REVIEW
ONCOLOGY

Diseases & Research

A Comprehensive Review Linking Colorectal Cancer and Serum Vitamin D Metabolic Pathways

Nuzhat Tamanna[1], Sumaiya Tasnim[2], Anoma Barua[2], Tasmia Afrin[2], Newaz Sabbih[3], Salma Khan[4,#]

[1] The Grand Rehabilitation and Nursing at Southpoint, Island Park, NY 11558, USA
[2] Research Ambitions, Bangladesh Medical Association of North America, NY 11427, USA
[3] Buffalo Medical PC, Buffalo, NY 14211, USA
[4] Loma Linda University School of Medicine, Loma Linda, CA 92354, USA

Abstract: Vitamin D, a secosteroid hormone, is well-known for its regulatory effects on various immune cells, as well as its established roles in the metabolism of calcium and bone. It has come to light as a crucial factor in the treatment and prevention of colorectal cancer (CRC), influencing cancer cell growth and immune responses. This review aims to investigate the connection involving vitamin D binding protein and receptor polymorphisms in relation to development of colorectal cancer over the past decade, drawing from observational and epidemiological research, including both live and laboratory based clinical trials. in vi- and in vitro clinical trials According to the American Cancer Society low dietary vitamin D which is a modifiable contributing factor for colorectal cancer warrants an in-depth analysis of its receptors, binding proteins, and genetic polymorphisms. The active form of vitamin D, 1,25 -dihydroxy vitaminD3, influences gene transcription via the vitamin D receptor (VDR), impacting immune responses, cellular protection. Clinical studies have shown varying correlations between VDR polymorphism of vitamin D receptor, vitamin D binding protein and colorectal cancer risk in different populations. Vitamin D shows a complex function in preventing as well as treating colorectal cancer through affecting cell growth, inflammation, and immune modulation. Adequate vitamin D levels are linked to a lower risk of colorectal cancer, improved prognosis, and better survival outcomes. Therefore, maintaining optimal amount of vitamin D levels through a proper diet, adequate sun exposure, as well as supplementation could be a crucial aspect of colorectal cancer management strategies.

Keywords: Vitamin D; Colorectal cancer; Vitamin D binding protein; Vitamin D receptor; Polymorphism; 1,25-hydroxylase.

Introduction

Colorectal cancer is a significant public health concern. and is known as the third most prevalent cancer globally, resulting in more than 1.8 million new diagnoses and 915,880 fatalities each year[1]. Although the primary functions of Vitamin D are related to metabolism of calcium and maintaining bone health, vitamin D and its analogs have been extensively studied as potential therapeutic alternatives or substitutes over the last ten years[2]. Vitamin D is hypothesized to reduce cancer development by promoting cell differentiation and apoptosis and interfering with inflammation and the immune system[3]. According to some studies, derivatives of vitamin D have been shown to influence the onset of CRC and progression by stimulating Wnt/β-catenin pathway and the innate immune reaction[4]. Most of the vitamin D is synthesized in the skin when 7-dehydrocholesterol is exposed to ultraviolet B rays, although it can also be found in oily fish, eggs, fortified dairy and cereal products, supplements, etc.[5]. The primary type of vitamin D present in circulation is 25-hydroxyvitamin D (25(OH)D), which is considered as the most reliable predictor of a person's vitamin D status because it represents a comprehensive assessment of vitamin D received through different sources[5]. The vitamin D receptor (VDR) and CYP24 (that catalyzes the first step in the catabolism of 1α,25-[OH]2-vitamin D, are now known to be widely expressed in the colon and a variety of organs[6,7]. The activated VDR forms a heterodimer with the retinoid X receptor alpha (RXRA)[3]. Common VDR gene polymorphisms have been hypothesized to interfere with expression and function of VDR, resulting in varying effects of vitamin D on different people[7]. According to several studies, VDR polymorphisms such as TaqI, BsmI, and Tru91 are linked to CRC risk[8]. Targeted or localized vitamin D deficiency may be caused by blocking the VDR signal or inhibiting the colon's ability to synthesize active vitamin[9]. Previous research studies have shown the significance of Vitamin D metabolic pathways in several other malignancies, including thyroid cancer health disparities. This may be useful in treating or preventing inflammation-associated colon cancer by identifying the protective mechanism that may potentially uncover novel therapeutic targets for IBD and CRC[9].

Methodology

We have conducted this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-

Correspondence: Salma Khan. E-mail: salmakhan@llu.edu. Address: Center for Health Disparities & Molecular Medicine, Loma Linda University School of Medicine, 11085 Campus St., Loma Linda, CA 92354, USA.
Received 18 October 2024; Revised 19 November 2024; Accepted 27 November 2024; Available Online 11 December 2024
DOI: 10.54457/DR.202402011

Analyses (PRISMA) protocols[10]. The search approach was built utilizing the above-mentioned keywords from two electronic databases including PubMed and Google Scholar. Inclusion criteria: Publications from the last 10 years (2014-2024) were included. We selected articles written in English, clinical trials in humans & animals (mice), reviews, systemic reviews, meta-analyses, and randomized control trials. Exclusion criteria: Publications before 2014, pediatric population, papers published in languages other than English, incomplete or ongoing study, editorials, comments, papers, book chapters & documents, letter, conference abstract. Initially, 144 articles were selected following the above-mentioned criteria. Three reviewers screened the study to prevent duplication and assessed the titles and abstracts of the initial publications. Then, three independent individuals reviewed the full-text publications, and one primary reviewer resolved any disagreements and finalized 54 articles for data extraction in manuscript writing. Due to the variability of the data, we were unable to conduct a meta-analysis. In this study, we performed a narrative analysis of the function of vitamin D at the cellular level and polymorphisms of VDR and VDBP at different stages that may influence colorectal cancer. Fig. 1 Provides a flow diagram that outlines the process of selecting studies.

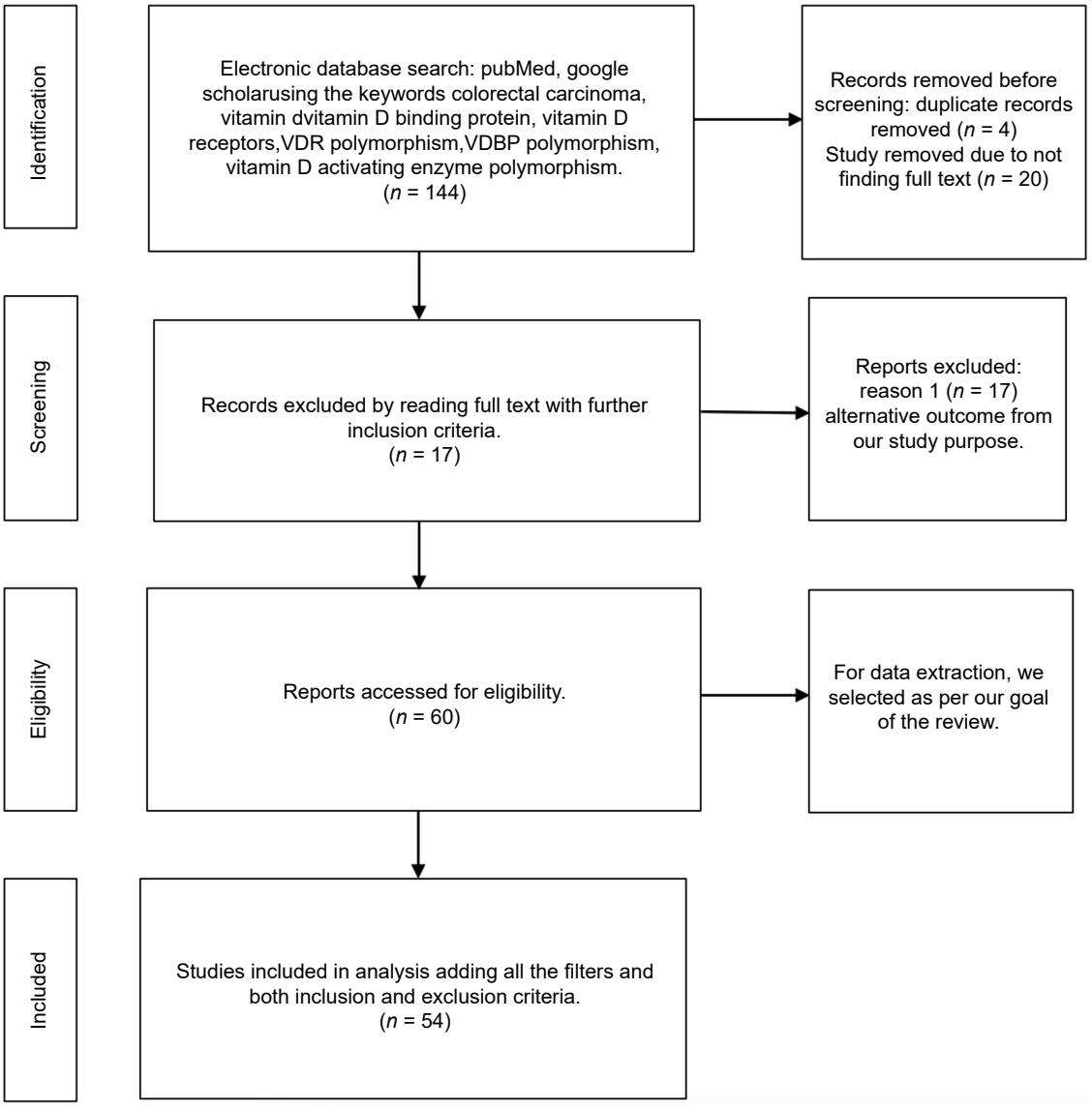

Fig. 1. Preferred Reporting Items for Literature Reviews and Meta-Analysis (PRISMA) flow diagram shows the study selection process.

Overview of vitamin D in CRC

Epidemiology and Influencing Factors of Colorectal Cancer in Relation to Vitamin D

According to National Cancer Institute statistics, in 2024, the projected number of colorectal cancer cases was 152,816, which is around 7.6% of all new cancer cases. The connection between colon cancer and vitamin D was initially noted by Garland and his colleagues, who found higher death rates caused by colon cancer in the north-eastern U.S., where sunlight is low compared to southern regions, correlating with lower sunlight exposure[11,12]. Colorectal cancer incidence is highest in men over 50 but is also

rising in younger adults aged 20-29, around 2.4% annually, with a five-year survival rate improving to 65% due to advancements in diagnosis and treatment but remains a significant issue in both males and females under 40[13]. Different lifestyles significantly impact colorectal cancer (CRC) risk, and the survival rates depend on CRC stage, ethnicity, cancer subtype, and genetic factors, involving both unchangeable factors (like family history and age) and adjustable factors (such as the intake of processed and red meat, heavy alcohol consumption, salt and salty foods, obesity, and gamma radiation)[1,13,14]. The occurrence of colorectal cancer has risen in several Asian countries due to lifestyle changes, involving a significant portion of individuals of East Asia with a deficiency of vitamin D, while a few studies propose a negative association between vitamin D levels and the risk of colorectal conditions[15]. The rates of incidence and mortality from colorectal cancer are increasing in developing and low-income nations, particularly in China, where new cases and deaths have increased due to their dietary habit. However, the age-adjusted mortality rate has experienced a slight reduction, falling from 10.01 per 100,000 in 2005 to 9.68 per 100,000 by 2020[16,17]. Vitamin D deficiency, affecting around 30-50% of children and adults globally, is a contributing factor for IBD and colon cancer, furthermore, vitamin D supplementation reduces colitis symptoms[18].

Cellular Mechanism of the Active Form of Vitamin D

Vitamin D is formed in the skin through ultraviolet B exposure or absorbed from the diet, undergoing hydroxylation steps to become 1,25-dihydroxyvitamin D, the active form. This active form attaches to the vitamin D receptor (VDR) in cells, forming dimers with Retinoid X receptor (RXR) as well as activating gene transcription through VDRE binding in the nucleus[18]. By VDR-mediated genomic action, the active form of vitamin D can provide protective, therapeutic, and adjuvant effects against cellular oncogenic transformation[2]. It helps fight cancer by stopping the multiplication and tumors from growing by interfering with signals by blocking angiogenesis, triggering apoptosis and autophagy, and alleviating inflammation[19]. The mitogenic effects of epidermal growth factor and Ras signaling cascade can be blocked by Calcitriol and downregulate the mRNA expression of Cyclin D1 in oncogenic Coca-2 cell lines[2]. On a cellular scale within human colorectal cells, the studies showed notable variances in the activation of two luciferase systems based on VDR, under various amounts of 1,25(OH)2D as well as a fixed amount of 25(OH)D, by GC isotype[20]. Active Vitamin D inhibits cancer cell growth by inducing G1 cell cycle arrest through upregulating cell cycle inhibitors like p21WAF1/CIP and p27KIP that directly regulate p21 gene expression via VDREs and enhance TGF-β1 receptor expression to restore sensitivity and inhibit epithelial cell proliferation in colorectal cancer[21]. The Wnt/β-catenin signaling pathway regulates cell functions crucial for embryo development and normal cell behavior, however, its dysregulation is related to cancers, including colorectal cancer, involving mutations in β-catenin genes[22]. VDR controls function of β-catenin in the nucleus of the cell where higher VDR levels have been shown to reduce β-catenin levels, potentially inhibiting CRC progression by suppressing Wnt/β-catenin pathway and the expression of cyclin D1 which promotes formation of cancer[22]. Transcription and expression of hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor (VEGF) are inhibited by calcitriol while triggering antiangiogenic effects through NF-κB signaling, and thus the nuclear proteins fork into headbox M1 (FOXM1) and Dickkopf 4 (DKK4)[21]. Fig. 2 illustrates the mechanism by which vitamin D shows its anticancer effects at the cellular level.

Serum Vitamin D Levels Among Patients with Colorectal Cancer

Elevated total 25(OH)D levels have been associated with improved 5-year overall survival, although this benefit does not last throughout the entire follow-up period[23]. The connection between cancer in colorectal region and vitamin D levels is probably not a direct cause-and-effect relationship but might instead reflect poor overall health or ongoing inflammation, with the inverse association could indicate reverse causality, where the cancer or its treatment lowers vitamin D concentrations[24]. Elevated total vitamin D levels were correlated with a better five-year survival rate, although this effect was not sustained throughout longer follow-up periods[23]. Studies using animal models and human tissues have explored the underlying mechanisms. For instance, research on mice has shown that 1,25-(OH) D3 exhibits anti-cancer properties. enhance the ratio of APC and β-catenin, elevate levels of E-cadherin and induces apoptosis[25]. According to a case-control study by Chen and Jin, lower serum 25(OH)D concentration in patient population with colorectal region were inversely related to the ratios of Treg and Th17 cells as well as relevant cytokine levels[17].

Clinical Studies on The Association between Vitamin D levels And Colorectal Cancer

Both epidemiological and preclinical research have recommended a connection between deficiency of vitamin D in serum and an excessive risk of inflammatory bowel diseases, various extra-skeletal conditions, and certain cancers, notably colorectal cancer, this connection has been reinforced by experimental findings using carcinoma cell lines and models of animal with colorectal cancer, highlighting the extensive protective effects of calcitriol as well as other vitamin D receptor agonists[26]. Evidence shows a high prevalence of vitamin D deficiency amid individuals positive for colorectal cancer, as clinical research conducted with 515 advanced colorectal cancer patients from the United States and Canada reported that 82% had vitamin D levels below 30 ng/mL, classifying them as insufficient, at the same time 50% were categorized as deficient with levels under 20 ng/mL, the study also found 20 ng/mL as median plasma 25(OH)D concentration[27]. A case-control study embedded within a larger cohort of female participants revealed that patients diagnosed with colorectal cancer had notably lower average serum 25(OH)D levels compared to those in the control group (21.9 vs 23.9 ng/mL, $p = 0.01$), additionally increased levels of vitamin D were connected to a lower risk of development of malignancy in colorectal region with OR = 0.45 (CI: 0.25 to 0.81; trend significance: $p = 0.02$); A current meta-analysis comprised with 23 studies established an inverse correlation between 25(OH)D levels in serum and the occurrence of adenomas in colorectal region with RR 0.80 (95% CI, 0.71–0.89), this correlation is significant in female populations and populations in Europe and America but not in males or Asi-

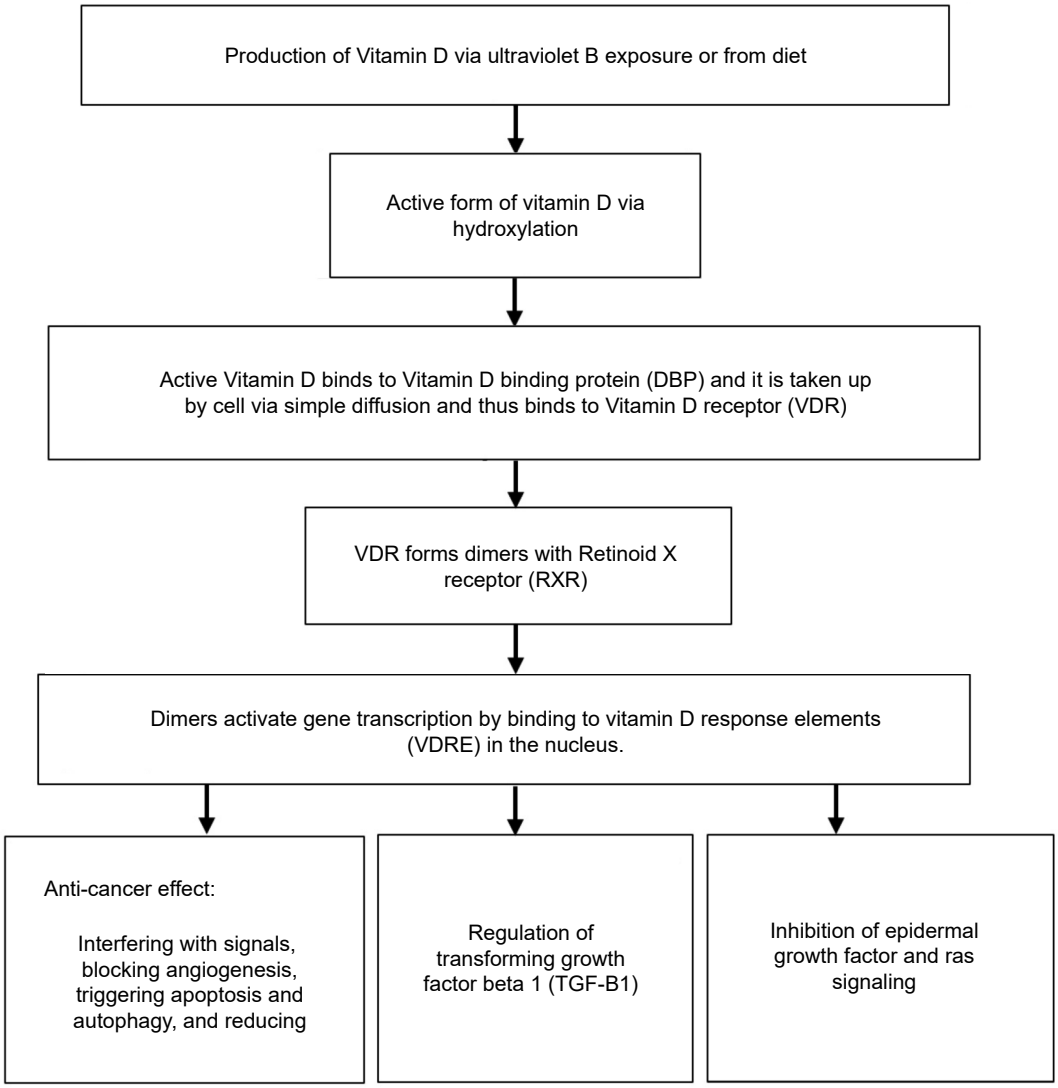

Fig. 2. Mechanism of vitamin D at the cellular level.

an populations[21]. Another study, led by Hamada et al., involving 869 colorectal cancer cases in the US, found that post-diagnosis scores of 25(OH)D were more firmly linked with survival amid CRC patients with lower peritumoral lymphocytic reaction though not with overall mortality. This suggests individual variations in vitamin D's anti-tumor effects based on the immune response, which may influence personalized intervention strategies for cancer patients[28]. 1 Study by Weinstein et al. showed a counter relation between circulating vitamin D concentration in serum and malignancy risk in colon and rectal region, however, this study did not identify any connection between the risk of colorectal carcinoma and circulating levels of DBP or the molar ratio between 25(OH)D and VDBP; while increased vitamin D levels were affiliated with a lower risk of cancer in colorectal area, VDBP did not appear to have a straight or modifying role[29]. Research by Song et al. highlighted the opposite connection between plasma 25(OH)D levels and malignancy in the specific colorectal region of body characterized by a robust immune reactivity, underscoring vitamin d's role in cancer immunoprevention particularly focusing on the interaction between the immune response of the host and the tumor[30]. In a randomized trial with advanced colorectal cancer patients, no significant difference in progression-free survival was found between those getting high-dose vitamin D3 and chemotherapy and those receiving standard-dose vitamin D3, although the hazard ratio for progression-free survival was 0.64[31].

The summary of all the clinical trials conducted showing association between serum vitamin D level and CRC is given in Table 1.

Polymorphism in the genes that encode enzymes

The enzyme breaks down 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D 24-hydroxylase (encoded by CYP24A1)[32]. A 2014 study linked genetic variations in Vitamin D metabolism to CRC risk in African Americans, which identified a significant association between CRC and the SNP rs12794714 in the CYP2R1 gene, along with two other SNPs, rs16847024 in the GC gene and rs6022990 in the CYP24A1 gene[33]. The elevated CYP27B1 expression indicates possible benefits from vitamin D treatment, especially in well and moder-

Table 1. Studies showing serum Vitamin D level and CRC association.

Author (Year)	Study Design	Number of Cases	Association	P-values
Savoie et al. (2019)[27]	Cohort	94	Primary endpoint: occurrence of vitamin D deficiency in patients with recently diagnosed CRC.	Vitamin D status was significantly associated with CRC stage at diagnosis. $p = 0.02$; Relationship between vitamin D supplement dose and baseline 25(OH)D level; Spearmanr2 = 0.39, $p < 0.045$
Weinstein et al. (2015)[29]	Nested Case-control	476	OR = 0.60 [95% CI: 0.38-0.94] for highest vs. lowest quantile	$p = 0.01$
Song et al. (2015)[30]	Nested Case-control	318	The association varied depending on the extent of immune response within the tumor- highest vs. lowest tertile of immune response. High lymphocytic reaction OR = 0.10 (CI: 0.03–0.35) Mild and absent lymphocytic reaction	$p < 0.001$ $p_{trend} > 0.50$
Jung et al. (2014)[3]	Prospective cohort	1059 incident colorectal cancer cases	Highest vs. Lowest Quintile of predicted 25(OH)D scores: Multivariate HR (CRC risk): 0.48 (0.30–0.78) for VDR-negative tumor 0.56 (0.42–0.75) for VDR-positive tumor	
Young Na et al. (2022)[21]	Nested case-control	274	OR = 0.45 [95% CI: 0.25–0.81] For quartile 4 vs. quartile 1	$p = 0.02$

ately differentiated tumors[34]. Conversely, the low CYP27B1 expression in poorly differentiated colorectal cancer suggests resistance of the cancer cells to calcitriol actions[34]. Inhibiting CYP24A1 could enhance calcitriol's anti-tumor effect[34]. CYP27B1 affects the tissue-level exposure to Vitamin D and has anti-tumor activity potential[35]. A study by Jacobs et al. revealed that compared to wild-type control, four of five CYP27B1 SNPs (R107H, A129T, S356N, and V374A) showed decreased enzymatic action while one (V166L) showed increased activity[35]. All four tested polymorphisms of CYP24A1 SNPs were associated with lower enzyme activity[35]. Latacz conducted a study with 325 cases and discovered a statistically significant association between genetic variation in the CYP27B1 gene and reduced occurrence of colon malignancy[36]. Vidigal and his colleagues conducted a study that reported that VDR, CYP24A1, and CYP27B1 polymorphisms were linked to increased malignancy in the colon region[37].

Vitamin D binding protein (VDBP) in CRC

VDBP level in serum of patients with CRC

Vitamin D binding protein is an essential carrier molecule that transports vitamin D metabolite in serum, and its weight ranges from 52 to 59 kDa; GC-globulin (GC), also called vitamin D binding globulin, is an α2-globulin made up of 458 amino acids and is predominantly synthesized by liver parenchymal cells[20,38]. Around 88% of circulating 25(OH)D is attached to VDBP, with 12% loosely bound to albumin besides transporting vitamin D metabolites, DBP also exhibits anti-inflammatory and immunoregulatory properties, potentially influencing various chronic diseases[5]. Experimental studies show that VDBP may suppress tumor growth through different mechanisms, including actin scavenging, activation of macrophages, chemotaxis, and angiogenesis suppression, though its exact role in colonic carcinogenesis remains unclear[23,38]. Several in vitro studies showed that DBP is a co-chemotactic factor that significantly improves the neutrophil chemotactic response of C5a and its derivative, C5a des Arg[39]. In vivo studies of DBP report that DBP's chemotactic cofactor activity is not limited to C5a but also other leukocyte chemo attractants[39]. Colon epithelial cells facilitate the access of DBP-bound 25(OH)D into colon cells through the Megalin and Dab2 receptors, which endocytose the complex[5]. A comprehensive analysis of 28 studies found that higher VDBP levels (mean serum VDBP level 383 microgram/ml showed less mortality) are related to a borderline decreased risk of multiple cancers, including colorectal cancer, and increased survival, potentially due to VDBP prolonging the anti-cancer properties of 25(OH)D by extending its half-life and facilitating its cellular uptake via the Megalin receptor[23].

Vitamin D- binding protein genetic polymorphisms

Two frequently studied GC polymorphisms (rs4588 and rs7041) result in amino acid alterations at positions 416 and 420, producing three prevalent phenotypic alleles (1F, 1S, and 2) and encoding the DBP protein isoforms Gc1s, Gc1f, and Gc2, which are associated with in vitamin D metabolism[20,39]. The affinity for vitamin D is different for GC isotypes. It varies significantly by race-ethnicity, as White individuals exhibit a lower prevalence of the 1F isotype than 1S but frequent allele 2, which is the least common overall[20]. Combining data from studies involving colonoscopy, we found that increased 25(OH)D3 levels were inversely linked to the risk of colorectal adenomas in people with specific Gc2 trait but not in individuals possessing only Gc1 trait; thus, people who have Gc2 isoform can maintain higher25(OH)D3

concentrations for adenoma prevention[40]. Individuals with specific DBP isoforms, such as 2_2, may experience more efficient metabolite delivery and release at the cellular level, even with lower 25(OH)D levels, due to efficient GC-megalin interaction, potentially impacting health outcomes like colon cancer[20].

Clinical studies on vitamin D-binding protein concentrations CRC patients

A clinical trial of 'Ursodeoxycholic Acid (UDCA)' consisting of 403 participants showed that cellular uptake of vitamin D significantly varies depending on genetic variation (Gc isotype) in different concentrations and conditions ($p < 0.01$)[20]. Another study included 104 CRC cases, showing that higher serum VDBP levels are linked to a less aggressive tumor trait in African American cases, particularly indicated by reduced expression of tumor Ki67, potentially indicating a role in anti-tumor immunity through VDBP-MAF complex formation, warranting further investigation in longitudinal studies for CRC survival implications[41]. Gc-MAF, formed from DBP after de-glycosylation through β-galactosidase and sialidase of the B and T lymphocytes, can activate the tumoricidal activity of macrophages[42]. It can inhibit angiogenesis (one of the drivers of carcinogenesis) induced by pro-inflammatory prostaglandin E1 by interacting with the CD36 receptor, with promising benefits as novel anticancer immunotherapy in several clinical studies[42]. A clinical trial consisting of 627 eligible patients with a total of 25(OH)D levels and 603 with available VDBP levels showed that higher VDBP levels were significantly linked to enhanced overall survival along with CRC-specific survival, in individuals with the highest quartile of VDBP having a lower risk of mortality relative to those in the reduced quartile[23]. A case-control study by Gibbs and colleagues published in 2019 (1710 incident CRC cases) explored the inverse association between increased circulating 25-hydroxyvitamin-D levels and CRC occurrence with respect to the functional GC-rs4588*A (Thr436Lys) variant that encodes the vitamin D–binding protein-2 isoform and DBP2 isoform were more likely related to reduced 25(OH)D levels than the DBP1 isoform due to less renal absorption of 25(OH)D, shorter circulation time in serum, and minimal affinity constant to 25(OH)D[43]. A study in China (212 CRC patients) found no significant link between circulating VDBP levels and colorectal cancer risk but did find that higher levels of total 25(OH)D were linked to a lower risk of CRC, suggesting that while VDBP may not be directly related to CRC risk, it does affect the levels of free and bioavailable 25(OH)D[44]. Table 2 summarizes the studies that examine the association between vitamin D binding protein and CRC.

VDR Influences Colorectal Cancer Progression Outcomes

Serum VDR levels in colorectal cancer

The active byproduct of vitamin D, $1,25(OH)_2D_3$, modulates downstream gene expression by binding to VDR and plays a role in immune response, cell death, cellular differentiation, maturation, and cancer development[45]. VDR, a nuclear receptor, is present in colorectal epithelial and various cells[46]. The VDR gene is situated on the long arm of chromosome 12 (12q13-14), covering about 75 kb. It has nine exons with several SNPs linked to VDR function, including five common ones[47]. According to

Table 2. Studies show the association between serum vitamin D binding protein and CRC.

Author (Year)	Study Design	Number of Cases	Association with CRC
Ying et al. (2015)[44]	Nested case-control	212 incident CRC patients	Highest (Q4) vs Lowest Quartiles (Q1) of serum VDBP level was not linked to the occurrence of CRC; $p = 0.944$, OR = 0.93 [95% CI:0.51–1.69] for Q4:Q1; Similar results even after adjustment for 25(OH)D. Highest (Q4) vs Lowest Quartiles (Q1) of: • Total 25(OH)D in plasma and the risk of CRC; $p = 0.027$, OR = 0.53 [95% CI:0.29–0.98] • Free 25(OH)D and the risk of CRC; $p < 0.001$, OR = 0.42 [95% CI:0.22–0.82] • Bioavailable 25(OH)D and the risk of CRC; $p = 0.006$, OR = 0.29 [95% CI:0.15–0.56] Similar results were obtained even after adjustment for VDBP.
Gibbs et al. (2018)[40]	Pooled data from 3 case-control studies	418 patients with adenoma	Elevated levels of 25(OH)-D3 were linked to decreased risk of colorectal adenoma inGc2 trait of the gene encoding DBP: per 10 ng/mL rise in 25(OH)D3, OR = 0.71, 95% CI:0.56–0.90; *p*-value for Interaction = 0.03; No association with Gc1 isoforms: OR = 1.07 (95% CI:0.87–1.32)
Gibbs et al. (2019)[43]	Nested case-control	1710 incident CRC cases	Correlation between 25(OH)D levels below 50 nmol/L for each DBP2-encoding variant (rs4588*A) inherited: OR = 1.43 [95% CI:1.27–1.62] $t_{trend} = 1.2 \times 10^{-8}$ 53% reduced likelihood of CRC in people with the DBP2 insomnia: RR = 0.47 [95% CI:0.33–0.67]; 12% lower risk among those without the DBP2 isoform: RR = 0.88 [95% CI:0.61–1.27] $h_{eterogeneity} = 0.01$
Yuan et al. (2020)[23]	Nested case-control	603 white participants with incident CRC cases	Correlations between the serum status of vitamin D-related biomarkers before CRC diagnosis and survival: Lowest quartile vs. Highest quartile of VDBP: • CRC-specific mortality HR = 0.58 (95% CI:0.37–0.91) $p_{trend} = 0.02$ Similar results after adjustment for a total of 25(OH)D levels. No link between bioavailable or free 25(OH)D levels and mortality in CRC cases; $p_{trend} > 0.15$
Lawler et al. (2023)[41]	Nested case-control	104 CRC cases	25-hydroxyvitamin D were not linked to: Elevated Ki67 (OR per 1-SD increase [95% CI:1.35 [0.86–2.11]); p53 (OR = 0.75 [0.47–1.20]); COX-2 expression (OR = 1.25 [0.78–2.01]); Metastatic disease (OR = 1.04 [0.59–1.81]) Biomarker level was not correlated with 25-hydroxyvitamin D ($p_{trend} \geq 0.09$); In African Americans: Higher VDBP levels were linked to reduced odds of high Ki67 expression, OR = 0.53 [95% CI: 0.28–0.98]; $p_{trend} = 0.04$

most studies on human cancer cells, the expression of VDR and CYP27B1 increases initially at the transformative stage of the cancer. However, the more aggressive the tumor becomes, the VDR and CYP27B1 levels decline, and CYP24A1 slowly increases[48]. While no statistically significant correlation was found among Asians, the VDR BsmI allele and genotype were linked to a decreased incidence of colorectal cancer in Caucasians, suggesting that carriers of the BsmI B-allele provided a safeguarded factor in Caucasians[45].

VDR gene Polymorphisms in patients with CRC

Over 60 SNPs have been identified in the VDR gene[45]. Recently Several molecular studies have discovered many single-nucleotide polymorphisms (SNPs) in the human VDR and CASR genes including FokI (rs10735810), BsmI (rs1544410), TaqI (rs731236) in VDR and A986S (rs1801725) and R990G (rs1042636) in CASR[46,49]. The FokI polymorphism at the 5' end of exon 2 is a nonsynonymous SNP associated with the VDR protein frameshift[45]. Zhang and his colleagues showed no interaction between different types of VDR genes (such as FokI, BsmI, ApaI, and TaqI) and CRC occurrence. However, some relation was found between the ApaI form of VDR and vitamin D intake with respect to colon cancer occurrence[50]. A mutation in CDX-2, an intestinal-specific transcription factor found in the VDR's 5′ region, causes G > A sequence diversification and controls the action of the promoter at exon 1, and compared to the A allele, the promoter containing the Cdx-2 G allele has 30% less transcriptional activity[45].

Clinical studies of VDR Polymorphism in individuals with colorectal cancer

Control study (n = 364) held in Bangkok, Thailand, between 2014 and 2015 showed no substantial connection in allele and genotype frequency in VDR SNP. In contrast, the AGGT haplotype was markedly correlated with reduced CRC risk. (odds ratio 0.24, 95% confidence interval 0.07–0.81, $p = 0{:}01$)[47]. This study found that the haplotype AGGT of BsmI, Tru9I, ApaI, and TaqI was strongly correlated with CRC. However, the correlation was weak, with only 0.9% and 3.6% allele frequencies, respectively[47]. A study on the Newfoundland population assessed TaqI and BsmI polymorphisms in one block for CRC survival and found no significant association[46]. In a clinical trial conducted in Saudi Arabia, all colorectal cancer patients (n = 50) had prior treatment experience and had completed their entire chemotherapy regimen; healthy controls (n = 50) were also included[51]. It showed that the homozygous (aa) version of the ApaI VDR polymorphism aligned with total vitamin D levels but not with 25(OH)D3 concentrations in CRC patients, and Ca levels were found to be notably decreased in CRC patients with the Aa genotype compared to those with AA or aa genotypes ($p = 0.04$)[51]. Peripheral blood was collected from 397 colorectal cancer patients (202 with stage II/III and 195 with stage IV), along with control samples from 40 patients with adenomatous polyps and 100 healthy donors, and PCR-RFLP was employed to genotype both patient and control samples[52]. Table 3 offers an overview of studies emphasizing the connection between vitamin D receptors and colorectal cancer.

In vivo studies of CRC in mice model with vitamin D Receptor

One of the previous studies has indicated that low intestinal VDR protein levels or VDR targeted deletion in the intestinal epithelial may result in dysbiosis, reduced autophagy, and a decrease in the inflammatory bowel disease risk ATG16L1 (autophagy-related 16 like 1)[53,54]. The researchers investigated the effects and mechanisms of intestinal epithelial VDR in healthy and inflamed conditions using cell culture models, which is a targeted VDR deletion mouse model, colitis models, and human samples[53]. In another trial, researchers created lentivirus-delivered VDR silencing and overexpression in SW480 cells, identified critical genes involved in Wnt/β-catenin signaling, and tracked tumor formation in nude mice exposed to VDR-OE SW480 cells by using various techniques like Co-immunoprecipitation and Chromatin showing VDR interacts with β-catenin and activates LEF-1 transcription in vitro where VDR overexpression significantly decreases tumor growth in nude mice by suppressing the expression of β-catenin, cyclin D1, and LEF-1 Immunoprecipitation[22].

Conclusion

Calcitriol, the active vitamin D, fights cancer by inhibiting tumor growth, blocking angiogenesis, inducing apoptosis and autophagy, and reducing inflammation. It also downregulates oncogenic pathways like Ras and Wnt/β-catenin signaling and suppresses cell cycle regulators. Epidemiological studies have consistently shown an opposing link between serum 25-hydroxyvitamin D [25(OH)D] levels and colorectal cancer risk. While vitamin D receptor (VDR) polymorphisms influence colorectal cancer susceptibility and progression, their precise effects can vary due to genetic and environmental factors, highlighting the need for further research to clarify their clinical significance. Continued research is crucial to uncover new perceptions of the tumor-suppressing mechanisms of vitamin D and to determine patient populations that may benefit most from this adjunctive therapy. Additional clinical studies focusing on common single nucleotide polymorphisms (SNPs) in the VDR gene related to colorectal cancer could provide valuable insights. Furthermore, clinical trials have identified a link between genetic polymorphisms in vitamin D metabolizing enzymes and colorectal cancer, particularly in African American populations, suggesting the need for further exploration across other populations. Addressing the clinical demand for vitamin D uptake variations due to genetic differences involves a multifaceted approach that integrates personalized medicine, public health strategies, and advanced diagnostic tools: (1) Identifying variations in genes involved in vitamin D metabolism (e.g., *CYP2R1*, *GC*, *VDR*) can help determine individual needs for vitamin D; (2) Pair vitamin D levels with genetic data to understand the functional impact of genetic variations; (3) Develop initiatives for at-risk populations, such as certain ethnic groups or individuals with low sun exposure; (4) Develop vitamin D analogs or targeted therapies that bypass genetic limitations; (5) Use drug delivery systems that optimize bioavailability for individuals with absorption or metabolic challenges; (6) Invest in research to understand the interaction between genetic variants and environmental factors affecting vitamin D metabolism. By combining these strategies, healthcare systems can effectively address the variability in vitamin D uptake due to genetic differences, improving health outcomes and

Table 3. Studies showing association between Vitamin D receptor and Cancer in colorectal Region.

Author (Year)	Study Design	Number of Cases	Association and Findings			
			Polymorphism	Comparison between different isoforms	OR [95% CI]	*p*-value
Yang et al. (2023)[45]	Meta-analysis (45 studies)	19,673	Bsml variant and CRC risk	B vs b	0.94 [0.90–0.99]	0.013
				BB vs bb	0.88 [0.79– 0.97]	0.01
				BB vs Bb/bb	0.89 [0.81–0.98]	0.014
			FokI polymorphism and CRC risk	Ff vs FF	0.86 [0.84–0.93]	< 0.001
				Ff/Ff vs FF	0.88 [0.79–0.98]	0.022
				Ff vs Ff/FF	0.9 [0.82–0.99]	0.033
			Cdx-2 polymorphism and CRC risk	C vs c	0.5 [0.33–0.75]	0.001
				CC vs cc	0.09 [0.01–0.77]	0.028
				Cc vs cc	0.49 [0.30–0.81]	0.006
				CC/Cc vs cc	0.45 [0.28–0.74]	0.001
Suksawatamnuay et al. (2020)[47]	Case-control	182	No significant allele and genotype association in VDR SNPs. AGGT haplotype associated with decreased CRC risk p = 0.01 [95% CI: 0.07–0.81], OR = 0.24			
Al-Ghafari et al. (2019)[51]	Case-control	50	aa version of the ApaI VDR polymorphism has correlation with total level of vitamin D, p < 0.0001 No correlation with 25(OH)D3 in CRC patients (p = 0.12) Calcium levels were lower in Aa genotype CRC patients compared to AA or aa, (p = 0.04)			
Messaritakis et al. (2020)[52]	Retrospective cohort	397	All the homozygous mutant genotypes (aa, bb, ff or tt) were significantly associated with CRC particularly stage IV, leading to lower survival (p < 0.001) All four polymorphisms were significantly associated with TLR and KRAS variants Independent factors associated with lower overall survival (OS), tt (p = 0.01), aa (p < 0.001), ff (p = 0.01)			

reducing the burden of diseases associated with vitamin D deficiency.

The current limited clinical research on vitamin D binding protein (VDBP), VDR gene expression, and vitamin D activating enzymes indicates that more research could advance the development of vitamin D3 analog-based therapies for more effective colorectal cancer prevention and treatment.

Abbreviations

1,25 (OH)D, 1,25-hydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; APC/β-catenin, Adenomatous polyposis coli/β-catenin; CI, Confidence interval; CRC, Colorectal cancer; CYP, Cytochrome P; DBP, Vitamin D Binding Protein; HIF-1, Hypoxia-inducible factor-1; IBD, Inflammatory Bowel Disease; KRAS, Kirsten rat sarcoma viral oncogene; MAF, Macrophage activating factor; NF-κB, Nuclear Factor-κB; RR, Relative risk; OR, Odds ratio; SNP, Single nucleotide polymorphism; TGF-β1, Transforming growth factor-β1; TLR, Toll-like receptor; UDCA, Ursodeoxycholic Acid; UVB, Ultraviolet B radiation; VDBP, Vitamin D Binding Protein; VDR, Vitamin D receptor; VDRE, Vitamin D response element; VEGF, Vascular Endothelial Growth Factor.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Acknowledgments

The authors would like to express their gratitude to the 'Research Ambition Group BMANA', Dr. Tahsin Tabassum, and Dr. Tonima Ashrafi for their guidance and assistance in data collection and structuring this research paper. Their expertise and insights have been instrumental in shaping the clarity and organization of the content.

Authors' contributions

This review topic was conceptualized and designed by SK. Data acquisition was performed by ST, NT, AB and NS. Data was analyzed and interpreted by NT, ST, AB and TA. The manuscript was written, reviewed and revised by NT, ST, AB, TA and SK. All tables were prepared by AB, TA, ST and figures by NT, ST.

References

[1] Guo LL, Chen SS, Zhong LX, et al. Vitamin D intake as well as circulating 25-hydroxyvitamin D level and risk for the incidence and recurrence of colorectal cancer precursors: A meta-analysis. Front Med, 2022, 9: 877275.

[2] Haidari F, Abiri B, Iravani M, et al. The Effects of UVB and Vitamin D on Decreasing Risk of Colorectal Cancer Incidence and Mortality: A Review of the Epidemiology, Clinical Trials, and Mechanisms. Nutr Cancer, 2019, 71(5): 709-717.

[3] Jung S, Qian ZR, Yamauchi M, et al. Predicted 25(OH)D score and colorectal cancer risk according to vitamin D receptor expression. Cancer Epidemiol Biomark Prev, 2014, 23(8): 1628-37.

[4] Ferronato MJ, Alonso EN, Gandini NA, et al. The UVB1 Vitamin D analogue inhibits colorectal carcinoma progression. J Steroid Biochem Mol Biol, 2016, 163: 193-205.

[5] Anic GM, Weinstein SJ, Mondul AM, et al. Serum vitamin D, vitamin D binding protein, and risk of colorectal cancer. PLoS One, 2014, 9(7): e102966.

[6] Bostick RM. Effects of supplemental vitamin D and calcium on normal colon tissue and circulating biomarkers of risk for colorectal neoplasms. J Steroid Biochem Mol Biol, 2015, 148: 86-95.

[7] Budhathoki S, Yamaji T, Iwasaki M, et al. Vitamin D Receptor Gene Polymorphism and the Risk of Colorectal Cancer: A Nested Case-Control Study. PLoS One, 2016, 11(10): e 0164648.

[8] Sheng S, Chen Y, Shen Z. Correlation between polymorphism of vitamin D receptor TaqI and susceptibility to colorectal cancer: A meta-analysis. Medicine, 2017, 96(26): e7242.

[9] Meeker SM, Seamons A, Treuting PM, et al. Effect of Chronic Vitamin D Deficiency on the Development and Severity of DSS-Induced Colon Cancer in *Smad3-/-* Mice. Comp Med, 2020, 70(2): 120-130.

[10] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. PLoS Med, 2021, 18(3): e1003583.

[11] Mohr SB, Gorham ED, Kim J, et al. Could vitamin D sufficiency improve the survival of colorectal cancer patients? J Steroid Biochem Mol Biol, 2015, 148: 239-44.

[12] Meeker S, Seamons A, Paik J, et al. Increased dietary vitamin D suppresses MAPK signaling, colitis, and colon cancer. Cancer Res, 2014, 74(16): 4398-408.

[13] Cruz-Pierard SM, Nestares T, Amaro-Gahete FJ. Vitamin D and Calcium as Key Potential Factors Related to Colorectal Cancer Prevention and Treatment: A Systematic Review. Nutrient, 2022, 14(22): 4934.

[14] Yusefi AR, Bagheri Lankarani K, Bastani P, et al. Risk Factors for Gastric Cancer: A Systematic Review. Asian Pac J Cancer Prev, 2018, 19(3): 591-603.

[15] Choi YJ, Kim YH, Cho CH, et al. Circulating levels of vitamin D and colorectal adenoma: A case-control study and a meta-analysis. World J Gastroenterol, 2015, 21(29): 8868-77.

[16] Fang Y, Song H, Huang J, et al. The clinical significance of vitamin D levels and vitamin D receptor mRNA expression in colorectal neoplasms. J Clin Lab Anal, 2021, 35(11): e23988.

[17] Chen B, Jin L. Low serum level of 25-OH vitamin D relates to Th17 and treg changes in colorectal cancer patients. Immun Inflamm Dis, 2022, 10(11): e723.

[18] Meeker S, Seamons A, Maggio-Price L, et al. Protective links between vitamin D, inflammatory bowel disease and colon cancer. World J Gastroenterol, 2016, 22(3): 933-48.

[19] Chen A, Davis BH, Sitrin MD, et al. Transforming growth factor-beta 1 signaling contributes to Caco-2 cell growth inhibition induced by 1, 25(OH)(2)D(3). Am J Physiol Gastrointest Liver Physiol, 2002, 283(4): G864-74.

[20] Hibler EA, Jacobs ET, Stone AD, et al. Associations between vitamin D-binding protein isotypes, circulating 25(OH)D levels, and vitamin D metabolite uptake in colon cancer cells. Cancer Prev Res, 2014, 7(4): 426-34.

[21] Na SY, Kim KB, Lim YJ, et al. Vitamin D and Colorectal Cancer: Current Perspectives and Future Directions. J Cancer Prev, 2022, 27(3): 147-156.

[22] Yu J, Sun Q, Hui Y, et al. Vitamin D receptor prevents tumour development by regulating the Wnt/β-catenin signalling pathway in human colorectal cancer. BMC Cancer, 2023, 23(1): 336.

[23] Yuan C, Song M, Zhang Y, et al. Prediagnostic Circulating Concentrations of Vitamin D Binding Protein and Survival among Patients with Colorectal Cancer. Cancer Epidemiol Biomark Prev, 2020, 29(11): 2323-2331.

[24] Vaughan-Shaw PG, Zgaga L, Ooi LY, et al. Low plasma vitamin D is associated with adverse colorectal cancer survival after surgical resection, independent of systemic inflammatory response. Gut, 2020, 69(1): 103-111.

[25] Marques da Costa P, Martins I, Neves J, et al. Serum vitamin D levels correlate with the presence and histological grading of colorectal adenomas in peri and postmenopausal women. Clin Nutr, 2019, 38(3): 1390-1397.

[26] Fernández-Barral A, Costales-Carrera A, Buira SP, et al. Vitamin D differentially regulates colon stem cells in patient-derived normal and tumor organoids. FEBS J, 2020, 287(1): 53-72.

[27] Savoie MB, Paciorek A, Zhang L, et al. Vitamin D Levels in Patients with Colorectal Cancer Before and After Treatment Initiation. J Gastrointest Cancer, 2019, 50(4): 769-779.

[28] Hamada T, Liu L, Nowak JA, et al. Vitamin D status after colorectal cancer diagnosis and patient survival according to immune response to tumour. Eur J Cancer, 2018, 103: 98-107.

[29] Weinstein SJ, Purdue MP, Smith-Warner SA, et al. Serum 25-hydroxyvitamin D, vitamin D binding protein and risk of colorectal cancer in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Int J Cancer, 2015, 136(6): E654-64.

[30] 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.

[31] Ng K, Nimeiri HS, McCleary NJ, et al. Effect of High-Dose vs Standard-Dose Vitamin D3 Supplementation on Progression-Free Survival Among Patients with Advanced or Metastatic Colorectal Cancer: The SUNSHINE Randomized Clinical Trial. JAMA, 2019, 321(14): 1370-1379.

[32] Christakos S, Dhawan P, Verstuyf A, et al. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiol Rev, 2016, 96(1): 365-408.

[33] Pibiri F, Kittles RA, Sandler RS, et al. Genetic variation in vitamin D-related genes and risk of colorectal cancer in African Americans. Cancer Causes Control, 2014, 25(5): 561-70.

[34] Dou R, Ng K, Giovannucci EL, et al. Vitamin D and colorectal cancer: molecular, epidemiological and clinical evidence. Br J Nutr, 2016, 115(9): 1643-60.

[35] 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): 2563-73.

[36] Latacz M, Snarska J, Kostyra E, et al. *CYP27B1* Gene Polymorphism rs10877012 in Patients Diagnosed with Colorectal Cancer. Nutrients, 2020, 12(4): 998.

[37] Vidigal VM, Silva TD, de Oliveira J, et al. Genetic polymorphisms of vitamin D receptor (VDR), CYP27B1 and CYP24A1 genes and the risk of colorectal cancer. Int J Biol Markers, 2017, 32(2): e224-e230.

[38] Martin P, Noonan S, Mullen MP, et al. Predicting response to vascular endothelial growth factor inhibitor and chemotherapy in metastatic colorectal cancer. BMC Cancer, 2014, 14: 887.

[39] Kew RR. The Vitamin D Binding Protein and Inflammatory Injury: A Mediator or Sentinel of Tissue Damage? Front Endocrinol, 2019, 10: 470.

[40] Gibbs DC, Fedirko V, Um C, et al. Associations of Circulating 25-Hydroxyvitamin D3 Concentrations with Incident, Sporadic Colorectal Adenoma Risk According to Common Vitamin D-Binding Protein Isoforms. Am J Epidemiol, 2018, 187(9): 1923-1930.

[41] Lawler T, Su T, Cai Q, Steinwandel MD, et al. Associations between serum vitamin D biomarkers and tumor expression of Ki67, p53, and COX-2 in colorectal cancer cases from the Southern Community Cohort Study. J Steroid Biochem Mol Biol, 2023, 225: 106201.

[42] Saburi E, Saburi A, Ghanei M. Promising role for Gc-MAF in cancer immunotherapy: from bench to bedside. Caspian J Intern Med, 2017, 8(4): 228-238.

[43] Gibbs DC, Song M, McCullough ML, et al. Association of Circulating Vitamin D With Colorectal Cancer Depends on Vitamin D-Binding Protein Isoforms: A Pooled, Nested, Case-Control Study. JNCI Cancer Spectr, 2019, 4(1): pkz083.

[44] 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.

[45] Yang M, Ji W, Xu N, et al. Association of vitamin D receptor polymorphisms with colorectal cancer susceptibility: A systematic meta-analysis. Medicine, 2023, 102(1): e32575.

[46] Zhu Y, Wang PP, Zhai G, et al. Vitamin D receptor and calcium-sensing receptor polymorphisms and colorectal cancer survival in the Newfoundland population. Br J Cancer, 2017, 117(6): 898-906.

[47] Suksawatamnuay S, Sriphoosanaphan S, Aumpansub P, et al. Association between Vitamin D Receptor Single-Nucleotide Polymorphisms and Colorectal Cancer in the Thai Population: A Case-Control Study. Biomed Res Int, 2020, 2020: 7562958.

[48] Al-Ghafari AB, Balamash KS, Al Doghaither HA. Serum vitamin D receptor (VDR) levels as a potential diagnostic marker for colorectal cancer. Saudi J Biol Sci, 2020, 27(3): 827-832.

[49] Aggarwal A, Prinz-Wohlgenannt M, Tennakoon S, et al. The calcium-sensing receptor: A promising target for prevention of colorectal cancer. Biochim Biophys Acta, 2015, 1853(9): 2158-67.

[50] Zhang X, Fang YJ, Feng XL, et al. Interactions Between Vitamin D and Calcium Intake, Vitamin D Receptor Genetic Polymorphisms, and Colorectal Cancer Risk. Dig Dis Sci, 2021, 66(6): 1895-1905.

[51] Al-Ghafari AB, Balamash KS, Al Doghaither HA. Relationship between Serum Vitamin D and Calcium Levels and Vitamin D Receptor Gene Polymorphisms in Colorectal Cancer. Biomed Res Int, 2019, 2019: 8571541.

[52] Messaritakis I, Koulouridi A, Sfakianaki M, et al. The Role of Vitamin D Receptor Gene Polymorphisms in Colorectal Cancer Risk. Cancers, 2020, 12(6): 1379.

[53] Wu S, Zhang YG, Lu R, et al. Intestinal epithelial vitamin D receptor deletion leads to defective autophagy in colitis. Gut, 2015, 64(7): 1082-94.

[54] Sun J. The Role of Vitamin D and Vitamin D Receptors in Colon Cancer. Clin Transl Gastroenterol, 2017, 8(6): e103.