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Vitamin D Receptor Polymorphisms and Renal Cancer Risk in Central and Eastern Europe

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Abstract

Previous studies investigated the role of vitamin D intake and cancer risk. The kidney is a major organ for vitamin D metabolism, activity, and calcium homeostasis, therefore, it was hypothesized that dietary vitamin D intake and polymorphisms in the vitamin D receptor (*VDR*) gene may modify renal cell carcinoma (RCC) risk. Three common *VDR* gene polymorphisms (*BsmI*, *FokI*, *TaqI*) were evaluated among 925 RCC cases and 1,192 controls enrolled in a hospital-based case-control study conducted in Central and Eastern Europe. Overall associations with RCC risk were not observed, however subgroup analyses revealed associations after stratification by median age of diagnosis and family history of cancer. Among subjects over 60 years, reduced risks were observed among carriers of the *f* alleles in the *FokI* SNP (OR = 0.61 for *Ff* and OR = 0.74 for *ff* genotypes) compared to subjects with the *FF* genotype (P-trend = 0.04; P-interaction = 0.004). Subjects with the *BB BsmI* genotype and a positive family history of cancer had lower risk compared to subjects with the *bb* allele (OR=0.60; 95% CI: 0.33-1.1; P trend = 0.05). Genotype associations with these subgroups were not modified when dietary sources of vitamin D or calcium were considered. Additional studies of genetic variation in the *VDR* gene are warranted.

Keywords

VDR polymorphisms; *FokI*; *BsmI*; *TaqI*; RCC; renal cancer; kidney

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Introduction

The kidney is a major organ for vitamin D metabolism, activity and calcium homeostasis (Klassen and Watkins, 2001). The anti-carcinogenic properties of vitamin D include inhibition of clonal tumor cell proliferation, hematopoieses, induction of immune cell differentiation and apoptosis (Valdivielso and Fernandez, 2006; Walters, 1992). Vitamin D activity is mediated through binding to vitamin D receptors (*VDR*), transcriptional factors that are part of the nuclear hormone receptor family which influence the behavior of genes involved in cell regulation, growth, and immunity (Valdivielso and Fernandez, 2006; Walters, 1992; Thibault et al, 2006).

Several epidemiologic studies of breast, prostate and colorectal cancer examined the relationship between cancer risk and dietary vitamin D intake (Kim et al, 2001; Slattery et al, 2004(b); Tseng et al, 2005; Divisier al, 2006; Lin et al, 2007; Shin et al, 2002) but the direction of risk has not been consistent. There are currently no studies that investigated the association between dietary vitamin D intake and renal cancer given that the kidney is the major organ of vitamin D metabolism and activity. However, dietary intake of vitamin D may not be a good measure of vitamin D exposure since sunlight exposure induces synthesis of vitamin D. Yet, since vitamin D activity is mediated by the vitamin D receptor, analysis of genetic variation in *VDR* may elucidate the role of vitamin D in RCC etiology. Three *VDR* polymorphisms have been commonly investigated. Each polymorphism is named by the restriction sites that were initially used to identify them. The *FokI* (Ex4+4T>C) polymorphism is located at the 5′ end of the *VDR* gene. This polymorphism alters the transcription initiation site of the *VDR* protein.

The protein associated with the *FokI f* variant is three amino acids shorter than the *F* allele and functions with higher activity as a transcription factor than the wild-type (*FF*) protein (Arai et al, 1997; Jurutka et al, 2000); evidence from previous epidemiological studies indicate the *FokI f* polymorphism to be associated with decreased cancer risk (Huang et al, 2006; Liu et al, 2005). Furthermore, *BsmI* (IVS10+283G>A) and *TaqI* (Ex11+32T>C) polymorphisms are highly correlated to each other and are both located near the 3′ end of the gene. Like many tagging SNPs, *BsmI* and *TaqI* polymorphisms are not known to have functional relevance yet they are thought to be in linkage disequilibrium with functional variants in the 3'UTR which modify mRNA stability (Uitterlinden et al, 2004).

In this study, the role of common *VDR* polymorphisms within one of the largest RCC studies with biological samples to date was examined to evaluate whether genetic variants were associated with RCC risk overall or within particular case subgroups. In addition, interactions between *VDR* polymorphisms and dietary intake frequency of vitamin D and calcium rich foods were assessed.

Materials and Methods

Details regarding this study population were previously described (Moore et al, 2007). Briefly, a hospital-based case-control study of renal cell cancer was conducted between 1999 and 2003 in 7 centers in 4 Central and Eastern European countries (Moscow, Russia; Bucharest, Romania; Lodz, Poland; and Prague, Olomouc, Ceske-Budejovice, and Brno, Czech Republic). This is an area with the highest incidence of RCC in the world (Hung et al, 2007). A total of 1,097 newly diagnosed and histologically confirmed RCC (IDC-O-2 codes C64) cases, aged 20-88 years were recruited for this study. Controls were selected among individuals admitted as in-patients or out-patients from the same hospitals as cases. Eligible controls (N=1,476) were recruited with non-tobacco related conditions and frequency-matched to cases on gender, age (+/- 3 years), center and place of residence. No single disease made up more than 20% of the control group. All participants were of Caucasian decent. Using lifestyle and food frequency

questionnaires, consumption of food-specific items were categorized into: never, low (<1 a month), medium (≥1 a month but <1 a week), and high (≥1 a week). Dietary sources of vitamin D were estimated based on intake frequency of liver, fish and egg. Dietary sources of calcium were estimated based on intake frequency of yogurt, milk and cheese. Additional details on the dietary questionnaire were previously reported (Hsu et al, 2006).

Laboratory Analysis

Genotyping of *VDR* polymorphisms was conducted at IARC and at NCI's Core Genotyping Facility (CGF). Blood samples were stored at -80°C and shipped to the NCI on dry ice. DNA for genotyping assays were extracted from buffy coat and whole blood samples using phenol-chloroform extraction. Methods for all genotype assays can be found at: http://snp500cancer.nci.nih.gov/home.cfm (Packer, 2004). DNA from RCC cases and controls were blinded and randomized on PCR plates for genotyping analyses. Genotyping of a randomly selected 5% duplicate samples was conducted for quality control. A total of 925 (84.2%) cases and 1,192 (80.7%) controls were genotyped. All three *VDR* variants were in Hardy-Weinberg Equilibrium ($p<0.05$), and duplicates were highly concordant. Call rates for *BsmI* IVS10+283G>A (94%), *FokI* Ex4+4T>C (98%), and *TaqI* Ex11+32T>C (92%) were similar for RCC cases and controls.

VDR genotypes are expressed using nomenclature derived from restriction-fragment length polymorphism (RFLP) analysis studies. Upper-case letters (i.e. *B*, *F*, *T*) specify alleles coded for the restriction polymorphisms previously observed that also refers to a specific base change. Specifically, the *BsmI* (IVS10+283G>A) polymorphism *A* allele is equivalent to "*B*" using the RFLP nomenclature. The *FokI* (Ex4+4T>C) *C* allele is equivalent to "*F*" allele from the RFLP nomenclature, and the *TaqI* (Ex11+32T>C) T allele is equivalent to "*T*" allele using RFLP nomenclature.

Statistical Analysis

Hardy-Weinberg equilibrium was tested by the goodness of fit χ^2 test. Pairwise linkage disequilibrium (LD) between SNP was estimated based on D′ and r^2 values using Haploview (http://www.broad.mit.edu/mpg/haploview/index.php). Of the 3 SNP genotyped, *BsmI* and *TaqI* were highly correlated (r^2 <0.95). Haplotype analysis for *BsmI* and *TaqI*, which reside within a region of high linkage disequilibrium (Uitterlinden Ag, 2004), were estimated in R, adjusted for age, gender and center (version 2.4.0; http://www.r-project.org). Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated using unconditional logistic regression models adjusting for gender, age, center, self-reported hypertension (yes, no), smoking status (never, ever) and body mass index (BMI). Interactions were tested comparing regression models with and without interaction terms using a likelihood ratio test (LRT). Polytomous logistic regression was used to estimate OR and 95% CI for histologically defined case subgroups. Heterogeneity between risk factor OR for case subgroups was assessed using logistic regression analyses restricted to cases. An extension of the polytomous logistic regression model was used to evaluate heterogeneity in risk factor ORs by multiple tumor characteristics simultaneously (Chatterjee, 2004). This method allowed simultaneous evaluation of several correlated tumor features (i.e. histopathologic subtype, stage, and grade) as determinants of risk. All analyses were conducted in STATA 8.0 unless otherwise specified (STATA Corporation, College Station, TX).

Results

A description of study subjects is presented in Table 1. Cases and controls were comparable in age; however, cases had a higher prevalence of hypertension, having a first degree relative with cancer, and high BMI. Overall, none of the *VDR* polymorphisms investigated were

significantly associated with RCC risk (Table 2). After stratification by mean age (60 years), reduced RCC risk was observed among older subjects with the *f* allele in the *FokI* SNP (OR = 0.61 for *Ff*; OR = 0.74 for *ff* genotypes) compared to those with the *FF* genotype (P trend = 0.04; P interaction = 0.004). Among subjects with a familial history of cancer, risks were lower among carriers of the *B* allele in the *BsmI* SNP (OR = 0.72 for *Bb*; OR = 0.60 for the *BB* genotypes) compared with the *bb* genotype (P trend = 0.05). Lower risk was observed among subjects with the *t* allele in the *TaqI* SNP (OR = 0.79 for *Tt*; OR = 0.62 for the *tt* genotypes) compared to the *TT* genotype (P trend = 0.07). *VDR* polymorphisms did not modify associations between RCC and known risk factors such as hypertension, BMI, or tobacco. Genotype associations overall or within subgroups were not modified when dietary vitamin D or calcium intake frequencies were considered (data not shown). Results did not differ after stratification by tumor histology, stage or grade (data not shown).

Discussion

In this study, RCC risk was not associated with the *BsmI*, *FokI*, or *TaqI VDR* polymorphic variants evaluated. However, after subgroup analysis by age, lower risks were observed among subjects older than 60 years of age with the *FokI f* allele compared to those with the *F* allele. Among subjects with a familial history of cancer, lower risks were observed among subjects the *BsmI B* and *TaqI t* allele.

The *FokI f* polymorphism results in a protein that is three amino acids shorter and with higher transcriptional activity than the wild-type protein (Arai et al, 1997; Jurutka et al, 2000; Uitterlinden et al, 2004; Hu et al, 2003). Epidemiological studies showed *FokI F* polymorphism is associated with elevated risk among older prostate and head and neck cancer cases compared to carriers of the *ff* allele (Huang et al, 2006; Liu et al, 2005). Among the elderly, vitamin D levels tend to decrease due to reduced dermal production of vitamin D, reduced solar exposure and outdoor activity, and reduced intake of vitamin D rich foods (Holick, 1989; Lips, 2001). While most epidemiological studies show an association between the *FokI F* polymorphism and increase cancer risk, the relationship may be modified with age. Because vitamin D levels generally decrease with age, genetic contributions may provide greater protection among the elderly than among younger populations with adequate intake levels (Mosekilde, 2005).

No significant associations among *VDR* variant genotypes among subjects with a positive family history of cancer were observed in previous colon and prostate cancer studies (Cheteri et al, 2004; Slattery ML, 2004(a)), however, a case-control study of 483 breast cancer patients in Finland found significantly lower cancer risk among women with a family history of breast cancer, among women with an *a* allele in the *VDR ApaI* SNP compared with carriers of the *AA* genotype (Sillanpaa et al, 2004). The authors of this study speculated that a novel interaction between the *VDR ApaI* genotype and breast cancer 1 (*BRCAI*) or breast cancer 2 (*BRCA2*) genes exist (Sillanpaa et al, 2004). Similarly, significant association with the *BsmI* genotype and RCC among those with a familial history of cancer may reflect an association with other genes predisposing to family renal cancer, such as the von Hipple-Lindau (*VHL*) gene.

A Japanese study observed higher RCC risk among subjects with the *TaqI TT* polymorphism, particularly among RCC cases with rapid compared to slow-growth tumors (Ikuyama et al, 2002). In our study, prevalence of *VDR* polymorphisms did not differ by tumor stage or grade.

Strengths of this study include (1) high rates for participation and biological specimen collection, (2) inclusion of histologically confirmed cancer cases, and (3) a large sample size. This study also had sufficient statistical power to detect relatively small genotype associations overall and within subgroups, although power to detect multiplicative interactions was limited. Furthermore, the assessment of vitamin D and calcium intake was evaluated using a food

frequency questionnaire of specific food items which limited the ability to accurately assess intake.

In conclusion, the data showed that the *FokI f* polymorphism was associated with lower RCC risk among older subjects and that *BsmI B* and *TaqI t* polymorphisms were associated with lower risk among individuals with a family history of cancer. Additional studies are warranted to elucidate the role of genetic variation in *VDR* and RCC risk.

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Table 1

General characteristics of participants genotyped in the Central and Eastern European Renal Cell Carcinoma Study

Variables	Cases		Controls		
	n	%	n	%	P-value
Participants Genotyped	925	43.7	1,192	56.3	
Gender					
Male	550	59.5	766	64.3	
Female	375	40.5	426	35.7	0.02
Age at Interview (years)					
≤60	472	51.0	620	52.0	
>60	453	49.0	572	48.0	0.65
Mean Age (std)	**59.5 years (10.4)**		**59.3 years (10.4)**		
Center					
Romania-Bucharest	90	9.7	125	10.5	
Poland-Lodz	80	8.7	195	16.4	
Russia-Moscow	288	31.1	366	30.7	
*Czech Republic	467	50.5	506	42.4	<.001
BMI at Interview					
<25	267	28.9	432	36.2	
25-29.9	404	43.7	493	41.4	
30+	254	27.5	267	22.4	<.001
Tobacco Status					
Never	433	46.9	486	40.8	
Ever	490	53.1	705	59.2	0.01
Hypertension					
No	507	54.9	737	61.8	
Yes	417	45.1	455	38.2	0.001
Familial History of Cancer					
No 1st degree relative with cancer	623	67.4	861	72.2	
1st degree relative with cancer	302	32.6	331	27.8	0.02
° **Dairy Intake**					

Variables	Cases		Controls		
	n	%	n	%	P-value
Low: <1/mo	264	29.3	403	33.2	
Medium: < 1/week	324	36.0	405	33.4	
High: ≥1/week	312	34.7	406	33.4	0.15
° **Yogurt Intake**					
Low: <1/mo	361	39.1	537	43.1	
Medium: < 1/week	182	19.7	212	17.0	
High: ≥1/week	381	41.2	498	39.9	0.18
° **Milk Intake**					
Low: <1/mo	203	22.0	292	23.4	
Medium: < 1/week	133	14.4	157	12.6	
High: ≥1/week	588	63.6	798	64.0	0.76
• **Egg Intake**					
Low: <1/mo	33	3.6	92	7.4	
Medium: < 1/week	297	32.1	314	25.2	
High: ≥1/week	594	64.3	841	67.4	0.80
• **Fish Intake**					
Low: <1/mo	244	27.1	355	29.2	
Medium: < 1/week	356	39.6	444	36.6	
High: ≥1/week	300	33.3	415	34.2	0.71
• **Liver Intake**					
Low: <1/mo	406	43.9	508	40.7	
Medium: < 1/week	373	40.4	487	39.1	
High: ≥1/week	145	15.7	252	20.2	0.02

* Brno, Olomouc, Prague, Ceske

° Dietary sources of calcium intake

• Dietary sources of vitamin D intake

Table 2

ects, Age, and Familial History of Cancer

Effects		Age: 20-60 Years			Age: > 60 Years				No Familial History of Cancer			‡ Familial History of Cancer			
s	OR (95%CI)	*Cases	*Controls	OR (95%CI)	*Cases	*Controls	OR (95%CI)	P-int§	*Cases	*Controls	OR (95%CI)	*Cases	*Controls	OR (95%CI)	P-int§
	1.00	174	216	1.00	150	191	1.00		204	296	1.00	120	111	1.00	
	0.97 (0.79-1.18)	182	256	0.85 (0.64-1.13)	188	218	1.13 (0.84-1.53)		263	347	1.11 (0.87-1.41)	107	127	0.72 (0.49-1.06)	
	0.85 (0.61-1.18)	39	60	0.70 (0.44-1.12)	42	52	1.05 (0.65-1.70)		55	78	0.97 (0.65-1.44)	26	34	0.60 (0.33-1.11)	
	0.38			*0.10*			*0.59*	*0.28*			*0.79*			*0.05*	*0.16*
	1.00	129	190	1.00	157	148	1.00		198	249	1.00	88	89	1.00	
	0.90 (0.73-1.11)	212	253	1.27 (0.95-1.71)	164	239	0.61 (0.45-0.83)		246	359	0.87 (0.67-1.12)	130	133	0.93 (0.62-1.39)	
	0.91 (0.69-1.19)	72	105	1.11 (0.76-1.62)	77	94	0.74 (0.50-1.09)		100	138	0.97 (0.70-1.34)	49	61	0.79 (0.48-1.30)	
	0.41			*0.41*			*0.04*	*0.004*			*0.66*			*0.37*	*0.56*
	1.00	173	214	1.00	147	188	1.00		206	295	1.00	114	107	1.00	
	1.00 (0.82-1.24)	176	225	0.93 (0.70-1.24)	185	213	1.12 (0.83-1.51)		254	319	1.12 (0.87-1.44)	107	119	0.79 (0.53-1.16)	
	0.87 (0.64-1.18)	45	74	0.70 (0.45-1.07)	52	63	1.10 (0.71-1.70)		67	95	1.00 (0.69-1.44)	30	42	0.62 (0.35-1.08)	
	0.49			*0.14*			*0.55*	*0.35*			*0.73*			*0.07*	*0.20*

orted hypertension (yes, no), BMI (continuous), and smoking status (ever never)

yes, no), BMI (continuous), and smoking status (ever never)

ous), center, self reported hypertension (yes, no), BMI (continuous), and smoking status (ever never)

o missing data

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