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Vitamin D receptor (VDR) Polymorphisms and Risk of Ovarian Cancer in Caucasian and African American women

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Abstract

Background—Polymorphisms in the vitamin D receptor (*VDR*) gene have been shown in some studies to be associated with the risk of epithelial ovarian cancer (EOC) in Caucasian women. This association among African American women has been understudied.

Methods—Case-control data from the North Carolina Ovarian Cancer Study were analyzed using logistic regression to determine the association between seven *VDR* polymorphisms of functional significance and EOC in both Caucasians (513 cases, 532 controls) and African Americans (74 cases, 79 controls). In a follow-up analysis, associations were assessed between six SNPs in proximity of the *Apal* variant and a larger sample of African-Americans (125 cases, 155 controls).

Results—African American women who carried at least one minor allele of *Apal* (rs7975232) were at higher risk for invasive EOC controlling for age and admixture with an odds ratio (OR) for association under the log-additive model of 2.08 (95% confidence interval (CI) = 1.19, 3.63, $p = 0.010$). No association was observed between any of the *VDR* variants and EOC among Caucasians. A follow-up analysis in a larger sample of African American subjects revealed a nearly two-fold increase in risk of invasive EOC in rs7971418, a SNP in proximity to the *Apal* SNP ($R^2 = 0.369$) with a log-additive OR of 1.87 (95% CI = 1.20, 2.93, $p = 0.006$).

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Conclusion—This is the first report showing *VDR* variants associated with ovarian cancer risk in African American women. A larger study of African American women is needed to confirm these findings.

Impact—Our results imply that vitamin D exposure is a possible modifiable risk factor of ovarian cancer among African Americans.

Keywords

ovarian cancer; vitamin D receptor; polymorphisms; population risk factors; linkage disequilibrium

Introduction

The nuclear vitamin D receptor (VDR) transduces the pleiotropic response of the biologically active form of the vitamin D hormone ($1\alpha,25$ -dihydroxyvitamin D_3 , also known as $1\alpha,25(OH)_2D_3$) as part of the vitamin D endocrine system that is important in calcium absorption, immunity and proliferation (1). Recent evidence shows that as a nuclear receptor, VDR may bind to over 2000 VDR binding sites, two thirds of which occur in the presence of the ligand $1\alpha,25(OH)_2D_3$, and result in the up-regulation of genes of the immune response and intracellular signaling cascades (2). The biologically active form of the vitamin D hormone is metabolized from the main circulating form, 25-hydroxyvitamin D_3 or 25(OH)D, which is the established marker of vitamin D status. In a case-control study from the National Health and Nutrition Examination Surveys (NHANES) with 28 ovarian cancer cases and 7245 controls, cases were nearly four times more likely to have low serum 25(OH)D levels than controls (OR=3.9, 95% CI=1.1, 13.9) (3).

Circulating 25(OH)D levels are modulated by both sun exposure and dietary intake. In particular, serum levels are increased by cutaneous synthesis of pre-vitamin D, 7-dehydrocholesterol that results from exposure to solar ultraviolet-B (UVB) radiation (4). Exposure to UVB varies geographically, hence individual levels of 25(OH)D may be influenced by residence in regions of high solar irradiance such as in the Western U.S. where an inverse relationship between UVB exposure and incidence of several cancers, including ovarian cancer, has been documented (5). Factors associated with higher 25(OH)D levels, including vitamin D from sunlight exposure and diet, are 46% lower among African Americans of high African ancestry (6).

Common variants in the *VDR* gene, such as *Apa1* (rs7975232), *Bsm1* (rs1544410), *Fok1* (rs2228570) and *Taq1* (rs731236) have been examined in relation to various cancers including ovarian cancer. One study showed that Caucasian women who carried at least one minor allele of the *Apa1* and *Fok1* polymorphisms were found to be at higher risk for developing epithelial ovarian cancer compared to non-carriers (7), while Clendenen et al. (8) found no evidence of association between the *Apa1* and *Fok1* variants and ovarian cancer. Two additional large case-control studies also reported statistically significant associations between *Fok1* and ovarian in Caucasian subjects with odds ratios (ORs) ranging from 1.09–1.26 (9, 10). Further, VDR protein expression in tissue from ovarian cancer patients has

been shown to be lower in tissues from ovarian cancer patients when compared to healthy women (11) supporting an etiological role.

Although 25(OH)D levels and vitamin D exposures from sunlight and diet are lower among African Americans, the influence of variants in the *VDR* gene on ovarian cancer risk is unknown. In this report, Caucasian and African American subjects enrolled in the North Carolina Ovarian cancer Study (NCOCS) were included in an initial analysis of 7 single nucleotide polymorphisms (SNPs), followed by a second analysis in African American women of 7 linked variants in the *VDR* gene.

Materials and Methods

Study Population

The participants in this study are from the North Carolina Ovarian Cancer Study (NCOCS), a population-based, case-control study of epithelial ovarian cancer conducted in a 48-county region of North Carolina. Identification and recruitment of ovarian cancer cases and controls has been described in detail in other reports (12). Briefly, newly diagnosed cases of primary epithelial ovarian cancer and low malignant potential (LMP) cancers diagnosed between January 1, 1999 and August 31, 2007 were identified through the North Carolina Central Cancer Registry using a rapid case ascertainment system. Consent to contact the women was requested from the treating physicians. Eligible cases were 20 to 74 years old at diagnosis, had at least one intact ovary, no prior history of ovarian cancer, resided in the study area and were cognitively able to give consent and complete an interview in English. All cases underwent centralized histopathologic review by the study pathologist to confirm their diagnosis. Controls were identified using list-assisted random digit dialing and were frequency-matched by age (5 year age categories) and race (African American or other) to the cases and resided in the same 48 county region. Nurse-interviewers conducted in-person visits with all study participants where they obtained written informed consent, administered a 90-minute standardized questionnaire, drew a blood sample and obtained anthropometric measurements. The study protocol was approved by the Duke University Medical Center Institutional Review Board and the human subjects committees at the North Carolina Central Cancer Registry and each hospital where cases were identified.

Genotyping

Genomic DNA was isolated according to a previously published protocol (12). The initial analysis of Caucasian and African American subjects focused on seven common *VDR* variants: *Apal* (rs7975232), *FokI* (rs2228570), *TaqI* (rs731236), *BsmI* (rs1544410), rs2239179, rs3782905, and rs7968585 (see Table 1). The follow-up study focused on *VDR* variants in LD ($R^2 > 0.8$) with *Apal* (rs7975232) in either the YRI or CEU populations. We identified twenty such variants and after removing redundant variants and those that were not designable were left with six variants in addition to *Apal*; rs10783215, rs2248098, rs2525044, rs7305032, rs7971418, and rs987849. All genotyping was accomplished using commercially available TaqMan assays (Applied Biosystems) on a 384 7900HT platform using genomic DNA. For internal quality controls replica CEPH and patient samples were

genotyped with each plate. Genotyper 2.0 software was used to call genotypes for each sample.

Statistical Analysis

We utilized intercontinental ancestry scores calculated using the program LAMP (13) as part of another study involving NCOCS subjects (14) to identify African American subjects and to adjust for degree of European admixture. Participants estimated to have greater than 10% Asian ancestry were removed from the analysis. In this report, participants were considered to be of European ancestry if they had a greater fraction of European ancestry than African ancestry and of African ancestry if the opposite was true. We used unconditional multivariable logistic regression models to measure the evidence of association between each *VDR* polymorphism and ovarian cancer risk; all analyses were adjusted for age at diagnosis/interview and LAMP score. We report odds ratios (OR) and 95% confidence intervals (CI) for heterozygote and homozygote genotypes, and under dominant and log-additive models for the minor allele using the homozygous major allele as the reference group.

Results

All SNPs genotyped in this study are listed in Table 1. Most of the SNPs are in Hardy-Weinberg-Equilibrium (HWE) in Caucasian controls. Among African Americans controls, *Apal* (rs7975232), *BsmI* (rs1544410) and rs7968585 had borderline significant p-values, likely due to small sample size. These subjects form a subset, of the larger sample of African American controls used in the follow-up analysis in which the HWE p-value for *Apal* (rs7975232) was no longer statistically significant. A comparison of the *Apal* genotyping results found in the subset of subjects that were included in both the initial analysis and in the follow-up showed 100% concordance for the rs797232 SNP genotypes.

Subjects in the initial analysis of 7 *VDR* variants included 513 Caucasian cases and 532 Caucasian controls and 74 African American cases and 79 African American controls. The initial analysis was conducted before data collection was complete and included those subjects who completed enrollment at that time. *VDR* SNPs *Apal* (rs7975232), *FokI* (rs2228570), *TaqI* (rs731236), *BsmI* (rs1544410), rs7968585, rs2239179, and rs3782905 (Table 1) were chosen for their functional significance and/or *Apal* (rs7975232) linkage and included in the initial analyses.

Table 2 provides summaries of the study population used in the initial analysis. Most African American and Caucasian cases were invasive tumors (77% and 78.7%, respectively) and there were similar proportions of invasive and LMP ovarian cancer cases in both racial groups. Most invasive cases were of the serous histologic subtype and diagnosed at stage III or IV. Table 2 also provides summaries of the follow-up sample of African Americans. The proportion of these cases (76.8%) diagnosed with invasive tumors is similar to those of both racial groups in the initial analysis (Table 2). As in the initial sample, most invasive cases were serous and stage III or IV at diagnosis. Not shown in Table 2, the mean age at diagnosis of African American cases (52.5 years, standard deviation (SD) = 11.6 years) was similar to the mean age at interview for controls (54.1 years, SD = 12.9 years), (p-value =

0.41). The comparison of the age at diagnosis/interview between Caucasian cases (55.3 years, SD = 11.4 years) and controls (54.5 years, SD = 12.7 years) also showed no difference ($p = 0.30$).

An initial analysis of Caucasians (Table 3a) and African Americans (Table 3b) was done to compare the association of *VDR* variants within each racial group. No statistically significant associations were observed between any of the 7 SNPs and ovarian cancer among Caucasian women (Table 3A). In contrast, we found evidence of association between the *Apal* risk variant (rs7975232) and ovarian cancer among African American women. In particular, we estimated the per-allele OR under the log-additive model of association to be 1.88 (95% CI = 1.14, 3.12, $p = 0.014$) for all cases and 2.08 (95% CI = 1.19, 3.63, $p = 0.010$) when restricted to invasive cases. We further restricted the analysis to serous invasive cases ($n = 63$) and found that the association was attenuated (data not shown). The *Apal* (rs7975232) variant's association with ovarian cancer remained significant after Bonferroni correction. In the follow-up study of 125 African American cases and 155 controls from the NCOCS, we focused on *VDR* variants in LD ($R^2 > 0.8$) with *Apal* (rs7975232) in either the YRI or CEU populations. We identified twenty such variants and after removing redundant variants and those that were not designable, we were left with six variants (rs10783215, rs2248098, rs2525044, rs7305032, rs7971418, rs987849) in addition to *Apal* (rs7975232) (see Table 4). Associations with *Apal* remained, but were diminished in the larger follow-up set; under the log-additive model of association we observed an OR=1.35 (95%CI = 0.95, 1.92) among all cases and an OR=1.39 (95%CI = 0.94, 2.05) among invasive cases. In addition, we found evidence of association between rs7305032 and ovarian cancer under the log-additive model in all cases (OR=1.64, 95%CI = 1.09, 2.47) and when restricted to invasive cases (OR=1.87, 95% CI = 1.20, 2.93). Further, several variants (rs2525044, rs7305032 and rs7971418) showed evidence of association under a dominant model. No association with risk for ovarian cancer was observed when the analysis was restricted to serous invasive cases (63 cases). These results suggest the existence of an allele at this locus that is associated with increased risk for ovarian cancer among African American women.

The follow-up study SNPs, rs10783215, rs2525044, rs2248098, rs7305032, rs7971418 and rs987849 demonstrated only modest linkage with the *Apal* rs7975232 polymorphism ($R^2 = 0.200, 0.397, 0.063, 0.369, 0.299, \text{ and } 0.275$, respectively) among the African American controls. We found stronger patterns of linkage disequilibrium among the SNPs neighboring *Apal* (rs7975232). In particular, rs2525044, rs987549 and rs7305032, the latter the most strongly associated SNP, had pairwise R^2 values ranging from 0.72 to 0.80. This suggests that the underlying risk allele is more likely to be in LD with the variants in this cluster than with *Apal*.

Discussion

The association of *VDR* polymorphisms was determined in two analyses: first an assessment of risk for ovarian cancer in Caucasian and African American women conferred by 7 *VDR* variants (4 of them with functional significance) and second, a follow-up assessment of risk for ovarian cancer in African Americans associated with 6 additional *VDR* SNPs in LD to

the *Apa1* (rs7975232) SNP which was the only SNP found to be significantly associated with risk of ovarian cancer in the initial analysis.

To date, most studies that have examined the association between polymorphism in the *VDR* gene and ovarian cancer have been in Caucasians, with some studies supporting an association with at least one genetic variant (7, 10) while others have not (8). In the current report we were not able to detect an association with any of the initial seven SNPs we genotyped for their potential functional significance in the Caucasians subjects enrolled in the NCOCS. However, we did detect a significant association with the *Apa1* (rs7975232) *VDR* variant among African American women. The association was stronger when the analysis was restricted to invasive ovarian cancer cases. The follow-up analysis of *VDR* variants in LD with *Apa1* in a larger sample of African Americans revealed one SNP, rs7305032, that was significantly associated with ovarian cancer but in modest LD with *Apa1* rs7975232 ($R^2 = 0.369$). This variant was in high LD with rs2525044 ($R^2 = 0.721$) and rs987849 ($R^2 = 0.768$). The odds of developing ovarian cancer increased by a factor of more than 1.6 for every copy of the minor allele of rs7305032 an African American subject carried. The association was stronger when the analysis was restricted to invasive cases.

To our knowledge, there have been no published reports of the association of *VDR* polymorphisms and ovarian cancer in African American women. However, *VDR* polymorphisms have been investigated for risk in Japanese women (94 cases, 173 controls) that were heterozygous carriers of *VDR* polymorphism *Cdx2* (rs11568820) risk allele. A significantly reduced risk of ovarian cancer was detected (OR=0.5, 95%CI = 0.3, 0.9) when compared to controls. No association was observed with *Apa1* (rs7975232) and *FokI* (rs2228570) SNPs in the same study (7).

Previous studies have examined the association of *VDR* polymorphisms in African Americans and Caucasians in other cancers. One study that included African Americans (488 breast cancer cases and 448 controls) found no association between the *VDR* variant, *BsmI* (rs1544410) and breast cancer in African Americans while a significant relationship was observed in Caucasians (1143 breast cancer cases and 987 controls) (15). A large multi-ethnic study including pooled data from 6 prospective studies which included approximately 6,300 cases and 8,100 controls (of which 325 cases and 419 controls were African Americans) found a significant association only between the *FokI* (rs2228570) polymorphism and breast cancer (OR=1.16, 95%CI=1.04, 1.28) in a study sample of both Caucasians and African Americans combined (16). In a more recent study 1,777 cases and 1,839 controls, the *FokI* (rs2228570) polymorphism was found to be protective against breast cancer risk in Caucasian individuals homozygous for that allele (OR=0.71, 95%CI=0.57, 0.88) (17). In a meta-analysis of *VDR* variants, *Apa1*, *BsmI*, *FokI*, *TaqI*, and *Cdx2* polymorphisms *TaqI* risk and *BsmI* major alleles were associated with reduced prostate cancer risk among all study subjects regardless of race (18). In another study of men less than 65 year of age at diagnosis that included both African Americans and Caucasians, African Americans homozygous for the wild type allele of the *FokI* (rs2228570) polymorphism had increased risk for prostate cancer (OR=1.9, 95%CI=1.0–3.3), but not Caucasians (19). The risk allele of the *TaqI* (rs731236) polymorphism showed a modest association in risk for prostate cancer in a study that included 253 African American prostate

cancer cases and 297 controls (OR = 1.3; 95% CI = 1.0, 1.7) but the significance of that association was removed upon adjustment for age and individual ancestry (Bonilla et al., 2011).

While associations with specific *VDR* variants were observed among African American subjects with breast or prostate cancer, no significant associations were noted for the *Apal* (rs7975232) SNP. The *VDR* variants assessed in this study may be associated with a functional phenotype that is specific to ovarian cancer. Log-additive analyses of the *Apal* SNP (rs7975232) in the initial analysis and in the follow-up suggest that the risk alleles may contribute to *VDR* gene function, although in the follow-up analysis, the association with the *Apal* allele was attenuated and was of borderline significance. In the follow-up analysis we found evidence that rs7305032 was associated with ovarian cancer; however rs7305032 was not in strong LD with the *Apal* SNP (rs7975232) in the study population. A larger fine mapping analysis in African Americans coupled with a comprehensive functional characterization of the locus is necessary to confirm and localize the associations we observed.

The ethnic differences in the *VDR* association with disease suggest that race may be an effect modifier that may impact the vitamin D system. Because the Caucasian and African Americans subjects are North Carolina residents, the differences in association to risk for ovarian cancer may stem from alterations in *VDR* activity although we cannot rule out the effect of exposure to UVB irradiation due to skin pigmentation and latitude, absorption and diet. While African ancestry has been linked to lower circulating 25(OH)D levels, (in part because of darker skin pigmentation that blocks essential UVB exposure) other evidence suggests that the relationship may be associated with baseline 25(OH)D and cholesterol levels (20). An average level of 25(OH)D (115 nmol/l) were measured in traditional populations living in Tanzania who wear moderate degree of clothing and spend the major part of the day outdoors (21). These levels are much higher than the concentration of 25(OH)D (>50 nmol/l) recommended by the US Institute of Medicine (22). These data suggest a role for western lifestyle in modifying 25(OH)D levels.

The main limitation of this study is the small sample size of African American subjects which may have limited our ability to detect modest, but potentially important associations. We also did not have environmental vitamin D exposure assessment, which may have been associated ovarian cancer risk in African Americans since differences in circulating 25(OH)D have been lower in African Americans, possibly reflecting a gene-environment interaction.

In our analyses potential population stratification was addressed by adjusting for population admixture using European and African assignments for intercontinental ancestry which decreases the possible confounding effects of population stratification. In what we report, we define African Americans to be those subjects with an African ancestry Lamp score of 0.5 or greater and adjust for the fraction of European ancestry. We repeated the analysis after sub setting to those subjects with an African ancestry Lamp score of 0.8 or larger to assess whether confounding due to population admixture could explain the associations we observed. The results of the two analyses were consistent, while the key associations

between rs7305032 and ovarian cancer were stronger with the stricter genetic definition (all cases OR=1.84; 95% CI=1.11, 3.08; invasive cases OR=2.14; 95% CI=1.23, 3.72). This study suggests that there may be differences in genetic predisposition to ovarian cancer among women of African ancestry due to variants in the *VDR* gene. As *VDR* has not been a major locus identified in GWAS studies in ovarian cancer, the association in Africans may have been missed as only samples of European ancestry are included in those studies.

In summary, our results suggest that risk to ovarian cancer may be altered by *VDR* polymorphism and race. Future studies should include larger samples sizes of African Americans. Additionally, future studies should be designed to explore modifying effects of environmental factors such as diet, dietary supplements, and UVB exposure, on the association between *VDR* variants and ovarian cancer risk. Future functional studies could elucidate the underlying impact on *VDR* gene expression of the intronic *VDR* variants associated with increased risk for ovarian cancer.

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Table 1
Characteristics of Vitamin D Receptor SNPs genotyped in the Initial and Follow-up Analyses by Ancestry*

SNP	Function class	Position	Minor allele	MAF European Ancestry	HWE p-value	MAF African Ancestry	HWE p-value
Initial analysis							
rs7975232 <i>Apal</i>	intron	48238837	C	0.4765	0.7014	0.3101	0.0585
rs2228570 <i>FokI</i>	nonsyn *	48272895	A	0.3766	0.5383	0.1772	0.6888
rs731236 <i>TaqI</i>	syn *	48238757	C	0.3972	0.3276	0.2595	0.8516
rs1544410 <i>BsmI</i>	intron	48239835	T	0.3996	0.5259	0.2692	0.0355
rs2239179	intron	48257766	C	0.4301	0.4960	0.2885	0.7786
rs3782905	intron	48266167	C	0.3184	0.7879	0.2215	0.4636
rs7968585	intergenic	48232093	G	0.4906	0.2620	0.3861	0.0234
Follow-up analysis							
rs7975232 <i>Apal</i>	intron	48238837	C	-----	-----	0.3247	0.4117
rs10783215	unknown	48231898	C	-----	-----	0.3581	0.7604
rs2248098	intron	48253356	A	-----	-----	0.4710	0.6016
rs2525044	intron	48242256	A	-----	-----	0.1600	0.9226
rs7305032	intron	48249860	G	-----	-----	0.2086	0.4812
rs7971418	intron	48245235	C	-----	-----	0.3816	0.3242
rs987849	intron	48254676	G	-----	-----	0.1916	0.7348

* nonsyn (nonsynonymous); syn (synonymous); MAF (minor allele frequency); HWE (Hardy-Weinberg Equilibrium)

Histological Characteristics of Ovarian Cancer Cases participating in the North Carolina Ovarian Cancer Study: Initial and Follow-up Analyses

Table 2

	African American Cases *		Caucasians Cases		African American Cases **	
	N	(%)	N	(%)	N	(%)
All Cases Tumor Behavior	74		513		125	
Invasive tumor	57	(77.0)	400	(78.0)	96	(76.8)
Low-malignant-potential tumor	17	(23.0)	111	(21.6)	29	(23.0)
missing	0		2	(0.4)	0	
Invasive Cases only Histology						
Serous	33	(57.9)	236	(59.0)	57	(59.4)
Clear cell	2	(3.5)	37	(9.3)	2	(2.1)
Endometrioid	10	(17.5)	59	(14.8)	16	(16.7)
Mucinous	2	(3.5)	21	(5.3)	4	(4.2)
other	10	(17.5)	47	(11.8)	17	(17.7)
missing						
Invasive Cases only Stage						
I or II	11	(19.3)	116	(29.0)	20	(20.8)
III or IV	45	(79.0)	283	(70.8)	74	(77.1)
missing	1	(1.7)	1	(0.2)	2	(2.1)
Grade						
Well differentiated	9	(15.8)	50	(12.5)	17	(17.7)
Moderately differentiated	16	(28.1)	118	(29.5)	29	(30.2)
Poorly differentiated or undifferentiated	30	(52.6)	219	(54.8)	47	(49.0)
missing	2	(3.5)	13	(3.2)	3	(3.1)

* Initial study

** Follow-up study

Age- and European ancestry-adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for associations between VDR variants and Ovarian Cancer among Caucasians

Table 3A

	Cases				Controls		Age- and Ancestry-adjusted			
	All*		Invasive**		All		All*		Invasive**	
	N	(%)	N	(%)	N	(%)	OR	(95%CI)	OR	(95% CI)
rs975232 <i>Apal</i>										
AA	138	(27.2)	105	(26.8)	148	(27.8)				
AC	262	(51.7)	204	(52.0)	261	(49.1)				
CC	107	(21.1)	83	(21.2)	123	(23.1)				
AC/CC	369	(72.8)	287	(73.2)	384	(72.2)				
Log-additive							0.97	(0.82, 1.15)	0.97	(0.80, 1.17)
Total	507		392		532					
rs2228570 <i>FokI</i>										
GG	197	(38.5)	158	(39.9)	203	(38.2)				
AG	250	(48.8)	185	(46.7)	256	(48.2)				
AA	65	(12.7)	53	(13.4)	72	(13.6)				
AG/AA	315	(61.5)	238	(60.1)	328	(61.8)				
Log-additive							0.98	(0.82, 1.17)	0.97	(0.80, 1.17)
Total	512		396		531					
rs731236 <i>TaqI</i>										
TT	168	(32.9)	131	(33.2)	198	(37.4)				
TC	266	(52.1)	205	(51.9)	243	(45.8)				
CC	77	(15.1)	59	(14.9)	89	(16.8)				
TC/CC	343	(67.1)	264	(66.8)	332	(62.6)				
Log-additive							1.06	(0.89, 1.27)	1.06	(0.88, 1.28)
Total	511		395		530					
rs1544410 <i>BsmI</i>										
CC	165	(33.1)	129	(33.5)	192	(36.7)				
CT	257	(51.6)	197	(51.2)	244	(46.7)				
TT	76	(15.3)	59	(15.3)	87	(16.6)				

	Cases				Controls		Age- and Ancestry-adjusted			
	All*	Invasive**		All	N	(%)	All*	Invasive**		All*
	N	(%)	N	(%)	N	(%)	OR	(95%CI)	OR	(95% CI)
CT/TT	333	(66.9)	256	(66.5)	331	(63.3)				
Log-additive							1.05	(0.88, 1.25)	1.05	(0.87, 1.27)
Total	498		385		523					
rs2239179										
TT	142	(28.1)	111	(28.4)	168	(31.8)				
TC	275	(54.3)	211	(54.0)	267	(50.5)				
CC	89	(17.6)	69	(17.6)	94	(17.8)				
TC/CC	364	(71.9)	280	(71.6)	361	(68.2)				
Log-additive							1.08	(0.90, 1.29)	1.08	(0.89, 1.31)
Total	506		391		529					
rs3782905										
GG	214	(42.2)	171	(43.6)	243	(46.2)				
GC	237	(46.7)	177	(45.2)	231	(43.9)				
CC	56	(11.0)	44	(11.2)	52	(9.9)				
GC/CC	293	(57.8)	221	(56.4)	283	(53.8)				
Log-additive							1.13	(0.94, 1.36)	1.11	(0.91, 1.35)
Total	507		392		526					
rs7968585										
AA	132	(26.0)	101	(25.7)	144	(27.2)				
AG	262	(51.6)	203	(51.7)	252	(47.5)				
GG	114	(22.4)	89	(22.6)	134	(25.3)				
AG/GG	376	(74.0)	292	(74.3)	386	(72.8)				
Log-additive							0.97	(0.81, 1.15)	0.97	(0.81, 1.17)
Total	508		393		530					

* including all peritoneal cases
** including serous invasive peritoneal cases

Age- and African Ancestry-adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for associations between VDR variants and Ovarian Cancer Risk among African Americans

Table 3B

	Cases				Controls				Age-and Ancestry-adjusted			
	All*		Invasive**		All		Invasive**		All*		Invasive**	
	N	(%)	N	(%)	N	(%)	N	(%)	OR	(95%CI)	OR	(95%CI)
rs7975232 Apa I												
AA	23	(31.1)	16	(29.1)	34	(43.0)						
AC	36	(48.6)	27	(49.1)	41	(51.9)						
CC	15	(20.3)	12	(21.8)	4	(5.1)						
AC/CC	51	(68.9)	39	(70.9)	45	(57.0)						
Log-additive									1.88	(1.14, 3.12)	2.08	(1.19, 3.63)
Total	74		55		79							
rs2228570 Fok I												
GG	47	(63.5)	35	(63.6)	54	(68.4)						
AG	22	(29.7)	16	(29.1)	22	(27.8)						
AA	5	(6.8)	4	(7.3)	3	(3.8)						
AG/AA	27	(36.5)	20	(36.4)	25	(31.6)						
Log-additive									1.25	(0.72, 2.16)	1.26	(0.70, 2.26)
Total	74		55		79							
rs731236 Taq I												
TT	43	(58.1)	32	(58.2)	43	(54.4)						
TC	25	(33.8)	18	(32.7)	31	(39.2)						
CC	6	(8.1)	5	(9.1)	5	(6.3)						
TC/CC	31	(41.9)	23	(41.8)	36	(45.6)						
Log-additive									0.95	(0.57, 1.59)	1.01	(0.58, 1.77)
Total	74		55		79							
rs1544410 Bsm I												
CC	44	(60.3)	34	(63.0)	38	(48.7)						
CT	26	(35.6)	17	(31.5)	38	(48.7)						
TT	3	(4.1)	3	(5.6)	2	(2.6)						

	Cases				Controls				Age-and Ancestry-adjusted			
	All*		Invasive**		All		All*		All*		Invasive**	
	N	(%)	N	(%)	N	(%)	N	(%)	OR	(95%CI)	OR	(95%CI)
CT/TT	29	(39.7)	20	(37.0)	40	(51.3)						
Log-additive									0.72	(0.40, 1.29)	0.73	(0.39, 1.38)
Total	73		54		78							
rs2239179												
TT	34	(45.9)	27	(49.1)	40	(51.3)						
TC	34	(45.9)	23	(41.8)	31	(39.7)						
CC	6	(8.1)	5	(9.1)	7	(9.0)						
TC/CC	40	(54.1)	28	(50.9)	38	(48.7)						
Log-additive									1.09	(0.66, 1.82)	1.10	(0.64, 1.89)
Total	74		55		78							
rs3782905												
GG	49	(66.2)	37	(67.3)	49	(62.0)						
GC	22	(29.7)	16	(29.1)	25	(31.6)						
CC	3	(4.1)	2	(3.6)	5	(6.3)						
GC/CC	25	(33.8)	18	(32.7)	30	(38.0)						
Log-additive									0.81	(0.46, 1.41)	0.83	(0.45, 1.54)
Total	74		55		79							
rs7968585												
AA	26	(35.1)	19	(34.5)	25	(31.6)						
AG	33	(44.6)	25	(45.5)	47	(59.5)						
GG	15	(20.3)	11	(20.0)	7	(8.9)						
AG/GG	48	(64.9)	36	(65.5)	54	(68.4)						
Log-additive									1.20	(0.74, 1.94)	1.20	(0.71, 2.04)
Total	74		55		79							

* including all peritoneal cases
** including serous invasive peritoneal cases

Follow-up Analysis of Age- and African ancestry-adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for associations between VDR variants and Ovarian Cancer Risk among African Americans

Table 4

	Cases			Controls			Age- and Ancestry-adjusted			
	All			All			Invasive**			
	N	(%)	N	(%)	N	(%)	OR	(95% CI)	OR	(95% CI)
rs7975232 Apal										
AA	47	(37.6)	35	(37.2)	68	(44.2)	1.00	(Reference)	1.00	(Reference)
AC	58	(46.4)	44	(46.8)	72	(46.8)	1.16	(0.70, 1.93)	1.19	(0.68, 2.08)
CC	20	(16.0)	15	(16.0)	14	(9.1)	2.07	(0.95, 4.51)	2.19	(0.95, 5.09)
CC/AC	78	(62.4)	59	(62.8)	86	(55.9)	1.31	(0.81, 2.12)	1.35	(0.80, 2.29)
Log-additive							1.35	(0.95, 1.92)	1.39	(0.94, 2.05)
Total	125		94		154					
rs10783215										
TT	45	(36.3)	32	(34.4)	63	(40.6)	1.00	(Reference)	1.00	(Reference)
CT	56	(45.2)	43	(46.2)	73	(47.1)	1.07	(0.64, 1.81)	1.11	(0.63, 1.97)
CC	23	(18.5)	18	(19.4)	19	(12.3)	1.70	(0.83, 3.49)	1.90	(0.87, 4.12)
CC/CT	79	(81.5)	61	(80.6)	92	(87.7)	1.21	(0.74, 1.97)	1.27	(0.74, 2.18)
Log-additive							1.25	(0.89, 1.76)	1.32	(0.91, 1.92)
Total	124		93		155					
rs2248098										
GG	28	(22.4)	20	(21.3)	45	(29.0)	1.00	(Reference)	1.00	(Reference)
AG	66	(52.8)	50	(53.2)	74	(47.7)	1.44	(0.81, 2.56)	1.52	(0.80, 2.89)
AA	31	(24.8)	24	(25.5)	36	(23.2)	1.38	(0.70, 2.71)	1.47	(0.70, 3.09)
AA/AG	97	(77.6)	74	(78.7)	110	(71.0)	1.42	(0.82, 2.45)	1.51	(0.82, 2.76)
Log-additive							1.18	(0.84, 1.65)	1.21	(0.84, 1.75)
Total	125		94		155					
rs2525044										
GG	74	(60.2)	54	(58.1)	106	(70.7)	1.00	(Reference)	1.00	(Reference)
AG	46	(37.4)	38	(40.9)	40	(26.7)	1.65	(0.98, 2.77)	1.95	(1.12, 3.41)
AA	3	(2.4)	1	(1.1)	4	(2.7)	1.08	(0.23, 4.97)	0.53	(0.06, 4.92)

	Cases				Controls			All		Age- and Ancestry-adjusted	
	All		Invasive**		N	N (%)	OR	(95% CI)	OR	Invasive** (95%CI)	
	N	(%)	N	(%)							
AA/AG	49	(39.8)	39	(41.9)	44	(29.3)	1.60	(0.96, 2.65)	1.82	(1.05, 3.16)	
Log-additive							1.44	(0.92, 2.26)	1.56	(0.95, 2.56)	
Total	123		93		150						
rs7305032											
GG	57	(46.0)	40	(42.6)	96	(63.6)	1.00	(Reference)	1.00	(Reference)	
AG	61	(49.2)	50	(53.2)	47	(31.1)	2.20	(1.33, 3.64)	2.69	(1.55, 4.68)	
AA	6	(4.8)	4	(4.3)	8	(5.3)	1.24	(0.41, 3.79)	1.34	(0.38, 4.80)	
AA/AG	67	(95.2)	54	(95.7)	55	(94.4)	2.06	(1.27, 3.35)	2.51	(1.46, 4.28)	
Log-additive							1.64	(1.09, 2.47)	1.87	(1.20, 2.93)	
Total	124		94		151						
rs7971418											
AA	34	(27.6)	25	(27.2)	61	(40.1)	1.00	(Reference)	1.00	(Reference)	
AC	70	(56.9)	53	(57.6)	66	(43.4)	1.92	(1.12, 3.29)	1.96	(1.08, 3.55)	
CC	19	(15.4)	14	(15.2)	25	(16.4)	1.36	(0.66, 2.82)	1.38	(0.61, 3.08)	
CC/AC	89	(72.3)	67	(72.8)	91	(59.8)	1.76	(1.06, 2.94)	1.79	(1.02, 3.16)	
Log-additive							1.28	(0.90, 1.81)	1.28	(0.88, 1.87)	
Total	123		92		152						
rs987849											
AA	68	(54.8)	50	(53.8)	100	(64.9)	1.00	(Reference)	1.00	(Reference)	
AG	53	(42.7)	42	(45.2)	49	(31.8)	1.59	(0.97, 2.62)	1.79	(1.04, 3.08)	
GG	3	(2.4)	1	(1.1)	5	(3.2)	0.89	(0.21, 3.87)	0.43	(0.05, 3.79)	
GG/AG	56	(45.2)	43	(46.3)	54	(35.1)	1.53	(0.94, 2.49)	1.67	(0.98, 2.84)	
Log-additive							1.36	(0.88, 2.10)	1.41	(0.88, 2.28)	
Total	124		93		154						

* including all peritoneal cases
** including serous invasive peritoneal cases