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RESEARCH ARTICLE

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The clinical significance of vitamin D levels and vitamin D receptor mRNA expression in colorectal neoplasms

Ying Fang[1] | Haojun Song[2] | Jian Huang[1] | Jianbo Zhou[1] | Xiaoyun Ding[2]

[1]Department of Gastroenterology, Yuyao People's Hospital of Zhejiang Province, Ningbo, China

[2]Department of Gastroenterology, Laboratory of Digestive Diseases, Ningbo First Hospital, Ningbo, China

Correspondence
Jianbo Zhou, Department of Gastroenterology, Yuyao People's Hospital of Zhejiang Province, 800 Chengdong Road, Yuyao City, Ningbo, 315400, China.
Email: zhoujianbowave@163.com

Xiaoyun Ding, Department of Gastroenterology, Laboratory of Digestive Diseases, Ningbo First Hospital, No. 59, Liuting Road, Ningbo, 315010, China.
Email: dyyyding@126.com

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Abstract

Background/Aim: This study aimed to investigate the clinical significance of changes in vitamin D [25(OH)D] levels and vitamin D receptor (VDR) mRNA expression in colorectal adenoma development.

Methods: Plasma concentrations of 25(OH)D and mRNA expression of VDR in tissues were determined by enzyme-linked immunosorbent assay (ELISA) and real-time fluorescence quantitative polymerase chain reaction (RT-qPCR), respectively. In addition, the concentration of plasma 25(OH)D and levels of VDR mRNA in tissues were compared among healthy individuals and adenoma and adenocarcinoma patients.

Results: Vitamin D receptor expression in colorectal adenocarcinoma tissues was significantly lower than that in para-cancerous tissues that were >5 cm away from malignant tumor sites ($p < 0.01$). The level of VDR expression in normal colorectal tissues from healthy individuals was significantly higher than that in colorectal adenomas ($p < 0.01$) and colorectal adenocarcinomas ($p < 0.01$); however, the VDR expression was not significantly different between colorectal adenomas and colorectal adenocarcinomas ($p = 0.106$). The concentration of 25(OH)D in healthy individuals was significantly higher than that in patients with colorectal adenomas ($p < 0.01$) and colorectal adenocarcinomas ($p < 0.01$); however, the concentration of 25(OH)D was not significantly different between colorectal adenomas and colorectal adenocarcinomas ($p = 0.489$). A low concentration of 25(OH)D was considered a risk factor for colorectal adenoma and colorectal adenocarcinoma, with odds ratios of 4.875 and 2.925, respectively.

Conclusions: The 25(OH)D levels and VDR mRNA expression might be associated with the development of colorectal adenoma and its progression to adenocarcinoma.

KEYWORDS
colorectal adenocarcinoma, colorectal adenoma, vitamin D, vitamin D receptor

Ying Fang and Haojun Song contributed equally to this study.

1 | INTRODUCTION

Colorectal cancer is a common malignancy, with global incidence ranks of 3 and 2 among men and women, respectively.[1] Currently, the incidence and mortality rates of colorectal cancer in developing and low-income countries have exhibited a continuously increasing trend.[2] This trend is especially evident in China, where lifestyle changes have led to a significantly increased incidence of colorectal cancer.[3]

Colorectal adenomas are closely associated with colorectal cancer. The risk of colorectal cancer decreases when the detection of colorectal adenomas increases.[4] The entire process of the development and progression of colorectal cancer involves multiple stages, from abnormal hyperplasia of the intestinal mucosal epithelia to the formation of the final neoplasm. Vitamin D [25(OH)D] is a special fat-soluble vitamin that was previously considered to be associated with the development and progression of colorectal cancer.[5] 25(OH)D functions by binding to the vitamin D receptor (VDR). The binding product mediates the regulation of proliferation, metaplasia, apoptosis, and the colonic epithelial cell cycle, which influences the development and progression of colorectal cancer.[6-8] Two studies have investigated the role of 25(OH)D in the prevention of colorectal adenoma, but reported different results; thus, the role of 25(OH)D in the prevention and treatment of precancerous lesions (adenoma) has not been established.[9,10]

In this study, the clinical changes in 25(OH)D levels and VDR mRNA expression in colorectal adenomas and colorectal adenocarcinomas were investigated to determine the possible functions of 25(OH)D in the development and progression of colorectal neoplasms.

2 | MATERIALS AND METHODS

2.1 | Patient selection

The current study used the case-control method to randomly enroll 49 patients with colorectal adenomas and 55 patients with colorectal adenocarcinomas who were admitted to the Ningbo First Hospital in Zhejiang, China between 2013 and 2015. For analysis and comparison, 59 healthy individuals were randomly recruited as the normal control group. Healthy individuals were determined when they presented with good physical results after routine medical examinations at our hospital. Participants from the same province who were admitted to the hospital during the sunny seasons and who did not take calcium tablets and dietary 25(OH)D were included in this study. The institutional review boards of the Ningbo First Hospital approved the study, and all 163 participants provided written informed consent.

Biopsy specimens were obtained from patients who underwent colonoscopy. Colorectal adenocarcinoma tissues were collected directly from the tumor site by colonoscopy, while the para-cancerous tissues were collected >5 cm away from the malignant tumor site. Patients were first diagnosed with colorectal adenomas or colorectal adenocarcinomas; thus, they did not receive any type of treatment modality at the time of sample collection. Normal colorectal tissues were collected from the colorectum of healthy individuals using colonoscopy.

The inclusion criteria for the group of colorectal adenomas were as follows: (1) patients diagnosed with colorectal adenoma by colonoscopy and with a biopsy specimen confirmed to be colorectal adenoma after pathological examination[11]; (2) patients without any recent acute inflammation and liver or kidney dysfunction; and (3) patients without history of tumors, immune diseases, cardiovascular diseases, various acute and chronic inflammations, liver and kidney diseases, severe skin diseases, other major diseases, or surgery. Patients with familiar polyposis or black spot polyp syndrome were excluded.

The inclusion criteria for the group with colorectal adenocarcinoma were as follows: (1) patients diagnosed with colorectal cancer by colonoscopy and with a biopsy specimen confirmed to be colorectal adenoma by pathological examination[11]; (2) patients without any recent acute inflammation and with normal liver and kidney functions; and (3) patients without history of tumors other than colorectal cancer, immune diseases, cardiovascular diseases, liver or kidney diseases, serious skin diseases, other major diseases, or surgery. Patients with colorectal cancer that was aggravated by familial polyposis and black-associated polyp syndrome were excluded.

The inclusion criteria for the normal control group were as follows: (1) participants with good health status, normal colonoscopy results, and no recent inflammation or liver and kidney dysfunction; participants who had recently completed physical examinations were preferred; and (2) participants without history of tumors, immune diseases, cardiovascular diseases, various acute and chronic inflammations, liver and kidney diseases, severe skin diseases, other major diseases, or surgery.

2.2 | Detection of plasma 25(OH)D concentration by enzyme-linked immunosorbent assay

Blood samples from all participants were collected. Briefly, 3–5 mL of blood was collected in standard EDTA tubes from each participant. Plasma samples were then extracted by centrifugation and stored at −80°C. Plasma concentrations of 25(OH)D were determined by enzyme-linked immunosorbent assay (ELISA). The human 25(OH)D ELISA kit was purchased from Shanghai Qiaodu Biotechnology Co. Ltd., China (Cat#: DRE10185), and the 25(OH)D concentration was measured according to the manufacturer's protocol. The 25(OH)D concentrations in healthy individuals ranged between 20 and 150 ng/mL. 25(OH)D concentrations between 20 and 30 ng/mL indicates 25(OH)D insufficiency, concentrations between 10 and 20 ng/mL indicates 25(OH)D deficiency, and concentrations <10 ng/mL indicates severe 25(OH)D deficiency.[12]

2.3 | Detection of VDR mRNA levels in tissues by reverse-transcription quantitative PCR

Twenty-three cases of normal intestinal mucosa, 41 adenomas, and 45 adenocarcinomas and para-cancerous tissues were used to detect VDR mRNA levels. The collected colorectal tissues were stored in 2 mL centrifuge tubes containing 1 mL RNAlater® Stabilization Solution (Thermo Fisher Scientific, Waltham, MA, USA) at −80°C. RNA was then extracted using the TRIzol method and reverse-transcribed into cDNA using a reagent kit purchased from Takara (Cat#: RR047A; Shiga-ken, Japan). The primer sequences for glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) and *VDR* genes are listed in Table 1. Primer sequences were obtained from the NCBI database (http://www.ncbi.nlm.nih.gov/), and the primers were synthesized by Shanghai Invitrogen Biological Engineering Co., Ltd. (Shanghai, China). *GAPDH* was used as the reference gene for the quantification of the *VDR* gene in tissues. A Takara reagent kit was used for reverse-transcription quantitative PCR (RT-qPCR). The PCR mixture included 10 μL SYBR Premix Ex Taq II, 0.8 μL of each primer (10 μM), 0.4 μL of ROX Reference Dye II, 2 μL of the cDNA solution, and 6 μL of RNA-free H_2O. After the RT-qPCR reaction system was established, amplification was performed by qPCR in an Applied Biosystems Step One Plus Real-Time PCR System (Chicago, Illinois, USA). Each sample was tested in triplicate. The thermocycling program was set as follows: (1) 30 s at 95°C for initial denaturation; (2) 40 cycles of 5 s at 95°C for denaturation, 15 s at 55°C for annealing, and 19 s at 72°C for extension; and (3) 15 s at 95°C, 1 min at 60°C, and 15 s at 95°C for final dissociation. The Ct values were recorded, and the relative mRNA expression levels were analyzed using the $2^{-\Delta\Delta Ct}$ method.[13]

2.4 | Statistical analysis

The normality of the data was tested when the sample size was ≤40. SPSS version 19.0 was used for the statistical analyses of data using universal descriptions. All data are expressed as the mean ± standard deviation (mean ± SD). For sample size >40, data were analyzed using the *t* test between the two groups and one-way analysis of variance (ANOVA) among more than two groups. For sample size ≤40, the data were analyzed using the Wilcoxon rank-sum test. Correlation analysis was performed using Spearman's rank correlation analysis. Statistical significance was set at $p < 0.05$.

TABLE 1 Primer sequences for the *GAPDH* and *VDR* genes

Primer name	Sequence
GAPDH forward primer	GGAAGGTGAAGGTCGGAGTC
GAPDH reverse primer	AATGAAGGGGTCATTGATGG
VDR forward primer	CTGACCCTGGAGACTTTGAC
VDR reverse primer	TTCCTCTGCACTTCCTCATC

Abbreviations: GAPDH, glyceraldehyde-3-phosphate dehydrogenase; VDR, vitamin D receptor.

3 | RESULTS

3.1 | Distribution of plasma 25(OH)D in the three groups

Among the 163 participants, 24, 75, 12, and 52 had 25(OH)D insufficiency (14.6%), 25(OH)D deficiency (46%), severe 25(OH)D deficiency (7.4%), and normal 25(OH)D levels (31.9%), respectively. In the normal control group, 25(OH)D insufficiency, 25(OH)D deficiency, severe 25(OH)D deficiency, and normal 25(OH)D levels accounted for 13%, 30.5%, 3.4%, and 53.1%, respectively. In the adenoma group, 25(OH)D insufficiency, 25(OH)D deficiency, severe 25(OH)D deficiency, and normal 25(OH)D levels accounted for 10.2%, 57.1%, 14.3%, and 18.4%, respectively. In the adenocarcinoma group, 25(OH)D insufficiency, 25(OH)D deficiency, severe 25(OH)D deficiency, and normal 25(OH)D levels accounted for 18.2%, 54.5%, 5.5%, and 21.8%, respectively (Figure 1). A correlation analysis between the 25(OH)D levels (concentration <20 ng/mL) and the presence of neoplasms in the adenoma group showed that the odds ratio (OR) was 4.875 and the 95% confidence interval (CI) was 2.144–11.084 ($p < 0.01$). Between the 25(OH)D levels (concentration <20 ng/ml) and the presence of neoplasms in the adenocarcinoma group, the OR was 2.925 and the 95% CI was 1.364–6.271 ($p < 0.01$). These results suggest that 25(OH)D deficiency is a risk factor for the development of colorectal adenoma and colorectal adenocarcinoma.

3.2 | Comparison of plasma 25(OH)D concentrations among the three groups

The plasma 25(OH)D concentration in the normal control group (41.35 ng/mL ± 4.570 ng/mL) was significantly higher than that in the colorectal adenoma group (22.28 ng/mL ± 2.445 ng/mL, $p < 0.01$) and the colorectal adenocarcinoma group (26.01 ng/mL ± 2.927 ng/mL, $p < 0.01$); however, no significant difference was observed between the adenoma and adenocarcinoma groups ($p = 0.47$ and $p > 0.05$, respectively; Figure 2). Furthermore, the plasma 25(OH)D concentrations in the colorectal adenoma and colorectal adenocarcinoma groups did not correlate with patients' age, sex, smoking history, alcohol consumption history, location, tumor size, tumor differentiation level, lymph node metastasis, or neoplasm pathologic type (Table 2).

3.3 | Level of VDR expression in tissues

In the 45 paired colorectal adenocarcinoma and para-cancerous tissues, we observed that the level of VDR mRNA expression in the adenocarcinoma group was 0.305 ± 0.06-fold greater than that in the para-cancerous group ($p < 0.01$; Figure 3). When normal tissues were used as the control, the level of VDR mRNA expression in normal tissues (1.00 ± 0.22) was significantly higher than that in

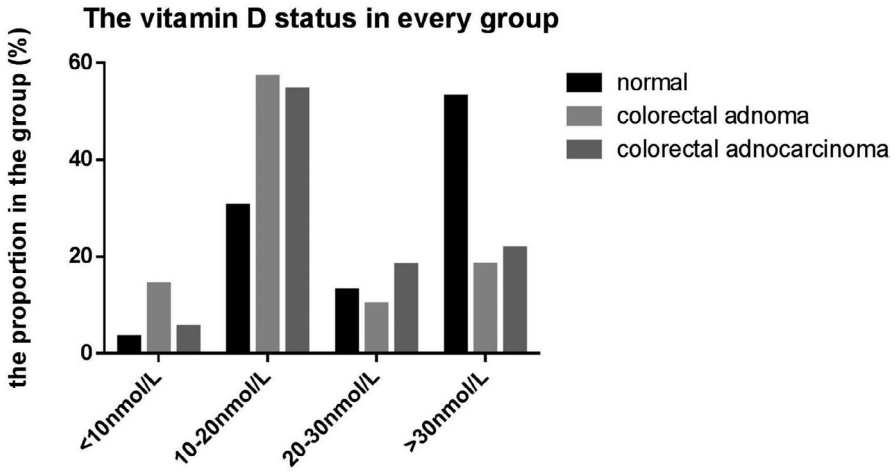

FIGURE 1 Distribution of plasma 25(OH)D in the healthy individuals (n = 59), adenoma patients (n = 55), and adenocarcinoma patients (n = 49)

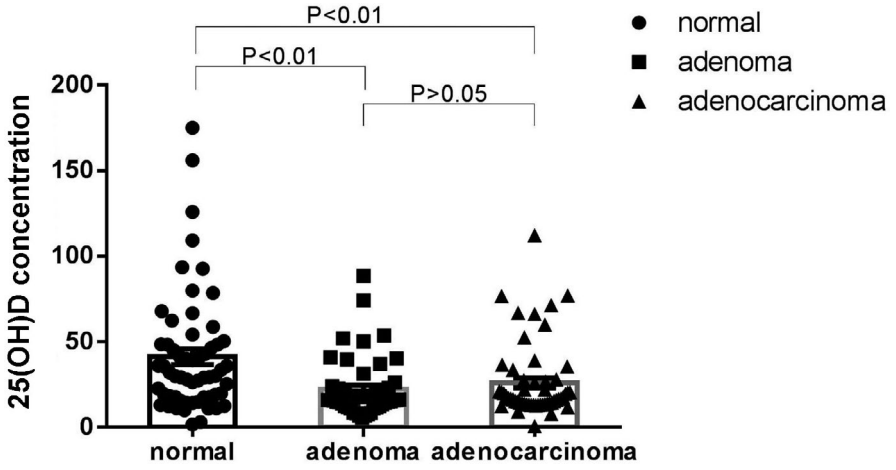

FIGURE 2 Comparison of plasma 25(OH)D concentrations among the healthy individuals (n = 59), adenoma patients (n = 55), and adenocarcinoma patients (n = 49). The statistical analysis was performed using the Student's *t* test, and statistical significance was set at $p < 0.05$

adenoma (0.52 ± 0.08, $p < 0.01$) and adenocarcinoma (0.37 ± 0.07, $p < 0.05$) tissues; however, the differences between the adenoma and adenocarcinoma groups were not statistically significant ($p > 0.05$; Figure 4). The results revealed no correlation between VDR mRNA expression and patients' age, sex, smoking history, alcohol consumption history, tumor size, tumor differentiation level, lymph node metastasis, or neoplasm pathologic type in the colorectal adenocarcinoma and adenoma groups (Table 3).

4 | DISCUSSION

In the current study, the expression of VDR in colorectal adenocarcinoma tissues was significantly lower than that in para-cancerous tissues, and the level of VDR expression in normal colorectal tissues was significantly higher than that in colorectal adenomas and colorectal adenocarcinomas. The concentration of 25(OH)D in healthy individuals was significantly higher than that in patients with colorectal adenomas and colorectal adenocarcinomas; however, the 25(OH)D concentration and VDR expression were not significantly different between colorectal adenomas and colorectal adenocarcinomas.

The development and progression of colorectal neoplasms involve a process that is associated with multiple steps and factors. The incidence of colorectal neoplasms is rising, and advanced adenomas tend to be found predominantly in the distal colorectum in patients aged 45–49 years.[14] In recent years, the function of 25(OH)D in the development and prevention of colorectal neoplasms has received considerable attention. The nested control study conducted by Jenab et al.[15] supports the notion that 25(OH)D levels in circulating blood are negatively correlated with the risk of developing colorectal cancer. A meta-analysis also concluded that increased 25(OH)D uptake helps in reducing the development of colorectal cancer.[16] The results of our study confirmed that the 25(OH)D levels in patients with colorectal adenoma and colorectal adenocarcinoma were significantly lower than those in healthy individuals, and the 25(OH)D concentrations between the two were not significantly different. Furthermore, 25(OH)D deficiency was shown to be a risk factor for the development of colorectal adenomas (OR, 4.875) and colorectal adenocarcinoma (OR, 2.925). Colorectal adenomas are precancerous lesions of colorectal cancer.[4] Therefore, colorectal cancer patients might already be 25(OH)D deficient at the time when colorectal adenomas are present, and 25(OH)D deficiency would not worsen as the disease progresses.

25(OH)D has been reported for years to be associated with the regulation of calcium phosphate homeostasis. It is also involved in the regulation of immune response and brain development, such as

TABLE 2 Correlation between plasma 25(OH)D concentration and the clinicopathologic characteristics of patients in the colorectal adenoma and colorectal adenocarcinoma groups

	Colorectal adenoma			Colorectal adenocarcinoma		
Classification	**N**	**25(OH)D (ng/mL)**	**P**	**N**	**25(OH)D (ng/mL)**	**P**
Age (years)						
<60	22	20.23 ± 2.84	0.101	25	24.41 ± 3.88	0.372
≥60	33	29.87 ± 4.41		24	20.06 ± 2.95	
Sex						
Male	33	24.14 ± 3.21	0.203	34	23.09 ± 3.19	0.494
Female	22	28.82 ± 5.56		15	20.45 ± 3.48	
Alcohol consumption						
Yes	11	20.84 ± 3.14	0.318	13	24.94 ± 5.27	0.569
No	44	27.31 ± 3.56		36	21.31 ± 2.76	
Smoking						
Yes	15	25.48 ± 3.77	0.865	15	23.6 ± 2.96	0.527
No	40	26.21 ± 3.91		34	19.28 ± 4.37	
CEA						
Negative	29	25.97 ± 3.81	0.867			
Positive	26	26.06 ± 4.58				
CA-199						
Negative	39	27.41 ± 3.22	0.392			
Positive	16	22.61 ± 6.39				
Adenocarcinoma differentiation						
High	8	24.42 ± 3.15	0.409			
Medium	38	28.10 ± 4.01				
Low	9	18.71 ± 1.14				
Lymph node metastasis						
N0	36	26.99 ± 3.86	0.653 69			
N1–3	19	24.16 ± 4.27				
Invasion level						
T1	3	16.48 ± 3.50	0.464			
T2	8	28.15 ± 6.12				
T3	26	27.61 ± 4.85				
T4	18	24.3 ± 3.56				
TNM stage						
I, II	33	24.02 ± 3.57	0.535			
III, IV	22	26.60 ± 4.31				
Location						
Colon	28	25.88 ± 3.93	0.872	34	22.83 ± 2.91	0.803
Rectum	27	26.15 ± 4.42		15	21.01 ± 4.66	
Adenocarcinoma size						
≥5 cm	20	27.2 ± 4.28	0.375			
<5 cm	35	23.92 ± 3.93				
Neoplastic grade						
Low grade				33	22.05 ± 3.09	0.893
High grade				16	22.74 ± 4.07	

(Continues)

TABLE 2 (Continued)

	Colorectal adenoma			Colorectal adenocarcinoma		
Classification	**N**	**25(OH)D (ng/mL)**	**P**	**N**	**25(OH)D (ng/mL)**	**P**
Adenoma size						
<1 cm				27	20.84 ± 2.96	0.410
≥1 cm				22	24.04 ± 4.10	
Solitary/multiple						
Solitary				17	18.85 ± 2.14	0.218
Multiple				32	24.10 ± 2.55	
Pathologic classification						
Tubular				39	23.36 ± 2.68	0.691
Tubulovillous				7	20.05 ± 5.16	
Villous				3	13.32 ± 5.89	

Data are expressed as numbers or means ±standard deviations (SDs). 25(OH)D, vitamin D; CEA, carcinoembryonic antigen; CA-199, carbohydrate antigen 199; TNM stage, tumor, lymph node, and metastasis stage. Correlation analysis was performed using Spearman's rank correlation analysis. Statistical significance was set at $p < 0.05$.

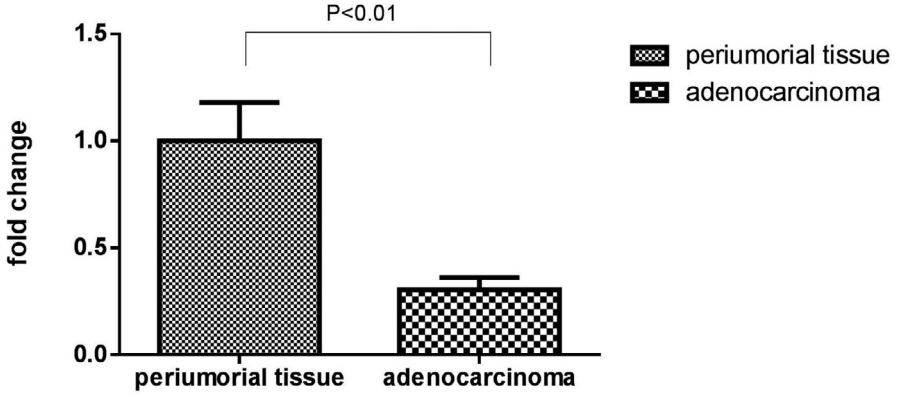

FIGURE 3 Comparison of the expression of VDR mRNA between the para-cancerous (n = 45) and adenocarcinoma tissues (n = 45). The VDR mRNA expression level in para-cancerous tissues was set as 1. The fold change was defined by calculating the ratio of VDR mRNA level in adenocarcinoma over that in para-cancerous tissues. The statistical analysis was performed using a Student's *t* test, and statistical significance was set at $p < 0.05$

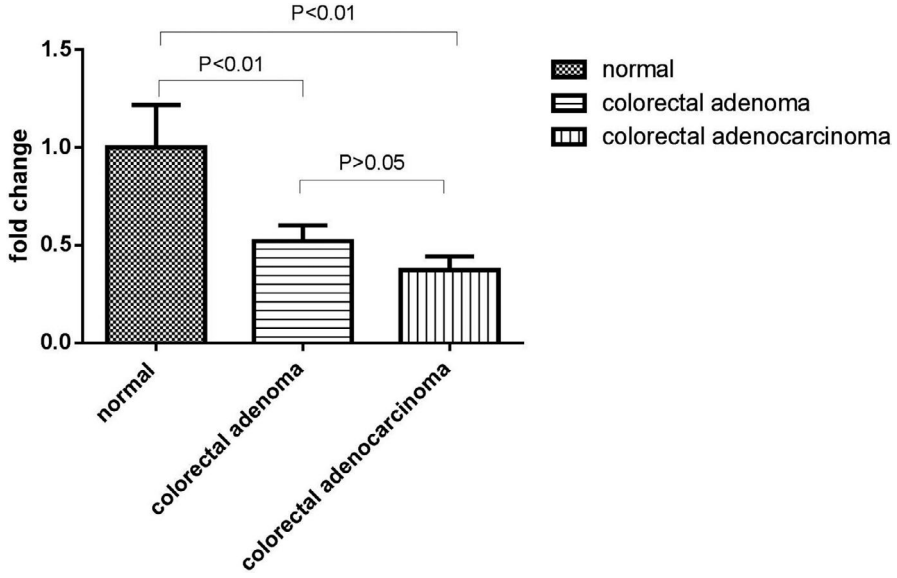

FIGURE 4 Comparison of the fold change in the VDR mRNA expression among normal (n = 23), adenoma (n = 41), and adenocarcinoma tissues (n = 45). The VDR mRNA expression level of the normal colorectal tissues in healthy individuals was set as 1. The fold change was defined by calculating the ratio of VDR mRNA level in the adenoma or adenocarcinoma over that in normal colorectal tissues. The statistical analysis was performed using a Student's *t* test, and statistical significance was set at $p < 0.05$

the immunomodulation of Th1 and Th2 cell proliferation and inflammatory cytokine secretion.[17-19] 25(OH)D is also highly associated with cancer, although 25(OH)D supplementation alone does not reduce the incidence of cancer and cancer mortality, even after long-term follow-up.[20] The effect of 25(OH)D on colorectal adenoma prevention cannot be estimated because of the different results shown

TABLE 3 Correlation between the level of VDR expression and the clinicopathologic characteristics of patients in the colorectal adenoma and adenocarcinoma groups

	Colorectal adenoma			Colorectal adenocarcinoma		
Classification	**N**	**Fold change**	**P**	**N**	**Fold change**	**P**
Age (years)						
<60	15	0.31 ± 0.14	0.294	17	0.33 ± 0.07	0.117
≥60	30	0.41 ± 0.08		24	0.65 ± 0.12	
Sex						
Male	22	0.41 ± 0.08	0.386	21	0.41 ± 0.10	0.183
Female	23	0.33 ± 0.14		20	0.64 ± 0.13	
Alcohol consumption						
Yes	9	0.27 ± 0.08	0.193	11	0.47 ± 0.15	0.428
No	36	0.40 ± 0.08		30	0.54 ± 0.10	
Smoking						
Yes	11	0.43 ± 0.18	0.205	15	0.58 ± 0.14	0.336
No	34	0.35 ± 0.07		26	0.49 ± 0.10	
25(OH)D level[a]						
<20 ng/mL	13	0.32 ± 0.24	0.249	13	0.54 ± 0.15	0.103
≥20 ng/mL	8	0.50 ± 0.12		6	0.92 ± 0.24	
CEA						
Negative	21	0.27 ± 0.05	0.193			
Positive	24	0.46 ± 0.12				
CA-199						
Negative	28	0.38 ± 0.09	0.810			
Positive	17	0.36 ± 0.11				
Adenocarcinoma differentiation						
High	3	0.16 ± 0.10	0.208			
Medium	37	0.34 ± 0.07				
Low	5	0.75 ± 0.30				
Lymph node metastasis						
N0	31	0.28 ± 0.08	0.127			
N1–3	14	0.41 ± 0.09				
Invasion level						
T1	3	0.25 ± 0.14	0.749			
T2	5	0.29 ± 0.10				
T3	25	0.45 ± 0.12				
T4	12	0.28 ± 0.08				
TNM stage						
I, II	29	0.44 ± 0.10	0.175			
III, IV	14	0.25 ± 0.07				
Location						
Colon	26	0.48 ± 0.11	0.122	37	0.56 ± 0.09	0.103
Rectum	19	0.22 ± 0.05		4	0.2 ± 0.16	
Adenocarcinoma size						
≥5 cm	13	0.43 ± 0.20	0.730			
<5 cm	32	0.36 ± 0.06				

(Continues)

TABLE 3 (Continued)

	Colorectal adenoma			Colorectal adenocarcinoma		
Classification	N	Fold change	P	N	Fold change	P
Neoplastic grade						
Low grade				34	0.49 ± 0.09	0.147
High grade				7	0.72 ± 0.23	
Adenoma size						
<1 cm				18	0.56 ± 0.13	0.693
≥1 cm				23	0.50 ± 0.10	
Solitary/multiple						
Solitary				8	0.63 ± 0.22	0.621
Multiple				33	0.50 ± 0.09	
Pathologic classification						
Tubular				33	0.52 ± 0.09	0.802
Tubulovillous				6	0.49 ± 0.23	
Villous				2	0.67 ± 0.66	

Data are expressed as numbers or means ±standard deviations (SDs). 25(OH)D, vitamin D; CEA, carcinoembryonic antigen; CA-199, carbohydrate antigen 199. TNM stage, tumor, lymph node, and metastasis stage. The fold change was determined by calculating the ratio of VDR mRNA levels in the adenoma or adenocarcinoma to that in normal colorectal tissues. Correlation analysis was performed using Spearman's rank correlation analysis. Statistical significance was set at $p < 0.05$.

[a]Both the 25(OH)D concentration and the level of VDR mRNA expression in 21 patients in the colorectal adenocarcinoma group and in 19 patients in the colorectal adenoma group were detected.

in clinical trials. An investigation demonstrated that vitamin D3 (1000 IU daily) did not cause changes in intestinal barrier function-related biomarker expression in a subset of 105 participants from a large colorectal adenoma recurrence chemoprevention clinical trial.[9] Other clinical trials have shown that no association exists between daily vitamin D3 supplementation and the risk of colorectal adenomas over a period of 3–5 years.[10,21] Another study suggested that vitamin D3 supplementation prevents colorectal adenoma, which may vary according to the VDR genotype.[22] The mechanism underlying the effect of 25(OH)D on human colorectal adenomas warrants further study.

The VDR is necessary for 25(OH)D to exert its biological effects. 25(OH)D regulates downstream target genes by binding to VDR.[23] Previous studies comparing VDR expression between colorectal adenocarcinoma and normal tissues have yielded conflicting results. Barry et al.[22] reported that the effect of vitamin D3 supplementation on colorectal adenoma prevention was a function of the VDR genotype. Castellano-Castillo et al.[24] showed that VDR mRNA is expressed at high levels in normal colon tissues and low levels in colorectal cancer tissues; however, Cross et al.[25] and Kure et al.[26] reported contradicting results. The results of the present study showed that the VDR mRNA expression level in adenocarcinoma tissues was lower than that in para-cancerous tissues. In addition, the VDR mRNA expression level in adenoma tissues was lower than that in normal tissues. The tissue levels of VDR mRNA expression in para-cancerous and normal tissues were significantly higher than those in adenoma and adenocarcinoma tissues. The amount of VDR that can bind to 25(OH)D decreases when VDR expression in colorectal adenomas and adenocarcinomas decreases. Consequently, the biological effects of 25(OH)D are affected, and the anti-neoplastic and apoptosis-promoting functions of 25(OH)D significantly decrease, suggesting that VDR deficiency also participates in the development and progression of colorectal neoplasms. This finding is consistent with the opinion of Merchan et al.[22] Therefore, low VDR expression in adenocarcinoma tissues and reduced plasma 25(OH)D concentrations in patients with colorectal adenocarcinoma promotes the development and progression of colorectal neoplasms. This pathway may persist through the progression of colorectal adenoma to adenocarcinoma, or even colorectal cancer. Šutalo et al.[27] showed that 25(OH)D prevents tumor progression in normal colorectal mucosa and hyperplastic polyps, while the antitumor and chemopreventive effects are progressively weakened and ultimately absent in colorectal carcinoma. Nonetheless, studies are needed to investigate the role of 25(OH)D in different stages of colorectal neoplasms.

One limitation of our study was that the plasma 25(OH)D concentration may be affected by the body status; however, screen-detected adenomas and adenocarcinomas were selected using a standardized procedure, and the results were reliable. Another limitation was the small study population; multicenter and large-scale population trials are needed to confirm our study findings. Moreover, because colorectal adenoma and adenocarcinoma tissues were obtained from patients and the VDR expression and 25(OH)D concentration were not significantly different between colorectal adenoma and colorectal adenocarcinoma, the mechanism underlying the progression of colorectal adenoma to adenocarcinoma in the same patient has not been investigated. Further studies on this topic will facilitate a better understanding of the role of 25(OH)D in colorectal cancer.

5 | CONCLUSION

The present study elucidated the correlation between the levels of plasma 25(OH)D and the development and progression of colorectal neoplasms. The findings showed that low plasma 25(OH)D level is a risk factor for both colorectal adenomas and colorectal adenocarcinomas. In addition, the tissue levels of VDR mRNA expression in patients with colorectal adenomas and adenocarcinomas were significantly lower than in the normal population. The reduction in VDR mRNA expression might prevent 25(OH)D from exerting the proliferation-suppressing, apoptosis-promoting, and differentiation-promoting functions of colorectal neoplasms. Furthermore, 25(OH)D might affect the development and progression of colorectal adenoma to adenocarcinoma in parallel with VDR mRNA expression.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Ying Fang, Haojun Song involved in conceptualization of the study. All authors involved in experiments and data acquisition. Jian Huang involved in data analysis and interpretation, and writing of first draft. Jianbo Zhou, Xiaoyun Ding involved in interpretation and critical All authors have approved the final draft of the article and have agreed to the submission.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Jianbo Zhou https://orcid.org/0000-0003-2824-9169
Xiaoyun Ding https://orcid.org/0000-0002-3731-3508

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