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RESEARCH ARTICLE

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The association of serum vitamin D–binding protein and 25-hydroxyvitamin D in pre-operative and post-operative colorectal cancer

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Abstract

Background: The association between vitamin D–binding protein (VDBP) and 25-hydroxyvitamin D (25 (OH)D) with colorectal cancer (CRC) is still ambiguous. This study was to further investigate the relationship between serum VDBP, 25 (OH)D levels and the clinical and pathological features of patients with CRC.

Methods: Enzyme-linked immunosorbent assay (ELISA) and chemiluminescence immunoassay were used to analyze the VDBP and 25(OH)D concentrations in serum. Pearson's correlation analysis was applied to evaluate the association between serum VDBP and 25(OH)D levels in CRC. Conditional logistic regression was performed to analyze the prediction value of serum VDBP or 25(OH)D as a risk factor for CRC.

Results: The serological levels of 25(OH)D in patients were significantly lower than in healthy individuals, while VDBP levels were significantly higher than in healthy controls. The serum VDBP in pre-operative was significantly lower than in post-operative samples, while the serum 25(OH)D from pre-operative patients was significantly higher than post-operative patients. Patients with tumors with higher stage and increased lymph node involvement had lower serum post-operative VDBP levels. In addition, our results showed that the pre-operative VDBP level is a risk factor of CRC.

Conclusions: The levels of serum 25(OH)D and VDBP were both associated with CRC. Thus, serum 25(OH)D and VDBP levels might be of value in evaluating the pathogenesis and risk of CRC in the future. Moreover, serum VDBP or 25(OH)D levels were associated with patient's clinical and pathological features providing data for risk and prognostic prediction.

Liang and Jiang are contributed equally to this work.

KEYWORDS
25-hydroxyvitamin D, clinical-pathological features, colorectal cancer, risk, vitamin D–binding protein

1 | INTRODUCTION

Colorectal cancer (CRC) is a common type of cancer worldwide.[1] In China, the estimated new cases and deaths of CRC were 376 300 and 191 000, respectively, in 2015.[2] Benefited by the development of screening tools for early detection, more and more patients could be treated at an early stage; however, the incidence and mortality of CRC among adults aged under 50 years is increasing in the United States.[3] Accumulating evidence indicates that high levels of circulating vitamin D is an anti-cancer factor, which may reduce the risk of CRC.[4-6]

Vitamin D (VD) is photochemically synthesized in the skin when exposed to ultraviolet B (UVB) radiation or ingested from food and/or supplements. Once getting into blood circulation, VD is hydroxylated and forms 25-hydroxyvitamin D [25(OH)D] in the liver, the well-known biomarker of VD status. Then, 25(OH)D is hydroxylated and forms 1,25-dihydroxyvitamin D [1,25(OH)2D] in the kidney and other organs, the bioactive form of VD.[7] Recent studies found that free 25(OH)D may be an independent CRC prognostic biomarker.[8]

Vitamin D—binding protein (VDBP), primarily vitamin D carrier protein, is mainly synthesized and secreted by the liver, which belongs to the albumin gene family. Moreover, VDBP is the precursor to the Gc protein–derived macrophage-activating factor (Gc-MAF) that can activate macrophages against cancer cell.[9,10] Recently, several studies have reported that serum VDBP was associated with prostate, pancreatic, and bladder cancers as well as acute leukemia.[11-14] Several papers have pointed that VDBP was not associated with CRC.[15,16] However, it has been reported that VDBP played a role in the modulation of serum 25(OH)D levels although it was not directly corrected with the risk of CRC.[17] So far, the expression levels of 25(OH)D and VDBP in CRC, and their association with CRC pathogenesis and risk are still ambiguous. In this study, we analyzed the serum 25(OH)D and VDBP levels in pre- and post-operative CRC patients and correlated them with clinical features and the risk of CRC.

2 | MATERIALS AND METHODS

2.1 | Patients

Seventy-eight patients diagnosed with colorectal cancer were enrolled consecutively in this study in a period of time from May 2017 to July 2018. The diagnosis was made by pathologic examination. During hospitalization, all patients had no outdoor activity and were provided hospital diet without calcium or vitamin D supplements by the department of food and nutrition. Ninety healthy individuals, ranging from 45 to 87 years old, who had regular diet without calcium or vitamin D supplements before blood drawing, were selected as controls with matched ages and genders to the patient group. The study was approved by the Institutional Review Board of the People's Hospital of Guangxi Zhuang Autonomous Region for the use of human materials.

2.2 | Blood sample collection

Fasting blood samples were obtained either the day before surgical operation or other treatments (baseline) and on day 5 after surgery, respectively, using the serum separation tube (BD healthcare). All patients with CRC had paired pre-operative and post-operative blood samples. The blood samples were transported to the Department of Laboratory Medicine within 30 minutes of collection. The samples were then centrifuged at 1500 *g* at 4°C for 10 minutes; the serum was collected into a 2 mL of centrifuge tube and stored at −80°C until analysis.

2.3 | Enzyme-linked immunosorbent assay (ELISA)

Serum vitamin D–binding protein (VDBP) was measured by using the Quantikine ELISA Human Vitamin D BP Immunoassay (Catalog number DVDBP0) kit from R & D Systems, Inc following the manufacturer's instructions. In brief, 100 μL of Assay Diluent RD1-19 was added to each well in the microplate; then, 50 μL of standard, control, or sample were added per well and covered with the adhesive strip to incubate for 1 hour at room temperature on a horizontal orbital microplate shaker; all the liquid was aspirated and washed by adding 400 μL Wash Buffer for 4 times; after the last wash, inverted and blotted against the plate through clean paper towels to drain the remaining wash buffer; added 200 μL of Human Vitamin D BP Conjugate to each well and covered with a new adhesive strip to incubate for 2 hours at room temperature on the shaker; repeated the aspiration and wash; then added 200 μL of Substrate Solution to each well to incubate for 30 minutes at room temperature on the benchtop by protecting from light; following this step, 50 μL of stop solution was added to stop the color development; and finally, measured the plate immediately on a microplate reader at OD 450 nm.

2.4 | Chemiluminescence immunoassay

In clinical laboratory, chemiluminescence immunoassay is widely used to measure serum vitamin D (VD) because of its automatic capability with clinical satisfaction. In this study, serum VD was quantitatively analyzed on a Roche cobas E601 electrochemiluminescence

immunoassay platform using a Roche cobas Elecsys Vitamin D total (25 Hydroxyvitamin D, REF 05 894 913 190, Roche Diagnostics GmbH) assay kit. All the tests abovementioned were performed following our laboratory standard operating procedures described previously.[14]

2.5 | Statistical analysis

IBM SPSS Statistical 20.0 (SPSS Inc Chicago) was performed for statistical analysis. Differences in basic characteristics of patients were evaluated by using independent samples *t* test. Paired samples *t* test was performed to compare the difference in each parameter of paired pre- and post-operative serum VDBP or 25(OH)D levels. Moreover, Pearson's correlation analysis was applied to evaluate the association between serum VDBP and 25(OH)D levels in CRC. The pre- and post-operative 25(OH)D and pre- and post-operative VDBP (≥median and <median) levels were stratified by using conditional logistic regression (multivariate analysis) to evaluate whether serum VDBP or 25(OH)D is a risk factor for CRC, which estimated odds ratios (OR) and 95% confidence intervals (CI). A *P*-value of <.05 was considered as statistically significant.

Serum 25(OH)D and VDBP levels were correlated with clinical and pathological features including age, gender, lesion site, tumor stage, tumor size, lymph node involvement, vascular and nerve invasion, and cell differentiation.

2.6 | Ethics statement

The study was approved by the Institutional Review Board of the People's Hospital of Guangxi Zhuang Autonomous Region for the use of human materials.

3 | RESULTS

3.1 | Correlation of serum VDBP and 25(OH)D levels with clinical-pathological features in CRC patients

The correlation of serum VDBP and 25(OH)D levels with clinical-pathological features from 78 patients with CRC were summarized as shown in Table 1. Of 78 patients with CRC, there were 33 females and 45 males with ages ranging from 32 to 86 years (a median age of 64 years). In this study, colon was the main lesion site of the tumor (49/78), and 63 cases were found to be moderately differentiated according to histopathologic grading.

According to the median or feature of the parameters we collected, we divided each parameter into two or three groups, which was analyzed through univariate analysis (displayed in Table 1). In independent samples test, our data showed that the groups, tumor stage III-IV and lymph node involvement, had distinctly lower serum post-operative VDBP levels than the groups, stage I-II and no lymph node involvement, with $P = .006$ and $P = .004$, respectively. As for the levels of pre-operative serum 25(OH)D, males and rectal tumor groups were significantly higher ($P = .003$, $P = .007$, respectively). While with post-operative 25(OH)D levels, males, rectal tumors, and tumor size <5.0 cm had significantly higher levels ($P = .007$, $P = .032$, and $P = .040$, respectively). In paired samples test, the pre-operative VDBP concentration of patients with age <64, males, rectal tumors, tumors stage I-II, moderate cell differentiation, tumor size ≥5.0 cm, no lymph node involvement, no vascular invasion, and no nerve invasion were significantly lower than the post-operative VDBP levels, all with $P < .05$. And as shown in Table 1, except for the high cell differentiation and low cell differentiation groups, the levels of pre-operative 25(OH)D were distinctly higher than post-operative 25(OH)D ($P < .05$).

3.2 | Serum VDBP and 25(OH)D levels in pre- and post-operative CRC patients

Table 2 shows that the serum VDBP in pre- and post-operative CRC patients were significantly higher than the controls ($P < .001$ for both). While serum 25(OH)D in both pre- and post-operative CRC patients were significantly lower than the controls ($P = .001$ and $P < .001$, respectively). In addition, the VDBP levels in pre-operative CRC patients was significantly lower than the post-operative levels ($P = .005$). However, the level of pre-operative 25(OH)D was significantly higher than post-operative 25(OH)D ($P < .001$).

3.3 | Serum VDBP and 25(OH)D levels and the risk of CRC

In order to understand whether serum VDBP and 25(OH)D is a risk factor for CRC, multivariate analysis and conditional logistic regression were performed and the results are displayed in Table 3. The results showed that the pre-operative VDBP level is a risk factor for CRC (OR = 13.264, CI = 1.72-102.28, $P = .013$), while the post-operative 25(OH)D level is a protective factor (OR = 0.099, CI = 0.01-0.90, $P = .040$).

3.4 | Correlation between serum VDBP and 25(OH)D levels

Statistical analysis results showed that there was a weak correlation between both pre-operative VDBP and post-operative VDBP with 25(OH)D levels (Table 4, Pearson −.127 and .156, $P = .267$ and .172, respectively).

4 | DISCUSSION

The association between serum VD and cancer occurrence is still unclear to date. The function of VDBP is to bind and carry VD to

TABLE 1 Correlation of serum VDBP and 25(OH)D with clinical-pathological features

Parameters	Total (N = 78)	VDBP ($\bar{x} \pm s$ μg/mL) Pre-OP	VDBP ($\bar{x} \pm s$ μg/mL) Post-OP	P^2	25(OH)D ($\bar{x} \pm s$ nmol/L) Pre-OP	25(OH)D ($\bar{x} \pm s$ nmol/L) Post-OP	P^2
Age (y)							
≥64	40	330.98 ± 17.99	376.10 ± 24.90	.074	55.22 ± 5.02	41.08 ± 2.59	**.002***
<64	38	329.31 ± 19.35	391.47 ± 24.07	**.035***	48.38 ± 4.30	43.12 ± 3.38	**.009***
P^1		.950	.659		.306	.630	
Gender							
Female	33	343.50 ± 18.84	390.43 ± 25.78	.161	40.61 ± 3.33	35.55 ± 2.74	**.002***
Male	45	320.39 ± 18.07	378.57 ± 23.38	**.011***	60.16 ± 4.88	46.85 ± 2.86	**.001***
P^1		.387	.736		**.003***	**.007***	
Lesion site							
Colon	49	342.64 ± 17.50	384.59 ± 24.44	.102	45.11 ± 3.55	38.61 ± 2.61	**<.001***
Rectum	29	309.09 ± 18.90	381.89 ± 21.68	**.010***	63.35 ± 6.31	47.92 ± 3.33	**.013***
P^1		.218	.934		**.007***	**.032***	
TNM stage							
I-II	40	330.27 ± 17.42	429.33 ± 25.15	**.001***	50.22 ± 4.91	40.05 ± 2.85	**.017***
III-IV	38	330.06 ± 19.92	335.44 ± 21.13	.796	53.65 ± 4.49	44.20 ± 3.11	**<.001***
P^1		.994	**.006***		.608	.328	
Cell differentiation							
High	6	351.69 ± 36.15	361.42 ± 57.11	.912	69.12 ± 22.6	34.49 ± 6.88	.214
Moderate	63	327.64 ± 14.77	386.69 ± 18.60	**.006***	50.67 ± 3.16	43.17 ± 2.36	**<.001***
Low	9	333.54 ± 43.50	376.68 ± 60.09	.404	48.05 ± 11.7	39.41 ± 6.40	.199
P^1		.887	.920		.325	.501	
Tumor size							
≥5.0 cm	42	337.75 ± 17.71	403.62 ± 22.04	**.007***	49.42 ± 4.59	37.97 ± 2.24	**.007***
<5.0 cm	36	321.33 ± 19.64	360.22 ± 26.93	.207	54.78 ± 4.83	46.86 ± 3.60	**.001***
P^1		.536	.212		.424	**.040***	
Lymph node invasion							
Yes	38	328.02 ± 20.68	332.96 ± 21.00	.892	53.52 ± 4.50	43.93 ± 3.12	**<.001***
No	40	332.21 ± 16.60	431.68 ± 25.02	**.001***	50.35 ± 4.90	40.30 ± 2.85	**.019***
P^1		.874	**.004***		.636	.392	
Vascular invasion							
Yes	32	337.79 ± 22.48	352.72 ± 23.34	.577	50.52 ± 4.66	41.23 ± 3.27	**.001***
No	46	324.87 ± 15.95	405.06 ± 24.02	**.003***	52.84 ± 4.64	42.65 ± 2.77	**.008***
P^1		.631	.136		.734	.740	
Nerve invasion							
Yes	19	375.17 ± 32.28	389.61 ± 31.76	.679	58.24 ± 7.00	46.54 ± 5.11	**.006***
No	59	315.67 ± 13.50	381.65 ± 20.52	**.004***	49.85 ± 3.76	40.63 ± 2.24	**.003***
P^1		.051	.844		.281	.231	

Note: P^1 represents the comparison of intra-parameter. P^2 represents the comparison of VDBP and 25(OH)D in pre- and post-operative CRC.
Abbreviations: Post-OP, post-operative; Pre-OP, pre-operative.
*Means $P < .05$.

organs and tissues, and its role and relationship with VD are not fully understood either.

In this study, we found that both serologic levels of pre- and post-operative 25(OH)D in patients with CRC were significantly lower than in healthy individuals ($P = .001$ and $P < .001$, respectively, Table 2). Many studies found that there is an inverse association between serum 25(OH)D and the risk of CRC.[15,18,19] VD is associated with enhancing cellular differentiation and apoptosis, reducing cellular proliferation and inflammation in animal and cancer cells.[20-22] Furthermore, VD activates cytochrome P27B1 (CYP27B1) and

TABLE 2 Serum VDBP and 25(OH)D levels in pre- and post-operative CRC patients and controls

Number	Pre-OP VDBP ($\bar{x} \pm s$ μg/mL)	Post-OP VDBP ($\bar{x} \pm s$ μg/mL)	P^2	Pre-OP 25(OH)D ($\bar{x} \pm s$ nmol/L)	Post-OP 25(OH)D ($\bar{x} \pm s$ nmol/L)	P^2
Cases (n = 78)	330.17 ± 13.10	383.59 ± 17.25	**.005***	51.89 ± 3.32	42.07 ± 2.10	**<.001***
Controls (n = 90)	200.71 ± 6.48			66.58 ± 2.68		
P^1	<.001*	<.001*		.001*	<.001*	

Note: P^1 represents the difference between patients and controls. P^2 represents the difference between pre-operative VDBP or 25(OH)D and post-operative VDBP or 25(OH)D.

Abbreviations: Post-OP, post-operative; Pre-OP, pre-operative.

*Means $P < .05$.

TABLE 3 Evaluation of pre- and post-operative serum VDBP and 25(OH)D as a risk factor in CRC patients

Factor X	Regression coefficient B	OR	CI	Wald χ^2	*P*-value
Pre-OP VDBP	2.585	13.264	1.72-102.28	6.153	**.013***
Post-OP VDBP	10.531	37 455.601	0.00-1.48E + 38	0.071	.790
Pre-OP 25(OH)D	1.687	5.402	0.63-46.24	2.371	.124
Post-OP 25(OH)D	−2.313	0.099	0.01-0.90	4.205	**.040***

Abbreviations: CI, 95% confidence intervals; OR, odds ratios; Post-OP, post-operative; Pre-OP, pre-operative.

*Means $P < .05$.

TABLE 4 Comparison between serum VDBP and 25(OH)D in CRC by Pearson's correlation analysis

Paired	Pre-operative VDBP VS 25(OH)D	Post-operative VDBP VS 25(OH)D
Pearson correlation	−.127	.156
P-value	.267	.172

cytochrome P24A1 (CYP24A1), as well as vitamin D receptor (VDR) which are expressed in normal colorectal cells, suggesting that VD plays an important biological function in colorectal cells.[23-25] The expression of CYP27B1 in moderately and well-differentiated CRC samples is increased, which indicates a possible response to VD in these patients. While in poorly differentiated CRC, the expression of CYP27B1 is repressed, indicating that cancer cells may be resistant to calcitriol therapy.[26,27] CYP24A1 shows a strong negative feedback effect, so the inhibition of CYP24A1 may improve the anti-tumor effect of calcitriol.[26] VDR is abundantly present in colorectal epithelial cells which plays an important role in mediating the biological effects of calcitriol.[28] There is a hypothesis that alteration of VRD may change transcriptional control of 1,25(OH)2D3 and impact anti-tumor effect of VD.[29] Therefore, these results suggest that VD plays a role in inhibiting tumorigenesis of CRC.

Several studies have reported that serum VDBP was associated with prostate, pancreatic, bladder cancer, and acute leukemia.[11-14] As mentioned above, several studies found that there was no association between VDBP and CRC.[15,16] However, our study results showed that both serologic levels of pre- and post-operative VDBP in CRC patients were distinctly higher than the healthy controls ($P < .001$ for both, Table 2), suggesting that serum VDBP may be associated with the pathogenesis of CRC. We also found that pre-operative VDBP levels was a risk factor for CRC (OR = 13.264, CI = 1.72-102.28, $P = .013$, Table 3, respectively). VDBP plays an important role in macrophage activation, serving as an actin scavenger, anti-neoplastic, anti-angiogenic, pro-apoptotic, and immunomodulatory factors.[30-32] Following tissue injury and cell death, actin is released into circulation and can lead to vascular obstruction and organ dysfunction.[15] The ability of VDBP to rapidly sequester actin protects against these complications [33] which may account for its elevation in CRC. At this point, serum VDBP might be a potential biomarker to evaluate the risk and pathogenesis of CRC.

The serum concentration of pre-operative VDBP was much lower than the post-operative level ($P = .005$, Table 2), while the concentration of pre-operative 25(OH)D was much higher than the post-operative level ($P < .001$, Table 2). It seems that VDBP and 25(OH)D had an inverse association with the disease progression. Anic et al[16] and Ying et al[17] have pointed that VDBP may change the 25(OH)D concentration in CRC. However, there was no significant correlation between these two markers in the serum by Pearson's correlation analysis ($r = −.127$ and .156, $P = .267$ and .172, Table 4) in our study. Maybe the small sample volumes would reduce statistical power to define the relationship between VDBP and 25(OH)D. The surgical procedure may change the serum level of 25(OH)D and VDBP such as plasma loss and loss of proteins which may influence the results. There is one study suggested that the level of VDBP and 25(OH)D should be detected multiple times before and after treatment for CRC.[34] However, due to the limitations of patient management in our hospital, we were unable to measure the serum VDBP and 25(OH)D levels at multiple time points in this study. What is more, the patients' condition during pre- and post-surgery such as anxiety, stress, and fasting may affect the level of serum VDBP and 25(OH)D. However,

due to the limitation of access to medical records and difficulty in observation of patients' daily performance and manifestation, we were unable to exclude the stress factors mentioned above. Thus, it is necessary to consider these parameters and pay close attention on their effect on serum VD and VDBP in the future studies.

Results from univariate analysis showed that the serum concentration of pre- and post-operative 25(OH)D in male patients and rectal tumors were significantly higher (P = .003, P = .007, P = .007, and P = .032, respectively). Andersen et al found that the inverse association between serum 25(OH)D and CRC was more prominent in females than males.[6] A meta-analysis including 1248 cases of CRC suggested that 25(OH)D had stronger inverse associations with colon than with rectal tumors.[35] In other words, serum 25(OH)D shows higher levels in males than females, rectal than colon tumors, consistent with our study. In addition, higher stage (III-IV) tumors and patients with lymph node involvement had distinctly lower post-operative serum VDBP levels (P = .006 and P = .004, respectively). A report suggests that low VD levels were found in most cases of breast cancer with advanced tumor stage, large tumors, and positive lymph nodes.[36] To our knowledge, the relationship of clinical-pathological features and serum VDBP or 25(OH)D in CRC has been rarely reported and merits further investigation in the future.

In conclusion, our study found that there was a relationship between serum 25(OH)D and VDBP in CRC. Thus, serum 25(OH)D and VDBP levels might be of value in determining the pathogenesis and risk of CRC and requires further study.

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AUTHOR CONTRIBUTIONS

Yuanzi Liang carried out the serological studies, participated in the experiment design and statistical analysis, and drafted the manuscript. Liejun Jiang participated in the experiment design, serum sample collection, and the statistical analysis and helped to draft the manuscript. Xiaowei Chi and Feng Qiu carried out the patients' clinical and pathological information collection and participated in serum sample collection. Steven Hochwald carried out the English editing and participated in the manuscript revise. Yanfang Luo, Qiuwei Lu and Xiafang Yang performed the immunoassays. Huayi Huang and Junfa Xu conceived the study and participated in its design and coordination and manuscript revise. All authors read and approved the final manuscript.

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REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87-108.
2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *Ca A Cancer J Clin*. 2016;66(2):115.
3. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2017: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin*. 2017;67(2):100-121.
4. Song M, Nishihara R, Wang M, et al. Plasma 25-hydroxyvitamin D and colorectal cancer risk according to tumour immunity status. *Gut*. 2016;65(2):296-304.
5. Printz C. High vitamin D levels increase survival rates in patients with metastatic colorectal cancer. *Cancer*. 2015;121(13):2105.
6. Andersen SW, Shu XO, Cai Q, et al. Total and free circulating vitamin d and vitamin D-Binding protein in relation to colorectal cancer risk in a prospective study of african americans. *Cancer Epidemiol Biomarkers Prev*. 2017;26(8):1242-1247.
7. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266-281.
8. Yang L, Chen H, Zhao M, Peng P. Prognostic value of circulating vitamin D binding protein, total, free and bioavailable 25-hydroxy vitamin D in patients with colorectal cancer. *Oncotaget*. 2017;8(25):40214-40221.
9. Speeckaert MM, Speeckaert R, van Geel N, Delanghe JR. Vitamin D binding protein: A multifunctional protein of clinical importance. *Adv Clin Chem*. 2014;63:1-57.
10. Nagasawa H, Sasaki H, Uto Y, Kubo S, Hori H. Association of the macrophage activating factor (MAF) precursor activity with polymorphism in vitamin D-binding protein. *Anticancer Res*. 2004;24(5C):3361-3366.
11. Layne TM, Weinstein SJ, Graubard BI, Ma X, Mayne ST, Albanes D. Serum 25-hydroxyvitamin D, vitamin D binding protein, and prostate cancer risk in black men. *Cancer*. 2017;123(14):2698-2704.
12. Weinstein SJ, Stolzenberg-Solomon RZ, Kopp W, Rager H, Virtamo J, Albanes D. Impact of circulating vitamin D binding protein levels on the association between 25-hydroxyvitamin D and pancreatic cancer risk: A nested case-control study. *Cancer Res*. 2012;72(5):1190-1198.
13. Li F, Chen DN, He CW, et al. Identification of urinary Gc-globulin as a novel biomarker for bladder cancer by two-dimensional fluorescent differential gel electrophoresis (2D-DIGE). *J Proteomics*. 2012;77:225-236.
14. Jiang L, Zhang X, Chen Y, et al. Alteration of serum 25(OH) vitamin d, vitamin d binding protein, and c-reactive protein levels in acute leukemia patients. *Clin Lab*. 2018;64(9):1553-1559.
15. Song M, Konijeti GG, Yuan C, et al. Plasma 25-Hydroxyvitamin d, vitamin d binding protein, and risk of colorectal cancer in the nurses' health study. *Cancer Prev Res (Phila)*. 2016;9(8):664-672.
16. Anic GM, Weinstein SJ, Mondul AM, Mannisto S, Albanes D. Serum vitamin D, vitamin D binding protein, and risk of colorectal cancer. *PLoS ONE*. 2014;9(7):e102966.
17. Ying HQ, Sun HL, He BS, et al. Circulating vitamin D binding protein, total, free and bioavailable 25-hydroxyvitamin D and risk of colorectal cancer. *Sci Rep*. 2015;5:7956.
18. Chandler PD, Buring JE, Manson JE, et al. Circulating vitamin d levels and risk of colorectal cancer in women. *Cancer Prev Res (Phila)*. 2015;8(8):675-682.
19. Atoum MF, Tchoporyan MN. Association between circulating vitamin D, the Taq1 vitamin D receptor gene polymorphism and colorectal cancer risk among Jordanians. *Asian Pac J Cancer Prev*. 2014;15(17):7337-7341.
20. Manson JE, Mayne ST, Clinton SK. Vitamin D and prevention of cancer–ready for prime time? *N Engl J Med*. 2011;364(15):1385-1387.
21. Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. *Nat Rev Cancer*. 2007;7(9):684-700.

22. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer*. 2014;14(5):342-357.
23. Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat Rev Cancer*. 2003;3(8):601-614.
24. Jacobs ET, Van Pelt C, Forster RE, et al. CYP24A1 and CYP27B1 polymorphisms modulate vitamin D metabolism in colon cancer cells. *Cancer Res*. 2013;73(8):2563-2573.
25. Marques VV, Aguiar JP, Donizetti ST, et al. Genetic polymorphisms of vitamin D metabolism genes and serum level of vitamin D in colorectal cancer. *Int J Biol Markers*. 2017;32(4):e441-e446.
26. Dou R, Ng K, Giovannucci EL, Manson JE, Qian ZR, Ogino S. Vitamin D and colorectal cancer: Molecular, epidemiological and clinical evidence. *Br J Nutr*. 2016;115(9):1643-1660.
27. Bises G, Kallay E, Weiland T, et al. 25-Hydroxyvitamin D3–1alpha-hydroxylase expression in normal and malignant human colon. *J Histochem Cytochem*. 2004;52(7):985-989.
28. Wang Y, Zhu J, DeLuca HF. Where is the vitamin D receptor? *Arch Biochem Biophys*. 2012;523(1):123-133.
29. Poynter JN, Jacobs ET, Figueiredo JC, et al. Genetic variation in the vitamin D receptor (VDR) and the vitamin D-binding protein (GC) and risk for colorectal cancer: Results from the Colon Cancer Family Registry. *Cancer Epidemiol Biomarkers Prev*. 2010;19(2):525-536.
30. Speeckaert M, Huang G, Delanghe JR, Taes YE. Biological and clinical aspects of the vitamin D binding protein (Gc-globulin) and its polymorphism. *Clin Chim Acta*. 2006;372(1–2):33-42.
31. Gregory KJ, Zhao B, Bielenberg DR, et al. Vitamin D binding protein-macrophage activating factor directly inhibits proliferation, migration, and uPAR expression of prostate cancer cells. *PLoS ONE*. 2010;5(10):e13428.
32. Powe CE, Ricciardi C, Berg AH, et al. Vitamin D-binding protein modifies the vitamin D-bone mineral density relationship. *J Bone Miner Res*. 2011;26(7):1609-1616.
33. White P, Cooke N. The multifunctional properties and characteristics of vitamin D-binding protein. *Trends Endocrinol Metab*. 2000;11:320-327.
34. Iglar PJ, Hogan KJ. Vitamin D status and surgical outcomes: a systematic review. *Patient Saf Surg*. 2015;9:14.
35. Jenab M, Bueno-de-Mesquita HB, Ferrari P, et al. Association between pre-diagnostic circulating vitamin D concentration and risk of colorectal cancer in European populations: a nested case-control study. *BMJ*. 2010;340:b5500.
36. Thanasitthichai S, Chaiwerawattana A, Prasitthipayong A. Association of vitamin d level with clinicopathological features in breast cancer. *Asian Pac J Cancer Prev*. 2015;16(12):4881-4883.

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