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REVIEW

Vitamin D and Gastrointestinal Cancers: A Narrative Review

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Abstract
Calcitriol ($1,25(OH)_2D_3$) performs various activities throughout the body. Although low serum 25-hydroxyvitamin D [25(OH)D] levels are associated with several disease processes such as risk of fractures and falls, hypertension, cardiovascular disease, and diabetes mellitus, recent evidence attests that this important hormone also regulates several cellular pathways involved in cancer development and progression. Calcitriol modulates several genes controlling gut physiology and calcium homeostasis and also maintains the integrity of epithelial barriers, regulates the absorption of phosphate and calcium, and modulates host defense against pathogens and inflammatory response by interplaying with several types of secretory and immune cells. Vitamin D deficiency is significantly related to increased risk of developing certain types of cancer. This deficiency can be prevented by vitamin D supplementation which is both economical and safe. This can lower the risk of developing cancer and also improve the prognosis of patients with gastrointestinal malignancy, but epidemiological data remain inconsistent. Several retrospective observational studies have demonstrated the benefits of vitamin D supplementation, but a few randomized controlled trials have not seemingly supported the beneficial role of vitamin D supplementation in gastrointestinal cancers. Therefore, in this literature review, we aimed to examine the possible role of vitamin D in gastrointestinal malignancies, including gastric, esophageal, pancreatic, hepatic, and colorectal cancers.

Keywords Vitamin D · $1,25(OH)_2D_3$ · Calcidiol · [25(OH)D] · Gastrointestinal cancer · Calcitriol · VDR

Introduction

Vitamin D, a pluripotent fat-soluble prohormone, plays an essential role in various physiological and pathological processes in the human body. It mainly influences calcium homeostasis but also exhibits multiple pleiotropic actions in tissues of multiple body organs, like heart, stomach, brain, gonads, pancreas [1]. Vitamin D interplays with many cellular pathways implicated in cell differentiation, proliferation, and apoptosis. Thus, a low serum concentration of this hormone can lead to the development and progression of cancers; this will be more comprehensively discussed in the following parts of this article [2].

In most people, vitamin D can be obtained from the exposure to ultraviolet B radiation in sunlight. This is because the exposure to sun acts as a catalyst in the conversion reactions of 7-dehydrocholesterol in the skin to vitamin D_3 (cholecalciferol). Some amounts of vitamin D_3 can also be obtained from animal sources like fish or fortified dairy products. Another form of vitamin D, vitamin D_2 or ergocalciferol, can be found naturally in certain plants and fungi [3]. Vitamin D originating from the skin or dietary sources rapidly

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binds to the blood carrier of the hormone, i.e., vitamin D binding protein (DBP) [4]. Cholecalciferol/ergocalciferol is then hydroxylated to 25-hydroxyvitamin D [25(OH)D] (also known as calcidiol), which is the stable metabolite of vitamin D. The serum [25(OH)D] levels are typically monitored for assessing the individual status of vitamin D. It is further converted into 1, 25-dihydroxyvitamin D [1,25$(OH)_2$D] (also known as calcitriol, which is the most active metabolite of vitamin D) by using 1-α-hydroxylase in kidneys (*CYP27B1*) [2, 5–7]. Some other sites in the human body like immature keratinocytes, lymph node, hair follicles, adrenal medulla, islets of pancreas, Purkinje cells of the cerebellum, neurons of the cortex also possess 1-α-hydroxylase activity, rendering those important sites for the conversion of calcidiol into calcitriol [8]. Calcitriol is ultimately catabolized by *CYP24A1* (25-hydroxyvitamin D-24-hydroxylase) and becomes deactivated [5].

Vitamin D binds to its receptor (i.e., vitamin D receptor (VDR)) to exert its actions. VDR belongs to a family of transacting transcriptional regulatory factors that include thyroid hormone receptors, steroids, retinoic acid receptors, and retinoid-X receptors (RXR) [9, 10]. VDR is encoded by the gene located on chromosome 12 [11], containing a total of 14 exons (eight protein-coding exons numbering II–IX, other six encoding 5′ end of the VDR gene numbered IA–IF) directed by two promoter regions [12, 13]. The level of expression of VDR, along with its genetic variants, is an important determinant of both activity and function of vitamin D [14]. Vitamin D_3 binds with VDR and subsequently with RXR, after entering the cell via the plasma membrane proteins [15], to form a heterodimer [15–18]. The RXR and VDR interaction is essential for the transcriptional activity of VDR [15, 17]. The VDR–RXR complex reportedly binds to specific vitamin D response elements (VDRE) in the promoter regions of genes responsible for activation or suppression of specific cellular pathways implicated in tumorigenesis [15–18]. These pathways include various cell cycle-related processes like cellular growth, invasion, apoptosis, differentiation, and metastasis of tumor cells, modulating immune cell differentiation [19], inhibition of angiogenesis in malignant cells [20]. These functions implicate a kaleidoscope of genes like *p21/WAF1*, *c-myc*, *and c-jun*, which are important for cell cycle regulation and tumorigenesis [21–24]; it is not surprising that VDR gene polymorphisms and VDR-mediated signaling pathways play an important role in cancer biology [9, 25, 26]. The calcium-sensing receptor (CaSR), which is a G protein-coupled receptor, is partially responsible for the anti-proliferative effect of vitamin D on tumor progression, as two VDREs are present in the CaSR gene promoter region [27, 28].

Many epidemiological cohort studies have revealed a significant association between the low serum [25(OH)D] and the risk of colon [29–32], breast [33], pancreas [34], and prostate cancers [35]. Recent evidence also showed that the lack of VDR [36], or severe vitamin D deficiency, can lead to tumorigenesis [37, 38]. One interesting proposal postulated in the various ecological and geographical studies on different regions of the world is that exposure to "ultraviolet radiation (UVR)" has protective effects on certain cancers' mortality including some gastrointestinal cancers like esophageal, gastric, pancreatic, colon, rectal, and gallbladder cancers, possibly involving the mechanism of vitamin D synthesis [39–42]. However, some in vitro studies performed on transgenic mice have hypothesized about the independent effect of UVR without the role of vitamin D on the reduction in the progression of certain malignancies [43, 44]. Experimental studies showed that vitamin D acts as an anti-proliferative agent in skin, colon, breast, and prostate tumor cells, where it may also be effective in limiting the pro-inflammatory response [2]. Therefore, this review aimed at discussing the significance of vitamin D in gastrointestinal (GI) malignancies, including esophagus, liver, stomach, pancreas, colon, and rectal (colorectal) cancers.

Literature Search

We used keywords like "Vitamin D," "1,25$(OH)_2D_3$," "VDR," "Mechanism of action of vitamin D," "Gastrointestinal cancers," "Vitamin D in esophageal cancers," "Pancreatic cancers and vitamin D," "Vitamin D in liver cancers," "Vitamin D in gastric cancers," "Colorectal adenoma and carcinoma and vitamin D" and related terms to search articles written in English in Google Scholar, PubMed, and MEDLINE dated back from 1980 till present. Some additional publications were also included from the citations of the researched articles. The Cochrane Clinical Trials Registry and clinicaltrials.gov were followed electronically for any trials that are yet to be finished or published.

Esophageal Cancer

Except for a few experimental studies that suggested vitamin D and VDR are therapeutic targets in esophageal cancer, the majority of clinical studies on the association between vitamin D and esophageal cancer produced insufficient or controversial findings [45, 46].

Chen et al. [47] found that calcitriol supplementation was effective in inhibiting aggressive tumor behavior both in vivo and in vitro by reducing interleukin 6 (IL-6) expression in esophageal squamous cell carcinoma (ESCC). Another study has also shown the beneficial effects of vitamin D in ESCC through a mechanism involving the NF-KB pathway and culminating in down-regulation of glutathione peroxidase 1, an enzyme participating in the pathogenesis of several types of cancers [48] (Fig. 1). VDR expression in human

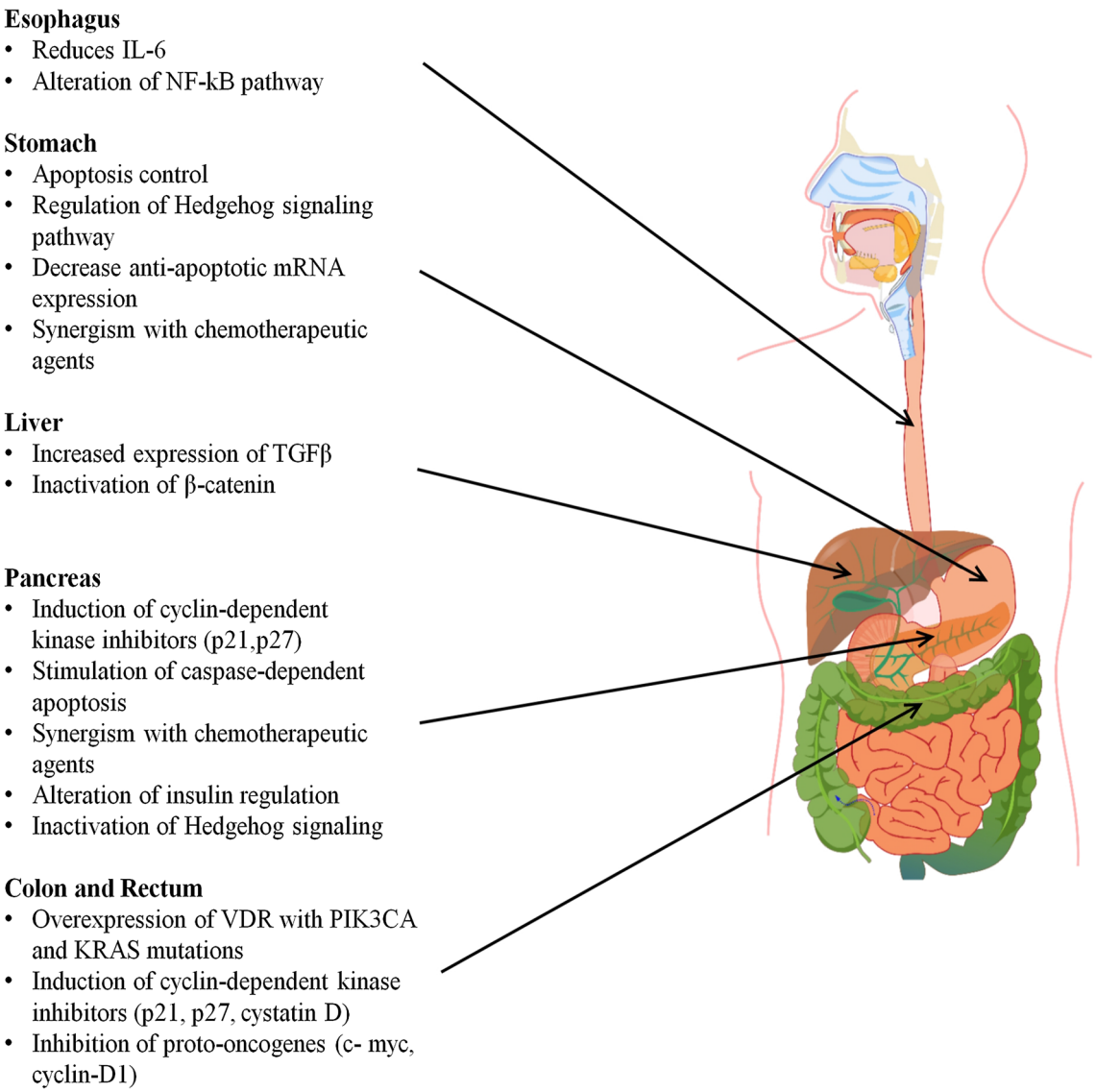

Fig. 1 Mechanisms through which vitamin D exerts its anti-tumorigenic effect on different gastrointestinal cancers [interleukin 6 (IL-6), transforming growth factor β (TGFβ), vitamin D receptor (VDR)]

esophageal adenocarcinomas has been found to decline with the dedifferentiation of the tumor; moreover, lower expression of VDR may act as a predictive marker of response to neoadjuvant therapy [49, 50].

Some studies have examined whether circulating serum [25(OH)D] levels are associated with the risk of developing esophageal dysplasia and both adenocarcinoma and squamous cell carcinoma. A French multicenter case–control study reported that higher estimated dietary vitamin D consumption was an independent protective factor against the development of ESCC [51]. Another prospective cohort study, including 47,800 men, showed that serum [25(OH)D] levels are significantly and inversely related to the incidence of esophageal cancer (relative risk (RR) 0.37, 95% confidence interval (CI) 0.17–0.80) [52]. Wang et al. carried out a longitudinal observational study to examine the effects of postoperative dietary supplementation of vitamin D on the quality of life (QOL) and survival of patients with esophageal cancer. QOL was found to be significantly better in patients taking dietary supplementation of vitamin D and was independently associated with improved disease-free survival (hazard ratio (HR) 0.610, 95% CI 0.381–0.978) [53]. However, a combined analysis of 1065 patients with upper GI cancers from eight cohorts revealed that 25(OH)D and the risk of developing upper GI cancer are not significantly associated [54]. Similarly, other studies published by Fanidi et al. and Thota et al. did not show any relationship between the risk of developing esophageal cancer and serum

levels of 25(OH)D [55, 56]. Another study conducted in China showed that increased serum [25(OH)D] levels might predict the risk of squamous dysplasia (i.e., a precursor condition of ESCC) [57]. In Barrett's esophagus, a well-known disease anticipating esophageal adenocarcinoma, VDR expression was found to be up-regulated compared with normal esophageal squamous epithelium [58]. In some retrospective studies, VDR was only detected in columnar epithelium and Barrett's esophagus but not in squamous mucosa [49, 58], thus demonstrating different roles of vitamin D in two histological subtypes of the epithelium. This conflicting evidence needs to be better explored in additional studies [59].

Gastric Cancer

Some types of gastric cancer are associated with *Helicobacter pylori* infection; dietary factors may also be associated with the risk of developing these types of malignancies [60–62]. As for esophageal cancer, many studies have reported that vitamin D is related to gastric cancer. However, doubts remain about the interplay between vitamin D and gastric tumorigenesis. Paricalcitol, a calcitriol analog, was found to inhibit the gastric cell line growth, via inducing apoptosis and suppressing inflammation but without producing the well-known hypercalcemic effects of calcitriol [63]. Bao et al. reported that the administration of 1,25-dihydroxy vitamin D_3 induced apoptosis in gastric cancer cells and enhanced VDR and *CYP24A1* expressions [64, 65]. Baek et al. also showed that vitamin D_3 treatment was effective in reducing the mRNA expression of *patched1* and *Gli1*. This suggests vitamin D_3 may regulate the Hedgehog (Hh) signaling pathway in gastric cancer cells. A synergistic effect on suppression of gastric cancer cell viability was also observed by combining vitamin D_3 and other anticancer drugs such as vinblastine, adriamycin, and paclitaxel [66] (Table 1). Using the rat model of gastric cancer, Ikezaki et al. [67] showed that 24R,25-dihydroxy vitamin D_3 [24R,25(OH)] exerts some chemopreventive effects on experimental stomach carcinogenesis.

A retrospective study conducted by Ren et al. [68] on 197 patients showed that gastric cancer stage and lymph node metastasis were inversely related to pretreatment [25(OH)D] levels. In gastric cancer patients, high serum [25(OH)D] ($\geq$50 nmol/L) was found to be associated with a higher overall survival rate than the lower serum [25(OH)D] levels (<50 nmol/L) ($p=0.018$). Notably, serum [25(OH)D] levels remained an independent prognostic factor of gastric cancer ($p=0.019$). Khayatzadeh et al. [69] failed to show any statistically significant relationship between gastric cancer risk and either intake of vitamin D or serum levels of 25(OH)D. A cohort study published by Giovannucci et al. [52] found that a nonsignificant inverse relationship existed between serum [25(OH)D] and the rate of stomach cancer. Studies have demonstrated the possible relationship between 25-hydroxyvitamin D levels and gastric cancer occurrence and progression, but the precise mechanism involved in the process needs to be further investigated.

Liver Cancer

Hepatocellular carcinoma (HCC), a primary liver tumor, usually results from chronic inflammation caused by any of the following alone or in combination: alcoholism, viral infections (i.e., hepatitis B and C viruses), and deposition of toxic substances such as fat, copper, and iron [70]. The liver is the predominant organ where the activation of vitamin D by 25-hydroxylation occurs and DBP is synthesized [71]. Severe functional hepatic injury in patients with liver fibrosis and cirrhosis (with occasional malignant transformation) could lead to decreased synthesis of several proteins, including DBP, as well as decreased hydroxylation of vitamin D to 25-OH-D [72]. Therefore, these patients are commonly diagnosed with vitamin D deficiency [71].

Studies on the beneficial effects of vitamin D on cholangiocarcinoma (CC) and HCC cells have revealed that both these cells overexpress the catabolic enzyme *CYP24A1*, which may lead to decreased intracellular 25-hydroxyvitamin D levels, predisposing to tumor growth [73, 74]. Some studies also showed that supplementation of vitamin D_3 leads to decreased proliferation of HCC and CC cell lines [75, 76]. Pourgholami et al. [77] conducted an in vitro study, showing that vitamin D strongly inhibited the growth of HCC in two human cell lines. Another in vitro study by Chiang et al. [78] found that 25(OH)D could inhibit HepG2 cell growth in liver cancer, and this action was potentiated by *CYP27B1* overexpression. Chen et al. [79] showed that vitamin D deprivation promoted the growth of in vivo liver tumor by disrupting the transforming growth factor β (TGFβ) pathway through increased expression of toll-like receptor 7 (TLR7) and activation of β-catenin.

A multicenter, prospective, nested case–control study on 520,000 European participants conducted by Fedirko et al. reported the inverse relationship of pre-diagnostic serum vitamin D concentration with the risk of developing HCC in later years. In the study, it was showed that lower concentration of vitamin D (<50 nmol/L) was significantly associated with HCC risk (RR 1.82, 95% CI 1.02–3.26) and higher levels of pre-diagnostic [25(OH)D] ($\geq$75 nmol/L) reduced the risk of HCC though statistically not significant (RR 0.73, 95% CI 0.25–2.13; $p=0.016$) [80]. Finkelmeier et al. showed that severe deficiency of vitamin D was related to enhanced risk of death from HCC (HR 2.25, 95% CI 1.331–3.179). It also indicated that very low levels

Table 1 Preclinical and clinical studies on the role of vitamin D in various gastrointestinal cancers

Gastrointestinal region	Studies favoring response of vitamin D in gastrointestinal cancers	Studies not favoring response of vitamin D in gastrointestinal cancers
Esophagus	Inhibition of tumor progression by reduced IL-6 expression [47] Alteration of NF-kB pathway by down-regulation of GPX1 (glutathione peroxidase) [48] Decreased VDR with tumor dedifferentiation [49] Independent protective factor for developing esophageal cancer [51, 52] Improved quality of life (QOL) with postoperative supplementation [53] Increased sensitivity of vitamin D in the Barrett's esophagus and columnar epithelium due to strong expression of VDR in these tissues [58]	Association of higher serum vitamin D with squamous dysplasia [54] Rising serum levels of 25(OH)D was a predictor for squamous dysplasia [57] No clear association found between the serum levels of 25(OH)D and high-grade dysplasia/esophageal adenocarcinoma [55, 56]
Stomach	Cancer prevention by controlling apoptosis [63] Induction of cellular apoptosis and increased VDR expression in cancer cells [65] Regulation of Hedgehog (Hh) signaling pathway by decreasing the level of certain anti-apoptotic mRNA expression (Glil, cyclin D1, Bcl2) [66] Synergistic effects with other chemotherapeutic agents (paclitaxel, adriamycin, vinblastine) [66] Chemopreventive effects of 24R, 25-dihydroxy vitamin D_3 [67] Inverse relationship between the serum levels of 25(OH)D with cancer stage and lymph node metastasis [68]	Increased serum levels of 25(OH)D decreased incidence of stomach cancer, but was statistically nonsignificant [52] No significant association between serum 25(OH)D level and cancer risk [69]
Liver	Potential of vitamin D as the prognostic marker of HCC/cirrhosis of liver Decreased proliferation of both HCC and CC cell lines by vitamin D_3 treatment [75] Inhibition of HCC cell line by vitamin D or its analog (seocalcitol) [76, 77] Progression of tumor growth by lower serum levels of 25(OH)D due to higher expression of *CYP24A1* [73, 74] Increased *CYP27B1* expression inhibited HepG2 cell growth [78] Tumorigenesis in vitamin D deficiency by inhibition of TGFβ pathway through activation of β-catenin and increased expression of TLR7 [79] Increased mortality risk with severe vitamin D deficiency [81] Positive prognostic value on CC tissue [82]	Accelerated disease progression associated with higher vitamin D levels [125]
Pancreas	Decreased cancer cell line in response to vitamin D_3 analog treatment [83, 85] Cell cycle arrest at G1 phase in the cancer cell line by a vitamin D analog (22-oxa-1,25-dihydroxyvitamin D_3) [84] Induce cyclin-dependent kinase inhibitor p21, p27 and induce cell cycle arrest at G1/S phase in pancreatic cell line [86] Poor prognosis in advanced pancreatic cancer with deficient serum levels of 25(OH)D [87] Inverse relationship between the intake of vitamin D and the incidence and prognosis of cancer [34] Synergistic therapeutic effect when combined with chemotherapeutic agent (gemcitabine), also boosted up caspase-dependent apoptosis [93] Increased risk of cancer in diabetic patients having a deficiency of vitamin D [94] Slow down the growth of pancreatic cancer cells by inactivating the Hedgehog signaling pathway [96]	Increased risk of pancreatic cancer with increasing level of vitamin D binding protein (DBP) or vitamin D [88]

Table 1 (continued)

Gastrointestinal region	Studies favoring response of vitamin D in gastrointestinal cancers	Studies not favoring response of vitamin D in gastrointestinal cancers
Colon and rectum	Occurrence and recurrence of colorectal adenoma in patients are inversely related to vitamin D [100, 102, 103] Favorable response of vitamin D may vary according to clinical stage [100] Increased colorectal cancer mortality with decreasing serum levels of 25(OH)D [101] Significant inverse relationship between CRC risk and serum levels of 25(OH)D [104] Reduction in incidence of colorectal cancer by half in patients with higher vitamin D [105] Reduced serum levels of 25(OH)D due to overexpression of *CYP24A1* leading to decreased anti-proliferative activity of vitamin D in colorectal adenocarcinoma [107] Mutation of *PIK3CA* and *KRAS* is associated with VDR overexpression in CRC progression [108] Suppression of tumor growth by inducing the expression of the cyclin-dependent kinase inhibitors (p21, p27) and inhibiting the proto-oncogenes like c-myc, cyclin-D1 [109] Malignant transformation due to decreased expression of calcium-sensing receptor (CaSR) in gut epithelium [110] VDR genotype may determine the beneficial role of vitamin D in advanced adenoma [115]	No effect on colorectal cancer incidence after vitamin D supplementation in post-menopausal women [31] No association between vitamin D intake or calcium level and risk of adenoma [126] No significant risk reduction in recurrent colorectal adenomas after vitamin D administration following adenoma removal [113]

of 25(OH)D_3 were independently associated with mortality [81]. Seubwai et al. [82] also reported a positive response of vitamin D treatment on CC cells lines with high expression of VDR, postulating possible usage of vitamin D as an adjuvant therapy in depressing the tumor progression.

The concept that vitamin D may be a therapeutic aid in HCC and CC is plausible due to its anti-proliferative, pro-differentiation, and pro-apoptosis effects on malignant cells. However, more studies are needed to elicit the mechanisms involved.

Pancreatic Cancer

Several studies described that vitamin D and its analogs inhibited the rate of proliferation of pancreatic cancer cell lines [83–85]. Schwartz et al. reported increased activity of the *CYP27B1* enzyme in normal and malignant pancreatic tissues. He showed an inhibitory effect of 25(OD)$_2D_3$ on the growth rate of three (out of the four) pancreatic tumor cell lines used in their experiment. They also showed that 25(OD)$_2D_3$ and the level of induction of cyclin-dependent kinase inhibitors *p21* and *p27* were correlated [86]. Another in vitro study using normal and cancerous pancreatic cells showed increased VDR expression in malignant tissues [83]. The administration of vitamin D_3 analog was also effective in reducing the growth of malignant cells. Some other studies pointed out a putative role of vitamin D pathways in the etiology of pancreatic cancer. Cho et al. [87] studied 178 patients and showed that a deficiency in vitamin D (i.e., <20 ng/mL) led to poor prognoses in patients with advanced pancreatic cancer (i.e., stages III and IV). Another epidemiological study performed by Skinner et al. [34] in two large US cohorts found that vitamin D intake was inversely associated with both the incidence and prognosis of pancreatic cancer. Nonetheless, Piper et al. [88] showed that subjects with high 25(OH)D levels (≥ 100 nmol/L) had a significantly higher risk (i.e., over threefold) of pancreatic cancer than those with lower values (i.e., 50 to <75 nmol/L). Thus, they suggested that there is no relationship between vitamin D and pancreatic cancer. However, it is possible that the confounding factors may affect the result of the study: One is supplementation with vitamin D at the later stages of disease progression but before taking the blood samples for measurement of vitamin D [89], and the other is too long follow-up time for chronic diseases like cancers that may affect the overall relationship of the vitamin D status during the disease process with that of the stage of the disease [90–92].

Unlike these findings, evidence shows that vitamin D has significant prognostic value and may also exert a synergistic therapeutic effect in combination with chemotherapeutic agents (i.e., gemcitabine), mainly by promoting caspase-dependent apoptosis in malignant pancreatic cells [93]. The association between vitamin D and obesity may also help in the better understanding of pancreatic cancer development and progression. It is known that vitamin D regulates insulin synthesis, binding, and response, thus modulating the interplay between pancreatic carcinogenesis and diabetes, since the latter condition is a risk factor for pancreatic malignancy [94]. Accordingly, it has been recently demonstrated that the decreased serum 25-hydroxyvitamin D level is associated with a higher risk of development of pancreatic cancer in diabetic patients [95]. Likewise in gastric cancer, vitamin D_3 may counteract pancreatic cancer cell growth in the dish by acting through the Hh signaling pathway [96]. However, these important findings could not be replicated in vivo studies [96].

Colorectal Adenoma and Cancer

Colorectal cancer (CRC) is prevalent in developed countries than in underdeveloped countries [97–99]. Some studies showed that higher serum level of 25(OH)D is related to lower incidence of colorectal adenoma and carcinoma and enhanced survival rate in CRC patients [100, 101]. Several meta-analyses have shown that vitamin D might play a role in CRC prevention and treatment [102, 103]. Gandini et al. [104] found that a 10 ng/mL increase in the serum levels of 25(OH)D resulted in a 15% decreased rate of CRC (RR 0.85, CI 0.79–0.91). Other studies have shown that there is an association between higher serum levels of 25(OH)D and a 50% lower incidence of CRC [105]. The National Cancer Institute (NCI) also emphasized that vitamin D has a potential protective effect in reducing CRC mortality [101].

Vitamin D reportedly regulates cell cycle, proliferation, differentiation, and apoptosis of CRC cells through direct binding to VDR [106, 107]. The overexpression of VDR in CRC has been shown to be associated with *PIK3CA* and *KRAS* mutations [108]. Moreover, evidence showed that vitamin D has an inhibitory effect on the growth of cancer cells that may be mediated by induced expression of cyclin-dependent kinase inhibitors such as *p21* and *p27*, which control cancer cell cycle and induce apoptosis by inhibition of other pro-oncogenes such as *c-myc* and *cyclin-D1* [109]. An in vitro study carried out in human CRC cell lines by Aggarwal et al. [110] showed that functional calcium-sensing receptors (CaSR) are important for the anti-tumorigenic effects of calcitriol (Table 1).

Some studies reported different data on the expressions of VDR and vitamin D_3 hydroxylases (*CYP27B1, CYP24A1*) in colon epithelium. The *CYP27B1* expression may increase during the early steps of tumorigenesis (i.e., adenomas and well-differentiated carcinomas) in colon epithelial cells compared to the normal surrounding tissue, but then the

expression sharply declines in advanced, poorly differentiated tumors [111]. On the other hand, *CYP24A1* was found to be almost completely absent in normal or benign epithelial mucosa, but its expression was significantly enhanced in malignant tissues [107, 111].

Though some interesting clinical data have been published regarding vitamin D in CRC prevention, other studies have reported inconclusive evidence [112]. For example, Jacobs et al. [100] showed that 25(OH)D serum concentration was not related to adenoma recurrence, demonstrating the putative effects of vitamin D against CRC development and the progression of CRC. Another study investigating the effect of vitamin D and calcium on the development of colorectal adenoma reported no significant reduction in adenoma risk with daily supplementation of calcium and vitamin D for 3–5 years [113]. Since only advanced adenomas showed significant risk of progression to colorectal carcinoma [rate ratio (RR) 2.7, 95% CI 1.9–3.7; $p < 0.001$] and while reviewing the risk of death from colorectal cancers, an increased risk has been shown by advanced adenomas compared with non-advanced ones [RR 2.6, 95% CI 1.2–5.7; $p = 0.01$] when subgroup analysis of patients with advanced adenomas was performed [114]. Specific VDR-related single gene polymorphisms (SNPs) in the study subjects revealed significant variation in the risk of advanced adenomas with different SNPs [115]. The "Women's Health Initiative Calcium-Vitamin D (WHI CaD)" study showed that those who were supplemented with 1 g calcium/400 IU of vitamin D every day but did not take personal calcium or vitamin D on randomization had a nonsignificantly decreased risk of CRC by 17% [112]. Another randomized clinical study involving 1156 women with vitamin D and calcium supplementation and 1147 women supplemented with placebo failed to show any significant lower risk of all types of cancer incidence (including colon cancer and colon and rectum cancer in situ) after 4 years of treatment. However, when the outcome was analyzed with respect to serum 25(OH)D concentration, women who achieved > 50 ng/mL had a significantly reduced risk of all-cancer incidence [116]. Interestingly, studies have discovered higher plasma vitamin D concentration in meat eaters compared to the non-meat eaters [117], though increased meat consumption is associated with the development and progression of CRC [117–119].

Evidence shows that physical activity is related to lower risk of CRC [120, 121]; this has prompted calls to review physical activity recommendations to reduce the incidence and improve the prognosis of cancer [122]. The relationship between physical activity and increased exposure to sunlight could be a hidden link between vitamin D and CRC. However, further randomized control trials are needed to explore the link between physical activity and CRC. Moreover, a thorough explanation of the biological mechanisms underlying the published clinical evidence would contribute to clarifying the role of vitamin D and VDR agonists as important players in cancer prevention and treatment. Controlling development and progression of CRC through lifestyle factors (i.e., physical activity) and nutrients such as vitamin D is an appealing perspective, though the efficacy of dietary supplementation of vitamin D remains inadequately proved in this clinical setting.

Conclusion

In this article, we have narratively reviewed the role of vitamin D in the prevention and treatment of GI cancers. The expression of a high level of VDR in most normal gut epithelial cell types and the local synthesis of $1,25(OH)_2D_3$ point out that vitamin D mainly affects the gut, which is suggestive for a kaleidoscope of intracrine, autocrine, and paracrine activities of $1,25(OH)_2D_3$. Maintaining satisfactory endogenous serum levels of 25(OH)D is essential in regulating gut homeostasis through a large number of regulatory effects including calcium and phosphate absorption, maintenance of epithelial barrier function, protection against infections through anti-inflammatory effects, and cell cycle regulation through pro-apoptotic and pro-differentiation activities. Most of these preventive actions are mediated through VDR.

The current scientific evidence indicates that dietary supplementation of vitamin D may inhibit tumor growth in squamous-type esophageal cancer, and it may also be effective in improving the QOL and survival in patients with esophageal cancer. An analog of vitamin D (paricalcitol) was found effective in the inhibition of gastric carcinoma cells by promoting apoptosis and attenuating the inflammatory response. Vitamin D was also found to exert a synergistic effect with some chemotherapeutics used for treating gastric carcinoma, albeit the exact dosage of supplementation of vitamin D remains uncertain. The possible benefits of vitamin D in liver cancers are currently limited to in vitro studies. A larger number of information has been published on vitamin D and its role in the prevention and treatment of CRC and HCC, but there is a lack of definitive proofs of evidence even for these types of cancer.

Multiple in vitro studies showed anti-tumorigenic effects of vitamin D through its effects on cell cycle regulation, cellular differentiation, apoptosis, and inhibition of angiogenesis. Similarly, some retrospective observational studies also demonstrated the beneficial effects of this "sunshine" vitamin D in the prevention and treatment of GI cancers. Though numerous observational studies have depicted the protective role of vitamin D in cancer incidence, only a few randomized controlled trials have showed any significant relationship between them [112, 116, 123] (Table 1). Inadequate designing of these trials and assessing only the dose of

vitamin D rather than changes in serum vitamin D concentration in cancer have been postulated as the cause of these failed results [123, 124]. Further large randomized clinical trials are necessary to elucidate the definitive role played by vitamin D in GI cancer development and progression, and also for identifying the optimal form and dosage of vitamin D supplementation that may generate an effective protection against cancer.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical statement This manuscript writing and submission is in compliance with the DDS Journal guidelines. This manuscript, as submitted or its essence in another version, is not under consideration for publication elsewhere and will not be published elsewhere while under consideration by *Digestive Diseases and Sciences*. All authors have made substantive contributions to the study, and all authors endorse the data and conclusions.

References

1. Holick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. *Am J Clin Nutr*. 2004;79:362–371.
2. Fleet JC. Molecular actions of vitamin D contributing to cancer prevention. *Mol Asp Med*. 2008;29:388–396.
3. Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. *Am J Clin Nutr*. 2004;80:1710S–1716S.
4. White P, Cooke N. The multifunctional properties and characteristics of vitamin D-binding protein. *Trends Endocrinol Metab*. 2000;11:320–327.
5. Jacobs ET, Van Pelt C, Forster RE, et al. CYP24A1 and CYP27B1 polymorphisms modulate vitamin D metabolism in colon cancer cells. *Cancer Res*. 2013;73:2563–2573.
6. Dudenkov DV, Yawn BP, Oberhelman SS, et al. Changing incidence of serum 25-hydroxyvitamin D values above 50 ng/mL: a 10-year population-based study. *Mayo Clin Proc*. 2015;90:577–586.
7. Rooney MR, Harnack L, Michos ED, Ogilvie RP, Sempos CT, Lutsey PL. Trends in use of high-dose vitamin D supplements exceeding 1000 or 4000 international units daily, 1999–2014. *JAMA*. 2017;317:2448–2450.
8. Zehnder D, Bland R, Williams MC, et al. Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. *J Clin Endocrinol Metab*. 2001;86:888–894.
9. Ingles SA, Ross RK, Yu MC, et al. Association of prostate cancer risk with genetic polymorphisms in vitamin D receptor and androgen receptor. *J Natl Cancer Inst*. 1997;89:166–170.
10. Haussler MR, Mangelsdorf DJ, Komm BS, et al. Molecular biology of the vitamin D hormone. *Recent Prog Horm Res*. 1988;44:263–305.
11. Taymans SE, Pack S, Pak E, et al. The human vitamin D receptor gene (VDR) is localized to region 12cen-q12 by fluorescent in situ hybridization and radiation hybrid mapping: genetic and physical VDR map. *J Bone Miner Res*. 1999;14:1163–1166.
12. Zmuda JM, Cauley JA, Ferrell RE. Molecular epidemiology of vitamin D receptor gene variants. *Epidemiol Rev*. 2000;22:203–217.
13. Crofts LA, Hancock MS, Morrison NA, Eisman JA. Multiple promoters direct the tissue-specific expression of novel N-terminal variant human vitamin D receptor gene transcripts. *Proc Natl Acad Sci USA*. 1998;95:10529–10534.
14. Rai V, Abdo J, Agrawal S, Agrawal DK. Vitamin D receptor polymorphism and cancer: an update. *Anticancer Res*. 2017;37:3991–4003.
15. Lips P. Vitamin D physiology. *Prog Biophys Mol Biol*. 2006;92:4–8.
16. Fleet JC, DeSmet M, Johnson R, Li Y. Vitamin D and cancer: a review of molecular mechanisms. *Biochem J*. 2012;441:61–76.
17. Picotto G, Liaudat AC, Bohl L, Tolosa de Talamoni N. Molecular aspects of vitamin D anticancer activity. *Cancer Invest*. 2012;30:604–614.
18. Davis CD. Vitamin D and cancer: current dilemmas and future research needs. *Am J Clin Nutr*. 2008;88:565S–569S.
19. Lamprecht SA, Lipkin M. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. *Ann N Y Acad Sci*. 2001;952:73–87.
20. Chung I, Han G, Seshadri M, 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*. 2009;69:967–975.
21. Reichrath J, Rafi L, Rech M, et al. Analysis of the vitamin D system in cutaneous squamous cell carcinomas. *J Cutan Pathol*. 2004;31:224–231.
22. Hansen CM, Binderup L, Hamberg KJ, Carlberg C. Vitamin D and cancer: effects of 1,25(OH)2D3 and its analogs on growth control and tumorigenesis. *Front Biosci*. 2001;6:D820–D848.
23. Osborne JE, Hutchinson PE. Vitamin D and systemic cancer: is this relevant to malignant melanoma? *Br J Dermatol*. 2002;147:197–213.
24. Lamprecht SA, Lipkin M. Chemoprevention of colon cancer by calcium, vitamin D and folate: molecular mechanisms. *Nat Rev Cancer*. 2003;3:601–614.
25. Taylor JA, Hirvonen A, Watson M, Pittman G, Mohler JL, Bell DA. Association of prostate cancer with vitamin D receptor gene polymorphism. *Cancer Res*. 1996;56:4108–4110.
26. Curran JE, Vaughan T, Lea RA, Weinstein SR, Morrison NA, Griffiths LR. Association of A vitamin D receptor polymorphism with sporadic breast cancer development. *Int J Cancer*. 1999;83:723–726.
27. Fetahu IS, Hummel DM, Manhardt T, Aggarwal A, Baumgartner-Parzer S, Kállay E. Regulation of the calcium-sensing receptor expression by 1,25-dihydroxyvitamin D3, interleukin-6, and tumor necrosis factor alpha in colon cancer cells. *J Steroid Biochem Mol Biol*. 2014;144:228–231.
28. Canaff L, Hendy GN. Human calcium-sensing receptor gene. Vitamin D response elements in promoters P1 and P2 confer transcriptional responsiveness to 1,25-dihydroxyvitamin D. *J Biol Chem*. 2002;277:30337–30350.
29. Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. *Am J Public Health*. 2006;96:252–261.
30. Wu K, Feskanich D, Fuchs CS, Willett WC, Hollis BW, Giovannucci EL. A nested case–control study of plasma 25-hydroxyvitamin D concentrations and risk of colorectal cancer. *J Natl Cancer Inst*. 2007;99:1120–1129.
31. Wactawski-Wende J, Kotchen JM, et al. Calcium plus vitamin D supplementation and the risk of colorectal cancer. *N Engl J Med*. 2006;354:684–696.
32. Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK, Gorham ED. Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. *Lancet*. 1989;2:1176–1178.

33. Engel P, Fagherazzi G, Boutten A, et al. Serum 25(OH) vitamin D and risk of breast cancer: a nested case–control study from the French E3N cohort. *Cancer Epidemiol Biomark Prev*. 2010;19:2341–2350.
34. Skinner HG, Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Vitamin D intake and the risk for pancreatic cancer in two cohort studies. *Cancer Epidemiol Biomark Prev*. 2006;15:1688–1695.
35. Gao J, Wei W, Wang G, Zhou H, Fu Y, Liu N. Circulating vitamin D concentration and risk of prostate cancer: a dose-response meta-analysis of prospective studies. *Ther Clin Risk Manag*. 2018;14:95–104.
36. Larriba MJ, Ordóñez-Morán P, Chicote I, et al. Vitamin D receptor deficiency enhances Wnt/β-catenin signaling and tumor burden in colon cancer. *PLoS ONE*. 2011;6:e23524.
37. Llor X, Jacoby RF, Teng BB, Davidson NO, Sitrin MD, Brasitus TA. K-ras mutations in 1,2-dimethylhydrazine-induced colonic tumors: effects of supplemental dietary calcium and vitamin D deficiency. *Cancer Res*. 1991;51:4305–4309.
38. Sitrin MD, Halline AG, Abrahams C, Brasitus TA. Dietary calcium and vitamin D modulate 1,2-dimethylhydrazine-induced colonic carcinogenesis in the rat. *Cancer Res*. 1991;51:5608–5613.
39. Grant WB, Garland CF. The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. *Anticancer Res*. 2006;26:2687–2699.
40. Garland CF, Garland FC. Do sunlight and vitamin D reduce the likelihood of colon cancer? *Int J Epidemiol*. 1980;9:227–231.
41. Neale RE, Youlden DR, Krnjacki L, Kimlin MG, van der Pols JC. Latitude variation in pancreatic cancer mortality in Australia. *Pancreas*. 2009;38:387–390.
42. Tran B, Lucas R, Kimlin M, Whiteman D, Neale R, Study AC. Association between ambient ultraviolet radiation and risk of esophageal cancer. *Am J Gastroenterol*. 2012;107:1803–1813.
43. Rebel H, der Spek CD, Salvatori D, van Leeuwen JP, Robanus-Maandag EC, de Gruijl FR. UV exposure inhibits intestinal tumor growth and progression to malignancy in intestine-specific Apc mutant mice kept on low vitamin D diet. *Int J Cancer*. 2015;136:271–277.
44. Makarova AM, Frascari F, Davari P, et al. Ultraviolet radiation inhibits mammary carcinogenesis in an ER-negative murine model by a mechanism independent of vitamin D. *Cancer Prev Res (Phila)*. 2018;11:383–392.
45. Polednak AP. Trends in survival for both histologic types of esophageal cancer in US surveillance, epidemiology and end results areas. *Int J Cancer*. 2003;105:98–100.
46. Chang CK, Mulholland HG, Cantwell MM, et al. Vitamin D receptor gene variants and esophageal adenocarcinoma risk: a population-based case–control study. *J Gastrointest Cancer*. 2012;43:512–517.
47. Chen PT, Hsieh CC, Wu CT, et al. 1α,25-dihydroxyvitamin D3 inhibits esophageal squamous cell carcinoma progression by reducing IL6 signaling. *Mol Cancer Ther*. 2015;14:1365–1375.
48. Gan X, Chen B, Shen Z, et al. High GPX1 expression promotes esophageal squamous cell carcinoma invasion, migration, proliferation and cisplatin-resistance but can be reduced by vitamin D. *Int J Clin Exp Med*. 2014;7:2530–2540.
49. Trowbridge R, Sharma P, Hunter WJ, Agrawal DK. Vitamin D receptor expression and neoadjuvant therapy in esophageal adenocarcinoma. *Exp Mol Pathol*. 2012;93:147–153.
50. Mulholland HG, Murray LJ, Anderson LA, Cantwell MM, group Fs. Vitamin D, calcium and dairy intake, and risk of oesophageal adenocarcinoma and its precursor conditions. *Br J Nutr*. 2011;106:732–741.
51. Launoy G, Milan C, Day NE, Pienkowski MP, Gignoux M, Faivre J. Diet and squamous-cell cancer of the oesophagus: a French multicentre case–control study. *Int J Cancer*. 1998;76:7–12.
52. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst*. 2006;98:451–459.
53. Wang L, Wang C, Wang J, Huang X, Cheng Y. Longitudinal, observational study on associations between postoperative nutritional vitamin D supplementation and clinical outcomes in esophageal cancer patients undergoing esophagectomy. *Sci Rep*. 2016;6:38962.
54. Abnet CC, Chen Y, Chow WH, et al. Circulating 25-hydroxyvitamin D and risk of esophageal and gastric cancer: cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am J Epidemiol*. 2010;172:94–106.
55. Fanidi A, Muller DC, Midttun Ø, et al. Circulating vitamin D in relation to cancer incidence and survival of the head and neck and oesophagus in the EPIC cohort. *Sci Rep*. 2016;6:36017.
56. Thota PN, Kistangari G, Singh P, et al. Serum 25-hydroxyvitamin D levels and the risk of dysplasia and esophageal adenocarcinoma in patients with Barrett's esophagus. *Dig Dis Sci*. 2016;61:247–254. https://doi.org/10.1007/s10620-015-3823-5.
57. Abnet CC, Chen W, Dawsey SM, et al. Serum 25(OH)-vitamin D concentration and risk of esophageal squamous dysplasia. *Cancer Epidemiol Biomark Prev*. 2007;16:1889–1893.
58. Trowbridge R, Mittal SK, Sharma P, Hunter WJ, Agrawal DK. Vitamin D receptor expression in the mucosal tissue at the gastroesophageal junction. *Exp Mol Pathol*. 2012;93:246–249.
59. Zgaga L, O'Sullivan F, Cantwell MM, Murray LJ, Thota PN, Coleman HG. Markers of vitamin D exposure and esophageal cancer risk: a systematic review and meta-analysis. *Cancer Epidemiol Biomark Prev*. 2016;25:877–886.
60. Risch HA, Jain M, Choi NW, et al. Dietary factors and the incidence of cancer of the stomach. *Am J Epidemiol*. 1985;122:947–959.
61. Nomura A, Grove JS, Stemmermann GN, Severson RK. Cigarette smoking and stomach cancer. *Cancer Res*. 1990;50:7084.
62. Scartozzi M, Galizia E, Verdecchia L, et al. Chemotherapy for advanced gastric cancer: across the years for a standard of care. *Expert Opin Pharmacother*. 2007;8:797–808.
63. Park MR, Lee JH, Park MS, et al. Suppressive effect of 19-nor-1α-25-dihydroxyvitamin D2 on gastric cancer cells and peritoneal metastasis model. *J Korean Med Sci*. 2012;27:1037–1043.
64. Anderson MG, Nakane M, Ruan X, Kroeger PE, Wu-Wong JR. Expression of VDR and CYP24A1 mRNA in human tumors. *Cancer Chemother Pharmacol*. 2006;57:234–240.
65. Bao A, Li Y, Tong Y, Zheng H, Wu W, Wei C. Tumor-suppressive effects of 1, 25-dihydroxyvitamin D3 in gastric cancer cells. *Hepatogastroenterology*. 2013;60:943–948.
66. Baek S, Lee YS, Shim HE, et al. Vitamin D3 regulates cell viability in gastric cancer and cholangiocarcinoma. *Anat Cell Biol*. 2011;44:204–209.
67. Ikezaki S, Nishikawa A, Furukawa F, et al. Chemopreventive effects of 24R,25-dihydroxyvitamin D3, a vitamin D3 derivative, on glandular stomach carcinogenesis induced in rats by N-methyl-N′-nitro-N-nitrosoguanidine and sodium chloride. *Cancer Res*. 1996;56:2767–2770.
68. Ren C, Qiu MZ, Wang DS, et al. Prognostic effects of 25-hydroxyvitamin D levels in gastric cancer. *J Transl Med*. 2012;10:16.
69. Khayatzadeh S, Feizi A, Saneei P, Esmaillzadeh A. Vitamin D intake, serum Vitamin D levels, and risk of gastric cancer: a systematic review and meta-analysis. *J Res Med Sci*. 2015;20:790–796.
70. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology*. 2007;132:2557–2576.

71. Kitson MT, Roberts SK. D-livering the message: the importance of vitamin D status in chronic liver disease. *J Hepatol*. 2012;57:897–909.
72. Imawari M, Akanuma Y, Itakura H, Muto Y, Kosaka K, Goodman DS. The effects of diseases of the liver on serum 25-hydroxyvitamin D and on the serum binding protein for vitamin D and its metabolites. *J Lab Clin Med*. 1979;93:171–180.
73. Horvath E, Lakatos P, Balla B, et al. Marked increase of CYP24A1 mRNA level in hepatocellular carcinoma cell lines following vitamin D administration. *Anticancer Res*. 2012;32:4791–4796.
74. Kennedy L, Baker K, Hodges K, et al. Dysregulation of vitamin D3 synthesis leads to enhanced cholangiocarcinoma growth. *Dig Liver Dis*. 2013;45:316–322.
75. Hammad LN, Abdelraouf SM, Hassanein FS, Mohamed WA, Schaalan MF. Circulating IL-6, IL-17 and vitamin D in hepatocellular carcinoma: potential biomarkers for a more favorable prognosis? *J Immunotoxicol*. 2013;10:380–386.
76. Ghous Z, Akhter J, Pourgholami MH, Morris DL. Inhibition of hepatocellular cancer by EB1089: in vitro and in vive study. *Anticancer Res*. 2008;28:3757–3761.
77. Pourgholami MH, Akhter J, Lu Y, Morris DL. In vitro and in vivo inhibition of liver cancer cells by 1,25-dihydroxyvitamin D3. *Cancer Lett*. 2000;151:97–102.
78. Chiang KC, Yen CL, Yeh CN, et al. Hepatocellular carcinoma cells express 25(OH)D-1α-hydroxylase and are able to convert 25(OH)D to 1α,25(OH)$_2$D, leading to the 25(OH)D-induced growth inhibition. *J Steroid Biochem Mol Biol*. 2015;154:47–52.
79. Chen J, Katz LH, Muñoz NM, et al. Vitamin D deficiency promotes liver tumor growth in transforming growth factor-β/Smad3-deficient mice through Wnt and toll-like receptor 7 pathway modulation. *Sci Rep*. 2016;6:30217.
80. Fedirko V, Duarte-Salles T, Bamia C, et al. Prediagnostic circulating vitamin D levels and risk of hepatocellular carcinoma in European populations: a nested case–control study. *Hepatology*. 2014;60:1222–1230.
81. Finkelmeier F, Kronenberger B, Köberle V, et al. Severe 25-hydroxyvitamin D deficiency identifies a poor prognosis in patients with hepatocellular carcinoma—a prospective cohort study. *Aliment Pharmacol Ther*. 2014;39:1204–1212.
82. Seubwai W, Wongkham C, Puapairoj A, Khuntikeo N, Wongkham S. Overexpression of vitamin D receptor indicates a good prognosis for cholangiocarcinoma: implications for therapeutics. *Cancer*. 2007;109:2497–2505.
83. Albrechtsson E, Jonsson T, Möller S, Höglund M, Ohlsson B, Axelson J. Vitamin D receptor is expressed in pancreatic cancer cells and a vitamin D3 analogue decreases cell number. *Pancreatology*. 2003;3:41–46.
84. Kawa S, Yoshizawa K, Tokoo M, et al. Inhibitory effect of 220-oxa-1,25-dihydroxyvitamin D3 on the proliferation of pancreatic cancer cell lines. *Gastroenterology*. 1996;110:1605–1613.
85. Ohlsson B, Albrechtsson E, Axelson J. Vitamins A and D but not E and K decreased the cell number in human pancreatic cancer cell lines. *Scand J Gastroenterol*. 2004;39:882–885.
86. Schwartz GG, Eads D, Rao A, et al. Pancreatic cancer cells express 25-hydroxyvitamin D-1 alpha-hydroxylase and their proliferation is inhibited by the prohormone 25-hydroxyvitamin D3. *Carcinogenesis*. 2004;25:1015–1026.
87. Cho M, Peddi PF, Ding K, et al. Vitamin D deficiency and prognostics among patients with pancreatic adenocarcinoma. *J Transl Med*. 2013;11:206.
88. Piper MR, Freedman DM, Robien K, et al. Vitamin D-binding protein and pancreatic cancer: a nested case–control study. *Am J Clin Nutr*. 2015;101:1206–1215.
89. Grant WB, Karras SN, Bischoff-Ferrari HA, et al. Do studies reporting 'U'-shaped serum 25-hydroxyvitamin D-health outcome relationships reflect adverse effects? *Dermatoendocrinology*. 2016;8:e1187349.
90. Grant WB. Effect of interval between serum draw and follow-up period on relative risk of cancer incidence with respect to 25-hydroxyvitamin D level: implications for meta-analyses and setting vitamin D guidelines. *Dermatoendocrinology*. 2011;3:199–204.
91. Grant WB. 25-hydroxyvitamin D and breast cancer, colorectal cancer, and colorectal adenomas: case–control versus nested case–control studies. *Anticancer Res*. 2015;35:1153–1160.
92. Grant WB. Effect of follow-up time on the relation between prediagnostic serum 25-hydroxyvitamin D and all-cause mortality rate. *Dermatoendocrinology*. 2012;4:198–202.
93. Yu WD, Ma Y, Flynn G, et al. Calcitriol enhances gemcitabine anti-tumor activity in vitro and in vivo by promoting apoptosis in a human pancreatic carcinoma model system. *Cell Cycle*. 2010;9:3022–3029.
94. Stolzenberg-Solomon RZ, Graubard BI, et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA*. 2005;294:2872–2878.
95. Ahmad S, Chowdhury TA, Boucher BJ. Diabetes and cancer: could vitamin D provide the link? *J Diabetes Complicat*. 2013;27:184–190.
96. Brüggemann LW, Queiroz KC, Zamani K, van Straaten A, Spek CA, Bijlsma MF. Assessing the efficacy of the hedgehog pathway inhibitor vitamin D3 in a murine xenograft model for pancreatic cancer. *Cancer Biol Ther*. 2010;10:79–88.
97. Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. *Eur J Cancer*. 2010;46:765–781.
98. Heidelbaugh JJ, Tortorello M. The adult well male examination. *Am Fam Phys*. 2012;85:964–971.
99. Whitlock EP, Lin JS, Liles E, Beil TL, Fu R. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2008;149:638–658.
100. Jacobs ET, Hibler EA, Lance P, Sardo CL, Jurutka PW. Association between circulating concentrations of 25(OH) D and colorectal adenoma: a pooled analysis. *Int J Cancer*. 2013;133:2980–2988.
101. Freedman DM, Looker AC, Chang SC, Graubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. *J Natl Cancer Inst*. 2007;99:1594–1602.
102. Wei MY, Garland CF, Gorham ED, Mohr SB, Giovannucci E. Vitamin D and prevention of colorectal adenoma: a meta-analysis. *Cancer Epidemiol Biomark Prev*. 2008;17:2958–2969.
103. Ma Y, Zhang P, Wang F, Yang J, Liu Z, Qin H. Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies. *J Clin Oncol*. 2011;29:3775–3782.
104. Gandini S, Boniol M, Haukka J, et al. Meta-analysis of observational studies of serum 25-hydroxyvitamin D levels and colorectal, breast and prostate cancer and colorectal adenoma. *Int J Cancer*. 2011;128:1414–1424.
105. Gorham ED, Garland CF, Garland FC, et al. Optimal vitamin D status for colorectal cancer prevention: a quantitative meta analysis. *Am J Prev Med*. 2007;32:210–216.
106. Kaler P, Galea V, Augenlicht L, Klampfer L. Tumor associated macrophages protect colon cancer cells from TRAIL-induced apoptosis through IL-1beta-dependent stabilization of Snail in tumor cells. *PLoS ONE*. 2010;5:e11700.
107. Horváth HC, Lakatos P, Kósa JP, et al. The candidate oncogene CYP24A1: a potential biomarker for colorectal tumorigenesis. *J Histochem Cytochem*. 2010;58:277–285.
108. Kure S, Nosho K, Baba Y, et al. Vitamin D receptor expression is associated with PIK3CA and KRAS mutations in colorectal cancer. *Cancer Epidemiol Biomark Prev*. 2009;18:2765–2772.

109. Klampfer L. Vitamin D and colon cancer. *World J Gastrointest Oncol*. 2014;6:430–437.
110. Aggarwal A, Höbaus J, Tennakoon S, et al. Active vitamin D potentiates the anti-neoplastic effects of calcium in the colon: a cross talk through the calcium-sensing receptor. *J Steroid Biochem Mol Biol*. 2016;155:231–238.
111. Bises G, Kállay E, Weiland T, et al. 25-hydroxyvitamin D3-1alpha-hydroxylase expression in normal and malignant human colon. *J Histochem Cytochem*. 2004;52:985–989.
112. Bolland MJ, Grey A, Gamble GD, Reid IR. Calcium and vitamin D supplements and health outcomes: a reanalysis of the Women's Health Initiative (WHI) limited-access data set. *Am J Clin Nutr*. 2011;94:1144–1149.
113. Baron JA, Barry EL, Mott LA, et al. A trial of calcium and vitamin D for the prevention of colorectal adenomas. *N Engl J Med*. 2015;373:1519–1530.
114. Click B, Pinsky PF, Hickey T, Doroudi M, Schoen RE. Association of colonoscopy adenoma findings with long-term colorectal cancer incidence. *JAMA*. 2018;319:2021–2031.
115. Barry EL, Peacock JL, Rees JR, et al. Vitamin D receptor genotype, vitamin D3 supplementation, and risk of colorectal adenomas: a randomized clinical trial. *JAMA Oncol*. 2017;3:628–635.
116. Lappe J, Watson P, Travers-Gustafson D, et al. Effect of vitamin D and calcium supplementation on cancer incidence in older women: a randomized clinical trial. *JAMA*. 2017;317:1234–1243.
117. Crowe FL, Steur M, Allen NE, Appleby PN, Travis RC, Key TJ. Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: results from the EPIC–Oxford study. *Public Health Nutr*. 2011;14:340–346.
118. Yang J, Yu J. The association of diet, gut microbiota and colorectal cancer: what we eat may imply what we get. *Protein Cell*. 2018;9:474–487.
119. Aune D, De Stefani E, Ronco A, et al. Meat consumption and cancer risk: a case–control study in Uruguay. *Asian Pac J Cancer Prev*. 2009;10:429–436.
120. Campbell PT, Patel AV, Newton CC, Jacobs EJ, Gapstur SM. Associations of recreational physical activity and leisure time spent sitting with colorectal cancer survival. *J Clin Oncol*. 2013;31:876–885.
121. World Cancer Research Fund/American Institute for Cancer Research. Continuous update project report. Food, nutrition, physical activity, and the prevention of colorectal cancer. 2011.
122. Sanchis-Gomar F, Lucia A, Yvert T, et al. Physical inactivity and low fitness deserve more attention to alter cancer risk and prognosis. *Cancer Prev Res*. 2015;8:105–110.
123. Grant WB, Boucher BJ. Randomized controlled trials of vitamin D and cancer incidence: a modeling study. *PLoS ONE*. 2017;12:e0176448.
124. Heaney RP. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. *Nutr Rev*. 2014;72:48–54.
125. Corey KE, Zheng H, Mendez-Navarro J, et al. Serum vitamin D levels are not predictive of the progression of chronic liver disease in hepatitis C patients with advanced fibrosis. *PLoS ONE*. 2012;7:e27144.
126. Hartman TJ, Albert PS, Snyder K, et al. The association of calcium and vitamin D with risk of colorectal adenomas. *J Nutr*. 2005;135:252–259.