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Vitamin D and colorectal cancer – A practical review of the literature

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ABSTRACT

Colorectal cancer (CRC) is the third leading cause of cancer-related mortality in the United States and the second cause worldwide. Its incidence rates have been decreasing in the overall population in the US in the past few decades, but with increasing rates in the population younger than 50 years old. Environmental factors are supposed to be involved in the development of the disease, with strong evidence favoring an influence of the diet and lifestyle. A diet high in red meat and calories, and low in fiber, fruits and vegetables increases the risk of CRC, as well as physical inactivity. The influence of low calcium intake and low levels of vitamin D on the risk of the disease and on the clinical outcomes of CRC patients has also been investigated. Hypovitaminosis D has been highly prevalent worldwide and associated with several chronic diseases, including malignancies. Vitamin D is a steroid hormone with the main function of regulating bone metabolism, but with many other physiological functions, such as anti-inflammatory, immunomodulatory, and antiangiogenic effects, potentially acting as a carcinogenesis inhibitor. In this review, we aim to describe the relation of vitamin D with malignant diseases, mainly CRC, as well as to highlight the results of the studies which addressed the potential role of vitamin D in the development and progression of the disease. In addition, we will present the results of the pivotal randomized clinical trials that evaluated the impact of vitamin D supplementation on the clinical outcomes of patients with CRC.

Introduction

Colorectal cancer (CRC) is the third leading cause of cancer-related mortality in the United States and the second cause worldwide [1,2]. Declining incidence rates have been observed in the US in the past few decades, but with ascending rates in the population of patients younger than 50 years old [3]. Despite significant advances in the systemic therapy of the disease in the past few years, its prognosis remains poor, with high recurrence rates and 5-year overall survival (OS) below 15% in advanced disease [3]. Sporadic disease accounts for the majority of cases and an association between countries' human development index and their incidence rates of CRC has been observed, which suggests an influence of environmental factors in the development of the disease [2].

Well-known risk factors for sporadic CRC are aging, obesity or overweight, tobacco and alcohol use, and ethnic background [3]. There is also strong evidence that diet and lifestyle factors influence the risk of developing CRC. A diet high in red meat and calories, and low in fiber, fruits and vegetables increases the risk of CRC, as well as physical inactivity [3]. Low calcium intake and levels of vitamin D are suspected to increase the risk of the disease [4].

Hypovitaminosis D has been highly prevalent worldwide and associated with several chronic diseases, including malignancies [5]. The relationship between vitamin D and CRC has been extensively explored in the past few decades. Several meta-analyses have reported an association of lower levels of vitamin D and CRC risk [6]. Recently, a meta-analysis including 28 studies revealed a 39% lower risk between levels of circulating vitamin D and CRC risk in case-control studies and a 20% reduced CRC risk in prospective cohort studies [6].

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Vitamin D is a steroid hormone with the main function of regulating bone metabolism. However, it has many physiological functions, such as anti-inflammatory, immunomodulatory, proapoptotic, and anti-angiogenic effects [5,7,8]. Preclinical studies have suggested that it might act as a carcinogenesis inhibitor, slowing tumor progression by promoting cell differentiation and inhibiting cancer cell proliferation [9–11]. Vitamin D may, therefore, inhibit tumor invasiveness and its propensity to metastasize, potentially leading to reduced cancer mortality [9,11,12].

In this review article, after briefly describing vitamin D physiology, we aim to explore its potential antineoplastic properties, mainly in CRC, as well as summarizing the prevalence of vitamin D deficiency in both the general and CRC population. We also present the results of the pivotal randomized clinical trials which addressed the impact of vitamin D supplementation on the clinical outcomes of patients with CRC (Fig. 2, Tables 1 and 2).

Vitamin D and colorectal cancer relationship history

Although Hippocrates had already observed the importance of sunlight in human health in ancient Greece, it was only in 1880 that the epidemiologist and missionary, Theodore Palm, described the absence of rickets among children from equatorial areas given their sunlight exposure [13]. Many years later, Elmer V. McCollum, a chemist, discovered the compound that is now known as vitamin D, whose deficiency is currently linked to several diseases. The knowledge that sunlight exposure could help in cancer prevention began in 1936, when Peller observed that U.S. Navy personnel who developed skin cancer had a lower incidence of other cancers [14]. But it was only when the National Cancer Institute (NCI) published maps of the geographical distribution of cancer mortality in the US, that noticed a strong latitudinal gradient within the United States for colon cancer mortality rates that Cedric Garland and Frank Garland noticed a higher mortality rate of CRC in the Northeastern and Northern parts of the country when compared to the South and Southwest. Both investigators hypothesized that the higher risk of CRC in colder areas of US was related to less sunlight exposure and consequently lower levels of serum vitamin D [15].

Vitamin D physiology

Vitamin D3 (cholecalciferol) is the natural form of vitamin D, produced in the skin from 7-dehydrocholesterol (Fig. 1). Its synthesis in the skin depends on the intensity of the ultraviolet irradiation. It can also be obtained by eating specific foods, but rarely reaching sufficient level without supplementation [16]. In fact, individual variability in circulating levels of vitamin D does not depend solely on sunlight exposure or dietary intake, since genetic and epigenetic variables may impact on different steps along vitamin D metabolic pathway [17–19].

In the blood, vitamin D is transported by vitamin D binding protein (VDBP) to the liver, where it is hydroxylated to produce 25-hydroxyvitamin D3 ($25(OH)D_3$), the major circulating form of vitamin D (Fig. 1). $25(OH)D_3$ is transported by VDBP to the kidney and is filtered by the glomerulus. In the proximal renal tubule, $25(OH)D_3$ is metabolized by CYP27B1 to $1,25(OH)_2D_3$ (calcitriol), the functional and hormonally active form of vitamin D (Fig. 1) [16]. In the kidney, CYP27B1 is regulated by parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and calcitriol itself. Cytokines such as interferon gamma (IFNγ), tumor growth factor alpha (TNFα), and transforming growth factor beta1 (TGFβ1) are the major inducers of CYP27B1 in nonrenal tissues, such as keratinocytes and macrophages [20]. The $25(OH)D_3$ can also be converted to 24.25(OH)2D3 by CYP24A1, limiting the amount of calcitriol when its circulating level is high [16].

The biological actions of calcitriol are mediated by the vitamin D receptor (VDR), which is a member of the steroid hormone receptor family [21]. The human VDR genes are localized on chromosome 12. Intestine is the organ with the highest expression of VDR [20]. Although initially identified in the small intestine, VDR was later found in essentially all tissues in which it was sought [20]. The principal action of both calcitriol and VDR is intestinal calcium absorption [16]. Aberrant expressions of CYP24A1, CYP27B1 and VDR genes have been associated with circulating vitamin D levels and cancer [22–25]. Other genes are also implicated in vitamin D metabolism. For example, both DHCR7 and CYP2R1 are crucial components of vitamin D-metabolizing enzymes and correlation between their single nucleotide polymorphisms (SNPs) and cancer susceptibility has been described [18,26]. Polymorphisms in VDBP, especially rs4588 and rs7041, also impact on 25-OHD levels [27].

One of the main functions of calcitriol is to maintain adequate concentrations of serum and extracellular calcium and phosphorus, ensuring a variety of metabolic functions. For this, calcitriol relies on its interaction with various organs, such as adrenal glands, intestines, kidneys and parathyroids. It is responsible for the intestinal absorption of phosphorus and calcium, the mobilization of calcium from the bones and the increase in renal absorption of calcium, regulating bone metabolism [21,28]. The progressive loss of renal function leads to calcitriol deficiency and homeostatic changes in calcium, phosphorus, FGF-23 and PTH, among others, and explains why vitamin D deficiency is widespread among adults with chronic kidney disease. All these changes may also influence VDR activation and the development of secondary hyperparathyroidism (SHPT) [29].

Over the course of the last decades, it has become increasingly clear that the effects of calcitriol are not limited to the maintenance of calcium and phosphorus homeostasis. Calcitriol regulates multiple cellular processes with effects on normal and malignant cell growth and differentiation [20]. Most cancer cells express VDR, CYP27B1, and CYP24A1, which allows the cells to locally regulate calcitriol metabolism.

Anticancer properties of vitamin D in CRC

Preclinical data has showed that calcitriol may inhibit carcinogenesis based on antimitotic, prodifferentiating and proapoptotic activity [30]. The active metabolite of vitamin D exerts transcriptional activation and repression of target genes by binding to the VDR, which regulates gene expression in a ligand-dependent manner [31]. Altered expression of VDR and other important proteins in vitamin D synthesis and catabolism have been observed in several tumor types [32]. CYP27B1 and VDR are highly expressed during early CRC progression in well differentiated tumors and decreased in poorly differentiated counterparts, while CYP24A1 is upregulated, suggesting an autocrine/paracrine growth control by active metabolites of vitamin D in colorectal tissue as a restriction against tumor progression [32]. There are data showing that the chromosomal region containing the CYP24A1 gene is amplified in breast cancer, and its mRNA expression is upregulated in lung, colon and ovarian cancers, suggesting that calcitriol levels are reduced in these cases, possibly modulating tumor growth in some tissues [33–35].

VDR is overexpressed or repressed in several types of cancer, demonstrating tissue-type variations in calcitriol signaling [36–38]. VDR expression increases in hyperplastic polyps and in the early stages of tumorigenesis, but declines in late-stage poorly differentiated tumors and is absent in associated metastases [39]. CRCs with the higher expression of VDR are more responsive to supplementation of calcitriol [9]. However, downregulation of VDR in CRC cells by some transcription factors reduces its anticancer effect [39,40].

Progression through the cell cycle is regulated by cyclins, and their associated cyclin-dependent kinases (CDKs) and CDK inhibitors (CKIs). Expression of the CKIs p21 (encoded by the gene CDKN1A) and p27 (CDKN1B) inhibits proliferation, in part by inducing G1 cell-cycle arrest and withdrawal from the cell cycle (G0). Human breast cancer cells (MCF7) treated with calcitriol increase the expression of CDKN1A and CDKN1B, and repress CCND1 (encoding cyclin D1), CCND3 (encoding cyclin D3), CCNA1 (which encodes cyclin A1) and CCNE1 (which encodes cyclin E1), leading to the inhibition of CDK activity,

Table 1
Main observational studies reporting on the association of serum 25(OH)D levels with relevant clinical outcomes among CRC patients.

Reference	Study design	Study population	Time of serum 25-OH-D measure	OutcomeHR (95% CI) *Comparing extreme tertile, quartiles or quintiles (higher with lower)*	Comments
Ng et al. (2008) (51)	Cohort, prospective	Stage I-IV CRC, USA $n = 304$	Pre-CRC diagnosis (>2 years before)	OS 0.52 (0.29–0.94) CRC-Specific Survival 0.61 (0.31–1.19)	Adjusted for age, sex, season, BMI, physical activity, race, stage, grade, tumor location, dietary vitamin D intake
Fedirko et al. (2012) (52)	Cohort, prospective	Stage I-IV CRC, Europe $n = 1202$	Pre-CRC diagnosis (>2 years before)	OS 0.67 (0.50–0.88) CRC-Specific Survival 0.69 (0.50–0.93)	Adjusted for age, sex, season, BMI, smoking, physical activity, stage, tumor location, grade, dietary calcium intake; VDR and CASR genotype analysis;
Mezawa et al. (2010) (47)	Cohort, prospective, pos-hoc analysis	Stage I-IV CRC, Japan $n = 257$	Pos-CRC diagnosis, at the time of surgery	Death rate 0.16 (0.04–0.63) CRC-Specific Survival 0.98 (0.89–1.08)	Adjusted for age, sex, season, BMI, physical activity, stage, tumor location, type of resection, number of lymph nodes with metastasis
Zgaga et al. (2014) (53)	Case-control, retrospective	Stage I-III CRC, Scotland $n = 1598$	Post-CRC diagnosis (median of 105 days after surgery)	All-cause mortality 0.70 (0.55–0.89) CRC-Specific Survival 0.68 (0.50–0.90)	Adjusted for age, sex, season, stage, tumor site, surgery, time between definitive treatment and sampling, BMI, physical activity; VDR and CASR genotype analysis
Cooney et al. (2013) (54)	Case-control, retrospective	Stage I-IV CRC, USA $n = 368$	Post-CRC diagnosis (at least 21 days after chemotherapy)	Death risk 1.06 (0.64–1.75) CRC-Specific Survival 1.01 (0.59–1.74)	Adjusted for age at diagnosis, stage, race, sex, smoking status, month of blood draw, log CRP
Maalmi et al. (2017) (59)	Cohort, prospective	Stage I-IV CRC, Germany $n = 2910$	Pos-CRC diagnosis, (median of 36 days after diagnosis)	OS 0.56 (0.44–0.71) CRC-Specific Survival 0.60 (0.45–0.80)	Adjusted for Sex, age, season, stage, comorbidities, tumor location, tumor detection mode, BMI, surgery, smoking, chemotherapy, physical activity, time between diagnosis and blood draw
Wesa et al. (2015) (56)	Retrospective series	Stage IV CRC, USA $n = 250$	Pos-stage IV CRC diagnosis, stores sera of CEA ± 30 days of diagnosis	OS (adequate vs deficient) 0.61 (0.38–0.98)	Adjusted for albumin, ECOG performance status
Fuchs et al. (2017) (57)	Cohort, prospective, analysis from CALGB 89,803 phase III trial	Stage III CRC, USA and Canada $n = 1016$	25(OH)D prediction score in completely resected patients	DFS 0.62 (0.44–0.86)	Adjusted for Race, geographic region, dietary and supplemental vitamin D intake, BMI, and physical activity; stratified by molecular tumor characteristics
Yuan et al. (2019) (58)	Cohort, prospective, analysis from CALGB 80,405 phase III trial	Stage IV CRC, USA and Canada $n = 1041$	Pos-stage IV CRC diagnosis, pre- treatment	OS 0.66 (0.53–0.83) PFS 0.81 (0.66–1.00)	Adjusted for age, sex, race, ECOG, chemotherapy, treatment arm, BMI, physical activity, season, region
Ng et al. (2011) (48)	Cohort, prospective, analysis from IT N9741 phase III trial	Stage IV CRC, USA and Canada $n = 515$	Post-stage IV CRC diagnosis, after chemotherapy	OS 0.94 (0.72–1.23)	Adjusted for age, sex, race, geographic region, number of metastatic sites, chemotherapy
Maalmi et al. (2018) (59)	Meta-Analysis, 11 studies	Stage I-IV CRC, USA, Canada, Europe and Asia $n = 7718$	Miscellaneous	OS 0.68 (0.55–0.85) CRC-Specific Survival 0.67 (0.57–0.78)	I^2=64% for OS I^2=0% for CRC-Specific-Survival
Wu et al. (2020) (60)	Meta-Analysis, 17 studies	Stage I-IV CRC, USA, Canada, Europe, Asia and Oceania $n = 17,770$	Miscellaneous	OS 0.64 (0.55–0.72) CRC-Specific Survival 0.65 (0.56–0.73)	I^2=52.6% for OS I^2=0% for CRC-Specific-Survival

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CEA, Carcinoembryonic Antigen; CI, confidence interval; CRC, colorectal cancer; CRP, C-reactive protein; ECOG, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; VDR, Vitamin D Receptor; CASR, calcium sensing receptor; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

Table 2
Mains clinical trials assessing the effect of vitamin D supplementation in CRC outcomes.

Study Acronym/ Reference	Population	Intervention	Comparator	Outcome HR (95% CI)	Comments
Vital Trial Song et al. (2021) (E3)	No cardiovascular or cancer history, USA $n = 25,871$	2000 IU vitamin D3 + 1 g marine ω−3 fatty acid daily	Placebo	Colon polyp risk 1.08 (0.92–1.27) Serrated polyp risk 1.02 (0.82–1.26) CRC risk 1.09 (0.73–1.62)	- Double-blind - Follow-up considered insufficient - Benefit for BMI<27 (prespecified analyses): 0.86 (95% CI, 0.75–0.99).
WHI trials Wactawski-Wende et al. (2006) (E12)	Post-menopausal women, USA $n = 36,282$	1000 mg of elemental calcium and 400 UI of vitamin D3, daily	Placebo	Invasive CRC-incidence 1.08 (0,86–1,34)	- Double-blind - CRC-incidence as secondary outcome
AMATERASU trial Urashima et al. (2019) (E20)	Stage I-III TGI cancers, Japan $n = 417$	2000 IU vitamin D3, daily	Placebo	Risk of relapse or death 0.76 (0.50–1.14)	- Double-blind - CRC-patients subgroup analysis: HR 0.69 (0.39–1.24)
SUNSHINE trial Ng et al. (2019) (E22)	Advanced or metastatic CRC, USA $n = 139$	High vitamin D3 dose (8000 IU for QT cycle 1 followed by 4000 IU/d for subsequent cycles, daily)	Standard vitamin D3 dose (400 IU, daily, all QT cycles)	PFS or death 13 vs 11 months 0.64 (0–0.90; $p = 0.02$)	-Double blind, phase II - OS as secondary outcome (median, 24.3 vs 24.3 months; log-rank $p = 0.43$)
Gulobic et al. (2018) (81)	Advanced or metastatic CRC, Croatia $n = 71$	2000 IU vitamin D3, daily	No supplementation	OS 1.0064 (0.38– 2.60)	-Open-label - PFS as secondary endpoint, no difference

Abbreviations: BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

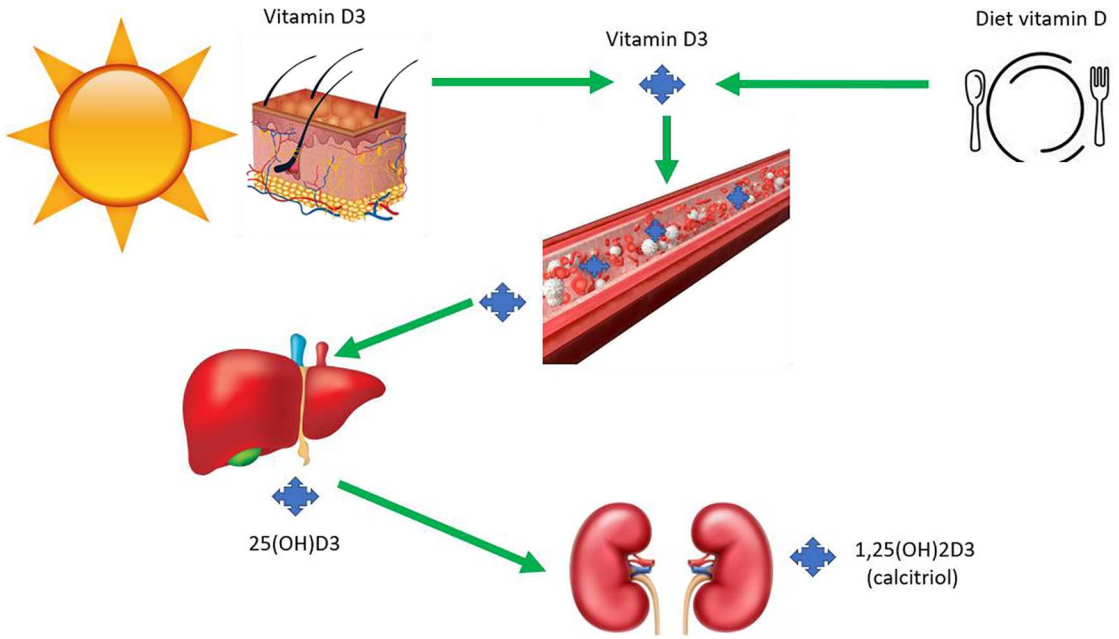

Fig. 1. Summarized physiology of vitamin D Vitamin D3 (cholecalciferol) is the natural form of vitamin D, produced in the skin from 7-dehydrocholesterol or, more rarely, obtained by eating specific foods. In the blood, vitamin D is transported by vitamin D binding protein (DBP) to the liver, where it is hydroxylated to produce 25-hydroxyvitamin D3 ($25(OH)D_3$), the major circulating form of vitamin D. $25(OH)D_3$ is transported by DBP to the kidney. In the proximal renal tubule, $25(OH)D_3$ is metabolized by CYP27B1 to $1,25(OH)_2D_3$ (calcitriol), the functional and hormonally active form of vitamin D.

phosphorylation of pRb and restraint of cell-cycle progression [41,42]. Other genes are transcriptionally affected by calcitriol in CRC, ovarian carcinoma and leukemia cells, such as the repression of genes involved in DNA replication (*TYMS*, which encodes thymidylate synthetase; *TK1*, which encodes thymidine kinase), activation of genes involved in G1 cell-cycle arrest (*INK4*, family of CKIs), downregulation of genes which target CKIs to ubiquitin-mediated proteasomal degradation (Cyclin E–CDK2; *SKP2*, S-phase kinase-associated protein 2) and repression of the protooncogene *MYC*. All of these gene transcription alterations significantly contribute to the antiproliferative effects of vitamin D [43–46]. Activation of the VDR by calcitriol can also inhibit tumor cell proliferation by inducing differentiation. In addition, calcitriol promoted differentiation through the induction of *CDH1* (which encodes E cadherin) in a cell line of *APC*-mutated human CRC. *CDH1* activation facilitates the translocation of β-catenin from the nucleus to the plasma membrane, allowing activated VDR to compete with β-catenin for transcription factor binding. Then, it inhibits the Wnt–β-catenin–TCF4 signaling pathway and lastly restrains cell-cycle progression and cell growth [47].

There is increasing evidence that calcitriol exerts antitumor effects by regulating key mediators of apoptosis, such as repressing the expression of the antiapoptotic/pro-survival proteins (BCL2 and BCL-

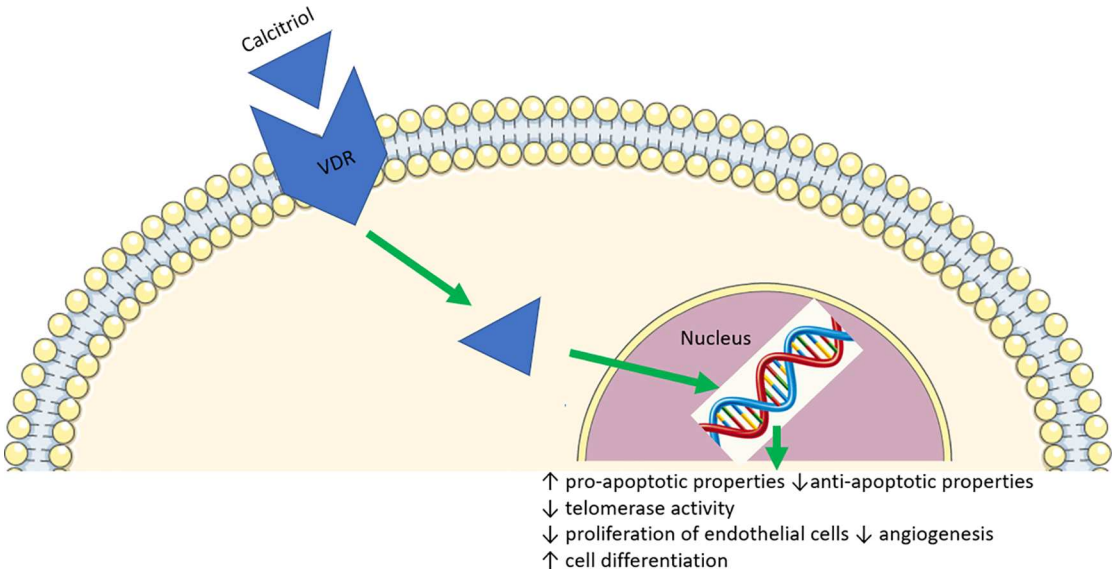

Fig. 2. Potential mechanisms of anticancer properties of vitamin D Calcitriol binds to VDR and results in transcriptional activation and repression of target genes, leading to increased apoptosis, decreased angiogenesis and cell differentiation.

XL), or inducing the expression of proapoptotic proteins (BAX, BAK and BAD). In epithelial ovarian cancer cells, a novel mechanism of telomerase-mediated apoptosis was proposed, showing that calcitriol destabilizes telomerase reverse transcriptase (TERT) mRNA, inducing apoptosis through telomere attrition resulting from the downregulation of telomerase activity [48]. Experimental evidence also suggests that vitamin D might potentiate the anticancer effects of many cytotoxic and antiproliferative anticancer agents [49].

Calcitriol also inhibits the proliferation of endothelial cells and thereby, angiogenesis. Vascular endothelial growth factor (VEGF)-induced endothelial cell tube formation and tumor growth are inhibited *in vivo* by administration of calcitriol to VEGF-overexpressing xenograft mouse models. Calcitriol also upregulates mRNA levels of the potent antiangiogenic factor thrombospondin 1 (THBS1) in human colon tumor cells [50,51]. In tumor-derived endothelial cells (TDECs), calcitriol induces apoptosis and cell-cycle arrest; however, these effects are not seen in endothelial cells from normal tissues, possibly because TDECs may be more sensitive to calcitriol through epigenetic silencing of CYP24A1 [52,53]. Lastly, direct effects of calcitriol on endothelial cells may have a primary role in its antitumor activity observed in animal models of cancer.

In summary, plausible mechanisms of antitumoral effects of vitamin D include induction of cell-cycle arrest, apoptosis of tumor cells, promotion of cell differentiation, inhibition of cancer cell proliferation and antiangiogenic effects. Other chemoprotective mechanisms are also worthy of consideration. These alternative mechanisms include enhancing DNA repair, antioxidant protection, anti-inflammatory and immunomodulation. In addition, other cell targets such as the stromal cells, endothelial cells, and cells of the immune system may be regulated by calcitriol and contribute to vitamin D mediated cancer prevention [54].

Prevalence of vitamin D deficiency in the general population and among colorectal cancer patients

It has been estimated that 1 billion people worldwide have vitamin D deficiency (< 20 ng/mL) or insufficiency (<30 ng/mL). In the US and Europe, approximately 40% to 100% of elderly people present with vitamin D deficiency, and approximately 70% to 97% of Canadians are estimated to harbor vitamin D insufficiency, although there has been recent improvement in vitamin D status in the North American population [55,56]. In addition, more than 50% of postmenopausal women taking medication for osteoporosis in the US have suboptimal levels of 25-hydroxyvitamin D [55]. In a Brazilian meta-analysis, the mean vitamin D concentration in the studied population was 27 ng/L. The prevalence of vitamin D deficiency and insufficiency were 28% and 45%, respectively [57]. In parallel, approximately 20% of the African population has low levels of the vitamin. Prevalence of vitamin D deficiency varied by region, with the highest risk reported in the countries in northern Africa and in the South Africa [58].

Similarly, another work suggests that vitamin D deficiency is widespread across Europe and its prevalence rates meet the criteria of a pandemic. Although there was considerable variation dependent on age group, ethnic background, and geographical location, 13% of the European population (n = 55,844) presented with vitamin D deficiency [59].

Likewise, vitamin D insufficiency has been found highly prevalent among patients with metastatic CRC. In a study including 257 patients from Japan, only 3% presented with sufficient levels of vitamin D [60]. Another study comprising 515 patients with advanced CRC accrued to a clinical trial throughout the US and Canada, the median plasma level of vitamin D was 20 ng/mL (range, 2.3 to 75.4 ng/mL). Indeed, 82% of those patients were vitamin D insufficient, while 50% of them were deficient [61]. Similarly, in another study from the US with 94 CRC patients, 65% of participants with a new diagnosis of CRC had vitamin D levels that were either insufficient or deficient [62]. A more recent study with 1733 CRC patients showed that the median serum vitamin D level at CRC diagnosis was 21.2 ng/mL [63].

Relationship between vitamin D levels and outcomes in CRC

Observational prospective studies have evaluated the association of vitamin D levels before and after the diagnosis of CRC and the prognosis of the patients. Study with 304 patients with stage I-IV CRC evaluated the vitamin D levels a mean of 6.0 years before the diagnosis. Those patients within the highest quintile of vitamin D levels had improved overall survival (OS) (HR:0.52, 95% CI 0.29–0.94) and decreased CRC-specific mortality (HR:0.61, 95% CI 0.31–1.19) compared to those within the lowest quintile [64]. Similarly, a second study measuring vitamin D 3.8 years prior to the diagnosis of CRC included 1202 patients with stages I-IV disease and reported that those with the highest quintile of vitamin D levels had prolonged OS (HR:0.67, 95% CI 0.50–0.88) and

CRC-specific survival (HR:0.69, 95% CI 0.50–0.93) compared to those with levels in the lowest quintile [65].

Other studies have measured vitamin D levels after the diagnosis of CRC. A Japanese prospective cohort of 257 patients measured vitamin D levels at the time of surgery. Those patients with levels in the highest quartile had a significant reduction in death rate (HR: 0.16, 95% CI 0.04–0.63) after multivariable adjustment for age, gender, month of blood sampling, cancer stage, residual tumor after surgery, time period of surgery, location of tumor, adjuvant chemotherapy and number of metastatic lymph nodes [60]. A prospective population-based case--control study measured vitamin D levels post-operatively in 1598 patients with stage I-III CRC who underwent surgery with curative intent. There was a strong association between vitamin D levels (highest vs lowest tertile) with all-cause mortality (HR: 0.70, 95% CI 0.55–0.89) and CRC-specific mortality (HR: 0.68, 95% CI 0.50–0.90). This study also genotyped VDR and detected gene-environment interactions between vitamin D concentration and rs11568820 genotype for CRC-specific mortality ($p = 0.022$) [66]. On the other hand, a population-based case-control study measured post-treatment levels of vitamin D in 368 patients with CRC, of which 3.5% had metastatic disease, and found that vitamin D levels were not associated with survival [67].

Studies with larger number of patients also investigated whether vitamin D levels were related to CRC outcomes. The association of pre-diagnostic vitamin D levels and CRC-specific and overall mortality in a prospective cohort of 1202 patients diagnosed with CRC was reported by the European Prospective Investigation into Cancer and Nutrition (EPIC) Group. The authors demonstrated that higher pre-diagnostic vitamin D levels were associated with a statistically significant reduction in CRC-specific mortality and overall mortality. Patients in the highest quintile (vs. lowest quintile) had an adjusted HR of 0.69 (95% CI 0.50–0.93) for CRC-specific mortality and of 0.67 (95% CI 0.50–0.88) for overall mortality [65]. Another prospective cohort of 2910 patients diagnosed with stages I-IV CRC had serum samples collected shortly after cancer diagnosis. Compared to patients in the highest vitamin D quintile, those in the lowest quintile demonstrated increased mortality. Adjusted HRs (95% CI) were 1.78 (1.39–2.27), 1.65 (1.24–2.21), 1.32 (1.03–1.71) and 1.48 (1.18–1.85) for all-cause mortality, CRC-specific mortality, recurrence-free and disease-free survival, respectively [68]. A retrospective series of 250 patients with stage IV CRC analyzed vitamin D levels from stored sera collected within ± 30 days of diagnosis. Higher levels of serum vitamin D (≥30 ng/mL) were associated with prolonged OS (HR: 0.61, 95% CI 0.38–0.98) compared to deficient levels [69].

Alliance (CALGB 89,803) phase III trial compared weekly 5FU/LV with 5FU/LV plus irinotecan (IFL) in stage III CRC patients. A post-hoc analysis investigated the prognostic value of vitamin D levels. In a population of 1106 patients, those in the highest quintile had an adjusted HR for CRC recurrence or mortality of 0.62 (95% CI, 0.44–0.86) compared to those in the lowest quintile. The benefit associated with higher levels remained significant even after adjusting for other prognostic factors and was consistent in several strata of clinical, pathologic, and molecular characteristics [70]. Vitamin D levels were also evaluated in the phase III CALGB 80,405 trial, which compared first-line chemotherapy (FOLFOX/FOLFIRI) with a biologic agent (cetuximab or bevacizumab) in patients with stage IV CRC. In a population of 1041 patients, 63% were vitamin D deficient (<20 ng/mL) and 31% were vitamin D insufficient (20 to <30 ng/mL). Patients in the top quintile of vitamin D (≥24.1 ng/mL) had a multivariable-adjusted HR of 0.66 (95% CI, 0.53–0.83) for OS and a more modest effect on progression-free survival (PFS), with a HR of 0.81 (95% IC, 0.66–1.00), compared to those in the bottom quintile (≤10.8 ng/mL) [71]. Differently, a randomized phase III trial (N9741) compared FOLFOX versus IFL as first-line regimen in 1379 patients with metastatic CRC, of which 515 patients had availability of plasma for vitamin D measurement. The analysis showed that vitamin D levels were not associated with survival (HR: 0.94, 95% CI 0.72–1.23) [61].

The AA genotype of GC rs4588 SNP has been linked to lower levels of 25-OHD [27]. In an interesting analysis of two phase III trials (FIRE-3 and TRIBE) in metastatic CRC, AA carriers treated with first-line FOLFIRI and bevacizumab (a monoclonal antibody with antiangiogenic properties) had inferior outcomes compared with C allele carriers. The author hypothesized that the inhibitory effect on VEGF- independent angiogenesis is smaller among AA carriers [72], who also have lower circulating levels of vitamin D.

Several meta-analyses have reported association between vitamin D levels and clinical outcomes in CRC. Meta-analysis including 11 studies with 7718 patients reported improvement in OS with increasing vitamin D levels. Comparing the highest versus the lowest categories, pooled HRs (95% CI) were 0.68 (0.55–0.85) for OS and 0.67 (0.57–0.78) for CRC-specific survival [73]. A larger meta-analysis of 17 studies with 17,770 patients also demonstrated improved OS and CRC-specific survival comparing the highest versus lowest levels of vitamin D. The pooled HR was 0.64 (0.55–0.72) for OS and 0.65 (0.56–0.73) for CRC-specific survival [74].

Clinical data of vitamin D supplementation and outcomes in CRC

Vitamin D supplementation and development of colon polyps

There are conflicting results from studies addressing the association of vitamin D intake and development of colon polyps. An analysis of 141,143 participants from three large prospective trials evaluated the association of risk factors of CRC and colon polyps. The participants had undergone colonoscopy and were followed up until diagnosis of a first polyp. Thirteen risk factors were assessed, including vitamin D intake. This study showed that vitamin D intake was inversely associated with serrated polyps (OR 0.92, 95% CI, 0.86–0.98) and conventional adenomas (OR, 0.85; 95% CI, 0.80–0.90) [75].

Likewise, an observational study with 1409 participants who had undergone screening colonoscopy suggested a protective effect of vitamin D intake on the development of colon polyps, with an adjusted OR of 0.57 (95% CI, 0.33–0.96). Meeting the recommended daily intake of vitamin D (600IU) was also protective (adjusted OR of 0.57; 95% CI 0.33–0.96). The impact of supplementation may be especially important on this specific population due to high prevalence of vitamin D insufficiency among individuals living in high latitude locations [76].

A recent large prospective trial did not confirm the benefit of vitamin D supplementation on the primary endpoints of incidence of cancer and cardiovascular disease. The VITAL trial randomized 25,871 adults to receive vitamin D3 2000 IU daily and marine n-3 fatty acid 1 g daily or placebo. There was no association between vitamin D supplementation and the secondary endpoint of colon polyps (OR for adenoma, 1,08; 95% CI, 0.92–1.27 and for serrated polyp, 1.02; 95% CI 0.82–1.26). A potential benefit of supplementation was observed among individuals with 25(OH)D serum levels below 30 ng/ml (OR for adenoma was 0.82 (95% CI, 0.60–1.13)) [77].

The effects of vitamin D supplementation may vary according to calcium intake. This interaction was shown in a case control study with 980 subjects in which a protective effect of vitamin D for distal colon adenoma recurrence was evident only among those with calcium intake below the median (OR: 0.40 for highest versus lowest quartile, 95% CI, 0.22–0.71, p for trend = 0.005) [78].

Vitamin D supplementation and recurrence of colon polyps

Overall, prospective studies do not show strong evidence that vitamin D supplementation reduces the risk of colon cancer recurrence. The Polyp Prevention Trial was a randomized multicenter clinical trial designed to determine the effects of diet on the recurrence of adenomatous polyps in the large bowel of 1905 patients. Supplementation of calcium and vitamin D during follow-up were inversely associated with adenoma recurrence (OR 0.82; 95% CI 0.68–0.99). Among the control

group, the multivariate OR for any use of supplemental vitamin D was 0.71 (95% CI 0.54–0.98) compared with 0.95 (95% CI 0.73–1.24) for the intervention group, showing no significant effect of calcium and vitamin D intake on the risk of adenoma recurrence [79].

A large placebo-controlled chemoprevention study randomized 2259 patients with one or more adenoma at baseline to receive 1200 mg/day of elemental calcium, 1000 IU/day of vitamin D3, both or neither agent. Treatment continued for 3 or 5 years, at which time a surveillance colonoscopy was performed to assess for recurrence of polyps. During this treatment phase, there was no effect of either calcium or vitamin D on incidence of sessile adenomas or polyps. However, during the later observational phase, elevated risk of sessile serrated adenomas was observed with calcium and vitamin D treatment (adjusted RR 3.81; 95% IC; 1.25–11.64), but not with vitamin D alone (adjusted RR 1.30; 95% IC; 0.81–2.09), suggesting a late deleterious effect of combined supplementation [80]. The potential benefit of the vitamin D supplementation on the prevention of advanced colorectal adenomas may vary according to polymorphisms of the VDR [81].

Dietary vitamin D and colorectal cancer incidence

The association of dietary vitamin D and risk of CRC has been studied in the past few decades. Nineteen-year prospective study with 1954 men reported 29 cases of CRC, who had lower dietary vitamin D compared to the participants who did not develop the disease ($p \leq 0.05$). Risk of CRC was inversely correlated with dietary vitamin D and calcium ($p \leq 0.05$). This association remained significant even after adjustment for age, daily cigarette consumption, body mass index, ethanol consumption, and percentage of calories obtained from fat [82].

Similarly, a meta-analysis with 31 original studies reported a significant 25% lower risk of developing CRC comparing the highest vs. the lowest dietary vitamin D consumption (OR 0.75 – 95% CI 0.67–0.85) in case-control studies, whereas a non-significant association was described for prospective studies (HR 0.94 – 95% CI 0.79- 1.11) [83].

A prospective study containing 60,866 men and 66,883 women drawn from the Cancer Prevention Study II Nutrition Cohort showed that higher total vitamin D intake was associated with reduced risk of CRC in men ($p = 0.02$). Nearly half of all men and women in the highest quintile of total vitamin D intake were long-term multivitamin users ($\geq$ 4 pills/week in 1982 and 1992) [84].

A meta-analysis with 8 prospective studies on vitamin D intake showed a risk reduction of 0.79 (95% CI, 0.67–0.90) and 0.78 (95% CI, 0.63–0.93) for colon and rectal cancer occurrence, respectively. The overall RR was 0.88 (95% CI, 0.80–0.96) [85]. In parallel, a systematic review with 14 observational studies of the association between pre-diagnostic oral intake of vitamin D and risk of CRC suggested that 1000 IU/day vitamin D3 supplement was associated with a 50% reduction in CRC ($p = 0.0001$). This study included many different trials and, since oral intake of vitamin D was quite low, extrapolation was needed to determine its estimated effective dose [86]. However, this reported impact was not confirmed in prospective clinical trials of vitamin D supplementation, as shown below.

Vitamin D supplementation and CRC incidence

Randomized clinical trial addressed the potential protective effect of vitamin D intake on the incidence of CRC. Population of 36,282 postmenopausal women from 40 Women's Health Initiative Centers in the US were randomized to receive 1000 mg of elemental calcium and 400 IU of vitamin D3 or a matching placebo for an average of 7 years. The incidence of invasive CRC, which was designed as a secondary outcome, did not differ significantly between the two groups. Among the 322 CRC cases, 168 were in the supplementation group versus 154 in the placebo group, with a HR of 1.08 (95% CI, 0.86–1.34; $p = 0.51$). The characteristics of CRC, including stage, were similar in both groups. The high intake of calcium and vitamin D among all the participants at baseline may have limited the ability to assess the effect of the study driven supplementation. Participants were not restricted from taking vitamin D supplements on their own and their mean intake at enrollment was twice the national average at that time [87].

The VITAL trial also did not show a reduced risk of CRC among the 12,927 patients assigned to receive daily vitamin D 2000 IU and marine n-3 fatty acid 1 g supplementation (HR 1.09; 95% CI, 0.73–1.62). Differences regarding cancer stage were not significant. Prespecified subgroup analyses showed differences according to body-mass index (BMI): normal-weight participants who received vitamin D had a lower CRC incidence compared to those who received placebo – HR of invasive cancer of any type in participants with BMI <27.1 was 0.86 (95% CI, 0.75–0.99), compared to HR 1.08 among those with BMI ≥27.1 (95% CI, 0.94–1.24), suggesting that BMI may modify the effect of vitamin D. Given the long latency for cancer development, the 5.3 years follow-up of the trial may have not been sufficient to show a protective effect [88]. Trials evaluating the effect of vitamin D supplementation on all-type cancer incidence have also failed to show benefit [89–91].

In contrast to the aforementioned trials, a more recently published meta-analysys including 37 case-control studies reported a 4% decrease in the risk of CRC per 100 IU/day of vitamin D [92]. In addition, another meta-analysis demonstrated a protective role of vitamin D on the incidence of CRC (OR 0.87 – 95% CI 0.82–0.92) with either dietary or supplemental sources [93]. Further studies are needed to best address the question whether vitamin D supplementation reduces the risk of CRC.

Vitamin D supplementation in CRC patients

Single-arm prospective study involving 453 patients with stage II CRC evaluated the impact of the supplementation of vitamin D on the risk of recurrence or mortality. Despite the results suggested potential positive impact on the quality of life, it did not demonstrate influence of supplementation on cancer recurrence or survival [94].

Randomized clinical trials did not show impact of vitamin D supplementation on CRC mortality [87,95]. Likewise, neither the aforementioned VITAL trial nor the RECORD trial that randomized 5292 participants to receive 800 IU/day vitamin D3, 1100 mg calcium, both or placebo in a secondary fracture prevention study [88,96].

The AMATERASU trial randomized 417 patients with stage I-III gastrointestinal cancers, including 201 patients with CRC to receive 2000 IU/day of vitamin D supplementation or placebo. Patients received standard oncological treatment and were regularly screened for cancer relapse. Vitamin D supplementation did not significantly reduce the risk of relapse or death (HR 0.76; 95% CI, 0.50–1.14, $p = 0.18$). Subgroup analyses of CRC patients also did not show any benefit (HR 0.69; 95% CI, 0.39–1.24) [97].

Randomized clinical trial with 71 patients with metastatic CRC compared standard chemotherapy alone versus the addition of 2000 IU/day vitamin D3 for 2 years. After a median follow-up of 46 months, no benefit in OS or PFS was shown [98]. Likewise, the larger double-blind phase 2 SUNSHINE trial examined the addition of high-dose (4000 IU/day) versus standard dose (400 IU/day) vitamin D3 to mFOLFOX6 plus bevacizumab in 139 patients with advanced or metastatic CRC. Median follow-up was 16.1 months. Patients randomized to receive high-dose vitamin D had longer PFS than those in the standard-dose group, with HR of 0.66 (95% CI, 0.45–0.99; $p = 0.02$), after multivariate adjustment for prognostic variables [99]. The phase 3 trial SOLARIS is currently underway, comparing high-dose versus standard-dose of vitamin D3 in previously untreated patients with metastatic CRC under treatment with mFOLFOX6 + bevacizumab, and its results will help elucidate this question (NCT04094688).

Conclusions

CRC is a multifactorial disease whose carcinogenesis is a result of a

complex interplay between genetic and environmental factors. Epidemiological studies suggest that diet and lifestyle are key factors for the development of the disease. Nevertheless, the identification of dietary elements involved in the carcinogenesis and their potential influence on clinical outcomes are challenging, even with well-designed and well-conducted randomized clinical trials. Despite data derived from preclinical and initial prospective studies showed an association between low levels of vitamin D and CRC, suggesting that vitamin D might have inhibitory effects on colorectal carcinogenesis, randomized clinical trials have not demonstrated impact of vitamin D supplementation on CRC incidence, recurrence, progression, or mortality. However, many questions remain unanswered and the ongoing clinical trials may shed lights on this obscure relationship between vitamin D and CRC.

CRediT authorship contribution statement

Renata D'Alpino Peixoto: Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Supervision. **Leandro Jonata de Carvalho Oliveira:** Writing – original draft, Writing – review & editing. **Thaís de Melo Passarini:** Writing – original draft, Writing – review & editing. **Aline Chaves Andrade:** Writing – original draft, Writing – review & editing. **Paulo Henrique Diniz:** Writing – review & editing. **Gabriel Prolla:** Writing – original draft, Writing – review & editing. **Larissa Costa Amorim:** Writing – original draft, Writing – review & editing. **Mariana Gil:** Writing – original draft, Writing – review & editing. **Flora Lino:** Writing – review & editing. **Bernardo Garicochea:** Writing – review & editing. **Alexandre Jácome:** Writing – original draft, Writing – review & editing. **Kimmie Ng:** Writing – review & editing, Supervision.

Declaration of Competing Interest

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References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2020, CA Cancer J. Clin. 70 (1) (2020) 7–30, https://doi.org/10.3322/caac.21590.
[2] H. Sung, J. Ferlay, R.L. Siegel, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA Cancer J. Clin. 71 (3) (2021) 209–249.
[3] R.L. Siegel, K.D. Miller, A. Goding Sauer, et al., Colorectal cancer statistics, 2020, CA Cancer J. Clin. 70 (3) (2020) 145–164.
[4] N. Keum, D. Aune, D.C. Greenwood, W. Ju, E.L. Giovannucci, Calcium intake and colorectal cancer risk: dose–response meta-analysis of prospective observational studies, Int. J. Cancer 135 (8) (2014) 1940–1948.
[5] A. Mithal, D.A. Wahl, J.P. Bonjour, et al., Global vitamin D status and determinants of hypovitaminosis D, Osteoporos. Int. 20 (11) (2009) 1807–1820.
[6] P. Hernández-Alonso, H. Boughanem, S. Canudas, et al., Circulating vitamin D levels and colorectal cancer risk: a meta-analysis and systematic review of case-control and prospective cohort studies, Crit. Rev. Food Sci. Nutr. (2021) 1–17, https://doi.org/10.1080/10408398.2021.1939649. Jul 5.
[7] G. Bivona, L. Agnello, M. Ciaccio, The immunological implication of the new vitamin D metabolism, Cent. Eur. J. Immunol. 43 (3) (2018) 331.
[8] I. Chung, G. Han, M. Seshadri, et al., Role of vitamin D receptor in the antiproliferative effects of calcitriol in tumor-derived endothelial cells and tumor angiogenesis *in vivo*, Cancer Res. 69 (3) (2009) 967–975.
[9] D. Feldman, A.V. Krishnan, S. Swami, E. Giovannucci, B.J. Feldman, The role of vitamin D in reducing cancer risk and progression, Nat. Rev. Cancer 14 (5) (2014) 342–357, https://doi.org/10.1080/10408398.2021.1939649.
[10] H. Pols, J. Birkenhäger, J. Foekens, J. Van Leeuwen, Vitamin D: a modulator of cell proliferation and differentiation, J. Steroid Biochem. Mol. Biol. 37 (6) (1990) 873–876.
[11] M.D. Griffin, W.H. Lutz, V.A. Phan, L.A. Bachman, D.J. McKean, R. Kumar, Potent inhibition of dendritic cell differentiation and maturation by vitamin D analogs, Biochem. Biophys. Res. Commun. 270 (3) (2000) 701–708.
[12] L.L. Ooi, H. Zhou, R. Kalak, et al., Vitamin D deficiency promotes human breast cancer growth in a murine model of bone metastasis, Cancer Res. 70 (5) (2010) 1835–1844.
[13] T.A. Palm, The geographical distribution and aetiology of rickets, Practitioner 45 (270–279) (1890) 321–342.
[14] Peller S., Stephenson C.S. Skin irritation and cancer in the US Navy. 1937.
[15] C.F. Garland, F.C. Garland, Do sunlight and vitamin D reduce the likelihood of colon cancer? Int. J. Epidemiol. 9 (3) (1980) 227–231.
[16] S. Christakos, P. Dhawan, A. Verstuyf, L. Verlinden, G. Carmeliet, Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects, Physiol. Rev. 96 (1) (2016) 365–408.
[17] I.S. Carvalho, C.I. Gonçalves, J.T. Almeida, et al., Association of vitamin D pathway genetic variation and thyroid cancer, Genes 10 (8) (2019) 572 (Basel).
[18] T.J. Wang, F. Zhang, J.B. Richards, et al., Common genetic determinants of vitamin D insufficiency: a genome-wide association study, Lancet N. Am. Ed. 376 (9736) (2010) 180–188.
[19] P. Gnagnarella, S. Raimondi, V. Aristarco, et al., Ethnicity as modifier of risk for Vitamin D receptors polymorphisms: comprehensive meta-analysis of all cancer sites, Crit. Rev. Oncol. Hematol. 158 (2021), 103202.
[20] D.D. Bikle, Vitamin D: newer concepts of its metabolism and function at the basic and clinical level, J. Endocr. Soc. 4 (2) (2020) bvz038.
[21] L.O. Galvão, M.F. Galvão, C.M.S. Reis, C. Batista, L.A. Casulari, Considerações atuais sobre a vitamina D, Brasília Med. 50 (4) (2013) 324–332.
[22] F.U. Afshan, A. Masood, B. Nissar, et al., Promoter hypermethylation regulates vitamin D receptor (VDR) expression in colorectal cancer-a study from Kashmir valley, Cancer Genet. 252 (2021) 96–106.
[23] M. Latacz, J. Snarska, E. Kostyra, et al., Single nucleotide polymorphisms in 25-hydroxyvitamin D3 1-alpha-hydroxylase (CYP27B1) gene: the risk of malignant tumors and other chronic diseases, Nutrients 12 (3) (2020) 801.
[24] I.A. Voutsadakis, Vitamin D receptor (VDR) and metabolizing enzymes CYP27B1 and CYP24A1 in breast cancer, Mol. Biol. Rep. 47 (12) (2020) 9821–9830.
[25] Y.H. Bai, H. Lu, D. Hong, C.C. Lin, Z. Yu, B.C. Chen, Vitamin D receptor gene polymorphisms and colorectal cancer risk: a systematic meta-analysis, World J. Gastroenterol. 18 (14) (2012) 1672.
[26] J. Wen, J. Li, X. Liang, A. Wang, Association of polymorphisms in vitamin D-metabolizing enzymes DHCR7 and CYP2R1 with cancer susceptibility: a systematic review and meta-analysis, Dis. Markers. 2021 (2021), 6615001, https://doi.org/10.1155/2021/6615001 eCollection 2021.
[27] D. Rozmus, J. Płomiński, K. Augustyn, A. Cieślińska, rs7041 and rs4588 Polymorphisms in Vitamin D Binding Protein Gene (VDBP) and the Risk of Diseases, Int. J. Mol. Sci. 23 (2) (2022) 933.
[28] A. Hossein-nezhad, M.F. Holick, Vitamin D for Health: A Global Perspective, Elsevier, 2013, pp. 720–755.
[29] J. Bover, J. Egido, E. Ferández-Giráldez, et al., Vitamin D, vitamin D receptor and the importance of its activation in patients with chronic kidney disease, Nefrología 35 (1) (2015) 28–41 (English Edition).
[30] K.K. Deeb, D.L. Trump, C.S. Johnson, Vitamin D signalling pathways in cancer: potential for anticancer therapeutics, Nat. Rev. Cancer 7 (9) (2007) 684–700.
[31] R.M. Evans, The steroid and thyroid hormone receptor superfamily, Science 240 (4854) (1988) 889–895.
[32] H.S. Cross, G. Bises, D. Lechner, T. Manhardt, E. Kállay, The vitamin D endocrine system of the gut-its possible role in colorectal cancer prevention, J. Steroid Biochem. Mol. Biol. 97 (1–2) (2005) 121–128.
[33] D.G. Albertson, B. Ylstra, R. Segraves, et al., Quantitative mapping of amplicon structure by array CGH identifies CYP24 as a candidate oncogene, Nat. Genet. 25 (2) (2000) 144–146.
[34] M.M. Weiss, A.M. Snijders, E.J. Kuipers, et al., Determination of amplicon boundaries at 20q13. 2 in tissue samples of human gastric adenocarcinomas by high-resolution microarray comparative genomic hybridization, J. Pathol. A J. Pathol. Soc. G. B. Irel. 200 (3) (2003) 320–326.
[35] M.G. Anderson, M. Nakane, X. Ruan, P.E. Kroeger, J.R. Wu-Wong, Expression of VDR and CYP24A1 mRNA in human tumors, Cancer Chemother. Pharmacol. 57 (2) (2006) 234–240.
[36] M. Friedrich, L. Rafi, T. Mitschele, W. Tilgen, W. Schmidt, J. Reichrath, Analysis of the vitamin D system in cervical carcinomas, breast cancer and ovarian cancer. Vitamin D Analogs in Cancer Prevention and Therapy, Springer, 2003, pp. 239–246.
[37] T. Mitschele, B. Diesel, M. Friedrich, et al., Analysis of the vitamin D system in basal cell carcinomas (BCCs), Lab. Investig. 84 (6) (2004) 693–702.
[38] J. Reichrath, L. Rafi, M. Rech, et al., Analysis of the vitamin D system in cutaneous squamous cell carcinomas, J. Cutan. Pathol. 31 (3) (2004) 224–231.
[39] D. Matusiak, G. Murillo, R.E. Carroll, R.G. Mehta, R.V. Benya, Expression of vitamin D receptor and 25-hydroxyvitamin D3-1α-hydroxylase in normal and malignant human colon, Cancer Epidemiol. Biomark. Prev. 14 (10) (2005) 2370–2376.
[40] H.G. Pálmer, M.J. Larriba, J.M. García, et al., The transcription factor SNAIL represses vitamin D receptor expression and responsiveness in human colon cancer, Nat. Med. 10 (9) (2004) 917–919.
[41] L. Verlinden, A. Verstuyf, R. Convents, S. Marcelis, M. Van Camp, R. Bouillon, Action of 1, 25 (OH) 2D3 on the cell cycle genes, cyclin D1, p21 and p27 in MCF-7 cells, Mol. Cell. Endocrinol. 142 (1–2) (1998) 57–65.
[42] S.S. Jensen, M.W. Madsen, J. Lukas, L. Binderup, J. Bartek, Inhibitory effects of 1α, 25-dihydroxyvitamin D3 on the G1–S phase-controlling machinery, Mol. Endocrinol. 15 (8) (2001) 1370–1380.
[43] H.G. Pálmer, M. Sánchez-Carbayo, P. Ordóñez-Morán, M.J. Larriba, C. Cordón-Cardó, A. Muñoz, Genetic signatures of differentiation induced by 1α, 25-dihydroxyvitamin D3 in human colon cancer cells, Cancer Res. 63 (22) (2003) 7799–7806.

[44] Q.M. Wang, J.B. Jones, G.P. Studzinski, Cyclin-dependent kinase inhibitor p27 as a mediator of the G1-S phase block induced by 1, 25-dihydroxyvitamin D3 in HL60 cells, Cancer Res. 56 (2) (1996) 264–267.
[45] P. Li, C. Li, X. Zhao, X. Zhang, S.V. Nicosia, W. Bai, p27Kip1 stabilization and G1 arrest by 1, 25-dihydroxyvitamin D3 in ovarian cancer cells mediated through down-regulation of cyclin E/cyclin-dependent kinase 2 and Skp1-Cullin-F-box protein/Skp2 ubiquitin ligase, J. Biol. Chem. 279 (24) (2004) 25260–25267.
[46] M.A. Caligo, G. Cipollini, M. Petrini, P. Valentini, G. Bevilacqua, Down regulation of NM23. H1, NM23. H2 and c-myc genes during differentiation induced by 1, 25 dihydroxyvitamin D3, Leuk. Res. 20 (2) (1996) 161–167.
[47] H.G. Pálmer, J.M. González-Sancho, J. Espada, et al., Vitamin D3 promotes the differentiation of colon carcinoma cells by the induction of E-cadherin and the inhibition of β-catenin signaling, J. Cell Biol. 154 (2) (2001) 369–388.
[48] F. Jiang, J. Bao, P. Li, S.V. Nicosia, W. Bai, Induction of ovarian cancer cell apoptosis by 1, 25-dihydroxyvitamin D3 through the down-regulation of telomerase, J. Biol. Chem. 279 (51) (2004) 53213–53221.
[49] G.D. Díaz, C. Paraskeva, M.G. Thomas, L. Binderup, A. Hague, Apoptosis is induced by the active metabolite of vitamin D3 and its analogue EB1089 in colorectal adenoma and carcinoma cells: possible implications for prevention and therapy, Cancer Res. 60 (8) (2000) 2304–2312.
[50] D. Mantell, P. Owens, N. Bundred, E. Mawer, A. Canfield, 1α, 25-dihydroxyvitamin D3 inhibits angiogenesis *in vitro* and *in vivo*, Circ. Res. 87 (3) (2000) 214–220.
[51] N.I. Fernandez-Garcia, H.G. Palmer, M. Garcia, et al., 1α, 25-Dihydroxyvitamin D3 regulates the expression of Id1 and Id2 genes and the angiogenic phenotype of human colon carcinoma cells, Oncogene 24 (43) (2005) 6533–6544.
[52] R.H. Getzenberg, B.W. Light, P.E. Lapco, et al., Vitamin D inhibition of prostate adenocarcinoma growth and metastasis in the Dunning rat prostate model system, Urology 50 (6) (1997) 999–1006.
[53] I. Chung, A.R. Karpf, J.R. Muindi, et al., Epigenetic silencing of CYP24 in tumor-derived endothelial cells contributes to selective growth inhibition by calcitriol, J. Biol. Chem. 282 (12) (2007) 8704–8714.
[54] J.C. Fleet, M. DeSmet, R. Johnson, Y. Li, Vitamin D and cancer: a review of molecular mechanisms, Biochem. J. 441 (1) (2012) 61–76.
[55] M.F. Holick, Vitamin D deficiency, N. Engl. J. Med. 357 (3) (2007) 266–281.
[56] S. Christakos, P. Dhawan, Y. Liu, X. Peng, A. Porta, New insights into the mechanisms of vitamin D action, J. Cell. Biochem. 88 (4) (2003) 695–705.
[57] M. Pereira-Santos, J.Y.G. dos Santos, G.Q. Carvalho, D.B. dos Santos, A.M. Oliveira, Epidemiology of vitamin D insufficiency and deficiency in a population in a sunny country: geospatial meta-analysis in Brazil, Crit. Rev. Food Sci. Nutr. 59 (13) (2019) 2102–2109.
[58] R.M. Mogire, A. Mutua, W. Kimita, et al., Prevalence of vitamin D deficiency in Africa: a systematic review and meta-analysis, Lancet Glob. Health 8 (1) (2020) e134–e142.
[59] K.D. Cashman, K.G. Dowling, Z. Škrabáková, et al., Vitamin D deficiency in Europe: pandemic? Am. J. Clin. Nutr. 103 (4) (2016) 1033–1044.
[60] H. Mezawa, T. Sugiura, M. Watanabe, et al., Serum vitamin D levels and survival of patients with colorectal cancer: post-hoc analysis of a prospective cohort study, BMC Cancer 10 (1) (2010) 1–8.
[61] K. Ng, D.J. Sargent, R.M. Goldberg, et al., Vitamin D status in patients with stage IV colorectal cancer: findings from Intergroup trial N9741, J. Clin. Oncol. 29 (12) (2011) 1599.
[62] M.B. Savoie, A. Paciorek, L. Zhang, et al., Vitamin D levels in patients with colorectal cancer before and after treatment initiation, J. Gastrointest. Cancer 50 (4) (2019) 769–779.
[63] E. Wesselink, M.J. Bours, J.H. de Wilt, et al., Chemotherapy and vitamin D supplement use are determinants of serum 25-hydroxyvitamin D levels during the first six months after colorectal cancer diagnosis, J. Steroid Biochem. Mol. Biol. 199 (2020), 105577.
[64] K. Ng, J.A. Meyerhardt, K. Wu, et al., Circulating 25-hydroxyvitamin d levels and survival in patients with colorectal cancer, J. Clin. Oncol. 26 (18) (2008) 2984–2991.
[65] V. Fedirko, E. Riboli, A. Tjønneland, et al., Prediagnostic 25-hydroxyvitamin D, VDR and CASR polymorphisms, and survival in patients with colorectal cancer in western European populations, Cancer Epidemiol. Biomark. Prev. 21 (4) (2012) 582–593.
[66] L. Zgaga, E. Theodoratou, S.M. Farrington, et al., Plasma vitamin D concentration influences survival outcome after a diagnosis of colorectal cancer, J. Clin. Oncol. 32 (23) (2014) 2430–2439.
[67] R.V. Cooney, W. Chai, A.A. Franke, L.R. Wilkens, L.N. Kolonel, L. Le Marchand, C-reactive protein, lipid-soluble micronutrients, and survival in colorectal cancer patients, Cancer Epidemiol. Biomark. Prev. 22 (7) (2013) 1278–1288.
[68] H. Maalmi, V. Walter, L. Jansen, et al., Relationship of very low serum 25-hydroxyvitamin D3 levels with long-term survival in a large cohort of colorectal cancer patients from Germany, Eur. J. Epidemiol. 32 (11) (2017) 961–971.
[69] K.M. Wesa, N.H. Segal, A.M. Cronin, et al., Serum 25-hydroxy vitamin D and survival in advanced colorectal cancer: a retrospective analysis, Nutr. Cancer 67 (3) (2015) 424–430.
[70] M. Fuchs, C. Yuan, K. Sato, et al., Predicted vitamin D status and colon cancer recurrence and mortality in CALGB 89803 (Alliance), Ann. Oncol. 28 (6) (2017) 1359–1367.
[71] C. Yuan, K. Sato, B.W. Hollis, et al., Plasma 25-hydroxyvitamin D levels and survival in patients with advanced or metastatic colorectal cancer: findings from CALGB/SWOG 80405 (Alliance), Clin. Cancer Res. 25 (24) (2019) 7497–7505.
[72] M.D. Berger, S. Stintzing, V. Heinemann, et al., A polymorphism within the vitamin D transporter gene predicts outcome in metastatic colorectal cancer patients treated with FOLFIRI/Bevacizumab or FOLFIRI/Cetuximab Predictive significance of a vitamin D transporter SNP, Clin. Cancer Res. 24 (4) (2018) 784–793.
[73] H. Maalmi, V. Walter, L. Jansen, et al., Association between blood 25-hydroxyvitamin D levels and survival in colorectal cancer patients: an updated systematic review and meta-analysis, Nutrients 10 (7) (2018) 896, https://doi.org/10.3390/nu10070896. Jul 13.
[74] G. Wu, M. Xue, Y. Zhao, et al., Low circulating 25-hydroxyvitamin D level is associated with increased colorectal cancer mortality: a systematic review and dose–response meta-analysis, Biosci. Rep. 40 (7) (2020).
[75] X. He, K. Wu, S. Ogino, E.L. Giovannucci, A.T. Chan, M. Song, Association between risk factors for colorectal cancer and risk of serrated polyps and conventional adenomas, Gastroenterology 155 (2) (2018) 355–373, e18.
[76] R.L. Sutherland, J. Ormsbee, J. Pader, et al., Vitamin D supplementation reduces the occurrence of colorectal polyps in high-latitude locations, Prev. Med. 135 (2020), 106072.
[77] M. Song, I.M. Lee, J.E. Manson, et al., No association between vitamin D supplementation and risk of colorectal adenomas or serrated polyps in a randomized trial, Clin. Gastroenterol. Hepatol. 19 (1) (2021) 128–135, e6.
[78] A.J. Levine, J.M. Harper, C.M. Ervin, et al., Serum 25-hydroxyvitamin D, dietary calcium intake, and distal colorectal adenoma risk, Nutr. Cancer 39 (1) (2001) 35–41.
[79] T.J. Hartman, et al., The association of calcium and vitamin D with risk of colorectal adenomas, J. Nutr. 135 (2) (2005) 252–259.
[80] S.D. Crockett, E.L. Barry, L.A. Mott, et al., Calcium and vitamin D supplementation and increased risk of serrated polyps: results from a randomised clinical trial, Gut 68 (3) (2019) 475–486.
[81] E.L. Barry, J.L. Peacock, J.R. Rees, et al., Vitamin D receptor genotype, vitamin D3 supplementation, and risk of colorectal adenomas: a randomized clinical trial, JAMA Oncol. 3 (5) (2017) 628–635.
[82] C. Garland, E. Barrett-Connor, A. Rossof, R. Shekelle, M. Criqui, O. Paul, Dietary vitamin D and calcium and risk of colorectal cancer: a 19-year prospective study in men, Lancet N. Am. Ed. 325 (8424) (1985) 307–309.
[83] H. Boughanem, S. Canudas, P. Hernandez-Alonso, et al., Vitamin D intake and the risk of colorectal cancer: an updated meta-analysis and systematic review of case-control and prospective cohort studies, Cancers 13 (11) (2021) 2814 (Basel).
[84] M.L. McCullough, A.S. Robertson, C. Rodriguez, et al., Calcium, vitamin D, dairy products, and risk of colorectal cancer in the Cancer Prevention Study II Nutrition Cohort (United States), Cancer Causes Control 14 (1) (2003) 1–12.
[85] Y. Ma, P. Zhang, F. Wang, J. Yang, Z. Liu, H. Qin, Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies, J. Clin. Oncol. 29 (28) (2011) 3775–3782.
[86] E.D. Gorham, C.F. Garland, F.C. Garland, et al., Vitamin D and prevention of colorectal cancer, J. Steroid Biochem. Mol. Biol. 97 (1–2) (2005) 179–194.
[87] J. Wactawski-Wende, J.M. Kotchen, G.L. Anderson, et al., Calcium plus vitamin D supplementation and the risk of colorectal cancer, N. Engl. J. Med. 354 (7) (2006) 684–696.
[88] J.E. Manson, N.R. Cook, I.M. Lee, et al., Vitamin D supplements and prevention of cancer and cardiovascular disease, N. Engl. J. Med. 380 (1) (2019) 33–44.
[89] P.M. Rothwell, M. Wilson, C.E. Elwin, et al., Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials, Lancet N. Am. Ed. 376 (9754) (2010) 1741–1750.
[90] N. Keum, E. Giovannucci, Vitamin D supplements and cancer incidence and mortality: a meta-analysis, Br. J. Cancer 111 (5) (2014) 976–980.
[91] G. Bjelakovic, L.L. Gluud, D. Nikolova, et al., Vitamin D supplementation for prevention of mortality in adults, Cochrane Database Syst. Rev. (1) (2014), CD007470, https://doi.org/10.1002/14651858.CD007470.pub3.
[92] J.F. Lopez-Caleya, L. Ortega-Valín, T. Fernández-Villa, M. Delgado-Rodríguez, V. Martín-Sánchez, A.J. Molina, The role of calcium and vitamin D dietary intake on risk of colorectal cancer: systematic review and meta-analysis of case–control studies, Cancer Causes Control 33 (2) (2022) 167–182, https://doi.org/10.1007/s10552-021-01512-3. Epub 2021 Oct 27.
[93] Y. Xu, M. Qian, J. Hong, et al., The effect of vitamin D on the occurrence and development of colorectal cancer: a systematic review and meta-analysis, Int. J. Colorectal Dis. 36 (7) (2021) 1329–1344.
[94] C. Lewis, P. Xun, K. He, Vitamin D supplementation and quality of life following diagnosis in stage II colorectal cancer patients: a 24-month prospective study, Support. Care Cancer 24 (4) (2016) 1655–1661.
[95] D.P. Trivedi, R. Doll, K.T. Khaw, Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial, BMJ 326 (7387) (2003) 469.
[96] A. Avenell, G.S. MacLennan, D.J. Jenkinson, et al., Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D3 and/or calcium (RECORD trial), J. Clin. Endocrinol. Metab. 97 (2) (2012) 614–622.
[97] M. Urashima, H. Ohdaira, T. Akutsu, et al., Effect of vitamin D supplementation on relapse-free survival among patients with digestive tract cancers: the AMATERASU randomized clinical trial, JAMA 321 (14) (2019) 1361–1369.
[98] Z. Antunac Golubić, I. Baršić, N. Librenjak, S. Pleština, Vitamin D supplementation and survival in metastatic colorectal cancer, Nutr. Cancer 70 (3) (2018) 413–417.
[99] K. Ng, H.S. Nimeiri, N.J. McCleary, 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 321 (14) (2019) 1370–1379.