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SERUM 25(OH)D LEVELS, DIETARY INTAKE OF VITAMIN D, AND COLORECTAL ADENOMA RECURRENCE

Elizabeth T. Jacobs[1,2,*], **David S. Alberts**[1,3], **Jose Benuzillo**[2], **Bruce W. Hollis**[4], **Patricia A. Thompson**[5], and **María Elena Martínez**[1,2]

1 *Arizona Cancer Center, University of Arizona, Tucson, AZ, USA 85724*

2 *Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA 85724*

3 *College of Medicine, University of Arizona, Tucson, AZ, USA 85724*

4 *Medical College of South Carolina, Charleston, SC, USA, 29425*

5 *Department of Pathology, University of Arizona, Tucson, AZ, USA 85724*

Abstract

There is strong epidemiological and laboratory evidence that vitamin D may be protective against colorectal neoplasia. Therefore, we sought to assess the relationship between serum 25(OH)D levels, dietary intake of vitamin D, and colorectal adenoma recurrence in our Ursodeoxycholic Acid trial. A total of 568 participants were randomly selected for analysis of serum 25(OH)D levels. The range of total 25(OH)D was 5.5 to 66.1 ng/ml, with a median of 25.6 ng/ml. After categorizing 25(OH)D levels into tertiles based on the population distribution, the adjusted odds ratios (95% CI) for adenoma recurrence in the second and third tertiles were 0.88 (0.56–1.39) and 0.78 (0.49–1.24), respectively. The association between serum 25(OH)D and adenoma recurrence appeared to be stronger among women than men. As compared to those below the median value, women with serum 25(OH)D levels above the median had an OR (95% CI) of 0.59 (0.30–1.16); the corresponding OR (95% CI) for men was 0.95 (0.60–1.49). Analyses by dietary vitamin D intake revealed no statistically significant associations. In summary, the results of this study show a moderate, nonsignificant inverse association between serum 25(OH)D levels and reduced risk for colorectal adenoma recurrence, particularly among women.

Keywords

Vitamin D; 25(OH)D; colorectal adenoma

*Correspondence Elizabeth T. Jacobs, Ph.D., Mel and Enid Zuckerman College of Public Health, Arizona Cancer Center. University of Arizona, P.O. Box 245024, Tucson, AZ 85724-5024, Ph (520) 626-0341, Fax (520) 626-9275, jacobse@u.arizona.edu.

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INTRODUCTION

Colorectal cancer is one of the most common cancers in the United States, and it is estimated that up to 75% of these cancers could be avoided by implementation of dietary changes[1]. This has led to intensive study of the dietary risk factors for colorectal cancer. Epidemiological and clinical researchers have sought to investigate the potential association between vitamin D and risk of colorectal neoplasia. Low serum levels of 25(OH)D were found to be significantly associated with risk of both colorectal adenoma[2] and cancer[3] in two large cohort studies. Some studies have found an inverse nonsignificant association between dietary or total intake of vitamin D and colorectal adenomas or cancer[4–7], while others have not[8,9]. The most recent contribution to the vitamin D and colorectal neoplasia literature are results from the Women's Health Initiative (WHI)[10]. In this randomized, double-blind placebo-controlled trial of 36,282 women, participants were assigned to a supplement of 500 mg of calcium carbonate plus 200 IU of vitamin D_3 twice daily, or a placebo. The results showed that the intervention had no appreciable effect on colorectal cancer; however, in a nested case-control analysis, those within the lowest quartile of serum 25(OH)D levels at baseline had a significantly increased risk for development of colorectal cancer. Therefore, the association between 25(OH)D levels and risk for colorectal neoplasia remains equivocal. We sought to assess the relation between these levels and risk for colorectal adenoma recurrence in a study population residing in an area with high exposure to sunlight.

MATERIALS AND METHODS

Study Population and Design

Study participants were drawn from the Ursodeoxycholic Acid (UDCA) Trial, a Phase III, double-blind, randomized, placebo-controlled trial designed to assess the effect of UDCA treatment (8–10 mg/kg/day) for three years on risk of colorectal adenoma recurrence. Study participants were recruited from 4 clinics throughout Tucson and Phoenix, were aged 40–80, and had one or more adenomas removed within the 6 months prior to randomization. No effect of UDCA on recurrence of adenomatous polyps was observed among the 1196 participants that completed the trial[11]. A total of 568 participants were randomly selected for analyses of serum levels of vitamin D.

Analysis of Serum 25(OH)D Levels

For analysis of 25(OH)D, acetonitrile extraction was performed, and ^{125}I-labeled 25(OH)D derivative was added to the assay tubes [12]. After incubation with primary antibodies, 0.5 mL of the second-antibody complex was added, incubated, and counted with a gamma well-counting system [12]. The coefficient of variation for 25(OH)D analyses was less than 7.0%.

Dietary Intake

Dietary data for the UDCA trial were collected using the Arizona Food Frequency Questionnaire (AFFQ), a semi-quantitative, scannable instrument with 113 items which was previously evaluated for reliability and validity[13]. The AFFQ was self-administered by participants at baseline, with study participants asked to report their usual intake of foods for the prior 12-month period[14]. Nutrient intakes were calculated by multiplying the frequency of each item's consumption by the nutrient composition for the age- and sex-specific portion size[13]. Nutrient composition of foods that were added to the questionnaire were derived from the USDA's 1986 Continuing Survey of Food Intake of Individuals (CSFII) and the United States Department of Agriculture's National Food Consumption Survey (1987–1988)[15].

Statistical Analyses

The subset of participants that had serum levels of 25(OH)D analyzed was compared with the entire population from the UDCA trial using chi-square analyses for categorical variables and a Student's t-test for continuous variables. Serum 25(OH)D levels were broken into tertiles based upon the distribution of the total population. For the analyses by gender, serum levels were designated as "high" or "low" based upon the median level for each gender. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression modeling. Likelihood-ratio tests were used to determine the variables included in the final adjusted model. For the analyses of serum 25(OH)D levels, two models were constructed; one that included recurrence data from those colonoscopies that were performed after the blood draw only; and one that included occurrence data from all colonoscopies conducted at least 6 months after randomization into the UDCA trial, even if they occurred prior to the blood draw. For the analyses of dietary intake of vitamin D, all participants in the UDCA trial with complete baseline dietary data were included in the analyses (n=1192). Dietary intake was separated into quartiles by the distribution for the total population, and tertiles for gender-specific analyses. ORs and 95% CIs were calculated as described above.

RESULTS

Table 1 presents a comparison of all participants in the UDCA trial (n=1192) with the randomly-selected subset of participants (n=568) that had serum analyzed for 25(OH)D. Characteristics between the two groups were similar, with the exception of the rate of colorectal adenoma recurrences. For all UDCA participants, the percentage of those with recurrences was 42.3, while for those in the subset it was 36.8. Because those colonoscopies that occurred prior to the blood draw were excluded from the primary analyses of those in the subset of UDCA participants, it was expected that fewer recurrences would have been observed in the subset.

The ORs and 95% CIs for risk of adenoma recurrence by tertile of serum 25(OH)D are shown in Table 2. When including recurrence data solely from those colonoscopies occurring after the blood draw used for analyses of serum 25(OH)D levels, the adjusted ORs (95% CIs) for the second and third tertiles for the total population were 0.88 (0.56–1.39) and 0.78 (0.49–1.24), respectively, compared to those in the lowest tertile. For men above the median for serum 25(OH)D levels, the adjusted OR (95% CI) for adenoma recurrence was 0.95 (0.60–1.49); while among women, those above the median had an OR (95% CI) of 0.59 (0.30–1.16). When including all colonoscopies from the UDCA trial, the ORs (95% CIs) for the total population were 0.74 (0.47–1.16) and 0.74 (0.46–1.17) for the second and third tertiles compared to the reference group. Among women above the median, a statistically significantly reduced risk for colorectal adenoma recurrence (OR= 0.49; 95% CI=0.25–0.97) was observed; while for men there was no association (OR=0.97; 95% CI=0.62–1.52). An interaction term for gender and serum 25(OH)D levels was not statistically significant (p=0.38).

Table 3 shows the ORs (95% CIs) for adenoma recurrence by quantile of dietary vitamin D intake. For the total population, the adjusted ORs (95% CIs) were 1.18 (0.83–1.70), 1.07 (0.75–1.54), and 1.00 (0.68–1.47) for increasing quartile of dietary intake (p-trend 0.86). Among women, there was a nonsignificant decreased risk for adenoma recurrence associated with the second and third tertiles of vitamin D intake compared with the reference group: OR=0.90; 95% CI=0.51–1.60 and OR=0.71; 95%=0.38–1.32, respectively. The ORs (95% CIs) for men in the second and third tertiles were null, with values of 0.95 (0.65–1.37) and 0.95 (0.64–1.39), respectively.

DISCUSSION

The results of the current study show a moderate, non-significant inverse association between serum 25(OH)D levels and risk for colorectal adenoma recurrence. This relationship appeared to be stronger for women than for men, although an interaction term for 25(OH)D and gender was not statistically significant. Colonoscopies were used to ascertain adenoma recurrence events. In order to maintain a prospective design, we first excluded data from all colonoscopies that occurred prior to the blood draw used for analysis of 25(OH)D. It appears that this exclusion served only to decrease the statistical power of the study. Generally, it is believed that an adenoma recurrence takes a least six months to form [11], and as such is not a discrete event. Therefore, we performed a secondary analysis that included data from all colonoscopies that were conducted during follow-up, whether before or after the blood draw. These results revealed a significantly reduced risk for adenoma recurrence among women who had serum 25(OH)D levels above the median of 17.3 ng/ml. However, because of the nature of the study design, it is not possible to attribute a causal relationship between serum 25(OH)D and adenoma recurrence.

The results of this study are in agreement with some reports in the literature where no significant effect for serum 25(OH)D and colorectal adenoma [16,17], or cancer[18] was observed. However, others[2,3,10] have reported statistically significant inverse associations between serum 25(OH)D and colorectal neoplasia, most recently the report from the Women's Health Initiative (WHI)[10]. Although in the WHI no protective effect for colorectal cancer was observed with daily supplementation of 400 IU of vitamin D_3 and 1000 mg of calcium carbonate, a statistically significant increased risk for colorectal cancer was observed for those with baseline 25(OH)D levels in the lower quartiles compared to the highest, with an OR (95% CI) of 2.53 (1.49–4.32) for the lowest vs. the highest quartile[10]. These results indicate that protection from colorectal cancer appeared at serum 25(OH)D levels above 23.4 ng/ml; which is similar to what we observed in our study when we repeated our gender-specific analyses using tertiles. However, as we were unsure that the data were stable when tertiles were used, we did not present these data in a Table.

The reason for the suggestion of a differential effect of 25(OH)D in women compared to men in the current work is unclear. The range of serum 25(OH)D was similar between the genders, although the mean for men was slightly higher than for women (26.9 ± 8.4 and 25.1 ± 10.4, respectively). Another possibility could be related to differences in colonic location of polyps and tumors between men and women. A report using data from the Clinical Outcomes Research Initiative (CORI) to evaluate gender differences in polyp location showed that women were more likely than men to develop pure right-sided (proximal) polyps[19]. Therefore, we explored the possibility of differential effects of 25(OH)D by colon location, and found no significant results.

In the current investigation, there was no significant association between dietary intake of vitamin D and risk for colorectal adenoma recurrence, as was also observed by Martinez et al [4]. and Hartman et al.[5] for adenoma recurrence, Levine et al. for distal adenoma recurrence [17] and Kampman et al. for colorectal cancer[20]. The results for women in this report are similar to those reported by Bostick et al. in the Iowa Women's Health Study (IWHS)[7], where a non-significant adjusted relative risk (95% CI) of 0.73 (0.45–1.18) was observed. Conversely, in an analysis of the Nurses' Health Study, a significant inverse association was reported for dietary vitamin D intake and colorectal cancer among women[6].

CONCLUSION

We found a moderate, non-significant inverse association between serum 25(OH)D levels and colorectal adenoma recurrence that was confined to women. Future work will include investigation of effect modification by vitamin D receptor and retinoid X receptor polymorphisms.

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Table 1

Characteristics for participants with plasma vitamin D analyses compared with all participants in the Ursodeoxycholic (UDCA) acid trial.

Characteristic	UDCA Subset N=568	All UDCA Participants N=1192
Recurrence (yes)	211 (36.8)	504 (42.3)[a]
Treatment group (UDCA)	281 (49.3)	613 (51.4)
Age (yrs)	66.0 ± 8.5	66.2 ± 8.5
Male (yes)	367 (64.7)	804 (67.5)
Race (white)	526 (92.6)	1108 (94.5)
Aspirin use (yes)	168 (29.6)	331 (27.8)
Family history (yes)	163 (28.7)	327 (27.4)
Protein (g/d)	72.7 ± 30.7	73.4 ± 30.7
Carbohydrate (g/d)	277.0 ± 120.3	278.7 ± 121.1
Total fat (g/d)	64.0 ± 31.0	65.4 ± 32.7
Energy (kcal/d)	1970.4 ± 797.5	1992.6 ± 820.5
Alcohol (g/d)	8.3 ± 15.0	7.9 ± 13.8
Total Fiber (g/d)	22.0 ± 11.3	21.8 ± 10.7
Calcium (mg/d)	963.1 ± 459.2	971.1 ± 458.8
Dietary Vitamin D (IU/d)	135.7 ± 96.9	136.9 ± 99.4
Supplemental Vit D (IU/d)	249.9 ± 246.9	238.9 ± 250.7

[a] $p<0.05$

Table 2

Adjusted odds ratios (95% CIs) for colorectal adenoma recurrence by serum 25 (OH)D level among men and women (n=568).

25(OH)D (mean, ng/ml)	Recur/Total	Adjusted[a] OR (95% CI) Recurrence Analysis[b]	Adjusted[a] OR (95% CI) Occurrence Analysis[c]
Total Population			
1 (17.0)	75/192	1.00	1.00
2 (25.5)	71/188	0.88 (0.56–1.39)	0.74 (0.47–1.16)
3 (36.3)	64/188	0.78 (0.49–1.24)[d]	0.74 (0.46–1.17)[e]
Men			
Low (20.5)	73/186	1.00	1.00
High (33.4)	68/181	0.95 (0.60–1.49)	0.97 (0.62–1.52)
Women			
Low (17.2)	39/101	1.00	1.00
High (33.0)	30/100	0.59 (0.30–1.16)	0.49 (0.25–0.97)

[a] Adjusted for BMI, number of colonoscopies, previous polyps, season of blood draw, and gender (total population only).

[b] Includes recurrences/nonrecurrences that occurred only after the blood draw for 25(OH)D analyses. Data from colonoscopies prior to blood draw were not used in these analyses.

[c] Includes data from all colonoscopies, including recurrences/nonrecurrences from prior to blood draw.

[d] P-trend=0.29.

[e] P-trend=0.20.

Table 3

Adjusted odds ratios (95% CIs) for colorectal adenoma recurrence by dietary intake of vitamin D for men and women (n=1192).

Dietary vitamin D Intake (median, IU/d)	Recur/Total	Crude OR	Adjusted[a] OR	p-trend
Total Population				
1 (31.8)	120/298	1.00	1.00	
2 (85.3)	131/298	1.16 (0.84–1.61)	1.18 (0.83–1.70)	
3 (157.3)	127/298	1.10 (0.79–1.53)	1.07 (0.75–1.54)	
4 (271.9)	126/296	1.09 (0.78–1.51)	1.00 (0.68–1.47)	0.86
Women				
1 (30.5)	49/130	1.00	1.00	
2 (107.6)	51/129	1.08 (0.66–1.78)	0.90 (0.51–1.60)	
3 (234.2)	44/129	0.86 (0.51–1.42)	0.71 (0.38–1.32)	0.28
Men				
1 (45.5)	123/268	1.00	1.00	
2 (125.5)	115/268	0.89 (0.63–1.25)	0.95 (0.65–1.37)	
3 (257.0)	122/268	0.99 (0.70–1.38)	0.95 (0.64–1.39)	0.78

[a] Adjusted for gender, energy intake, number of colonoscopies, and previous polyps.