**BASIC RESEARCH**

**Vitamin D receptor gene Tru9I polymorphism and risk for incidental sporadic colorectal adenomas**

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**INTRODUCTION**

Colorectal cancer (CRC) is one of the most common cancers in the USA, with an annual incidence of 146,940 cases and 56,730 deaths[1]. It has been reported that in USA, CRC morbidity is greater in northern latitudes, which may in part be due to lower sun exposure[2]. Several epidemiological studies support the hypothesis that dermal vitamin D synthesis mediated by sunlight may protect against colorectal cancer; several found decreased risk for this disease with higher serum levels of vitamin D or with increasing dietary vitamin D intake[3-4]. The vitamin D receptor (VDR), a member of the steroid/thyroid receptor family, mediates genomic actions of the active metabolite of vitamin D \(25(OH)\_2D_3\), and thus regulates cellular proliferation and differentiation[5-6] and induces apoptosis[7]. Recent studies show that VDR functions as a sensor of the colorectal carcinogen, lithocholic acid (LCA), inducing \textit{in vivo} expression of the CYP3A family that detoxifies LCA in the liver and intestine[8]. Based on such findings, there has been increased interest in an interaction between vitamin D and the VDR gene and risk for colorectal cancer. Although contradictory results have been reported[9-13], evidence suggests that at least some VDR gene polymorphisms are related to the risk of CRC or adenoma[14-17].

Recently, a novel G>A polymorphism in the 3'-UTR region of the VDR gene was identified and designated as VDR \textit{Tru9I}[18]. It is thought that the polymorphisms in this region of the VDR gene may affect its mRNA stability, possibly through linkage to other variants[19]. So far, no previous study has been reported on investigating the function of this polymorphism. In a epidemiological...
study, Gyorffy et al.[20], found that the presence of the variant ‘u’ allele, combined with VDR Apol ‘a’ and BowI ‘b’ alleles, is associated with increased risk for type I diabetes mellitus in girls. To our knowledge, there has been no previously published study on a potential association between the VDR Trn91 polymorphism and colorectal adenoma risk. Previously, we found that different genetic polymorphisms might affect risk for colorectal adenoma: the cyclinD1 A/G polymorphism was associated with increased risk,[21], and the p53-inducible ribonucleotide reductase small subunit 2 (p53R2) ‘AA’ genotype was strongly associated with increased risk in those with lower dietary nutrients including vitamins and calcium intakes (paper submitted). Herein, we report data from this same North Carolina case-control study on the association of the VDR Trn91 polymorphism and colorectal adenoma risk, alone and in interaction with various environmental risk factors for colorectal neoplasms.

MATERIALS AND METHODS

Study design

From 1994 to 1997, the markers of adenomatous polyps (MAP) case-control study were conducted to assess the validity of colonic epithelial cell proliferation as a biomarker of risk for incident sporadic colorectal adenomatous polyps. Prior to beginning the study, MAP was approved by the Institutional Review Board of Wake Forest University, Bowman Gray School of Medicine in accordance with an assurance filed with and approved by the Department of Health and Human Services. Informed consent was obtained from each participant. Eligibility criteria for study subjects consisted of English speaking adults from 30 to 74 years of age, either sex or any race who were scheduled for elective outpatient colonoscopy by four large gastro-enterology practices in Winston-Salem and Charlotte, North Carolina. Patients were recruited for over 24 mo. Cases were identified. Of these, 669 were eligible on initial screening (eligibility rate 29.8%), and of these 633 were willing to discuss the study, 617 of these were contacted, and 417 of these signed consent and had study colonoscopies (consent rate 63.1%). Of the 417 participants, 259 had some type of polyp, and of these 179 had adenomatous polyps. Nine of the 417 patients were subsequently determined ineligible for the study, and an additional eight patients had incident colon cancer and were not eligible for the primary case-control analyses; thus, 400 possible patients were available for genotypic analysis. Of these 400 patients, viable DNA was isolated from 391 (171 cases and 220 controls) for genotyping.

Genotyping

Genomic DNA was obtained from stored WBCs digested in 500 μL of lysis buffer (50 mmol/L Tris-HCl, pH 8.5, 1 mmol/L EDTA, 0.2% SDS, 200 g/mL protease K) over night at 55 °C with shaking. The digestion was precipitated directly with isopropanol and the pellets were washed with 70% ethanol. The genomic DNA pellets (50-100 μg) were dissolved in 300-800 μL of TE buffer, of which about 1 μL was used for each PCR reaction. DNA was amplified following the primers designed for the exon 8 region of the VDR gene following the published DNA sequence (GenBank number: AY342401). An isoschizomer of Trn91, MstI, was used in this study. The PCR (50 μL volume) was carried out in 20 mmol/L Tris-HCl, pH 8.4, 50 mmol/L KCl, 1.5 mmol/L MgCl2, 0.2 mmol/L dNTP, 0.5 mmol/L of each primer (5'-GCA GGG TAC AAA ACT TTG GAG-3' as forward and a 5'-CCT CAT CAC CGA CAT CAT GTC -3' as reverse), 80-120 ng of DNA template, and 2.5 units Taq polymerase (Gibco-Invitrogen). The solution was heated to 94 °C for 2 min, followed by 35 cycles of 30 s at 94 °C, 30 s at 69 °C, and 30 s at 72 °C. The final reaction was extended 7 min at 72 °C. The PCR products (5 μL) were loaded onto a 3% 2:1 NuSieve-SeaKem gel for confirmation. The PCR products (10 μL) were then subjected to MstI restriction enzyme at 37 °C overnight. Bands for the wild-type (‘UU’) allele were not cut (177 bp); the ‘uu’ genotype was showed at 91 and 86 bp; and the heterozygote (‘Uu’) allele was cut into 177-, 91-, and 86-bp fragments.

Statistical analysis

Allelic frequencies for polymorphic VDR Trn91 G>A alleles were compared to those in previous study populations. VDR Trn91 G>A genotype (UU, Uu, uu) distributions for cases and controls were tested for adherence to the Hardy-Weinberg equilibrium.

All statistical inquiries were conducted using R language
version 1.9.0 from http://www.R-project.org. Descriptive comparisons (i.e., mean±SD, frequencies as percents) of cases and controls were conducted utilizing \( \chi^2 \) tests for categorical variables, and \( t \) test for continuous variables.

Multiple logistic regressions were utilized to calculate odds ratios (ORs) and corresponding 95% CI, adjusted for potential confounding factors, to estimate the strength of an association between VDR Tru9I genotype and risk for incident sporadic colorectal adenomas. The effect of VDR Tru9I genotype was analyzed utilizing a priori hypothesized low risk, common ‘UU’ genotype as the referent group. A \( \chi^2 \) test for trend was calculated across genotypes to detect a pattern of association.

Several risk factors were scrutinized as possible confounders or effect modifiers of the VDR Tru9I genotype-colorectal adenoma association. Among these were age, sex, race, body mass index, family history of colon cancer (FHCC), smoking, alcohol consumption, non-steroidal anti-inflammatory drug (NSAID) use, and total dietary intake of calcium and vitamin D. The criteria for inclusion of any covariate in the final model included: (1) biological plausibility; (2) whether it fits the model at \( P \leq 0.1 \); and (3) whether it altered the OR for the primary exposure variable by 10% or more. Final models for genotype main effects included age, sex, smoking status, drinking status, and FHCC.

Models involving in the assessment of possible interactions between genotypes and various anti- and pro-proliferative and other key risk factors included age, sex, FHCC, NSAIDs, smoking status, and total intake of calcium and alcohol.

To examine potential gene-environment interactions of VDR Tru9I genotype and certain risk factors, stratified analyses were conducted. Continuous variables were dichotomized on median values for controls; furthermore, continuous dietary variables were categorized as sex-specific. Criteria for assessing effect modifiers were based on previous literature, biological plausibility, and whether or not risk estimates differed substantially across strata.

**RESULTS**

Adenoma cases were similar to the controls in respect to race, education status, and most dietary intakes (Table 1). However, cases were more likely to be a little older, male, and current drinkers or smokers. Controls were more likely to have histories of colon cancer in first-degree relatives.

There were significant differences in NSAID use and dietary calcium intake between cases and controls. The polymorphism distribution in present population was in Hardy-Weinberg equilibrium \( (\chi^2 = 3.41, P = 0.07) \).

Table 2 presents the associations between VDR Tru9I

### Table 1  Selected characteristics of cases and controls, MAP study, 1994-1997

| Demographic factors | Cases (n = 171) | Controls (n = 220) | \( P \) |
|---------------------|----------------|-------------------|-------|
| Age (yr)\( ^1 \)   | 58.4 (8.4)    | 55.8 (10.2)       | 0.006 |
| Male (%)            | 60            | 36                | <0.001|
| White (%)           | 89            | 89                | 0.98  |
| College education (%) | 19        | 23                | 0.38  |
| Major risk factors  |               |                   |       |
| Family history of colon cancer (%) | 14    | 31                | <0.001|
| Currently smoke cigarettes (%) | 30    | 20                | 0.02  |
| Currently drink alcohol (%) | 75    | 55                | <0.001|
| NSAID use (%)       | 19            | 30                | 0.007 |
| Dietary intakes     |               |                   |       |
| Total energy (kcal/d) | 2 010 (30)  | 2 169 (1 999)     | 0.27  |
| Total fat (g/d)     | 71.3 (39.9)   | 72.6 (65.9)       | 0.80  |
| Total meat (serve/wk) | 4.4 (1.4)  | 4.5 (1.4)         | 0.57  |
| Total fruits and vegetables (serve/wk) | 6.1 (3.6)  | 7.4 (10.2)       | 0.09  |
| Total calcium (mg/d) | 736 (406.6) | 871 (757)        | 0.02  |
| Total vitamin D (IU/d) | 315 (258.2)| 359 (374)       | 0.16  |
| Total folate (mg/d) | 416.7 (241.6) | 467 (402) | 0.12 |
| Total alcohol (g/d) | 7.4 (15.1)    | 4.8 (20.8)        | 0.14  |

\( ^1 \) Adjusted for age, sex, total energy intake, history of colon cancer in a first degree relative, nonsteroidal anti-inflammatory drug use, current smoking status, and total calcium and alcohol intakes; \( ^2 \) mean±SD presented unless otherwise indicated, except for age, all other means are age adjusted; \( ^3 \) non-steroidal anti-inflammatory drug.

### Table 2  Frequencies of VDR Tru9I genotypes and associations with incident sporadic colorectal adenomas (MAP study), 1994-1997

| VDR Tru9I genotype | Cases (n = 171) | Controls (n = 220) | Adjusted OR\( ^1 \) | 95%CI\( ^2 \) |
|---------------------|----------------|-------------------|---------------------|-------------|
| UU                  | 144            | 171               | 1.00                | (0.17-4.55)\( ^1 \) |
| Uu                  | 23             | 45                | 0.88                | (0.38-1.25)\( ^1 \) |
| uu                  | 4              | 4                 | 0.69                | (0.40-1.25)\( ^1 \) |
| Uu+uu               | 27             | 49                | 0.71                | (0.40-1.25)\( ^1 \) |
| \( P \)-trend       |                |                   | 0.24                |             |

\( ^1 \) Odds ratios; \( ^2 \) 95% confidence interval; \( ^3 \) adjusted for age, sex, total energy intake, history of colon cancer in a first degree relative, nonsteroidal anti-inflammatory drug use, current smoking status, and total calcium and alcohol intake.
genotypes and colorectal adenoma risk. The frequencies of VDR 
Tru9I 'UU', 'Uu', and 'uu' genotypes were 84.2%, 13.5%, and 2.3% in cases, and 77.8%, 20.3%, and 1.9% in controls, respectively. There were equivalent allele distributions for cases ('U' = 90.9%, 'u' = 9.1%) and controls ('U' = 88%, 'u' = 12%). A 29% decreased multivariable-adjusted OR (0.71; 95%CI, 0.40-1.25) was observed in 'Uu' and 'uu' carriers, compared to 'UU' carriers.

We investigated the association of the polymorphism with colorectal adenoma risk according to characteristics of adenomatous polyps (Table 3). The inverse association of having at least one 'u' allele with risk for colorectal adenoma was more pronounced for adenoma that were multiple (OR, 0.51; 95%CI, 0.21-1.24), larger (OR, 0.37; 95%CI, 0.11-1.28), sessile (OR, 0.36; 95%CI, 0.13-0.97), and perhaps for adenomas with higher levels of dysplasia (OR, 0.68; 95%CI, 0.33-1.41).

Potential interactions of VDR Tru9I polymorphism and other risk factors for colorectal neoplasms and risk for adenomas are shown in Table 4. Compared to the 'UU'

### Table 3 Age-, sex-adjusted associations of VDR Tru9I genotypes and risk for incident sporadic colorectal adenomas according to adenoma characteristics, MAP Study, 1994-1997

| Tru9I genotypes | UU | Uu+uu |
|-----------------|----|-------|
| Multiplicity    |    |       |
| 1               | 85/171 | 1.00 |
| >1              | 59/171 | 1.00 |
| Shape           |    |       |
| Sessile         | 51/171 | 1.00 |
| Pedunculated    | 97/171 | 1.00 |
| Size (cm)       |    |       |
| <1.0            | 111/171 | 1.00 |
| ≥1.0            | 33/171 | 1.00 |
| Dysplasia       |    |       |
| Mild            | 73/171 | 1.00 |
| ≥Moderate       | 71/171 | 1.00 |
| Morphology      |    |       |
| Tubular         | 131/171 | 1.00 |
| Any villous     | 13/171 | 1.00 |

### Table 4 Multivariate-adjusted joint and combined associations of VDR Tru9I genotypes and various risk factors for colorectal neoplasms and risk for incident sporadic colorectal adenomas, MAP study, 1994-1997

| Age (yr) | Cases (n) | Controls (n) | OR/95%CI | Cases (n) | Controls (n) | OR/95%CI |
|----------|-----------|--------------|----------|-----------|--------------|----------|
| ≤57      | 58        | 83           | 1.00     | 12        | 31           | 0.60 (0.26-1.37) |
| >57      | 86        | 89           | 1.41 (0.86-2.31) | 15        | 18           | 1.09 (0.46-2.56) |
| Sex      |            |              |          |           |              |          |
| Male     | 85        | 60           | 1.00     | 15        | 16           | 0.65 (0.28-1.53) |
| Female   | 59        | 112          | 0.51 (0.30-0.85) | 12        | 33           | 0.38 (0.17-0.88) |
| Current smoker | 35     | 77           | 1.00     | 6         | 25           | 0.39 (0.13-1.23) |
| Yes      | 105       | 94           | 1.84 (1.07-3.17) | 20        | 24           | 1.56 (0.69-3.53) |
| Current drinker | 63     | 99           | 1.00     | 13        | 26           | 0.96 (0.44-2.08) |
| Yes      | 77        | 71           | 1.65 (1.01-2.69) | 12        | 22           | 0.90 (0.39-2.06) |
| NSAID use |            |              |          |           |              |          |
| No       | 118       | 117          | 1.00     | 21        | 38           | 0.64 (0.34-1.23) |
| Yes      | 23        | 54           | 0.48 (0.26-0.86) | 5         | 11           | 0.38 (0.12-1.25) |
| Total calcium intake | 92    | 84           | 1.00     | 13        | 23           | 0.53 (0.23-1.20) |
| Lower    | 49        | 86           | 0.53 (0.32-0.87) | 14        | 26           | 0.52 (0.23-1.14) |
| Higher   | 76        | 83           | 1.00     | 14        | 25           | 0.59 (0.26-1.33) |
| Total vitamin D intake | 65    | 87           | 0.78 (0.48-1.27) | 13        | 24           | 0.60 (0.27-1.38) |

1 Adjusted for age, sex, total energy intake, history of colon cancer in a first degree relative, nonsteroidal anti-inflammatory drug use, current smoking status, and total calcium and alcohol intakes; 2 odds ratio; 3 greatest diameter of largest adenoma; 4 dysplasia in adenoma with greatest degree of dysplasia; 5 if multiple adenomas, classified as "Any villous" if any adenoma villous or tubulovillous; 6 not available.
alter transcriptional activity and mRNA degradation identified. It has been reported that the polymorphisms in polymorphism may interact with these dietary micronutrients.

In the present study, we assessed, for the first time, VDR Tru9I variants as risk factor for colorectal adenoma. Our data suggest that the Tru9I mutant ‘u’ allele was associated with decreased risk for colorectal adenoma, particularly for adenomas that were larger, multiple, had moderate or greater dysplasia, or were sessile. Also, the ‘u’ allele was related to decreased risk for adenoma, particularly among persons who were younger, female, NSAID users or did not smoke.

Vitamin D is obtained from the diet or sunlight-induced synthesis, and hydroxylated first in the liver [forming 25-(OH)D], then subsequently in the kidney [forming 1,25-(OH)2D]. The hypothesis that vitamin D may provide reduced colorectal adenoma risk was first proposed in the early 1980s in light of an inverse ecologic association between CRC morbidity and solar exposure[2]. In vivo and in vitro studies found that vitamin D, promotes differentiation of colon carcinoma cells by inducing E-cadherin and inhibiting β-catenin signaling[7]. Experimental data also suggest that the active metabolite of vitamin D and its analogs can induce apoptosis in a colorectal adenoma cell line[9]. Vitamin D interacts with the VDR, which upregulates CYP3A expression, which in turn increases detoxification of secondary bile acids, including LCA[9]. Recent epidemiological studies have suggested inverse associations among calcium, vitamin D and CRC or adenoma risk; but results are mixed. In the present study, higher calcium and vitamin D intake were associated with lower risk for colorectal adenomas; however, there was no support for the hypothesis that the VDR Tru9I polymorphism has been associated with decreased risk for colorectal adenoma, modified by NSAID use[8]. So far, there have been no previous reports of investigations of an association of the Tru9I polymorphism with any cancer.

Many studies have reported that the VDR polymorphisms are associated with susceptibility for and prognosis of different cancers[13,34]. Hutchinson et al.[33], found that the VDR ‘ttff’ genotype (according to TaqI and FokI polymorphisms) was significantly associated with thicker malignant melanoma tumors. It has also been reported that the FokI polymorphism was more strongly related to large adenoma risk among subjects with lower dietary calcium intake[3].

Some limitations in this study should be considered in interpreting our results. First, the small sample size and consequent low power preclude drawing strong conclusions. Second, this study is colonoscopy-based, and the population may not be representative of the general population. People who worried about their positive family history were more likely to seek colonoscopy examination, leading to a family history bias that may have attenuated associations. Another potential limitation is that ultraviolet radiation exposure was not assessed in the present study; therefore, the dietary vitamin D intake may not reflect the true exposure to vitamin D. In light of the relationship between vitamin D and calcium, this may also impact the estimated calcium-adenoma association.

In conclusion, this is the first study to investigate an association between the VDR Tru9I polymorphism and risk for incident sporadic colorectal adenoma. Our data suggest that the VDR Tru9I polymorphism may be more related to progression than initiation of colorectal adenoma. Our study also focused on the interaction between the VDR gene polymorphism, Tru9I, and dietary calcium and vitamin D intakes; however, no such interaction was found. On the other hand, our data suggest possible interactions of VDR Tru9I genotypes with age, sex, smoking, drinking, and NSAID use. Further, larger studies are needed to verify the present data, to understand the biological mechanisms of VDR gene/calcium/vitamin D interactions.

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