Null Results in Brief

No Association Between Vitamin D Intake, VDR Polymorphisms, and Colorectal Cancer in a Population-Based Case-Control Study

Joseph H. Ashmore1, Carla J. Gallagher2,3, Samuel M. Lesko4,5, Joshua E. Muscat2, Terry J. Hartman6, and Philip Lazarus1

Abstract

Background: Epidemiologic evidence indicates that greater intakes of vitamin D may decrease the risk of colorectal cancer. Variants in the vitamin D receptor (VDR) gene have the potential to modify associations between vitamin D intake and colorectal cancer.

Methods: Associations between intakes of vitamin D and colorectal cancer were studied in a large case-control study conducted in central and northeastern Pennsylvania including 1,012 cases with histologically confirmed colorectal cancer and 1,080 population-based controls. Associations between 35 tagSNPs encompassing the VDR gene and risk for colorectal cancer as well as gene-diet associations were also assessed among a subset of the population (770 controls, 710 cases).

Results: No significant trends were observed between vitamin D intake and colorectal cancer risk. After adjustment for multiple comparisons, none of the SNPs or haplotypes within the VDR gene were associated with colorectal cancer. There were also no interactions between dietary factors and variants in the entire VDR gene.

Conclusions: Overall, results from this study suggest that vitamin D intake and variants in the VDR gene have little effect on risk for colorectal cancer.

Impact: Increasing vitamin D intake from the diet may not result in decreasing the incidence of colorectal cancer. Cancer Epidemiol Biomarkers Prev; 24(10): 1635-7. ©2015 AACR.

Introduction

Cancers of the colon and rectum (colorectal cancer) are currently ranked third for both cancer incidence and mortality in the United States. Previous epidemiologic studies have suggested that greater vitamin D intake is associated with reduced colorectal cancer risk, but these results are inconclusive. One possible explanation for the observed inconsistencies between studies is genetic variation within the vitamin D receptor gene (VDR). Individuals with decreased VDR activity could potentially have an increased risk for colorectal cancer compared with those with normal VDR activity, particularly at low vitamin D intakes.

The objectives of the present study were to comprehensively examine associations between colorectal cancer incidence and (1) consumption of supplemental, dietary, and total vitamin D (2), SNPs that tag the common variation in the gene (tagSNPs) in the VDR gene, and (3) the potential interactions between vitamin D intake and variants in the VDR gene, in a population-based case-control study in a high-risk region of central and northeastern Pennsylvania.

Materials and Methods

Detailed descriptions of this study have been previously described (1–3). Briefly, cases were identified from the Pennsylvania State Cancer Registry within 15 months of diagnosis. To be eligible, case participants had to have a first time, histologically confirmed diagnosis of colon, rectal, or colorectal cancer and be English-speaking. Controls were residents of the same region with no history of colorectal cancer and were identified by random digit dialing.

Participants completed a modified version of the Diet History Questionnaire (DHQ), a validated food frequency questionnaire (FFQ) developed by the NCI (4). This DHQ was modified to examine more comprehensively and accurately the distinct dietary intake habits of subjects recruited from the population of central and northeast Pennsylvania as described previously (3).

A total of 35 tagSNPs were selected for the VDR gene by analyzing individuals of northern and western European ancestry collected by the Centre d’Etude du Polymorphisme Humain (CEPH) from HapMap.org according to the following criteria: (i) SNPs were located in the VDR gene or within its 5-kb 5’ or 3’ flanking region, (b) had a minor allele frequency ≥ 0.05, and (c) the other unselected SNPs could be captured by one of the tagging SNPs with a linkage disequilibrium r2 ≥ 0.80 (mean r2 = 0.98). Correction for multiple comparisons was performed using the false-discovery rate (FDR) (5).

All analyses were two-sided and considered significant if P < 0.05 for all tests. Statistical analyses were performed using SAS statistical software (version 9.3; SAS Institute). The
Table 1. ORs and 95% CIs for the main effects of vitamin D intake and risk of colorectal cancer

<table>
<thead>
<tr>
<th>SNP</th>
<th>Cases</th>
<th>Controls</th>
<th>OR* (95% CI)</th>
<th>FDR P value</th>
<th>OR# (95% CI)</th>
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<tr>
<td>Total vitamin D</td>
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<tr>
<td>Quartile 1</td>
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<td>1078</td>
<td>0.98</td>
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<td>Quartile 4</td>
<td>1078</td>
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| Supplemental vitamin D |       |          |              |             |              |             |
| No use                | 0 (none) | 1095 | 1.00     |             | 1.00         |             |
| Any vs. none          | >1     | 1095 | 1.00     |             | 1.00         |             |
| Low vs. none          | ≤10    | 1095 | 1.00     |             | 1.00         |             |
| High vs. none         | >10    | 1095 | 1.00     |             | 1.00         |             |

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Institutional Review Boards at the participating institutes, the Northeast Regional Cancer Institute (Scranton, PA), and the Penn State College of Medicine (Hershey, PA), reviewed and approved all study procedures.

Results

Characteristics of the study participants have been described previously (1–3). Overall, controls were younger, better educated, and consumed greater amounts of supplemental and dietary calcium.
total vitamin D, calcium, and fiber. Controls also had lower body mass index (BMI), were more likely to regularly use NSAIDs, consumed more alcohol, and were less likely to have a family history of colorectal cancer. In multivariate analyses, there was no clear pattern of association between vitamin D intake and risk for colorectal cancer (Table 1). In the age- and sex-adjusted model, subjects consuming >10 μg/d of supplemental vitamin D were inversely associated with colorectal cancer (OR, 0.61; 95% confidence interval [CI], 0.48–0.78; FDR \( p_{\text{trend}} = 0.005 \)). Similarly, those with the highest intakes of total vitamin D (>15.5 μg/d) were inversely associated with colorectal cancer (OR, 0.68; 95% CI, 0.52–0.88; FDR \( p_{\text{trend}} < 0.001 \)); neither of these remained significant in the fully-adjusted model.

Because of insufficient genomic DNA obtained from some subjects, there were differences in the sample numbers for the epidemiologic and genotypic datasets. There were no major differences between the two datasets. There was no effect of race in the dataset as 98% of the epidemiologic dataset was Caucasian, and only Caucasians were used in the genotyped dataset. Of the 35 tagSNPs evaluated, only one was marginally associated with colorectal cancer; however, none remained statistically significant after FDR correction (Table 2). There were no significant gene–diet interactions, even at the \( P = 0.1 \) cutoff. No haplotypes were significant after correction for multiple comparisons.

**Discussion**

In this study, no significant trends were observed between dietary or total vitamin D intake and risk for colorectal cancer after adjustment for known colorectal cancer risk factors (Table 1). There were also no SNPs or haplotypes within the VDR gene associated with colorectal cancer after correction for multiple comparisons. The results from the present study do not support those from a recent meta-analysis showing an inverse association between dietary vitamin D intake and colorectal cancer as well as an inverse association between the BsmI polymorphism (BB vs. bb, rs15444110) and colorectal cancer (6); however, the decreased number of subjects in the present genetic dataset may have limited our power to detect modest associations.

Previous studies that have found inverse associations between dietary vitamin D intake and colorectal cancer have controlled for similar covariates in their multivariate model (6) as was performed in the present study. The addition of calcium to our model has the largest effect on observed associations. When calcium is removed from the model, a nonsignificant inverse association is observed for the upper two quartiles of total vitamin D intake with a near-significant inverse trend (FDR \( p_{\text{trend}} = 0.059 \); data not shown). Our results are similar to those from other studies which have controlled for calcium when evaluating the effect of vitamin D on colorectal cancer (7, 8). Further studies evaluating additional genes or using biomarker data may help elucidate the complex relationship between vitamin D and risk for colorectal cancer.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

**Authors’ Contributions**

**Conception and design:** C.J. Gallagher, S.M. Lesko, J.E. Muscat, T.J. Hartman, P. Lazarus

**Development of methodology:** J.E. Muscat

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** S.M. Lesko, J.E. Muscat, T.J. Hartman

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** J.H. Ashmore, C.J. Gallagher, T.J. Hartman, P. Lazarus

**Writing, review, and/or revision of the manuscript:** J.H. Ashmore, C.J. Gallagher, T.J. Hartman, P. Lazarus

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** J.H. Ashmore, S.M. Lesko

**Study supervision:** P. Lazarus, S.M. Lesko

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**References**


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