Review Article

Vitamin D and GI cancers: shedding some light on dark diseases

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Abstract: Vitamin D synthesis and signaling affects numerous cellular processes including: proliferation, differentiation and apoptosis. It is now commonly recognized that low levels of vitamin D are associated with a greater risk of tumorigenesis. Cancers of the gastrointestinal tract are most often difficult to diagnose and treat as patients typically present with progressed disease. Basic research, clinical trials and population studies have supported the concept that treatment with Vitamin D may be a therapeutic option when treating GI cancers, however treatments must be individualized and monitored closely as the side effects from Vitamin D treatment can be increasingly harmful. This review will highlight the most recent findings regarding Vitamin D signaling and GI cancers.

Keywords: Vitamin D; cancer; signaling; enzymes; esophagus; stomach; pancreas; liver; colon

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Vitamin D synthesis

Vitamin D exists in two major forms: vitamin D_2 (ergocalciferol) and D_3 (cholecalciferol) and can be obtained from diet or supplements (1-3). Besides from food and supplements, vitamin D is also derived from sunlight. This process involves the conversion of 7-dehydrocholesterol in the skin after exposure to sunlight (UV-B light). Both D2 and D3 forms of vitamin D utilize vitamin D binding proteins (VDBP) in the bloodstream to reach the liver where they are converted to 25(OH)D by the enzyme, 25-hydroxylase (1-3). The biologically active form of vitamin D [$1,25(OH)_2D_3$ (referred to as vitamin D_3 throughout this review) is synthesized in the kidney by 1a-hydroxylase (CYP27B1) and is metabolized by the enzyme, 24 hydroxylase (CYP24A1)], that limits calcitriol actions via catabolism. Renal CYP27B1 gene expression is regulated and activated by the parathyroid hormone. After its synthesis, vitamin D_3 is released into the serum and can act on the intestine, bone and kidney to regulate calcium metabolism (2,3). CYP27B1 and CYP24A1 are found in numerous tissues throughout the body including the skin, colon, pancreas, liver, brain and placenta allowing for vitamin D_3 synthesis and degradation. Vitamin D_3 is thought to be the metabolite responsible for the cellular anticancer actions of vitamin D (2,3).

Vitamin D receptor signaling

Vitamin D_3 binds to the vitamin D receptor (VDR). Vitamin D_3 and VDR form a heterodimer with the retinoid X receptor (RXR) and bind to the vitamin D responsive element on the respective responsive gene (1-3). After binding, transcription and translation occur leading to protein formation, for example the formation of the calcium binding protein or osteocalcin. Classically, vitamin D_3 enters the cell through membrane proteins. For example, in intestinal cells, vitamin D_3 binds to VDR synthesizing the calcium binding protein, which can regulate transport through the cell (2). While the VDR is predominantly

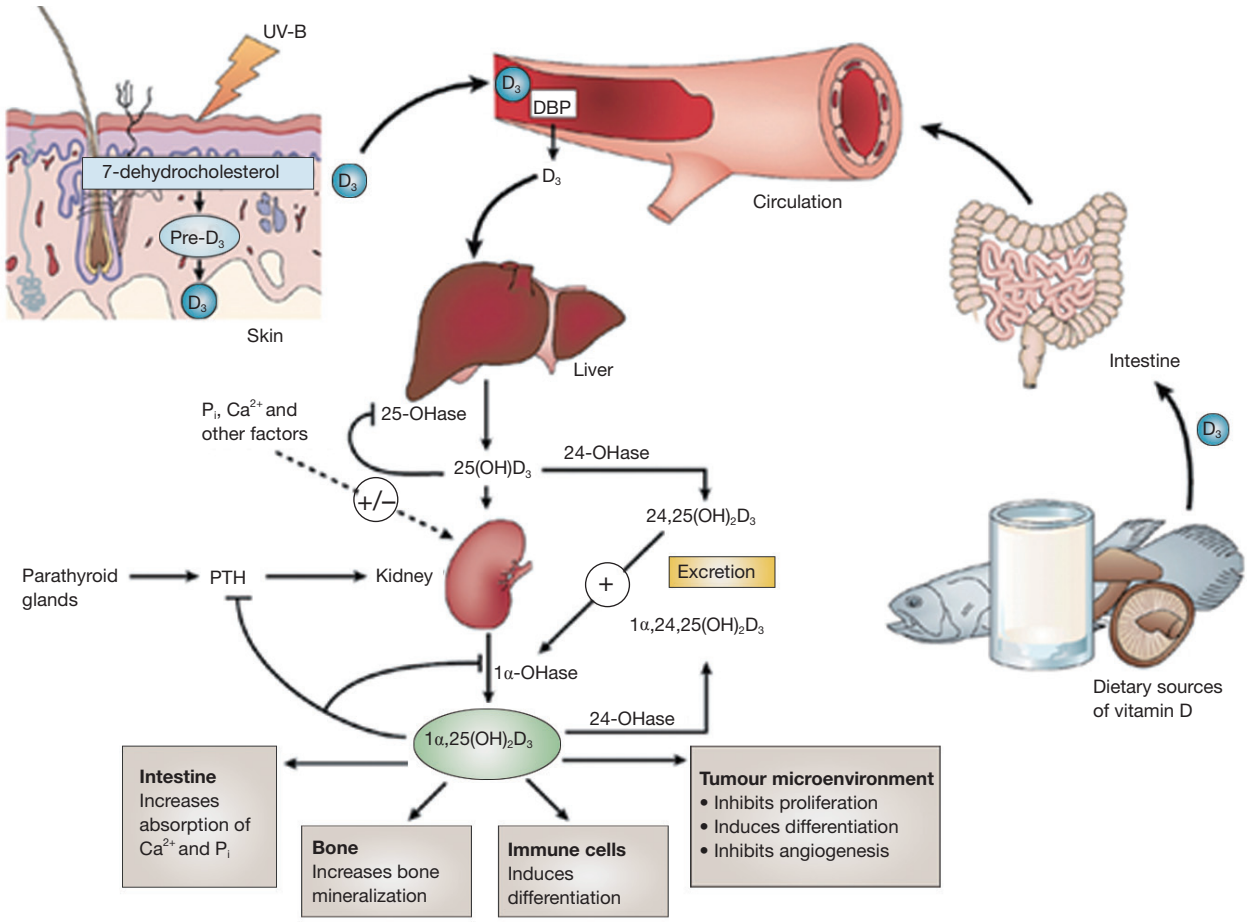

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Figure 1 Photochemical synthesis of vitamin D_3 (cholecalciferol, D_3) occurs cutaneously where pro-vitamin D_3 (7-dehydrocholesterol) is converted to pre-vitamin D_3 (pre-D_3) in response to ultraviolet B (sunlight) exposure. Vitamin D_3, obtained from the isomerization of pre-vitamin D_3 in the epidermal basal layers or intestinal absorption of natural and fortified foods and supplements, binds to vitamin D-binding protein (DBP) in the bloodstream, and is transported to the liver. D_3 is hydroxylated by liver 25-hydroxylases (25-OHase). The resultant 25-hydroxycholecalciferol [25(OH)D_3] is 1α-hydroxylated in the kidney by 25-hydroxyvitamin D_3-1α-hydroxylase (1α-OHase). This yields the active secosteroid 1α,25$(OH)_2D_3$ (calcitriol), which has different effects on various target tissues. The synthesis of 1α,25$(OH)_2D_3$ from 25(OH)D_3 is stimulated by parathyroid hormone (PTH) and suppressed by Ca^{2+}, P_i and 1α,25$(OH)_2D_3$ itself. The rate-limiting step in catabolism is the degradation of 25(OH)D_3 and 1α,25$(OH)_2D_3$ to 24,25(OH)D_3 and 1α,24,25$(OH)_2D_3$, respectively, which occurs through 24-hydroxylation by 25-hydroxyvitamin D 24-hydroxylase (24-OHase), encoded by the CYP24A1 gene. 24,25(OH)D_3 and 1α,24,25$(OH)_2D_3$ are consequently excreted [reprinted with permission from *Nature Reviews Cancer* 2007;7:684-700].

a nuclear protein, it has been found in the cytoplasm of vitamin D_3 target cells. The interaction between RXR and VDR is essential for VDR transcriptional activity (2,3). Vitamin D-response elements (VDREs) are also utilized to initiate gene transcription. The RXR-VDR complex recruits specific coactivator molecules like steroid receptor coactivators, histone acetyltransferases and the mediator complex subunit 1. The VDR-RXR complex translocates to the nucleus binding to VDREs that allows for promotion or suppression of specific cellular events, including tumorigenesis (1-3). *Figure 1* depicts the metabolism/catabolism and signaling pathway of vitamin D_3 (reprinted

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Vitamin D and cancer

The traditional role of vitamin D has been centered on the control of calcium and bone metabolism, however, recent studies have begun to elucidate the role that vitamin D plays in the development and progression of numerous cancers. Because vitamin D is known to participate in cell cycle regulation, cellular proliferation and apoptosis, angiogenesis and molecular cell signaling it stands to reason that this metabolite is involved in tumorigenic activity (1-3). It has been found that low serum vitamin D_3 levels are associated with increased cancers of the breast (4), colon (5) and prostate (6) and animals lacking VDR or with severe vitamin D deficiency are prone to increased tumorigenesis (7,8). In our review we will focus on the recently examined (within the last 5-10 years) role of vitamin D_3 in the cancers of the GI tract including: esophagus, gastric (stomach), liver, pancreas and colon.

Esophageal cancer

Cancer of the esophagus (esophageal cancer) is a relatively rare form of cancer that is characterized by two types: adenocarcinoma and squamous cell carcinoma. It has been shown that heavy smoking or alcohol use increases the incidence of squamous cell esophageal cancer (9). Typically the diagnosis, treatment and outcome for patients afflicted with esophageal cancers are difficult and grim. The majority of patients present in advanced stages of the disease with dysphagia (difficulty swallowing) being the main cause for seeking medical care. The five-year survival rate is approximately 15%, however, most patients do not survive the first year after diagnosis (10). Treatments depend upon the stage at which the diagnosis is made and may include esophagectomy, radiotherapy, and chemotherapy or laser photodynamic therapy (9). No reliable markers have been discovered for the detection of esophageal cancer, however, some studies suggest that vitamin D and VDR may allow for earlier detection or alternative therapeutic strategies. The majority of studies that examine the role that vitamin D may alter esophageal cancer are primarily done in specific population cohorts (11,12). Findings from these studies have been inconclusive and controversial. For example, in a study by Trowbridge *et al.* the authors found that in human esophageal adenocarcinomas VDR expression declined with tumor de-differentiation. The Authors also found that VDR translocated out to the cytoplasm during neoplastic transformation (13). While the Authors postulate that VDR expression may serve as a marker for neoadjuvant therapy they also disclose that these findings maybe aberrant and should be confirmed (13). A cohort study from Italy has found that increased dietary vitamin D intake (>3.5 mg/day) reduced the risk of esophageal cancer by ~40% suggesting a protective role for vitamin D in this cancer (14). In contrast, a study in China found that increased vitamin D serum levels predicted an increase in squamous dysplasia, the precursor for esophageal squamous cell carcinoma (15). The primary precursor to esophageal adenocarcinoma is Barrett's Esophagus and it has been found that VDR expression is upregulated in Barrett's mucosa when compared to the normal squamous epithelium of the esophagus (16) although no conclusive evidence regarding the definite role of vitamin D could be demonstrated. With regards to the role that might be played by the enzymes regulating vitamin D synthesis, a study found that overexpression of CYP24A1 coupled with low VDR expression is indicative of poor prognosis of esophageal cancer (17). These studies have provided preliminary insight into the potential impact that vitamin D may have on this GI cancer.

Gastric (stomach) cancer

Gastric cancer includes any cancer arising from any part of the stomach and is the fourth most common cancer worldwide (18). This cancer causes approximately 800,000 deaths worldwide and incurs poor prognosis, as most patients will present with advanced disease (18). The majority of gastric cancers arise from *Helicobacter pylori* infection, however, there are also dietary risks associated with gastric cancer. Smoking has also been found to significantly increase the risk of developing gastric cancer as well as alcohol consumption (19). Surgery is the most common treatment for stomach cancer wherein part or all of the stomach may be removed. Chemotherapy and radiotherapy are also utilized, however, there is no established standard of care (20). Similar to esophageal cancer, there are numerous studies linking vitamin D to gastric cancer, however, there is also confusion on the exact role and mechanism of vitamin D during tumorigenesis. A recent cohort study found that increased serum vitamin D levels were associated with decreased risk of gastric cancer and poor prognosis (21). It is also been shown that paricalcitol (an analog to calcitriol) suppresses the growth

of gastric cancer cells by regulating cell cycle, apoptosis and inflammation without inducing the hypercalcemia effects seen by calcitriol (22). Bao *et al.* found that direct usage of 1,25-dihydroxyvitamin D_3 induces cellular apoptosis in gastric cancer cells and also increased the expression of VDR and CYP24A1 (23) further supporting the anti-tumoral role that vitamin D may activate in gastric cancer. Evidence that vitamin D_3 may act through the hedgehog signaling pathway has also been demonstrated in gastric cancer cells. In this study, treatment with vitamin D_3 decreased cell viability by the inhibition of the expression of numerous hedgehog signaling target genes including patched1 and Gli1 in gastric cancer cells (24). A synergistic effect by vitamin D3 was also seen when it was combined with different chemotherapeutic drugs including paclitaxel (24). Finally, in an early study, treatment with vitamin D_3 was found to induce chemopreventative effects in rats with glandular stomach cancer by reducing both cancerous and precancerous lesions in the stomach (25). Taken together, these studies have laid important groundwork to continue the efforts in understanding the role of vitamin D in gastric cancers.

Pancreatic cancer

Cancer of the pancreas is a malignant neoplasm that arises from transformed cells of the pancreas. Adenocarcinoma arising within the exocrine component of the pancreas is the most common type of pancreatic cancer. It is the fourth most common cause of cancer-related deaths in the United States and eighth worldwide. The prognosis is very grim for patients that incur this disease. The 1-5-year survival rates are 25% and 6%, respectively and the median survival rate for advanced or metastatic pancreatic cancer is approximately 6-10 months. There are numerous risk factors related to pancreatic cancer including smoking, obesity, chronic pancreatitis and *H. pylori* infection. Similar to gastric cancer, surgery, radiation and chemotherapy treatments may all be utilized to offer care, however, treatments are dependent upon stage of cancer. Much work has been performed regarding vitamin D and pancreatic tumor progression. It has been demonstrated that the enzyme that catalyzes the conversion of 25(OH)D to 1,25-dihydroxy vitamin D is expressed in ductal cells in the pancreas in both normal and adenocarcinoma tissues and treatment with vitamin D3 decreases the growth of pancreatic cells *in vitro* (26). The vitamin D receptor, VDR, has been detected in numerous pancreatic cell lines and its expression is greatly decreased when compared to normal pancreatic cells (27). Further, treatment with a vitamin D analog, EB1089, induced a significant decrease in pancreatic cancer cell lines (27). Yu *et al.* demonstrated that calcitriol, in combination with the chemotherapy drug, gemcitabine increases caspase-dependent apoptosis of human pancreatic cancer cells both *in vitro* and *in vivo* (28). In a large cohort study it was found that increased plasma 25-hydroxyvitamin D levels are associated with a decreased risk for pancreatic cancer (29). This study was performed in 451 cases of pancreatic cancer along with over 1,000 controls and provides strong human data supporting the concept that lower vitamin D levels may increase susceptibility to developing pancreatic cancer especially when coupled with any of the known risk factors. In addition, there have been multiple cohort studies demonstrating that increasing serum vitamin D levels are coupled with decreased pancreatic risk, both in men and women (30-33). Interestingly, the link between obesity and vitamin D may offer some insight into pancreatic tumor development and progression. Vitamin D is involved in the regulation of insulin synthesis, binding and response, making insulin regulation directly relevant to pancreatic carcinogenesis since diabetes is also a known risk factor for this cancer (34,35). Evidence shows that low levels of vitamin D may increase the risk of cancer (including pancreatic) in people with diabetes (36). Similar to gastric cancer, vitamin D may act through the hedgehog-signaling pathway to inhibit pancreatic cancer cell growth by inactivating the receptor Smoothened, *in vitro*, however this effect was not recapitulated when *in vivo* models of vitamin D_3 treatment were used (37). There has been a causal link demonstrated to link vitamin D deficiency and pancreatic disease, including cancer. Kalpdor *et al.* found that in patients with pancreatic disease, serum vitamin D levels were significantly lower than those of controls, whereas both vitamin A and E levels were normal in all samples (38). Supplementation with vitamin D (dosed dependent upon disease stage) increased circulating vitamin D levels. Most studies stress the importance of monitoring serum vitamin D levels closely when used for treatments, as there can be other unwanted side effects from an overload of vitamin D (39-43). Because the sun is the main source for vitamin D production, treatment with sun exposure to increase serum vitamin D levels may appear to be a natural therapy, but it may not be without risk. A study from Sweden demonstrated that there is an increased risk of developing basal cell carcinoma from prolonged and repetitive sunlight exposure that has no weighted benefit in preventing internal cancers, including pancreatic (44).

Clinical studies have examined the potential added benefit of calcitriol to chemotherapy treatments. Blanke *et al.* demonstrated that out of 25 patients, three had a partial response and seven reached a stable disease state when given a combination of calcitriol and docetaxel (45). The median overall survival was 24 weeks and side effects were likely due to the chemotherapy drug and not calcitriol. While this is a modest effect, it warrants further studies to determine the benefits of vitamin D on pancreatic tumors. An early study using the vitamin D_3 analog, EB1089 suggested that, in patients with minimal stage disease, there was an increase in survival time and the duration of stable disease increased for a small number of patients, however advanced pancreatic tumors were not sensitized to this treatment (46). In summary, the investigation of the beneficial effects of vitamin D in pancreatic cancer remains unclear. Most studies support the concept that low levels of vitamin D can result in an increased risk of developing pancreatic cancer especially when coupled with a known risk like diabetes or obesity. Treatment with vitamin D (or one of its many analogs) must be monitored and specific to the patient and stage of disease. However, there may be promising therapies for patients suffering from pancreatic tumors within our reach.

Liver cancer

Most cancers found in the liver are metastatic tumors derived from other organs including breast, colon, lung, and kidney. The two primary cancers that arise from cells within the liver are hepatocellular carcinoma (arising from hepatocytes, HCC) and cholangiocarcinoma (CCH, derived from cholangiocytes, cells that line the bile ducts) (47-49). Hepatocellular carcinoma is a primary tumor of the liver that typically results from viral hepatitis infections or cirrhosis (47). Cholangiocarcinoma typically is the result of bile duct damage from diseases like primary sclerosing cholangitis (48,49). Both HCC and CCH are relatively rare; however liver cancer is the third leading cause of cancer death. Hepatocellular and cholangiocarcinomas are difficult to diagnose and typically are well advanced when found. The standard of care includes liver transplantation, partial hepatectomy (to resect tumors when possible), chemotherapy and radiotherapy (47-49). Like most GI cancers, the response to these treatments is minimal and dependent upon the stage of the disease. Numerous studies have been performed and are underway to determine the most beneficial treatment strategies for these cancers and this also involves the investigation of vitamin D on both CCH and HCC. Several studies have shown that both HCC and CCH express high levels of CYP24A1 (50,51). An increase in CYP24A1 can lead to lower levels of vitamin D thereby allowing for tumor growth. In these studies, treatment with vitamin D3 decreased the proliferative rate in numerous HCC and CCH cell lines (50,51). VDR is expressed in cholangiocarcinoma, increasing in expression during the development of CCH, whereas the expression of VDR in normal tissue is negligible (51,52). *Figure 2* depicts the expression of VDR, CYP24A1 and CYP27B1 in non-malignant and malignant tumor biopsies from human patient biopsies (reprinted with permission from Elsevier, *Digestive and Liver Disease*. Kennedy *et al.* Dysregulation of vitamin D_3 synthesis leads to enhanced cholangiocarcinoma growth. 2013;45:316-22). The expression of both VDR and the degrading enzyme are significantly increased compared to non-malignant tissues (*Figure 2*). In the study by Baek *et al.* they found that there was a synergistic effect when vitamin D_3 was combined with anti-cancer drugs decreasing cholangiocarcinoma cell proliferation (24). Besides using vitamin D_3 to reduce cholangiocarcinoma growth, the use of analogs has also proven to be effective. Stimulation with 22-0xa-D_3 induced cell cycle arrest of cholangiocarcinoma cell lines and also significantly inhibited tumor growth in CCH-inoculated mice without inducing hypercalcemia (53). Cellular apoptosis was also found in tissue samples from patients with CCH. These studies, though few, demonstrate the importance of examining the role of vitamin D in these malignancies. There are several numerous serum markers to aid in the detection of HCC. A recent study demonstrates that adding vitamin D levels to this list may be of help for physicians when diagnosing hepatocellular carcinoma as there was a significant decrease in vitamin D levels associated with progressive HCC (54). Because vitamin D can exert antiproliferative, pro-differentiation and pro-apoptosis effects on cancer cells that express VDR, the concept that vitamin D can aid in therapeutic development for HCC is also plausible. Numerous studies by Pourgholami *et al.*, have demonstrated that treatment with vitamin D decreases HCC proliferation *in vitro* and *in vivo* (55,56). They further looked at the role of vitamin D analogs including EB1089 and CB1093 and found a decrease of growth in hepatoblastoma cell lines and using *in vivo* models of HCC (55,57,58). Because of the toxicity and hypercalcemic effects of treatment with vitamin D, using analogs appears to be a much better approach to treat these cancers. Finally, a group reports that combining vitamin D with fish oil increases the antiproliferative on

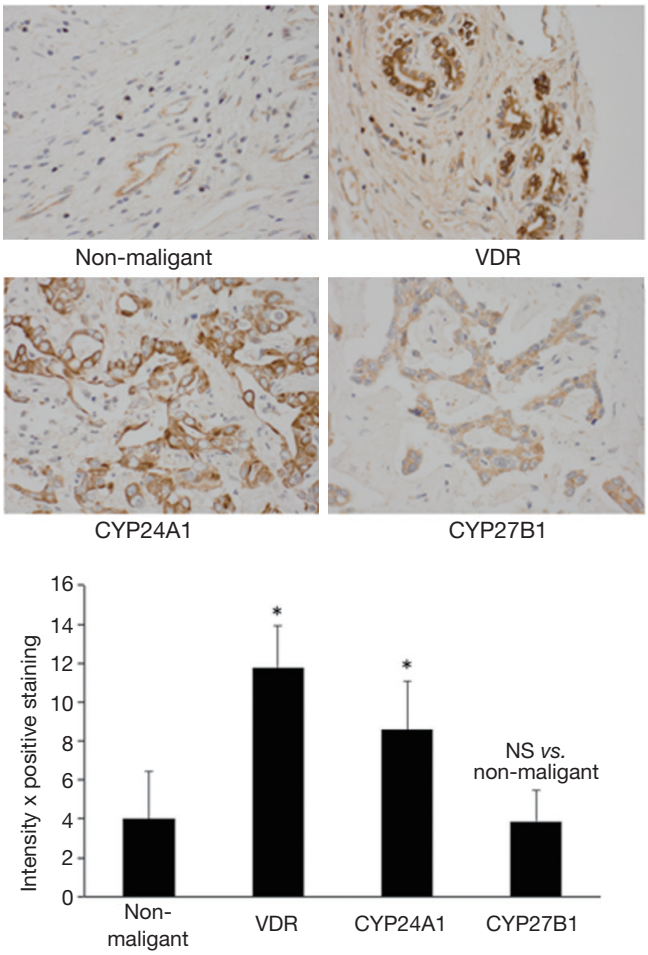

Figure 2 Immunohistochemistry was performed in human cholangiocarcinoma biopsy samples and compared to non-malignant controls. The protein expression of VDR and CYP24A1 are significantly increased in malignant biopsies compared to non-malignant, whereas CYP27B1 expression is decreased (*P<0.05 *vs.* non-malignant). Data are mean ± SE of 10-blinded evaluations of 10 randomly selected fields of three slides. Original magnification ×40 (reprinted with permission from Elsevier, Digestive and Liver Disease. Kennedy *et al.* Dysregulation of vitamin D3 synthesis leads to enhanced cholangiocarcinoma growth 2013;45:316-22).

human hepatoblastoma cells suggesting that delivery of vitamin D may also have beneficial effects on HCC (59).

Colon cancer

Finally, we examine the role of vitamin D in colon cancer. Colorectal cancer (CRC) is defined as cancer that arises from the color or rectum (parts of the large intestine) or in the appendix. CRC results in about 0.5 million deaths per year and is the second most common cause of cancer in women and third in men. Unlike a number of the other GI cancers, CRC is more common in developed countries rather than underdeveloped countries. Symptoms of CRC include increased worsening constipation, bloody stool, weight loss and loss of appetite. These symptoms increase with increasing age. Treatment strategies for CRC include surgery, chemotherapy, radiation and palliative care. Preventative care can significantly reduce the likelihood of developing CRC. Numerous studies involving vitamin D and CRC have been reported demonstrating a link between the two. It has been found that during CRC tumor progression, the regulating enzymes that metabolize and catabolize vitamin D are under epigenetic regulation and vitamin D (via VDR) regulates proliferation, differentiation and apoptosis in an autocrine fashion within colonic epithelium (60). An interesting study from Kaler *et al.* found that vitamin D_3 can enhance crosstalk between tumor epithelial cells and the microenvironment suggesting there is also a paracrine regulation by vitamin D (61). More recent work from this group has also found that treatment with vitamin D increases the sensitivity of tumor cells to TRAIL-induced cellular apoptosis (62). CYP24A1 expression was highly increased in adenocarcinomas from human patient samples when compared to normal colon mucosa and the increase in CYP24A1 was correlated with an increase in the proliferative marker, Ki-67 suggesting that degradation of vitamin D allows for tumor progression (63). The authors demonstrate that vitamin D disrupts the activation of STAT1 signaling and the production of Il-1beta in macrophages rendering them unable to activate the Wnt signaling pathway in colon carcinoma cells (61). VDR overexpression has also been found in CRC and was associated with PI3K-AKT pathway and KRAS mutations (64). Besides this finding, another study found that vitamin D actions are mediated via the TLR4 pathway in models of inflammatory bowel disease-induced CRC (65). To add more confusion, a recent study has shown that VDR activation may be dependent upon phosphatidylinositol 5-phosphate r-kinase type II beta (PIPKIIbeta) (66). *In vivo*, loss of VDR ($VDR^{-/-}$) in a model of intestinal tumor development (adenomatous polyposis coli (APC) knockout mice), increased tumor burden and the size of tumors compared to $APC^{-/-}$ alone providing strong proof that loss of VDR activation increases CRC tumorigenesis (67). Using a different model of CRC, Aberrant crypt Foci ($ACF^{-/-}$)

crossed with $VDR^{-/-}$, it was demonstrated that loss of VDR again increased tumor size and enhanced the Wnt/b-catenin pathway (68). Regardless of the pathway, it's clear that VDR is critical to regulate vitamin D effects on CRC. Like other GI cancers, treatment with vitamin D for CRC should be monitored closely and perhaps even personalized to the individual's genetic make-up. A recent study found that certain polymorphisms in CYP24A1 and CYP27B1 can regulate and alter vitamin D metabolism in colon cancer (69) and supports the concept of further studies to determine the exact mechanism of vitamin D effects in CRC.

Conclusions

In summary, the work regarding the role of vitamin D in GI cancers is growing and there is potential for therapeutic treatments to be established. However, there must be caution taken when treating with vitamin D and possible personalized treatments may be options for patients suffering from GI malignancies. Serum levels of vitamin D may be a useful biomarker for physicians, but this should also be taken into account with patient diet and sunlight exposure, as both of these are key regulators of vitamin D production. With a growing population of obese patients, vitamin D metabolism is at risk and therefore, the patients risk for developing GI cancers is also increased.

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