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Vitamin D Receptor Gene *Bsm*I and *Fok*I Polymorphisms in Relation to Ovarian Cancer Risk in the Polish Population

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Background: The role of vitamin D receptor (*VDR*) single-nucleotide polymorphisms (SNPs) in ovarian cancer has been studied in various populations; however, these results are discordant between different ethnicities. *Method:* Using the polymerase chain reaction–restriction fragment length polymorphism method, we studied the prevalence of the *VDR Fok*I (rs2228570) and *Bsm*I (rs1544410) SNPs in women with ovarian cancer ($n = 168$) and controls ($n = 182$) in a Polish population. *Results:* We found a significant contribution of the *Bsm*I SNP Bb + BB-versus-bb dominant inheritance model to ovarian cancer development ($p = 0.0221$, $p_{corr} = 0.0442$, odds ratio [OR] = 1.648 [95% confidence intervals, CI = 1.073–2.532]). However, we did not observe an association of the *Bsm*I SNP BB versus Bb + bb recessive inheritance model in patients ($p = 0.8059$, OR = 1.093 [95% CI = 0.538–2.218]). Moreover, there was no association of *Fok*I SNPs either in Ff + ff versus FF dominant or ff versus Ff + FF recessive inheritance models with ovarian cancer development ($p = 0.9924$, OR = 1.002 [95% CI = 0.628–1.599] and $p = 0.1123$, OR = 1.542 [95% CI = 0.901–2.638], respectively). The *p*-values of the trend test observed for the *VDR Bsm*I and *Fok*I SNPs in patients with ovarian cancer were $p_{trend} = 0.0613$ and $p_{trend} = 0.3655$, respectively. *Conclusion:* Our study indicates that the *VDR* B gene variant might be a moderate risk factor of ovarian cancer development in the Polish population.

Introduction

Ovarian cancer is the one of the most lethal gynecological malignancies in developed countries, with 225,500 new cases and 140,200 estimated deaths annually worldwide (Jemal *et al.*, 2011). Ovarian cancer may develop in different parts of the ovary; however, ~90% of malignant ovarian tumors arise from ovarian epithelium (Romero and Bast, 2012). Risk factors for ovarian cancer include advancing age, infertility, inflammation, environmental factors, positive family history of ovarian, uterine, breast, or colon tumors associated with mutations of *BRCA1* or *BRCA2*, mismatch repair genes, or *TP53* (Sueblinvong and Carney, 2009). Risk is also related to the number of ovulatory cycles and is halved in women using oral contraceptives, those with greater parity, or those who breast-fed long-term (Brekelmans, 2003; Sueblinvong and Carney, 2009; Romero and Bast, 2012).

Approximately 85% of ovarian cancer cases are sporadic, and 15% are familial, suggesting a significant role in the interaction between genetic factors and environmental exposure (Romero and Bast, 2012). The environmental factors may include diet, lifestyle, and exposure to chemicals or other toxins (Brekelmans, 2003). Recently, some studies have suggested the possible role of vitamin D in the development of cancers, including ovarian carcinogenesis (Grant, 2012).

The active form of vitamin D, 1,25-dihydroxyvitamin D3 [$1,25(OH)_2D_3$] transduces signals to target cells exploiting the vitamin D receptor (VDR) (Miyamoto *et al.*, 1997).VDR forms heterodimers with the related retinoid X receptors and initiates the transcription of various genes (Zhang *et al.*, 2011). It has been demonstrated that$1,25(OH)_2D_3$ is able to regulate the expression of tumor-related genes, mediating inhibition of growth of ovarian cancer cells (Zhang *et al.*, 2006). This may suggest that genetic variants of the *VDR* gene modulating the action of $1,25(OH)_2D_3$ may play a significant role in ovarian tumorigenesis. The *VDR* gene is situated on chromosome 12q, and some of the variants of this gene may affect the function of $1,25(OH)_2D_3$ in target cells (Uitterlinden *et al.*, 2004). The most frequently studied *VDR* single-nucleotide polymorphisms (SNPs) include rs10735810/rs2228570 (*Fok*I) and three other SNPs, namely rs1544410 (*Bsm*I), rs731236 (*Taq*I), and rs7975232 (*Apa*I), situated in the same linkage disequilibrium (LD) block (Uitterlinden *et al.*, 2004). In recent years, the relevance of *VDR* polymorphisms as risk factors for the development of various types of cancer, including ovarian cancer, has been evaluated in numerous population studies (Lurie *et al.*, 2007, 2011; Clendenen *et al.*, 2008; Köstner *et al.*, 2009; Tamez *et al.*, 2009; Tworoger *et al.*, 2009). However, these studies have demonstrated variable and inconsistent results (Lurie *et al.*, 2007, 2011; Clendenen *et al.*, 2008; Tamez *et al.*,

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2009; Tworoger *et al*., 2009). Therefore, we aimed to study whether the *Fok*I and *Bsm*I SNPs situated in the *VDR* gene can be a genetic risk factor of ovarian cancer in the Polish population.

Materials and Methods

Patients and controls

The patient group is composed of 168 women with histologically recognized ovarian carcinoma according to the International Federation of Gynecology and Obstetrics (FIGO). Histopathological classification, including the stage, grade, and tumor type, was performed by an experienced pathologist (Table 1). The controls encompassed 182 unrelated healthy female volunteers who were matched by age to the cancer patients (Table 1). Written informed consent was obtained from all participating individuals. The procedures of the study were approved by the Local Ethics Committee of the Poznan University of Medical Sciences. Patients and controls were Caucasian from the Wielkopolska area of Poland.

Genotyping

Genomic DNA was isolated from peripheral blood leukocytes by salt extraction. DNA samples were genotyped for the *Bsm*I (rs1544410) and *Fok*I (rs2228570) *VDR* SNPs (Supplementary Table S1; Supplementary Data are available online at www.liebertpub.com/gtmb). Genotyping of the *Bsm*I and *Fok*I *VDR* variants was conducted by polymerase chain reaction (PCR), followed by the appropriate restriction enzyme digestion (PCR–restriction fragment length polymorphism [RFLP]) according to the manufacturer's instructions (Fermentas, Vilnius, Lithuania). DNA fragments were separated in 2% agarose gels and visualized by ethidium bromide staining. Primer sequences and conditions for PCR-RFLP analyses are presented in Supplementary Table S2.

Table 1. Clinical Characteristics of Ovarian Cancer Patients and Healthy Controls

Characteristic	*Patients* (n = *168*)	*Controls* (n = *182*)
Mean age ± SD	55.6 ± 9.6	54.7 ± 8.7
Histological grade		
G1	31 (18.4%)	
G2	48 (28.6%)	
G3	46 (27.4%)	
Gx	43 (25.6%)	
Clinical stage		
I	46 (27.4%)	
II	37 (22.0%)	
III	58 (34.5%)	
IV	27 (16.1%)	
Histological type		
Serous	46 (27.4%)	
Mucinous	29 (17.3%)	
Endometrioid	50 (29.8%)	
Clear cell	19 (11.3%)	
Brenne	3 (1.8%)	
Mixed	11 (6.5%)	
Untyped carcinoma	10 (5.9%)	

Statistical analysis

For each SNP, the Hardy–Weinberg equilibrium (HWE) was assessed by Pearson's goodness-of-fit chi-square (χ^2) statistic. The differences in the allele and genotype frequencies between cases and controls were determined using χ^2 tests. SNPs were tested for association with ovarian cancer using the Cochran-Armitage trend test. The odds ratio (OR) and associated 95% confidence intervals (95% CI) were also calculated. The data were analyzed under recessive and dominant inheritance models. To adjust for the multiple testing, we employed a Bonferroni correction. Pairwise LD between selected SNPs was computed as both D' and r^2 values using HaploView 4.0 software (Broad Institute, Cambridge, MA). HaploView 4.0. software was also used for haplotype analysis. Only haplotypes with a frequency above 0.01 were analyzed. Statistical significance was assessed using the 10,000-fold permutation test.

Results

Association of the VDR Bsm*I and* Fok*I SNPs with ovarian cancer development*

The frequency of all studied genotypes did not exhibit deviation from the HWE between all investigated groups ($p > 0.05$). The number of genotypes, OR, and 95% CI evaluation for the *VDR Bsm*I and *Fok*I polymorphisms are presented in Table 2. The *p*-values of the trend test observed for the *VDR Bsm*I and *Fok*I SNPs were $p_{trend} = 0.0613$ and $p_{trend} = 0.3655$, respectively (Table 2). We found a significant contribution of *Bsm*I SNP in a dominant inheritance model to ovarian cancer development ($p = 0.0221$, $p_{corr} = 0.0442$, OR = 1.648 [95% CI = 1.073–2.532]) (Table 2). However, we did not observe an association of *Bsm*I SNP in a recessive inheritance model ($p = 0.8059$, OR = 1.093 [95% CI = 0.538–2.218]). Moreover, there was no association of the *Fok*I SNP, either in dominant or recessive inheritance models, with ovarian cancer development ($p = 0.9924$, OR = 1.002 [95% CI = 0.628–1.599] and $p = 0.1123$, OR = 1.542 [95% CI = 0.901–2.638], respectively) (Table 2).

Association of the VDR Bsm*I and* Fok*I haplotypes with ovarian cancer development*

Haplotype analysis of *VDR Bsm*I and *Fok*I polymorphisms did not reveal statistically significant differences in haplotype frequencies between cases and controls. The lowest *p*-value ($p = 0.0910$, $p_{corr} = 0.1736$) was observed for haplotypes composed of the Bf alleles (Table 3). However, these results were not statistically significant when permutations were used to generate empiric *p*-values. The *VDR Bsm*I and *Fok*I SNPs were in weak pairwise LD. This was calculated from the control samples, and had D' ranges of 0.004–0.106 for the *VDR Bsm*I and *Fok*I SNPs (Supplementary Table S3).

Discussion

The basic role of $1,25(OH)_2D_3$ is the homeostasis of calcium and maintenance of proper bone mineral densities (Uitterlinden *et al*., 2004; Maruotti and Cantatore, 2010). The VDR has been found in various tissues, including cardiac myocytes, β-cells in the pancreas, immune cells, and other peripheral tissues that indicate the broad role of $1,25(OH)_2D_3$ in human

Table 2. Association of Polymorphisms of the Vitamin D Receptor Gene with Ovarian Cancer

rs no.	*Alleles*[a]	*MAF*[b]	*Genotype*[c] *Cases*	*Genotype*[c] *Controls*	$OR_{dominant}$ (95% CI); p-*value*[d]	$OR_{recessive}$ (95% CI); p-*value*[d]	p_{trend} *value*[e]
rs1544410	A/G (B/b)	0.31	60/91/17	87/78/17	AG + AA vs. GG (Bb + BB vs. bb)	AA vs. AG + GG (BB vs. Bb + bb)	
					1.648 (1.073–2.532); 0.0221	1.093 (0.538–2.218); $p = 0.8059$	0.0613
rs2228570	C/T (F/f)	0.44	47/83/38	51/102/29	CT + TT vs. CC (Ff + ff vs. FF)	TT vs. CT + CC (ff vs. Ff + FF)	
					1.002 (0.628–1.599); 0.9924	1.542 (0.901–2.638); 0.1123	0.3555

Bold values are significant $p < 0.05$.
[a]Underline denotes the minor allele in the control samples.
[b]MAF, minor allele frequency calculated from the control samples.
[c]The order of genotypes: DD/Dd/dd (d is the minor allele).
[d]Chi-square analysis.
[e]Cochran-Armitage trend test.
CI, confidence interval; OR, odds ratio.

physiology, cardioprotection, immune system regulation, and cancer prevention (Uitterlinden *et al*., 2004; Maruotti and Cantatore, 2010). Moreover, the VDR has been also identified in different malignancies, which may draw attention to the role of vitamin D in growth control of various cancer cells (Wolden-Kirk *et al*., 2012). Recently, it has been demonstrated that $1,25(OH)_2D_3$ suppresses motility, invasion, and metastasis of squamous cell carcinoma in the murine model (Ma *et al*., 2012). In addition to these findings, Swami *et al.* (2012) observed that dietary vitamin D_3 and $1,25(OH)_2D_3$ displayed equivalent anticancer activity in murine xenograft models of breast and prostate cancer. Preclinical studies conducted by Zhang *et al.* (2006) demonstrated that the synthetic vitamin D analog EB1089 increased the apoptotic rate and decreased cell proliferation in human ovarian tumor xenografts in mice.

Vitamin D deficiency has been observed in patients with various cancer types and has been correlated with advanced stage of disease (Churilla *et al*., 2012). Reduced vitamin D status has been associated with either poor prognosis or development of lung, thyroid, breast, gastric, colon, and head and neck cancers (Cheng and Neuhouser, 2012; Imtiaz *et al*., 2012; Orell-Kotikangas *et al*., 2012; Pereira *et al*., 2012; Roskies *et al*., 2012; Ren *et al*., 2012). Decreased levels of vitamin D have also been found in patients with ovarian cancer as compared to the general population (Bakhru *et al*., 2010). Moreover, intake of total vitamin D was inversely associated with the risk of developing serous borderline and mucinous histological subtypes of ovarian tumors (Merritt *et al*., 2012). This may indicate that interaction between vitamin D levels and genetic variants of *VDR* may play a pivotal role in ovarian carcinogenesis.

We found a moderate association of the *Bsm*I *VDR* B gene variant with ovarian cancer in the Polish population. There was no *Bsm*I *VDR* polymorphism contribution to ovarian cancer development in the study conducted by Clendenen *et al.* (2008) in a Caucasian population (Clendenen *et al*., 2008). Moreover, the *Bsm*I *VDR* SNP was not associated with ovarian cancer development in cohorts from Massachusetts and New Hampshire in the United States (Tworoger *et al*., 2009).

However, we did not observe significant differences in the distribution of the *VDR Fok*I polymorphism between patients with ovarian cancer and controls. Our findings are consistent with the study results of Clendenen *et al.* (2008), who did not find that the *Fok*I SNP is a risk of ovarian cancer in a Caucasian population (Clendenen *et al*., 2008). However, in some studies, the *Fok*I polymorphism has been recognized as a risk factor of ovarian cancer (Lurie *et al*., 2007, 2011; Tworoger *et al*., 2009). Tworoger *et al.* (2009) observed that the TT (ff) genotype of the *Fok*I SNP was significantly associated with ovarian cancer risk in a population studied in Massachusetts and New Hampshire in the United States (Tworoger *et al*., 2009). Moreover, Caucasian women, but not Japanese women, having the heterozygous *Fok*I T (f) allele were also at increased risk for ovarian carcinoma compared with the homozygous CC (FF) carriers (Lurie *et al*., 2007). A recently conducted pooled analysis of five studies, including 1820 white non-Hispanic cases and 3479 controls, confirmed that the *Fok*I T (f) allele is associated with ovarian cancer (Lurie *et al*., 2011). In addition, Tamez *et al.* (2009) demonstrated that, in a Japanese population, the *Fok*I CC (FF) genotype was associated with better survival compared to the CT (Ff) or TT (ff) genotypes (Tamez *et al*., 2009).

The differences on the effect of the *Bsm*I and *Fok*I *VDR* SNPs on the increased risk of ovarian cancer development in various studies may be due to exposure of the analyzed groups to disparate environmental factors, group size, and genetic

Table 3. Analysis of Haplotypes in the *VDR* Gene and the Risk of Ovarian Cancer

Polymorphisms	*Haplotypes*	*Frequency*	*Case, control ratios*	χ^2	p-*Value*	p_{corr} *value*[a]
rs1544410_ rs2228570	GC (bF)	0.353	0.327, 0.378	1.995	0.1578	0.3149
	GT (bf)	0.307	0.301, 0.313	0.108	0.7422	0.9756
	AC (BF)	0.191	0.200, 0.183	0.331	0.5650	0.8896
	AT (Bf)	0.148	0.172, 0.126	2.857	0.0910	0.1736

[a]*p*-Value calculated using permutation test and a total of 10,000 permutations.
VDR, vitamin D receptor.

heterogeneity. Moreover, these differences might also result from confounding factors that are taken into consideration in these studies and include food habits, age, education, menopausal status, parity, body–mass index, use of oral contraceptives or hormone replacement therapy, tubal ligation, and others (Lurie *et al*., 2007, 2011; Tworoger *et al*., 2009).

The *Bsm*I or *Fok*I SNPs in *VDR* have been associated with breast, bladder, renal, carcinoma, and cutaneous malignant melanoma and nonmelanoma skin cancer (Mittal *et al*., 2007; Gandini *et al*., 2009; Tang *et al*., 2009; Arjumand *et al*., 2012). These polymorphisms were also recognized as risk factors of hepatocellular, head and neck, thyroid, prostate, and colorectal cancers (Liu *et al*., 2005; Mishra *et al*., 2005; Bai *et al*., 2009, 2012; Penna-Martinez *et al*., 2009; Falleti *et al*., 2010).

The effects of *Bsm*I and *Fok*I SNPs on the VDR protein function have already been studied (Arai *et al*., 1997; Luo *et al*., 2012; Monticielo *et al*., 2012). The *Fok*I SNP situated in exon 2 results in the formation of a second methionine start site that leads to the production of a shorter protein receptor (Arai *et al*., 1997). This VDR isoform displayed higher transcriptional activity than the longer-type receptor (Arai *et al*., 1997). The role of the *Fok*I SNP has recently been reinforced by Monticielo *et al.* (2012). They found that vitamin D concentration was remarkably elevated in bearers of the TT (ff) genotype versus individuals having the CC (FF) genotype (Monticielo *et al*., 2012). The *Bsm*I SNP may be associated with the different length polyadenylate sequence within the 3′-untranslated region of the *VDR* gene (Uitterlinden *et al.,* 2004). Recently, studies conducted by Luo *et al.* (2012) have indicated that the level of *VDR* mRNA was remarkably reduced in patients with the *VDR Bsm*I A (B) allele versus individuals bearing the GG (bb) genotype (Luo *et al*., 2012).

Our study demonstrates that the *Bsm*I, but not the *Fok*I, *VDR* SNP is a risk factor of ovarian cancer in the Polish population. However, this evaluation was conducted in a small size group, and this study should be replicated in other independent cohorts.

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Author Disclosure Statement

No competing financial interests exist.

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