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Genetic Polymorphisms in Vitamin D Receptor *VDR/RXRA* Influence the Likelihood of Colon Adenoma Recurrence

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Abstract

Low circulating levels of vitamin D affect colorectal cancer risk. The biological actions of the hormonal form of vitamin D, $1,25(OH)_2D_3$, are mediated by the vitamin D receptor (VDR), which heterodimerizes with retinoid X receptors (RXR). Using a single nucleotide polymorphism (SNP) tagging approach, we assessed the association between genetic variations in *RXRA* and *VDR* and odds of recurrent (metachronous) colorectal neoplasia in a pooled population of two studies. A total of 32 tag SNPs in *RXRA* and 42 in *VDR* were analyzed in 1,439 participants. A gene-level association was observed for *RXRA* and any ($P = 0.04$) or proximal ($P = 0.03$) metachronous neoplasia. No gene-level associations were observed for *VDR,* nor was any single SNP in *VDR* related to any metachronous adenoma after correction for multiple comparisons. In contrast, the association between *RXRA* SNP rs7861779 and proximal metachronous neoplasia was of borderline statistical significance [odds ratio (OR), 0.68; 95% confidence interval (95% CI), 0.53-0.86; unadjusted $P = 0.001$; adjusted $P = 0.06$], including when observed independently in each individual study. Haplotypes within linkage blocks of *RXRA* support an ~30% reduction in odds of metachronous neoplasia arising in the proximal colon among carriers of specific haplotypes, which was strongest ($OR_{proximal}$, 0.67; 95% CI, 0.52–0.86) for carriers of a CGGGCA haplotype (rs1805352, rs3132297, rs3132296, rs3118529, rs3118536, and rs7861779). Our results indicate that allelic variation in *RXRA* affects metachronous colorectal neoplasia, perhaps of particular importance in the development of proximal lesions. *Cancer Res; 70(4); 1496–504. ©2010 AACR.*

Introduction

A protective effect of vitamin D on colorectal cancer was first proposed in 1980 (1). Subsequent epidemiologic studies have reported significant inverse associations between measured blood levels of 25(OH)D, a biomarker used to approximate systemic vitamin D levels, and either colorectal cancer (2–6) or its precursor, colorectal adenoma (7). Several mechanisms of action for the putative antitumor properties of vitamin D have been proposed from extensive cell culture studies. The hormone metabolite of vitamin D, $1,25(OH)_2D_3$, has been shown to play a key role in the maintenance of cellular proliferation (8) and differentiation (9, 10), modulation of the cell cycle (11), and regulation of members of the Bcl-2 family, which are involved in apoptosis (10, 12). $1,25(OH)_2D_3$ has also been shown to upregulate E-cadherin, an important component of cellular adhesion (13, 14), resulting in the translocation of β-catenin from the nucleus to the plasma membrane (13, 15).

$1,25(OH)_2D_3$ mediates its action as a ligand by binding to the vitamin D receptor (VDR), which commonly forms a heterodimer with retinoid X receptors (RXR) such as RXRα, an isoform of RXR that has been implicated in colorectal carcinogenesis (16). Formation of VDR-RXR heterodimers releases corepressor proteins and recruits coactivators, resulting in increased VDR transcriptional activity at vitamin D-responsive elements (VDRE) in VDR target genes (17), including those involved in the regulation of vitamin D metabolites (18). Both VDR and RXRα are members of the steroid nuclear receptor superfamily (19), whose members and their ligands have been identified as potential targets for the prevention and treatment of several different cancers (17, 20). To date, the biological role of RXRα in relation to cancer has not been investigated as thoroughly as that of VDR, although RXR binding is absolutely required for transcriptional activation by VDR (21) and RXRα dysregulation has been identified to have carcinogenic effects in the colon (16). Thus, RXRα likely has a major regulatory role in pathways related to VDR, including effects on $1,25(OH)_2D_3$-mediated antineoplastic activities in the colon.

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Although a number of studies have evaluated limited candidate single nucleotide polymorphisms (SNP) in the *VDR* gene for their association with the development of colorectal adenoma (22–26), none have used a tag SNP approach (27) to evaluate allelic variation in *VDR* and odds of metachronous colorectal adenoma. In addition, despite the clear biological coupling of RXRα and VDR in mediating $1,25(OH)_2D_3$ activity at the cellular level, association of genetic variation in *RXRA* with cancer outcomes is limited to studies of prostate and biliary cancers (28, 29). Therefore, in the current work, a tag SNP approach was used to probe common genetic variation in the *RXRA* and *VDR* genes as well as to construct haplotype blocks where appropriate to determine the role of these genes in the development of metachronous colorectal neoplasia.

Materials and Methods

Subjects were drawn from participants of the Wheat Bran Fiber (WBF) and Ursodeoxycholic Acid (UDCA) trials conducted at the University of Arizona as described previously (30, 31). The WBF study was conducted to determine the effect of a high-fiber versus a low-fiber cereal supplement on metachronous colorectal neoplasia among participants in a randomized, double-blind clinical trial (30). Participants in the study had at least one histologically confirmed colorectal adenoma removed no more than 3 months before entry into the trial and were between 40 and 80 years of age. A follow-up colonoscopy was completed in 1,310 participants (32) and no effect of the fiber supplement on metachronous neoplasia was observed. The UDCA trial was a phase III, double-blind, placebo-controlled study conducted to determine the effect of ursodeoxycholic acid on colorectal metachronous neoplasia (31). A total of 1,192 participants completed the UDCA trial (31), with no effect of ursodeoxycholic acid on metachronous neoplasia. The University of Arizona Human Subjects Committee and Institutional Review Board approved both the WBF and UDCA trials.

End-point ascertainment. Metachronous colorectal neoplasia was defined as adenomas or cancers ($n = 7$) detected by colonoscopy at least 6 months after randomization to the parent trials. In the past, these lesions have been defined as "recurrences"; however, due to the possibility of some of the "recurrent" lesions having been those missed at baseline colonoscopy, it was recommended that the terminology be changed from "recurrent" to "metachronous". Personnel at each study site reviewed endoscopy and pathology reports and extracted data regarding size, histology, number, and location, followed by central pathology review at each site. Lesions were classified as proximal if they were located at or proximal to the splenic flexure; those distal to the splenic flexure, including the rectum, were categorized as distal.

SNP selection and genotyping. SNP selection for this platform used Haploview Tagger to identify bin tags from a European Caucasian population. Initial tag SNPs and linkage disequilibrium (LD) blocks were identified from HapMap data release 16c.1, June 2005, on National Center for Biotechnology Information B34 assembly, dbSNP b124. Tag SNPs from these data were identified using the following criteria: minor allele frequency >5%, pairwise r^2 >0.95, and at least 60 base pairs between neighboring SNPs (33, 34). SNPs located at the 5′ and 3′ ends of a LD block were also included. SNPs with little or no LD were selected from HapMap or dbSNP at a density of 1 per kb. In addition to this tag SNP selection strategy, high-interest SNPs that have been reported in the literature were also chosen, including *Bsm*I (rs1544410), *Taq*I (rs731236), and *Fok*I (rs2228570) restriction endonuclease sites, as well as the *Cdx-2* binding site in the promoter region (rs11568820).

Genotyping of the samples was performed on the Illumina Golden Gate platform (Illumina). Briefly, DNA was activated with streptavidin/biotin and added to a hybridization mixture. After hybridization, the samples were washed followed by extension, ligation, and cleanup. Universal primers labeled with Cy3 or Cy5 were used for PCR labeling of the DNA. Next, the labeled DNA was allowed to hybridize with the Sentrix Array Matrix and, finally, placed in the BeadArray Reader for quantitation of the fluorescence signal. Analysis of the output from the fluorescence reading was managed using Bead Studio software (Illumina). SNPs were considered to have failed genotyping if they met at least one of the following criteria: Illumina GenTrain score <0.4; 10% GC score <0.25; AB T Dev >0.1239, call frequency <0.95; intraplate replicate errors >2; parent-parent-child errors >2; or discordance with HapMap >3. Participants were genotyped for a total of 49 SNPs in *VDR* and 41 in *RXRA*.

The VDR *Fok*I polymorphism (rs2228570, 27823C>T) failed both the Illumina GoldenGate and the Sequenom Iplex technologies. We genotyped the sample set for high-interest SNPs that failed the Illumina GoldenGate platform using the GenomeLab SNPStream 12-plex technology from Beckman Coulter at the University of Arizona Genetics Core; because *FokI* is a commonly studied SNP and is not in high LD with any other SNP, it was included in the SNPStream platform. This technology couples base extension chemistry with a subsequent hybridization step to a glass slide. Genotype data passed quality control measures if they met the following criteria: distributed into three statistically significant clusters, failed to generate genotypes from all 181 blank wells, showed Mendelian consistency for Coriell CEPH trios, and showed >97% concordance among laboratory-blinded replicates. Any samples that exhibited low fluorescence intensity or generated an ambiguous genotype call were classified as failed and not included in the data. Genotype frequencies were found to be in Hardy-Weinberg equilibrium.

Statistical analysis. Participants from the WBF and UDCA trials with both genetic data and trial end-point data available were pooled, yielding 1,530 participants. Of these, a total of 91 participants reported a race/ethnicity other than white. Because the trials did not have adequate numbers of the other racial/ethnic groups to appropriately address the issue of population stratification, all genetic analyses were limited to the white participants, yielding a final sample size of 1,439 individuals. Before the statistical analysis, all SNPs that failed the criteria listed above, those that were monomorphic or had an excessive heterogeneity score, were excluded from the data set (*VDR* = 7; *RXRA* = 9), leaving a

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total of 42 *VDR* SNPs and 32 *RXRA* SNPs for inclusion in the final statistical analyses.

We used a multistage approach to test overall association of a gene through principal component analysis, finer resolution with a single SNP analysis, and characterization of effects through haplotype analysis. Principal components were generated to capture the set of available SNPs within each gene (32 on *RXRA*, 42 on *VDR*) in which the principal components are linear transformations of the original SNP data. The principal components were modeled using logistic regression, using an 80% explained-variance threshold in determining how many principal components to include in the models (35). Three different outcomes were modeled for each gene: any metachronous colorectal neoplasia, proximal metachronous neoplasia, and distal metachronous neoplasia. Proximal and distal lesions were evaluated as distinct outcomes based on *a priori* evidence that these may represent biologically disparate pathologies with potentially distinct genetic etiologies (36). Exclusion of rectal lesions from the distal end point did not result in any material changes to the point estimates; hence, they were included as distal colorectal lesions. A *P* value for the overall gene-outcome association was obtained from a likelihood ratio test comparing the model with principal components versus an intercept-only model, with degrees of freedom equal to the number of principal components.

Individual SNPs were evaluated using logistic regression models, using additive, dominant, and recessive modes of inheritance due to the lack of existing evidence regarding the true mode of inheritance for these SNPs. Preliminary statistical models were adjusted for age and sex; however, these covariates had no meaningful effect on the estimates, and crude models are presented in Results. After obtaining uncorrected *P* values for these associations, a multiple comparisons adjustment was used that is specifically designed for correlated tests due to LD and the exploration of different modes of inheritance (37).

LD plots were generated using the mapLD package available as part of the R project[7] to identify haplotype blocks. Haplotypes within each block were estimated with fastPHASE version 1.2 using default iteration settings (38). Haplotypes were evaluated for associations with any metachronous colorectal neoplasia as well as by colorectal subsite, using logistic regression to obtain odds ratios (OR) and 95% confidence intervals (95% CI). An overall *P* value for each haplotype block was obtained with a likelihood ratio test. All statistical analyses were conducted with R version 2.7.2 or SAS version 9.1. All statistical tests were two-sided and considered significant at a value of $P < 0.05$. D' values for SNPs were determined with Haploview 4.1.[8] Significant SNPs and haplotypes identified in the uncorrected analysis were evaluated separately in WBF and UDCA to assess heterogeneity between the two populations.

[7] http://www.r-project.org
[8] http://www.broad.mit.edu/mpg/haploview/

Results

Characteristics of the genotyped participants included in the pooled analysis of metachronous neoplasia are presented in Table 1. The mean age of the pooled study population was 66.2 ± 8.2, with 66.7% of the participants being male, 24.9% reporting a family history of colorectal cancer, and 43.7% having had a polyp before the baseline examination. At follow-up, 45.9% of the participants had a metachronous adenoma; of these, 33.1% had proximal lesions and 24.0% had distal neoplasia, with the remainder having had adenomas at both colon subsites. To evaluate the overall gene-level association of *VDR* and *RXRA*, principal component analysis was conducted with any, proximal, and distal metachronous neoplasia as the primary end points (Table 2). At the gene level, *RXRA* was significantly associated with any ($P = 0.04$) and proximal ($P = 0.03$), but not with distal, metachronous neoplasia. No significant association was observed at the gene level for *VDR* and metachronous neoplasia.

Next, the relationships between individual SNPs within each gene for any, proximal, and distal metachronous neoplasia were evaluated using additive, dominant, and recessive inheritance models for each SNP. After evaluating 32 SNPs in *RXRA* and 42 in *VDR*, a total of 5 SNPs in *RXRA* and 7 SNPs in *VDR* were significantly associated with metachronous neoplasia. Adjustment for multiple comparisons revealed one association of borderline statistical significance for *RXRA* (rs7861779) and proximal adenoma (OR, 0.68; 95% CI, 0.53–0.86; unadjusted $P = 0.001$; adjusted $P = 0.06$; Supplementary Table S1). Further, when this SNP was investigated in relation to proximal metachronous adenoma in the WBF and UDCA trials separately with unadjusted logistic regression models, this result was observed in each study separately, with an OR (95% CI) of 0.64 (0.45–0.91) in the WBF trial and 0.70 (0.50–0.98) in the UDCA trial. This SNP was also significantly associated with the presence of proximal lesions at baseline in cross-sectional analyses ($P = 0.05$; data not shown). Considering the potential implications of the differing proportions of participants with a family history of colorectal cancer or who reported previous polyps between the WBF and UDCA trials, the analyses for *RXRA* rs7861779 were repeated in separate models stratified by these variables. No material differences in the point estimate were observed between those with a family history and those without, nor for those who reported having previous polyps versus those who did not. No significant relationships were observed for any SNPs in *VDR* and metachronous adenoma after adjustment for multiple comparisons (Supplementary Table S2), including the following high-interest SNPs: *Taq*I (OR, 1.00; 95% CI, 0.86–1.17), *Bsm*I (OR, 1.01; 95% CI, 0.87–1.18), *Fok*I (OR, 0.93; 95% CI, 0.80–1.09), or the Cdx-2 binding site (OR, 0.95; 95% CI, 0.79–1.13).

We next constructed linkage blocks within each gene using the available SNP data to derive haplotype groups within each blockable region to evaluate the possibility of epistatic effects (see Supplementary Fig. S1 for the block structure using D' for both *VDR* and *RXRA*). Three major blocks on *RXRA* were identified, and *VDR* was also reduced to three blocks

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Table 1. Characteristics of the pooled population, WBF and UDCA

Characteristics	WBF *n* = 611	UDCA *n* = 828	Pooled *n* = 1,439
Mean age, y ± SD	66.0 ± 8.2	66.4 ± 8.2	66.2 ± 8.2
Sex, male, *n* (%)	403 (66.0)	560 (67.6)	963 (66.9)
Family history of colorectal cancer,* *n* (%)	113 (19.9)	234 (28.3)	347 (24.9)
Previous polyps,† *n* (%)	228 (41.2)	355 (45.5)	583 (43.7)
Any metachronous neoplasia,‡ *n* (%)	313 (51.2)	347 (41.9)	660 (45.9)
Proximal metachronous neoplasia, *n* (%)	225 (37.3)	248 (30.1)	473 (33.1)
Distal metachronous neoplasia, *n* (%)	160 (26.5)	183 (22.2)	343 (24.0)
Rectal metachronous neoplasia,§ *n* (%)	15 (2.5)	20 (2.4)	35 (2.4)

*History of colorectal cancer in parent or sibling.
†History of colorectal polyps before qualifying colonoscopy.
‡Colorectal adenoma or cancer detected during trial follow-up.
§Rectal adenoma only.

within which the SNPs were highly correlated. We next evaluated haplotype constructed within each of the primary blocks using the most common haplotype in that block as the reference group.

As shown in Table 3, for the *RXRA* gene, a GAGA haplotype in block 1 (rs11102986, rs11103473, rs10776909, and rs12004589) was associated with reduced odds for proximal metachronous neoplasia (OR, 0.70; 95% CI, 0.54–0.92; block global $P = 0.02$). In addition, a haplotype within block 2 of *RXRA* designated CGGGCA (rs1805352, rs3132297, rs3132296, rs3118529, rs3118536, and rs7861779) was similarly associated with a reduction in odds for any (OR, 0.74; 95% CI, 0.59–0.92; block global $P = 0.03$) and proximal (OR, 0.67; 95% CI, 0.52–0.86; block global $P = 0.0097$) metachronous neoplasia. A single haplotype in block 1 of *VDR*, designated GAA (rs11574143, rs731236, rs1544410), was related to reduced odds of proximal adenoma

Table 2. Association between *RXRA* and *VDR* genes and metachronous colorectal neoplasia

	Any metachronous neoplasia	Proximal metachronous neoplasia	Distal metachronous neoplasia
	OR (95% CI)	OR (95% CI)	OR (95% CI)
RXRA			
PC1	1.01 (0.96–1.05)	1.01 (0.97–1.06)	0.97 (0.93–1.03)
PC2	0.90 (0.83–0.99)	0.88 (0.80–0.97)	1.01 (0.91–1.12)
PC3	1.12 (1.00–1.25)	1.10 (0.98–1.24)	1.03 (0.91–1.17)
PC4*	1.09 (0.94–1.28)	1.10 (0.94–1.30)	1.15 (0.96–1.38)
LRT P†	0.04	0.03	0.49
VDR			
PC1	0.98 (0.93–1.03)	1.00 (0.95–1.06)	1.00 (0.94–1.06)
PC2	0.97 (0.92–1.02)	0.96 (0.91–1.02)	1.00 (0.93–1.06)
PC3	1.03 (0.95–1.10)	0.99 (0.92–1.07)	1.06 (0.98–1.16)
PC4	0.96 (0.88–1.04)	0.94 (0.86–1.03)	0.97 (0.88–1.07)
PC5	1.06 (0.93–1.19)	1.02 (0.89–1.16)	1.02 (0.88–1.18)
PC6	1.13 (0.99–1.30)	1.14 (0.99–1.31)	1.01 (0.86–1.17)
PC7	1.03 (0.89–1.20)	1.00 (0.85–1.16)	0.97 (0.82–1.15)
PC8*	1.19 (1.02–1.40)	1.21 (1.02–1.43)	0.98 (0.81–1.17)
LRT P†	0.11	0.18	0.96

Abbreviations: LRT, likelihood ratio test; PC, principal component.
*An 80% explained-variance threshold is used for including principal components in the model.
†P value for each model is from a likelihood ratio test with degrees of freedom equal to the number of principal components.

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Table 3. Haplotypes on *RXRA* and *VDR* genes and association with metachronous colorectal neoplasia

Haplotype	Count	Any metachronous		Proximal neoplasia		Distal neoplasia	
		n (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
RXRA, block 1*							
GTGC	1,857	857 (46.1)	1.00 (reference)	617 (33.5)	1.00 (reference)	428 (23.2)	1.00 (reference)
AAAC	523	252 (48.2)	1.09 (0.89–1.32)	185 (35.6)	1.10 (0.89–1.34)	132 (25.4)	1.12 (0.90–1.41)
GAGA	319	126 (39.5)	0.76 (0.60–0.97)	83 (26.1)	0.70 (0.54–0.92)	82 (25.8)	1.15 (0.87–1.51)
GAAC	86	45 (52.3)	1.28 (0.83–1.97)	34 (40.5)	1.35 (0.86–2.11)	22 (26.2)	1.17 (0.71–1.93)
GAGC	86	38 (44.2)	0.92 (0.60–1.43)	26 (30.2)	0.86 (0.54–1.38)	21 (24.4)	1.07 (0.64–1.77)
Rare	7	2 (28.6)	0.47 (0.09–2.41)	1 (14.3)	0.33 (0.04–2.75)	1 (14.3)	0.55 (0.07–4.59)
			$P = 0.1145$		$P = 0.0284$		$P = 0.8075$
RXRA, block 2†							
AGAACG	1,989	927 (46.6)	1.00 (reference)	674 (34.2)	1.00 (reference)	467 (23.7)	1.00 (reference)
CAGGAG	482	230 (47.7)	1.05 (0.86–1.28)	165 (34.5)	1.02 (0.82–1.25)	121 (25.3)	1.09 (0.87–1.38)
CGGGCA	383	150 (39.2)	0.74 (0.59–0.92)	98 (25.7)	0.67 (0.52–0.86)	91 (23.9)	1.01 (0.78–1.31)
Rare	24	13 (54.2)	1.35 (0.60–3.04)	9 (37.5)	1.16 (0.50–2.66)	7 (29.2)	1.33 (0.55–3.22)
			$P = 0.0325$		$P = 0.0097$		$P = 0.8246$
RXRA, block 3‡							
AAGGG	1,853	861 (46.5)	1.00 (reference)	622 (33.8)	1.00 (reference)	429 (23.3)	1.00 (reference)
GCAAA	501	234 (46.7)	1.01 (0.83–1.23)	169 (34.0)	1.01 (0.82–1.24)	122 (24.5)	1.07 (0.85–1.35)
GAGGA	249	112 (45.0)	0.94 (0.72–1.23)	77 (31.2)	0.89 (0.67–1.18)	66 (26.7)	1.20 (0.89–1.62)
GAGAA	186	73 (39.2)	0.74 (0.55–1.01)	49 (26.5)	0.70 (0.50–0.99)	45 (24.3)	1.06 (0.74–1.50)
GAGGG	35	18 (51.4)	1.22 (0.62–2.38)	15 (42.9)	1.47 (0.75–2.88)	7 (20.0)	0.82 (0.36–1.89)
AAAGG	23	9 (39.1)	0.74 (0.32–1.72)	4 (17.4)	0.41 (0.14–1.22)	8 (34.8)	1.75 (0.74–4.16)
AAGGA	12	4 (33.3)	0.58 (0.17–1.92)	3 (25.0)	0.65 (0.18–2.42)	3 (25.0)	1.09 (0.30–4.06)
Rare	19	9 (47.4)	1.04 (0.42–2.56)	7 (36.8)	1.14 (0.45–2.91)	6 (31.6)	1.52 (0.57–4.01)
			$P = 0.6040$		$P = 0.2091$		$P = 0.8086$
VDR, block 1§							
GAG	1,407	655 (46.6)	1.00 (reference)	457 (32.8)	1.00 (reference)	332 (23.8)	1.00 (reference)
GGA	1,106	508 (45.9)	0.98 (0.83–1.14)	376 (34.2)	1.07 (0.90–1.26)	258 (23.5)	0.98 (0.82–1.18)
AAG	306	130 (42.5)	0.85 (0.66–1.09)	101 (33.1)	1.02 (0.78–1.32)	73 (23.9)	1.01 (0.75–1.35)
GAA	41	18 (43.9)	0.90 (0.48–1.68)	7 (17.1)	0.42 (0.19–0.96)	16 (39.0)	2.05 (1.08–3.88)
Rare	18	9 (50.0)	1.15 (0.45–2.91)	5 (27.8)	0.79 (0.28–2.23)	7 (38.9)	2.04 (0.78–5.29)
			$P = 0.7591$		$P = 0.1792$		$P = 0.1537$
VDR, block 2‖							
GCCGG	1,018	482 (47.3)	1.00 (reference)	337 (33.4)	1.00 (reference)	253 (25.1)	1.00 (reference)
GCAAG	956	426 (44.6)	0.89 (0.75–1.07)	300 (31.5)	0.92 (0.76–1.11)	236 (24.8)	0.98 (0.80–1.21)
AACAA	381	169 (44.4)	0.89 (0.70–1.12)	120 (31.7)	0.92 (0.72–1.19)	93 (24.5)	0.97 (0.74–1.28)
GACAA	368	178 (48.4)	1.04 (0.82–1.32)	134 (36.9)	1.17 (0.91–1.50)	76 (20.9)	0.79 (0.59–1.06)
GCCAA	128	57 (44.5)	0.89 (0.62–1.29)	48 (37.5)	1.19 (0.82–1.75)	26 (20.3)	0.76 (0.48–1.20)
GACAG	18	6 (33.3)	0.56 (0.21–1.49)	5 (27.8)	0.77 (0.27–2.17)	1 (5.6)	0.18 (0.02–1.33)
Rare	9	2 (22.2)	0.32 (0.07–1.54)	2 (22.2)	0.57 (0.12–2.75)	1 (11.1)	0.37 (0.05–3.00)
			$P = 0.3939$		$P = 0.4642$		$P = 0.1518$

(*Continued on the following page*)

(OR, 0.42; 95% CI, 0.19–0.96) and increased odds of distal adenoma (OR, 2.05; 95% CI, 1.08–3.88), although the overall block was not statistically significant for either subsite ($P = 0.18$ and $P = 0.15$ for proximal and distal adenoma, respectively).

When examining associations in the WBF trial and UDCA trial independently, the magnitude of effect observed for each SNP or haplotype was similar for each study, although statistical significance was often shown in only one study or neither study (data not shown). As described above, a notable exception was *RXRA* SNP rs7861779, which exhibited a statistically significant association with proximal metachronous neoplasia in the WBF (OR, 0.64; 95% CI, 0.45–0.91) and UDCA (OR, 0.70; 95% CI, 0.50–0.98) trials individually. In addition, *RXRA* block 2 haplotype CGGGCA, which includes rs7861779, was significantly associated with any and proximal metachronous neoplasia across the separate and pooled studies.

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Table 3. Haplotypes on *RXRA* and *VDR* genes and association with metachronous colorectal neoplasia (Cont'd)

Haplotype	Count	Any metachronous		Proximal neoplasia		Distal neoplasia	
		n (%)	OR (95% CI)	*n* (%)	OR (95% CI)	*n* (%)	OR (95% CI)
VDR, block 3[¶]							
AAGAA	1,011	477 (47.2)	1.00 (reference)	334 (33.4)	1.00 (reference)	250 (25.0)	1.00 (reference)
GGGGA	977	433 (44.3)	0.89 (0.75–1.06)	307 (31.6)	0.92 (0.76–1.11)	237 (24.4)	0.97 (0.79–1.19)
AAAAG	649	291 (44.8)	0.91 (0.75–1.11)	224 (34.7)	1.06 (0.86–1.31)	148 (22.9)	0.89 (0.71–1.13)
AGGGA	184	93 (50.5)	1.14 (0.84–1.57)	61 (33.7)	1.02 (0.73–1.42)	40 (22.1)	0.85 (0.58–1.25)
Rare	57	26 (45.6)	0.94 (0.55–1.60)	20 (35.1)	1.08 (0.62–1.89)	11 (19.3)	0.72 (0.37–1.41)
			P = 0.4719		*P* = 0.7460		*P* = 0.7207

NOTE: Likelihood ratio test *P* values are for a model with these haplotypes versus an intercept-only model.
**RXRA*, block 1 includes rs11102986, rs11103473, rs10776909, and rs12004589.
[†]*RXRA,* block 2 includes rs1805352, rs3132297, rs3132296, rs3118529, rs3118536, and rs7861779.
[‡]*RXRA*, block 3 includes rs3118571, rs3118570, rs1536475, rs3132293, and rs877954.
[§]*VDR*, block 1 includes rs11574143, rs731236, and rs1544410.
[‖]*VDR*, block 2 includes rs11574026, rs10875695, rs11168293, rs4760655, and rs7299460.
[¶]*VDR*, block 3 includes rs4760658, rs4516035, rs11568820, rs7310552, and rs7970314.

Because of the biological relationship between VDR and RXRA, interactions between the statistically significant SNP in *RXRA*, rs7861779, and all of the SNPs in *VDR* were evaluated. After correction for multiple comparisons, no statistically significant interactions were observed (data not shown).

Discussion

In the current work, a statistically significant association between the *RXRA* gene and any and proximal metachronous neoplasia was observed, whereas there was no relationship for *VDR* at the gene level and neoplasia. After adjustment for multiple comparisons, one SNP in *RXRA* (rs7861779) was of borderline statistical significance in relation to proximal metachronous adenoma. Haplotype analyses showed that the *RXRA* block 1 haplotype GAGA, defined by rs11102986, rs11103473, rs10776909, rs12004589, was statistically significantly associated with a 24% reduced odds for proximal neoplasia. In addition, *RXRA* block 2 haplotype CGGGCA, defined by rs1805352, rs3132297, rs3132296, rs3118529, rs3118536, and rs7861779, was significantly related to a similar 26% lower odds of both any and proximal metachronous neoplasia. A single *VDR* haplotype in block 1 of *VDR* was related to reduced odds for proximal adenoma and increased odds for distal adenoma; however, the overall block was not significantly associated with lesions at either subsite.

Using a tagging approach, we found no consistent relationship between polymorphic variation in *VDR* and odds of metachronous colorectal adenoma, although there is substantial evidence for a role of VDR regulatory events in the development of colorectal neoplasia (39). For example, VDR has been reported to interact with β-catenin and inhibit β-catenin signaling events that are commonly disrupted in colonic cancers (13). In the nucleus, β-catenin binds to T-cell factor/lymphoid enhancer-binding factor (TCF/LEF), enabling the transactivation of target genes as part of the Wnt signaling pathway. Significantly, the activation of this Wnt signaling network, as well as β-catenin–mediated upregulation of proliferative genes, is suppressed in response to $1,25(OH)_2D_3$ through the nuclear VDR (13). Furthermore, while it is well-established that VDR heterodimerizes with RXR to exert transcriptional effects and promote cell differentiation (40), β-catenin also acts as a transcriptional coactivator of the RXR-VDR heterodimer, resulting in increased transactivation of VDRE-driven genes in the presence of $1,25(OH)_2D_3$ and causing enhanced antiproliferation (13, 41). Moreover, RXRα, an isoform expressed in the colonic epithelium, acts through agonists that enhance the interaction between RXR and β-catenin as well as increase the degradation of β-catenin (42, 43). RXR ligands have also been shown to modify the antiproliferative response of $1,25(OH)_2D_3$ in two colon cancer cell lines, exhibiting an increased proliferative response in Caco-2 cells but blocking it in HT-29 cells (44). The reasons for these differential responses are unclear but the data indicate that RXR acts as a potent modulator of VDR activity. Furthermore, an RXR ligand (9-*cis*-RA) can act synergistically with VDR-1,25D to induce VDR-mediated transactivation, enable recruitment of coactivators, and upregulate E-cadherin expression (45). These actions of the VDR/RXR heterodimer may offer insight into the biological mechanisms by which retinoids and vitamin D metabolites influence the development of colorectal neoplasia and how genetic variation in these genes may alter this activity (39). We therefore hypothesized that genetic variation in RXR likely affects the biological activity of VDR.

VDR is a highly polymorphic gene with more than 100 identified SNPs, of which only a handful have been studied

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to determine an association between genetic variation and risk of colorectal adenoma and colorectal cancer. Previous association studies have included *Bsm*I (rs1544410), *Taq*I (rs731236), *Apa*I (rs7975232), and *Fok*I (rs2228570) restriction endonuclease sites, as well as the *Cdx-2* binding site in the promoter region (rs11568820). None of these SNPs have been consistently independently associated with the risk of adenoma recurrence (23) or colorectal cancer (46); in a recent meta-analysis of *Fok*I and *Bsm*I and colorectal cancer, no significant associations were reported (46); another review of the literature indicated that the data for *VDR* SNPs and colorectal cancers may be weaker than for other malignancies (47). In the current work, no relationship between *Cdx-2, Bsm*I, or *Taq*I and metachronous colorectal adenoma were observed, although a single haplotype in *VDR* block 1, including *Taq*I, was observed to be statistically significantly associated with distal and proximal lesions, although in opposite directions. Although *Apa*I was not directly assessed in this population, this SNP has been shown to be in high LD with *Taq*I and *Bsm*I (47), neither of which was significantly related to metachronous neoplasia. Further, these results do not support a relationship between *Fok*I and the development of metachronous colorectal neoplasia, which is in line with recent reviews and meta-analyses of *Fok*I, which do not support a strong independent association with colorectal neoplasia (46, 47). Nonetheless, as this SNP may be important in gene-environment interactions, future work will include analyses of interactions between *Fok*I, circulating vitamin D concentrations, and other exposures.

Although the association between *VDR* polymorphic variation and cancer has been studied extensively, only two other studies have investigated the association of polymorphic variation in *RXRA* and cancer, although neither included colorectal cancer as an end point (28, 29). In the work by Ahn and colleagues, no relationship was observed for SNPs in *RXRA* and risk for prostate cancer (28); however, the study included only 11 SNPs in *RXRA*. Further, it is likely that the expression and activity of nuclear receptors like RXR vary in a tissue-specific manner (48). Chang and colleagues reported no significant associations between two *RXRA* SNPs (rs1536475 and rs1805343) and biliary tract cancers (29). The results of the present study also found no relationship between these two SNPs and risk of metachronous colorectal adenoma (Supplementary Table S1); however, the results showed that *RXRA* was significantly associated with colorectal neoplasia at the gene level. Further, after corrections for multiple comparisons, one high-interest SNP (rs7861779) was identified, and after characterizing haplotype block structure to assess the association between cocarriage of alleles and metachronous adenoma, *RXRA* block 1 was observed to be significantly associated with proximal metachronous adenoma. *RXRA* block 1 contains SNPs located in intron 1, whereas *RXRA* block 2, which was found to be significantly associated with any and proximal adenoma, contains SNPs located in introns 2, 4, and 5. SNPs located within introns can potentially affect alternative splicing of RNA (49–51).

Two *RXRA* haplotype blocks in our population showed significant associations with metachronous adenoma of similar magnitude. The two SNPs of highest interest (rs12004589 and rs7861779) from blocks 1 and 2, respectively, show strong LD ($D' = 0.87$) with one another, and as such are not likely to confer independent information. Replication of this work in another population is necessary to determine if the haplotypes and SNPs of interest in our population are generalizable to other populations and whether they are also related to cancer risk. When examined in the WBF and UDCA trials individually, the *RXRA* SNP rs7861779 was statistically significantly related to proximal metachronous neoplasia in both studies. Interestingly, rs7861779 was also statistically significantly associated with the presence of proximal adenomas at baseline in cross-sectional analyses ($P < 0.05$; data not shown). Of note, most of the SNPs selected for this investigation are tag SNPs; therefore, the SNPs in these haplotypes are likely not causal but rather serve as indicators for regions of interest. Therefore, if these data will be replicated in another population, then further identification of potential causal variants and their functional implications is warranted.

Taken together, laboratory and epidemiologic data support a protective role for vitamin D and its receptor, VDR, as well as the VDR heterodimeric partner, RXRα, in colorectal carcinogenesis. However, genetic variation in *VDR*, as measured here by a tag SNP approach, did not seem to play a major independent role in the formation of metachronous colorectal adenoma. In contrast, *RXRA* was significantly associated with colorectal neoplasia at the gene level, and these findings suggest a potentially important role of RXRα in the molecular processes, leading to colorectal carcinogenesis, particularly of the proximal colon. Because no statistically significant interactions between *RXRA* SNP rs7861779 and any *VDR* SNP were observed in the current work, it is possible that the associations observed are mediated through other RXRα heterodimer partners; these pathways should be investigated in future work.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Genetic Polymorphisms in Vitamin D Receptor *VDR/RXRA* Influence the Likelihood of Colon Adenoma Recurrence

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