control cell growth factors, such as *c-myc* and *c-fos*, or to elicit apoptosis by down-regulating *Bcl*-2 (46). VDR may also inhibit androgen receptor expression found in majority of ovarian tumors (12). A role of androgen in ovarian carcinogenesis has been suggested (47, 48), and Ahonen et al. (12) reported that vitamin D can antagonize the growth-promoting effects of dehydroandrostenedione in ovarian cancer cells.

VDR polymorphisms have been reported in association with breast, colon, and prostate cancer risk, suggesting a common link with ovarian cancer risk. VDR was found to be down-regulated in colon and breast tumors (49), but was found to be up-regulated in ovarian tumors (13, 49) when compared with nonmatched normal ovarian tissue. The basis for the up-regulation of VDR in ovarian tumors is not clear,

although higher levels of androgen in association with ovarian cancer may affect the expression of VDR (49). Dihydrotestosterone has been shown to increase VDR expression in the ovary (12). Studies comparing normal and cancerous tissue from the same individual might help to confirm if VDR is selectively up-regulated in ovarian tumors.

Strengths of this study include its population basis, histologic confirmation of all case diagnoses, and stringent laboratory quality control procedures. An advantage of our study design was its multiethnic nature, which might help to better understand genetic contributions to ovarian cancer risk. Although the study had sufficient power to detect significant associations in Caucasian and Japanese women, the number of women in other ethnic groups was small. Furthermore, power was limited to examine combinations of genetic variants. Larger studies are needed to explore the effects of these genetic variations.

Ovarian cancer is the fatal gynecologic malignancy, mostly because of its late clinical manifestations and absence of screening methods for early detection. As the majority of women who develop this cancer do not carry highly penetrant *BRCA* gene mutations, low-penetrant genes could be useful in detecting women at higher risk of ovarian cancer, allowing for an individualized approach to screening. Our study provides some evidence that the *VDR* gene might influence ovarian cancer susceptibility.

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