Neoplasma 2024; 71(4): 307–318

doi:10.4149/neo_2024_240531N240

Vitamin D supplementation in cancer prevention and the management of cancer therapy

Review

Ladislav KLENA[1], Kristina GALVANKOVA[1], Adela PENESOVA[1,2,*], Olga KRIZANOVA[1,3,*]

[1]*Institute of Clinical and Translational Research, Biomedical Research Center, Slovak Academy of Sciences, Bratislava, Slovakia;* [2]*Faculty of Physical Education and Sport, Comenius University, Bratislava, Slovakia;* [3]*Department of Physiology, Medical Faculty, Masaryk University, Brno, Czech Republic*

**Correspondence: adela.penesova@savba.sk, olga.krizanova@savba.sk*

Received May 31, 2024 / Accepted August 21, 2024

Vitamin D is an important steroid hormone that exerts immunomodulatory actions, controls calcium and phosphate homeostasis, and significantly affects human health. Vitamin D deficiency is a global health problem, affecting approximately 60% of adults worldwide, and has been implicated in a range of different types of diseases, e.g., cancer. Vitamin D is involved in the regulation of cell proliferation, differentiation, energetic metabolism, and different types of cell death (e.g., apoptosis, autophagy, etc.). In physiological conditions, it is also able to modulate immune responses, angiogenesis, etc., which belongs to fundamental cancer-related processes. Vitamin D deficiency has been associated with an increased risk of some types of cancer, e.g., colorectal, breast, ovarian, prostate, pancreatic, etc. The role of vitamin D in cancer prevention, carcinogenesis, and cancer treatment is still under investigation and depends on the type of cancer. This review summarizes the role of vitamin D in all three above-mentioned aspects and discusses the mechanism of action and potential possibilities in cancer treatment.

Key words: vitamin D; cancer; vitamin D receptor; obesity

Characterization and mechanism of action of vitamin D

Vitamin D is a group of steroid vitamins, occurring in two forms-D2 (ergocalciferol) and D3 (cholecalciferol). The major natural source of vitamin D originates from the skin, where cholecalciferol is synthesized in the lower layers of the epidermis after exposure to UV-B light. Vitamin D can also be supplemented in the body through dietary intake. The biologically active form of vitamin D, 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3-calcitriol), is formed from cholecalciferol by two hydroxylating steps (Figure 1). Vitamin D is important in the regulation and maintenance of calcium and phosphate homeostasis. Also, vitamin D is a significant modulator of the immune system. To identify vitamin D target genes, 25 healthy volunteers were subjected to bolus 80,000 IU vitamin D and after 24 hours, target genes were evaluated. From these, 61 genes participate in eight major pathways of innate immunity [1]. The function of vitamin D to influence innate immunity has been demonstrated in a large number of experimental models, but the molecular mechanisms involved in these processes are not yet fully understood. Nevertheless, appropriate vitamin D status in healthy individuals leads to suppression of innate immunity, e.g., suppression of inflammation [2].

The level of vitamin D in the body is determined by the serum 25(OH)D (calcifediol) concentration, with 25(OH)D having a relatively long circulating half-life of 15 days. Serum 25(OH)D concentrations can be measured either in nanomoles per liter (nmol/l) or nanograms per milliliter (ng/ml). The majority of the human population struggles with vitamin D deficiency when serum 25(OH)D concentrations are less than 30 nmol/l. Serum 25(OH)D concentrations greater than 125 nmol/l may be associated with adverse effects. Vitamin D is not eliminated from the body.

Two important enzymes are involved in the production of the active form of vitamin D-calcitriol. In the liver, cholecalciferol is converted to calcidiol by cytochrome P450 2R1 (vitamin D 25-hydroxylase; CYP2R1). Calcidiol is further hydroxylated to calcitriol (an active form of vitamin D3) in the liver by cytochrome P450 27B1 (25-hydroxyvitamin D 1-alpha-hydroxylase; CYP27B1) (Figure 1). Another enzyme, localized in mitochondria, cytochrome P450 family 24 subfamily A member 1 (CYP24A1), catalyzes hydroxylation reactions, which lead to the degradation of calcitriol. Calcitriol mediates its biological effects through the vitamin D receptor (VDR). This receptor belongs to the nuclear receptor family, which acts as a transcription factor after the binding of calcitriol [3]. The importance of all these enzymes and also VDR in cancer prevention and/or carcinogenesis was studied in various types of cancer.

Expression of VDR, CYP27B1, and CYP24A1 was studied in uveal melanoma, together with melanin levels. The inverse correlation between VDR, CYP24A1, CYP27B1, and melanin was found. The authors have further shown that vitamin D is metabolized in uveal melanoma [4]. Lower CYP27B1 expression was associated with a worse prognosis in melanoma patients, proving previous results and suggesting that CYP27B1 might be linked to the pathogenesis and progression of melanoma [5]. CYP27B1 was shown to be involved in various types of malignancies. Polymorphism of CYP27B1 was strongly associated with an increased risk of colorectal cancer [6]. Changes in the expression of CYP27B1 and CYP24A1 were also described in different types of breast cancer (for review see [7]). In breast cancer tumors, the expression of CYP27B1 was decreased, while the expression of CYP24A1 was upregulated [7].

VDR binds to the retinoid X receptor (RXR) and this heterotrimer forms the vitamin D-response element, which controls the gene expression of calcitriol-responsive genes [8]. Several teams investigated the role of the VDR in carcinogenesis. In digestive system tumors, VDR expression could be a prognostic indicator and may also be used as a reference for vitamin D supplementation. From 3,109 patients suffering from tumors in the digestive tract, those with high VDR expression have better overall survival compared to those with low VDR expression. VDR activated by vitamin D, or its analog, activates the downstream pathways thus resulting in the inhibition of tumor growth. VDR expression could be correlated with an intake of vitamin D, or its analogues. Although serum vitamin D levels can also be predictive markers of the prognosis of patients with digestive system tumors, their levels can be easily affected by other factors, such as diet, or sun exposure [9]. In mouse experimental models, VDR reduced the metastatic potential of human breast cancer cells [10]. Although most known actions of VDR require its ligand, the VDR with unbound ligand is also active. For example, in epidermal carcinogenesis, the suppressive influence of the unliganded VDR on the hedgehog and β-catenin pathways appears to play a major role as promoted by VDR on the DNA damage repair process [11, 12].

VDRs are overexpressed in breast cancer, which is associated with a low risk of death and a good prognosis. Therefore, VDR agonists may be potential agents for combination use with standard chemotherapy as these agents have demonstrated antiproliferative effects in various triple-negative breast cancer cell lines through enhanced apoptosis and cell cycle arrest [13]. VDR polymorphisms were shown to be associated with renal cell carcinoma mortality in the Japanese population [14], colorectal carcinoma [6], and also with high-grade glioma mortality [15]. Recently, a significant association between positive VDR staining of the nuclear

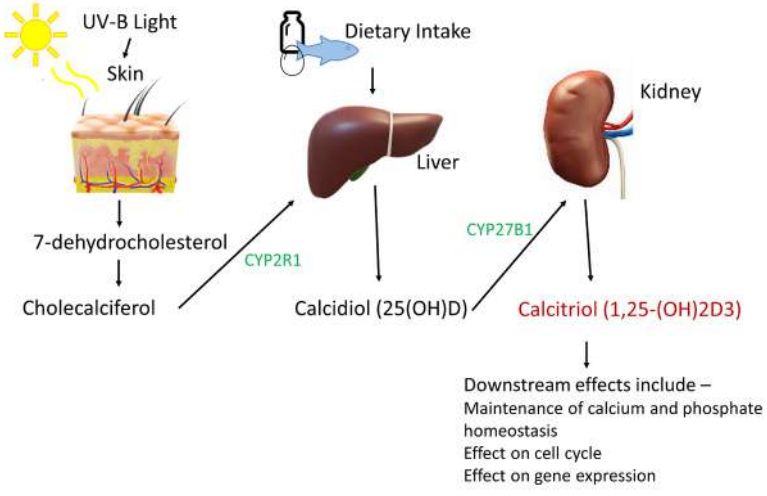

Figure 1. Cholecalciferol is produced in the skin but can also be taken by food or oral dietary supplements to prevent D3 deficiency. In the liver, cholecalciferol is converted to calcidiol by cytochrome P450 2R1 (vitamin D 25-hydroxylase; CYP2R1). Calcidiol is further hydroxylated to calcitriol (an active form of vitamin D3) in the kidney by cytochrome P450 27B1 (25-hydroxyvitamin D 1-alpha-hydroxylase; CYP27B1).

membrane in breast cancer with favorable tumor characteristics and a longer breast cancer-free interval and overall survival was published [16]. Positive nuclear VDR staining might be used to refine prognosis, especially of ER-positive cancer [16].

We obtained interesting results using the Tumor online Prognostic analyses Platform (http://www.biostatistics.online/topp/survival). From 33 different types of cancers, high levels of VDR were associated with increased overall survival in 6 types (lymphoid neoplasm diffuse large B-cell lymphoma, cholangiocarcinoma, stomach adenocarcinoma, esophageal carcinoma, bladder urothelial carcinoma, and lung adenocarcinoma). Interestingly, the association of the high levels of VDR with low overall survival was detected in 11 different types of cancers (pancreatic adenocarcinoma, thymoma, uveal melanoma, mesothelioma, brain lower grade glioma, cervical squamous cell carcinoma and endocervical carcinoma, glioblastoma multiforme, liver hepatocellular carcinoma, breast invasive carcinoma, acute myeloid leukemia, and lung squamous cell carcinoma). These results point to the need for more advanced studies on the role of VDR in different cancers, more oriented toward mechanisms of action.

Low vitamin D levels were determined in dark-skinned people living in temperate climates. Dark-skinned people are less efficient at making vitamin D because melanin in the skin hinders vitamin D synthesis [17]. Also, a higher incidence of certain types of cancers was described in the black population. African Americans have the highest death rate and shortest survival of any racial or ethnic group for most cancers [18]. Nevertheless, the connection between low levels of vitamin D and cancers in this population remains to be further elucidated.

Vitamin D interference with some other molecules

Vitamin D and calcium. Vitamin D significantly affects calcium homeostasis and metabolism. It was shown that calcium signaling in cancer cells can influence various processes important in cancer progression, such as proliferation, invasion, but also cell death [19].

The role of dietary supplementation of calcium in the development and progression of different types of cancer is abundantly discussed in the scientific literature. However, there are several controversial results. A variety of results proposed proliferative or proapoptotic effects.

Bernichtein et al. [20] provided evidence that a high-calcium diet dependently and dramatically promotes the progression of early prostate lesions. Remarkably, vitamin D supplementation had little protective effect *per se* but completely prevented the deleterious effects of a high-calcium diet in both mouse models. The authors have shown that these antagonistic effects are mediated by opposing regulation of 2 major mediators of calcium-induced cell proliferation, i.e., the calcium channel TRPC6 (transient receptor potential canonical 6) and the G-protein-coupled calcium-sensing receptor. This study predisposes at-risk patients with early-stage prostate cancer to careful consideration of calcium supplementation with vitamin D [20]. On the contrary, no association with the risk of total prostate cancer has been found in a dose-response meta-analysis examining calcium supplements. A significant positive association with fatal prostate cancer was found [21].

Liu et al. [22] found that vitamin D inhibited lung cancer tumor growth, migration, and proliferation by downregulating histidine-rich calcium-binding protein (HRC). HRC is deeply involved in the maintenance of calcium homeostasis in the cells. The upregulated expression of HRC correlated with the increased expression of the sodium-calcium exchanger. Inhibition of the calcium-binding role of HRC via vitamin D and VDR may affect the signal transduction of cancer pathways such as cyclin D1 [22].

In A431 squamous cell carcinoma, both VDR and protein disulfide isomerase family A member 3 (PDIA3) are required to regulate membrane response to active forms of vitamin D, possibly through CAMKIIα and impaired calcium influx [23]. The authors have shown that PDIA3 is required for 1,25(OH)2D3-induced calcium mobilization in A431 cells.

Vitamin D and cholesterol. Since 25(OH)D is a steroid compound, several teams attempted to compare serum 25(OH)D levels with lipid profiles. Yin et al. [24] used Mendelian randomization analysis to decipher the relationship between 25(OH)D and lipid levels. This study shows evidence of a link between vitamin D deficiency and an increased risk of high triglycerides, high total cholesterol, and high LDL-C lipids. Thus, a link between triglycerides, total cholesterol, and vitamin D is evident [24]. Recently a work by Zhang and Dong [25] reported that people working in agriculture, forestry, and fishing may benefit from maintaining adequate serum 25(OH)D levels to mitigate adverse lipid profiles and reduce cardiovascular risk, compared to miners or traffic drivers. Importantly, about two-thirds of people working in these fields were vitamin D-sufficient. Moreover, vitamin D was linearly associated with better HDL-C levels in vitamin D-sufficient individuals, females, and those without obesity. Nevertheless, the study has several limitations, e.g., seasonal variations of vitamin D, different lifestyle factors, etc. [25].

Cholesterol is an important steroid molecule performing various functions in the cell, from stabilization of membranes to serving as a precursor for steroid hormone synthesis, etc. Accumulating evidence shows that reprogramming of cholesterol synthesis is a common feature in breast cancer, but also in colon, rectal prostatic, and testicular cancers [26, 27]. LDL-C levels could serve as a prognostic factor in the diagnosis of breast cancer [28]. LDL levels can be useful in the identification and follow-up of high-risk groups, suggesting that cholesterol metabolism may be an important therapeutic target in patients with breast cancer.

Accumulating evidence suggests that anticancer drugs may exert their anti-proliferative activities at least in part by

reducing cholesterol content/biosynthesis [26]. Tamoxifen partially mediates its anticancer effect through 5,6β-epoxycholesterol, probably through the ROS-dependent mechanism [29]. Combinational treatment of chemotherapeutics and cholesterol-lowering drugs might be a promising novel tool in the treatment of cancers. It was shown that the administration of statins sensitizes anti-hormonal drugs in breast and prostate cancers. Statins have been considered an anticancer drug in recent decades, especially in older people [30].

Vitamin D and obese cancer patients, or patients with diabetes

Almost 20% of all cancer cases are caused by obesity [31–33]. The International Agency for Research on Cancer (IARC 2002) assessed that obesity represents a relative risk of many cancer cases, e.g., 11% of colon cancer, 9% of postmenopausal breast cancer, 39% of endometrial cancer, 25% of kidney cancer, and 37% of esophageal cancer. There is evidence that obesity is involved in the development of different types of cancer, including colorectal, renal, liver, esophageal, thyroid, melanoma, multiple myeloma, gallbladder, leukemia, lymphoma, and prostate in men; and postmenopausal breast and endometrial cancer in women [34–37].

Greater adiposity is associated with lower vitamin D status, and individuals with obesity frequently have marginal or deficient circulating 25(OH)D levels. According to a meta-analysis of Pereira-Santos et al. [38] prevalence of vitamin D deficiency was 35% higher in obese subjects compared to the normotrophic group and 24% higher than in the overweight group.

The mechanisms that drive etiologic pathways for these cancers in obesity are different and are not completely understood. Deficiency of vitamin D is thought to be one of them [32]. Meta-analysis of observational studies showed a consistent inverse relationship between serum vitamin D levels and colorectal cancer, however no association for prostate and breast cancer was found [39].

The genetic risk score (GRS) is a predictive model of genetic risk that can be calculated using an allelic scoring system that incorporates each risk allele identified as being associated with the studied phenotype. Recently, Almaghrbi et al. [40] systematically reviewed the association of the GRS of low-vitamin-D-risk alleles with different non-communicable diseases. They found the contribution of the single nucleotide polymorphisms (SNPs) of low-vitamin-D-risk as an accumulative factor associated with the risk of developing obesity, type 2 diabetes, cardiovascular diseases, and cancer.

Obesity often coexists with low calcium intake and vitamin D insufficiency [41], however, there are contradictions in the evidence regarding an association between calcium intake and body weight. According to one hypothesis, weight loss combined with increased calcium intake should result in reduced loss in fat-free mass and greater fat loss [42]. Some clinical trials showed a positive effect of calcium plus vitamin D3 supplementation, which facilitated fat loss in patients with overweight and/or obesity [42, 44]. Recently, Lee et al. [45] showed that excess intracellular Ca^{2+}, a known pathogenic factor in hypertension, acts as a critical negative regulator of insulin signaling by forming Ca^{2+}-phosphoinositides that prevent the membrane localization of AKT, a key serine/threonine kinase signaling molecule. Pharmacologically attenuated intracellular Ca^{2+} overload *in vivo*, by administering candesartan to obese mice successfully improved insulin resistance, dyslipidemia, hepatic steatosis, and inflammation by inhibiting dysregulated SOC-mediated Ca^{2+} entry and ectopic lipid accumulation [45]. Thus, there is robust evidence for the pleiotropic contribution of intracellular Ca^{2+} overload in the pathogenesis of insulin resistance and there are already approved drugs, e.g. candesartan that can act in the improvement also of insulin resistance and dyslipidemia. However, there is a need for more randomized control trials to examine the influence of vitamin D on body fat.

Together with other factors, orexigenic neuropeptide agouti-related protein (AgRP) that is associated with obesity might be involved in the development of colorectal cancer. Moreover, AgRP might be used as a diagnostic marker for this type of cancer [46]. Many studies dealt with ω-3 fatty acid intake, which potentially might have a protective effect on cancer risk. Nevertheless, usage of vitamin D and omega-3 fatty acids did not lower the risk of developing cancer during a 5.3-year trial [47]. Interestingly, this combination was effective in reducing aromatase inhibitors-associated arthralgia [48], which is important for postmenopausal patients with estrogen receptor-positive breast cancer treated by aromatase inhibitors.

Recent research has been focused on vitamin D supplementation in diabetes prevention and treatment. Supplementation with vitamin D had a promising effect in reducing glycated hemoglobin (HbA1c) in patients with type 1 diabetes, however, there was no significant impact on the incidence of type 2 diabetes or glycemic control in those patients [49]. According to guidelines [50], patients at high risk of diabetes or with diabetes should have a controlled level of serum vitamin D on a regular basis, and if needed vitamin D should be supplemented [51]. More longer-term trials and randomized controlled studies with bigger sample sizes are required to fully elucidate the beneficial effect of vitamin D supplementation in patients with diabetes.

Vitamin D in carcinogenesis

In general, vitamin D deficiency/insufficiency has been associated with an increased risk of many types of cancer, e.g., colorectal, breast, ovarian, prostate, pancreatic, etc. Information that vitamin D can have a protective effect against cancer was published a long time ago [52, 53]. Vitamin D is generally accepted as a substance with the potential ability to increase cellular resistance to malignant transforma-

tion and influence cancer treatment's efficacy depending on its supplementation [54]. It has been shown that increased pre-diagnostic serum vitamin D levels are associated with improved overall cancer survival [55]. However, some large-scale studies have suggested that the cancer-protective effects of vitamin D observed elsewhere, might not apply to overall cancer survival, but only to specific cancer types [56]. Barry et al. [57] suggested that the VDR genotype might affect the effectiveness of vitamin D3 supplementation in the prevention of colorectal adenoma recurrence [57]. There was no observed preventative effect of vitamin D on colorectal polyps or incident cancer was not observed in a cohort of overweight or prediabetic patients as well [58]. On the contrary, the incidence of metastatic or fatal cancer was reduced in the overall cohort with a high-dose supplementation of vitamin D for 5 years. The most prominent risk reduction was observed in normal-weight individuals [59]. It should be noted that despite the undoubted importance of these trials, they all suffer from distinct limitations-vitamin D dosing, racial differences, duration of the trials, etc.

The protective role in human carcinogenesis is boosted by the regulatory role of vitamin D on cell proliferation, apoptosis, cell differentiation, angiogenesis, autophagy, inflammation, oxidative and energy metabolism, as well as immune response modulation, which are fundamental cancer-related processes [60]. Vitamin D plays a preventive role in cervical cancer rather than a therapeutic [61].

The question arises about the optimal levels of vitamin D in cancer prevention. Torres et al. [62] reported that serum levels of vitamin D ≥40.26 ng/ml ± 14.19 ng/ml could exert a protective effect against breast cancer. Guyonnet et al. [63] reported that women with increased vitamin D intake had a 46% lower chance of developing breast cancer. It should be noted though, when looking at the role of vitamin D in breast cancer, different subtypes have to be considered. For example, vitamin D was found to have a significantly more protective effect in triple-negative breast cancer (TNBC) when compared to other subtypes [64]. Table 1 summarizes clinical studies and meta-analyses of such studies, which have aimed to determine the protective levels of vitamin D in various cancer types.

How does then vitamin D mediate cancer protective effects at the cellular level? As mentioned previously, the active form of vitamin D, 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3) or calcitriol, exerts its biological functions by binding to VDR. The VD_3-VDR complex can then regulate the transcription of a myriad of genes, which contain responsive elements VDREs. Cellular processes commonly deregulated in carcinogenesis, which are also commonly targeted by calcitriol, include cell cycle progression, cell proliferation, oxidative stress, immune function, cell migration, cellular adhesion, metabolism, angiogenesis, and apoptosis [78].

Effects on cell proliferation and the cell cycle. Cell cycle dysregulation and sustaining cell proliferation are prominent hallmarks of many cancers [79]. Several studies have reported that calcitriol can mediate the downregulation of aberrant proliferative signaling in a variety of cancers. It has been shown that calcitriol inhibits the NOTCH1 pathway in colorectal cancer (CRC) *in vitro,* thus inhibiting CRC cell proliferation, invasion, and migration [80]. Another study has reported that CRC cell proliferation is reduced by calcitriol acting downstream on SIRT1 deacetylase via VDR, which in turn mediates anti-proliferative activity [81]. In melanoma cell lines, calcitriol was found to transcriptionally inhibit *NSUN2* (NSUN2) by binding to VDR. NSUN2 has been linked to promoting cell proliferation and metastatic behavior in melanoma. Knocking down NSUN2 has been shown to reduce cell proliferation and the migratory ability of melanoma cells *in vitro*.

Aberrant WNT/β-catenin signaling has been well characterized to promote tumorigenesis in a variety of human cancers [82], including cell proliferation. A recent study has shown that in thyroid cancer, the activated form of VDR (activated by calcitriol), inhibits cell proliferation by binding E-cadherin and β-catenin, preventing TCF/LEF transcriptional activity and therefore the activation of aberrant WNT signaling [83]. This has been shown both *in vitro* and *in vivo*. Calcitriol has also been shown to reduce β-catenin expression in breast cancer *in vitro* [84]. Similarly, in colorectal carcinoma, VDR has been shown to bind β-catenin and prevent its nuclear accumulation, which is necessary to initiate WNT signaling by regulating the transcription of WNT target genes [85]. Similarly, calcitriol was reported to reduce the expression of β-catenin and therefore suppress aberrant WNT signaling in gastric cancer cells *in vitro* [86], and in colorectal cancer cells *in vitro* by the same mechanism [87].

Table 1. Clinical studies (bold letters) and meta-analyses (plain letters) reporting concentration-dependent protective effects of vitamin D.

Cancer type	Protective serum levels of vitamin D (nmol/l)	Sample size (n)	References
Breast cancer	≥100.65±35.48*	129,486	[62]
	30–70	**6,090**	**[64]**
Colorectal cancer	**25–50**	**403,170**	[65]
	≥50	7,718	[66]
	≥75*	2,819	[67]
Prostate cancer	**≥50**	**4,065**	**[68]**
Lung cancer	**41.05–59.85***	**445**	**[69]**
Glioblastoma	**66**	**1,704**	**[70]**
Melanoma	≥62.5*	12,297	[71]
Hepatocellular carcinoma	**≥50**	**431,807**	**[72]**
Pancreatic cancer	50–65*	529,917	[73]
Thyroid cancer	≥75*	402	[74]
Head and neck cancer	**≥75***	**81**	**[75]**
Bladder cancer	**≥60.35**	**115**	**[76]**
Leukemia	**≥75***	**125**	**[77]**

Note: *the following values were converted from ng/ml to nmol/l for consistency

Calcitriol has also been shown to reduce the proliferation of non-small-cell lung cancer both *in vitro* and *in vivo* in an elegant study by Songyang et al. [88]. The authors have shown that calcitriol inhibits lung cancer cell proliferation by interacting with the PI3K/AKT/mTOR pathway *in vitro*. The dysregulation of the PI3K/AKT/mTOR pathway in cancer is well characterized and known to drive cancer development and progression [89]. The individual components of this pathway were shown to be inhibited by calcitriol in a nearly similar way as if they were inhibited by synthetic inhibitors. Both cisplatin and calcitriol alone showed a similar effect on lung tumor size reduction *in vivo*.

In vivo and *in vitro* experiments on colorectal cancer have shown that vitamin D can cause cell cycle arrest by downregulating *CCND1* (Cyclin D1, which promotes cell cycle progression) and upregulating P21 (inhibits cyclin-dependent kinases, which results in cell cycle arrest at various stages) [90, 91]. Idris and colleagues [91] have also shown that vitamin D significantly downregulates *CCND3* (Cyclin D3 – promotes the cell cycle) and upregulates p27 (inhibitor of CDKs, resulting in cell cycle arrest) in several CRC cells i*n vitro*. Breast cancer cell lines treated with vitamin D *in vitro* exhibited cell cycle arrest in the sub-G0/G1 phase (apoptotic state) [92].

Apoptosis. Another hallmark of cancer is resisting cell death [79]. A number of studies have reported that vitamin D can interfere with cell death resistance in cancer. *In vitro* studies using breast cancer cell lines have shown that calcitriol mediates the upregulation of the pro-apoptotic BCL-associated X (*BAX*), caspase-3 (*CASP3*), and the downregulation of anti-apoptotic B-cell lymphoma 2 (*BCL2*) gene [93]. In another study, breast cancer cell lines treated with calcitriol induced apoptosis by activating caspase 3/7 [92]. A similar mechanism is also observed in ovarian cancer cells *in vitro* [94]. This study has also shown that in vitamin D-treated cells, elevated expression of P53 can be observed, together with decreased levels of BCL-2 and cyclin D1 (namely in TNBC). These results showed that vitamin D also induces apoptosis via P53 upregulation. Similar results were seen both *in vivo* and *in vitro* in CRC, where pro-apoptotic genes and proteins including cytochrome C were upregulated and the anti-apoptotic ones were downregulated [90]. In head and neck squamous cell carcinoma cells, vitamin D was found to increase the expression of pro-apoptotic BH3 domain only protein BIM in a number of cell lines *in vitro* [95]. Additionally, the authors supported this with *in silico* data, showing that higher BIM expression correlates with better survival, thus giving a more clinical relevance to the study. Idris et al. [91] have shown similar mechanisms of action of vitamin D on CRC cells *in vitro*. The study reported the downregulation of anti-apoptotic markers such as BCL2 and the upregulation of pro-apoptotic markers, BAX, cytochrome C, and caspase-3.

Metabolism. Reprograming cellular energetics is also a hallmark of cancer and a hot topic of research in the past decade [79]. Cancer cells have a tendency to rewire metabolic programs in their favor. Huang et al. [87] have shown that calcitriol can downregulate the Warburg effect in CRC cells *in vitro*. The Warburg effect is a metabolic phenomenon observed in cancer cells, where cancer cells switch from mitochondrial respiration to aerobic glycolysis in the presence of oxygen, thus producing more cellular energy to drive oncogenic processes [96]. The authors have shown that CRC cell lines treated with calcitriol displayed reduced expression of Glucose transporter 1 (GLUT1), Hexokinase 2 (HK2), and Lactate dehydrogenase (LDHA), and decreased extracellular acidification rate while increasing oxygen consumption rate and ATP production. These colorectal carcinoma cells have therefore switched back to mitochondrial respiration, thus reversing the Warburg effect. The same phenomena were observed *in vivo*, supporting the *in vitro* data, that calcitriol can indeed reverse the Warburg effect.

Calcitriol was also observed to suppress glycolysis in gastric cancer cells *in vitro* by downregulating GLUT1, HK2, and LDHA as in the previous study [97].

For an illustration of the whole process, see Figure 2.

Cell adhesion and cell migration. Increased cell plasticity and migratory capabilities are the cornerstone of metastasis of many cancers. A number of studies reported that calcitriol can reduce deregulated cell migration. Vitamin D-treated head and neck squamous carcinoma cells showed a significant reduction in migratory capability. The authors also showed that this could be the effect of E-cadherin levels being restored, which downregulated EMT and therefore the metastatic potential of these cells [95]. In invasive breast cancer cell lines, experiments have shown an upregulation of the epithelial marker E-cadherin and a downregulation of mesenchymal markers N-cadherin and P-cadherin, suggesting that calcitriol can reverse EMT [93]. In the same study, calcitriol was found to downregulate individual components of the mitogen-activated protein kinase (MAPK) pathway, namely JNK and p38, and upregulate the ERK1 (which can be beneficial for the survival of breast cancer patients). Furthermore, the study has shown that vitamin D downregulated Ras and MEK, the components of the Ras signaling pathway, which usually promotes oncogenic and metastatic processes in many cancer types when dysregulated.

Autophagy. Autophagy is responsible for removing potentially toxic and cancer-inducing waste from cells. This may include damaged or misfolded proteins, for example [98]. In cancer, it has been reported that autophagy may have a dual role, both in suppressing cancer progression and promoting it. In breast cancer, calcitriol has been found to suppress pro-survival autophagy [99]. This study has shown that breast cancer cell lines, as well as mice with mammary tumors treated with calcitriol, exhibited lower levels of autophagy markers (such as Beclin1, Atg5, and LC3B). Another study on breast cancer has revealed that supplementation with calcitriol induces autophagy in luminal-type breast cancer, which is similar to autophagy observed

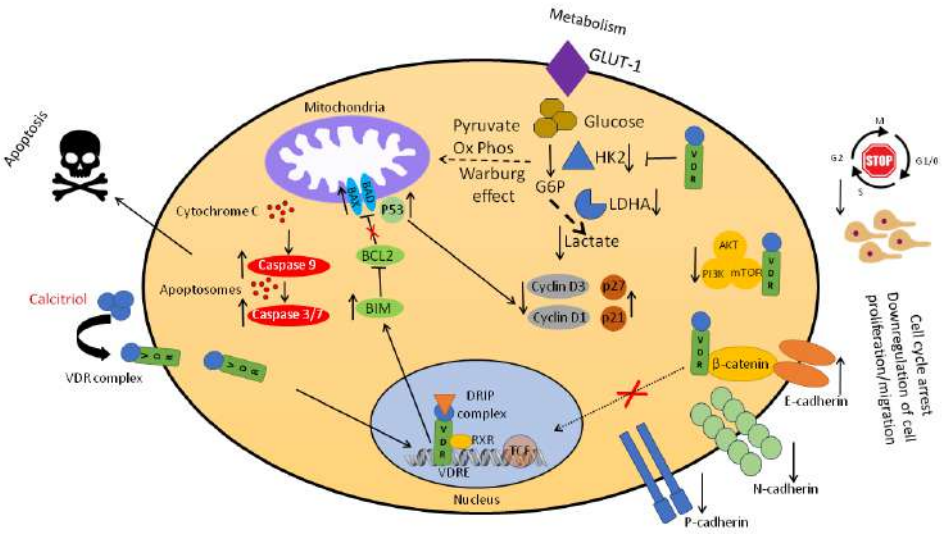

Figure 2. Scheme showing proposed mechanisms of calcitriol action at the cellular level in cancer cells. *Apoptosis*-Calcitriol binds the VDR and forms the VDR complex, which translocates into the nucleus and regulates the transcription of VDR responsive elements (VDREs) by binding to its co-activators-the DRIP complex (VDR-interacting proteins) and the RXR. Target genes regulating apoptosis, which contain VDREs, are activated. This causes the upregulation of BIM, which inhibits BCL-2, thus allowing the activation of BAD/BAX, which induces apoptosis and the mitochondrial release of cytochrome C into the cytoplasm. Cytochrome C activates Caspase-9, which subsequently activates Caspase 3/7 leading to cell death. *Metabolism*-The VDR complex downregulates glucose transporter 1 (GLUT-1) as well as hexokinase 2 (HK2) and lactate dehydrogenase A (LDHA), which promotes the conversion of lactate into pyruvate, thereby reversing the Warburg effect. *Cell cycle, proliferation, and migration*-The VDR complex binds β-catenin and inhibits its translocation to the nucleus, thereby preventing the transcription of WNT target genes. The VDR complex also increases the expression of E-cadherin and decreases the expression of epithelial-to-mesenchymal transition (EMT) markers P-Cadherin and N-Cadherin, suggesting a reverse of EMT. The VDR complex downregulates the individual components of the PI3K/AKT/mTOR pathway, decreasing cancer cell migration. Calcitriol also causes cell cycle arrest by upregulating the expression of P53, which mediates the downregulation of Cyclin D1 and Cyclin D3, and upregulates P21 and P27, which inhibit the cell cycle.

in normal breast tissue, which facilitates the suppression of breast cancer progression [100]. In prostate cancer, calcitriol was shown to potentiate the effects of sulforaphane in inducing autophagy and prostate cancer cell lines by upregulating the autophagy marker NRF2 [101]. Interestingly, in cervical cancer, calcitriol inhibits autophagy, which has been shown by p62 accumulation *in vitro* [102].

Angiogenesis. The formation of new blood vessels to facilitate oxygen and nutrients for tumors, also known as angiogenesis, is also a hallmark of cancer [79]. An *in vitro* study using ovarian cancer cell lines reported that cells treated with calcitriol exhibited reduced activity of the vascular endothelial growth factor (VEGF), which plays a part in angiogenesis signaling [94].

Vitamin D supplementation in the management of cancer therapy and in the treatment of side effects

The effect of vitamin D supplementation has been intensively studied in different types of breast tumors. Vitamin D deficiency is characteristic of all breast cancer patients, especially those with the most aggressive form of the tumor – TNBC. It has been shown that while vitamin D is an important factor in breast cancer prevention, its role in treatment is still unclear [13]. Vitamin D had no effect in inhibiting the proliferation of the TNBC cell lines MDA-MB-157, MDA-MB-231, and MDA-MB-468 [13].

Chemotherapy-induced peripheral neuropathy is an important burden during chemotherapy, especially in taxane-treated patients [103]. Jennaro et al. [104] published that vitamin D deficiency elevates the severity of paclitaxel-induced peripheral neuropathy. In general, patients with vitamin D insufficiency are more vulnerable to chemotherapy-induced peripheral neuropathy. Since the black population suffers from vitamin D hypovitaminosis, a higher incidence of chemotherapy-induced peripheral neuropathy might be, at least partially, explained by this fact [105]. The potential effectiveness of vitamin D supplementation for the prevention of chemotherapy-induced peripheral neurotoxicity remains to be further elucidated. However, considering the minimal toxicity and cost of vitamin D supplementation, and the use of vitamin D in the prevention of bone loss in patients with breast cancer receiving aromatase inhibitors, supplementation with vitamin D may be a reasonable intervention to prevent chemotherapy-induced peripheral neuropathy during paclitaxel treatment in some high-risk patients even in the absence of confirmatory clinical trial evidence [105].

Vitamin D analogs are also being studied by researchers. These may also possess the anticancer activity of vitamin D,

albeit without the toxic effects of high doses. One example is a current clinical trial, where both vitamin D and its analog paricalcitol alone or in combination with other treatments, including chemotherapy and immunotherapy are tested in patients with pancreatic cancer [106].

In summary, from the current knowledge about the role of vitamin D, it is clear that normal or higher levels of the vitamin are an effective preventive tool against some types of cancers e.g., breast cancer. Also, vitamin D hypovitaminosis is a negative predictive tool in obese people with cancer complications. Vitamin D can target different signaling pathways, which can result in decreased proliferation, cell cycle arrest, increased apoptosis, etc., that might help to combat tumor growth, or metastasis formation. However, it is clear that the beneficial effect of the vitamin D is not equal on all types of cancers. Also, a large number of other factors have to be taken into account, such as tumor type, severity of disease, dose, duration of vitamin D administration, seasonal variations of vitamin D, different lifestyle factors, race, gender, etc. Further investigation in this field might clarify the potential utilization of vitamin D as an anticancer drug.

Acknowledgments: The work of OK was supported by grants APVV-20-0176, VEGA 2/0040/22, and the work of AP was supported by grant APVV-22-0047 (the main investigator in the BMC).

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