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REVIEW

Vitamin D and potential effects on cancers: a review

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Abstract

Cancer is characterized by the abnormal and uncontrollable division and growth of cells that can infiltrate tissues and alter normal physiological function, which will become crucial and life-threatening if left untreated. Cancer can be a result of genetics, such as mutations or environmental causes, including smoking, lack of physical activity, as well as nutritional imbalance in the body. Vitamin D is one of the foremost nutrients that play a crucial role in a variety of biochemical pathways, and it is an important key factor in several diseases. Vitamin D is an essential nutrient for preventing malignancies and a complementary treatment for cancer through direct and indirect biochemical pathways. In this article, we summarized the correlation between vitamin D and various cancers using an extensive search on PubMed, Google Scholar, and Scopus. This paper reviews the role of vitamin D in different types of cancer.

Keywords Vitamin D · Prostate cancer · Breast cancer · Colorectal cancer · Melanoma · Hepatocellular cancer · Leukemia

Abbreviations

EMT	Epithelial-mesenchymal transition
HDAC2	Histone deacetylase 2
CLL	Chronic lymphoid leukemia
VDR	Vitamin D receptor
UVB	Ultraviolet blue
CML	Chronic myeloid leukemia
AML	Acute myeloid leukemia
TXNIP	Thioredoxin-interacting protein

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Introduction

Vitamin D is a fat-soluble vitamin associated with several Biochemical pathways and pathologies, and it can be obtained through the gastrointestinal tract (GI) or synthesized in the skin by direct ultraviolet (UV) Irradiation [1]. Vitamin D3, or cholecalciferol, and Vitamin D2, or ergocalciferol are the two main pre-forms of vitamin D in the body. The intermediate metabolite must undergo a 2-step hydroxylation to be converted to the active form of vitamin D. The first hydroxylation takes place in the liver by which Calcidiol or 25-hydroxyvitamin D is synthesized. This reaction is catalyzed by cytochrome P450 vitamin D 25-hydroxylases (i.e., CYP2R1, CYP2D11, and CYP2D25) [1]. Calcidiol is the most abundant form of vitamin D found in the blood, and therefore it can be used as an accurate indicator for measuring vitamin D status. Calcidiol is brought to the kidney via VDBP, where the second hydroxylation occurs. In this step, 1,25-dihydroxy vitamin D (calcitriol) is synthesized by 1-alpha-hydroxylase (CYP27B1) located primarily in the proximal tubule. Calcitriol is considered to be the physiologically active form of vitamin D in the body. The metabolic pathway of vitamin D is summarized in Fig. 1.

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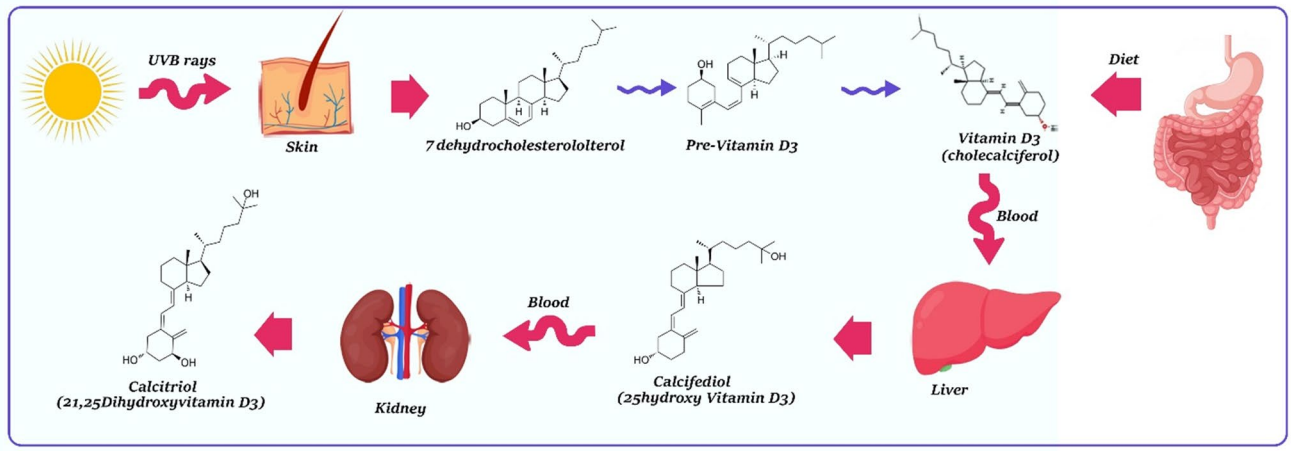

Fig. 1 A brief review of hydroxylation steps of intermediate metabolites and calcitriol synthesis. Vitamin D3 can be obtained either by absorption from the gastrointestinal tract or direct synthesis from 7-dehydrocholestrol. Afterward, vitamin D3 undergoes hydroxylation in the liver and kidney, respectively, synthesizing calcitriol, which is the active form of vitamin D; UVB: Ultraviolet blue

Vitamin D is found to play a role in regulating more than 1000 genes in a wide assembly of different cells and tissues [2]. A certain number of the included genes are involved in malignant cells' biochemical pathways. Vitamin D also regulates immune responses, cell proliferation, differentiation, and apoptosis [2]. Hence, the role of vitamin D in influencing malignant and tumor cells is undeniable.

Vitamin D also regulates phosphate, and sex hormone levels, and stimulates Calcium absorption in the GI tract through Its interaction with vitamin D receptor (VDR) [3]. Therefore, vitamin D deficiency will result in a Calcium deficit. In addition, vitamin D also promotes calcium and phosphate renal reabsorption. In cases where the concentration of phosphate in a person's serum is higher than usual, it leads to suppressing the synthesis of $1,25(OH)_2D$ [4]. Vitamin D also has an inverse association with parathyroid hormone synthesis. Vitamin D deficiency or Receptor abnormalities in the intestine will increase parathyroid hormone secretion. Vitamin D deficiency is frequently encountered among women of reproductive age [5]. A study reported a positive corresponding effect between serum vitamin D levels and Total testosterone as well as free androgen index [6].

1,25-dihydroxy vitamin D regulates steroid hormone synthesis (e.g., adrenal steroid hormones synthesis, sex hormones synthesis, and sex hormone signaling) by modulating various enzymes in the steroid hormone synthesis pathway [7]. A study conducted on Korean women concluded the level of 25-hydroxyvitamin D had a positive relationship with higher testosterone. No positive association between vitamin D levels and sex hormone E2 levels was observed. In contrast, another study revealed a contrary relation between 25-hydroxy vitamin D and E2 levels [8].

Vitamin D and cancer

Cancer is considered to be one of the foremost causes of death in today's world. The lifestyle changes brought by technological advancement are linked to the ever-increasing cancer incidences all around the globe. Several ongoing research are being conducted on this given subject by thousands of researchers in search of a cure. Some well-established treatments are already available. Vitamin D is found to be a crucial factor in cancer pathology through its regulatory and metabolic roles in the body (Fig. 2). Evidence and data on this vitamin on different types of cancer will be reviewed next.

Prostate cancer

Prostate cancer is currently the second most common cancer among men [9]. Various studies have investigated the link between dietary vitamin D as well as serum vitamin D with prostate cancer. However, there seems to be a conflict between the results. A study by Song et al. [10] reported that higher 25-hydroxy vitamin D levels were associated with a reduction in mortality in patients with prostate cancer. Also, vitamin D was reported to be a critical factor in protection against prostate cancer progression and prognosis. This statement is further backed up by Capiod et al. [11], showing that the advancement of early-stage tumors can be prevented by dietary vitamin D, Bao et al. [12] suggesting that vitamin D prevents metastasis in prostate cancer, and Woo et al. [13] which reported that vitamin

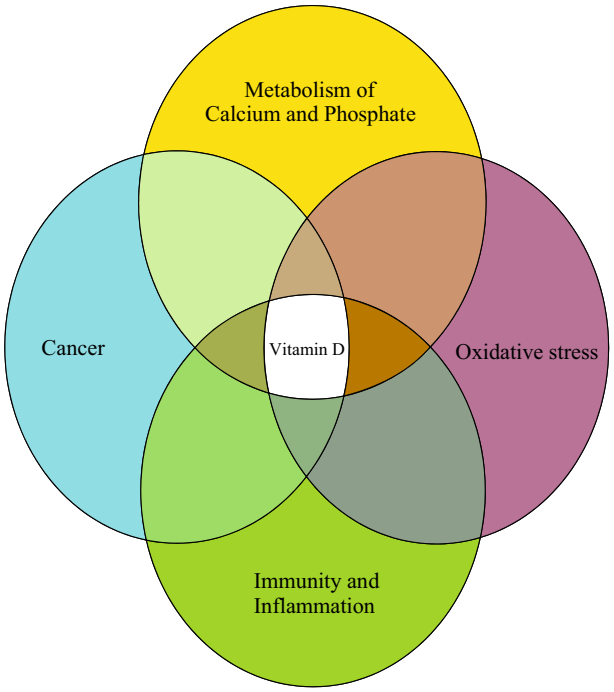

Fig. 2 Differential significant roles of vitamin D in the body are shown. Although each of the mentioned processes is interconnected and can affect each other either directly or indirectly, vitamin D acts as a common ground for all of the functions above

D remarkably improved PSA-doubling time. In addition, Bernichtein et al. [14] concluded that the Progression of early-stage prostate lesions as a result of a diet rich in calcium was reduced by calcitriol through its inhibitory effects on TRPC6 and calcium-sensing receptor expression. Also, a study by Barreto et al. reported Inhibitory effects of 25(OH)2D3 and 1,25(OH)2D3 in in vitro prostate cancer cell growth [15]. Ultraviolet blue (UVB) radiation and sunlight exposure have also been revealed to be oppositely related to prostate cancer risk [16]. The authors did not find dietary sources of vitamin D to be protective against prostate cancer, but they suggested that higher concentrations of vitamin D may be beneficial. However, a high intake of vitamin D can lead to hypercalcemia and vitamin D toxicity. Calcium is found to have a direct effect on the risk and development of prostate cancer [11]. Furthermore, a U-shaped association between 25-hydroxyvitamin D levels and cancer risk has been reported [17], suggesting that either an increase or decrease in serum 25-hydroxyvitamin D is associated with an increased risk for prostate cancer.

A meta-analysis found a correlation between increased vitamin D serum levels and elevation in the risk of prostate cancer [18].

A brief summarization of the findings is listed in Table 1 and 2. Overall, the results regarding the relationship between serum or dietary vitamin D and prostate cancer are rather conflicting, and further research is needed to establish a definitive conclusion.

Breast cancer

Breast cancer is one of the most frequent forms of cancer worldwide and is considered to be the leading cause of mortality among women cancer patients [19]. A high amount of research has gone into the link between vitamin D and breast cancer risk and progression. However, the results seem to be contradictory.

A considerable amount of Breast cancer cases progress into the metastatic phase over time. Mittal et al. demonstrated the importance of Vitamin D signaling and the epithelial-mesenchymal transition (EMT) process by inducing EMT-TF SLUG, a SNAIL zinc finger family member, expression in MCF7 and MDA-MB-468 cells, resulting in a significantly decreased level of VDR [20]. This finding is further backed up by Liu et al., showing that the downregulation of miR-1204 results in decreased distant metastasis through downregulating mesenchymal markers (N-cadherin/vimentin) and reduced cell proliferation followed by an increased VDR expression [21]. Furthermore, promoting the expression of epithelial markers such as E-cadherin is yet an additional way by which 1,25(OH)2D3 can inhibit EMT [22]. Lopes et al. Found that 1,25(OH)2D3 stimulates E-cadherin by demethylating cadherin-1 (CDH1) promoter in TNBC MDA-MB-231 cells [23]. It is suspected that an increase and decrease in E-cadherin and N-cadherin, respectively can result in reduced EMT [24]. 1,25(OH)2D can also regulate invasion and metastasis through inhibiting Tissue-type plasminogen, Urokinase-type plasminogen activator, and matrix metalloproteinase as well as induction of matrix metalloproteinase inhibitor-1 expression [25].

A study by Li et al. [26] in MMTV-PyMT mouse models fed with a vitamin D3-deficient diet found lung metastasis as early as eight weeks compared to those having a regular diet, which developed distant metastasis after 9–10 weeks. Vitamin D3 deficiency results in an increase in EMT marker levels in primary tumor tissue and metastatic long stromal tissue cells expressing CXCL12. Also, vitamin D3 deficiency resulted in an elevation in CXCL12/CXCR4 colocalization, leading to metastasis. In contrast, a study by Anisiewicz et al. [27] reported that metastasis in 4T1 mouse mammary gland cancer cells was elevated by treatment with 1,25(OH)2D3 and its low-calcemic analogs in young BALB/c-female mice. However, in another study, 1,25(OH)2D3 and both its analogs reduced the metastasis of 4T1 breast carcinoma cells to the lungs by decreasing OPN levels in old ovariectomized OVX mice [28]. These data may point to a link between 1,25(OH)2D3 and its analogs' activity and the

Table 1 Some of the available preclinical studies regarding the association between vitamin D and various cancers, which are mentioned throughout the text are summarized below

Objective	Result	Reference(s)
Prostate cancer		
Investigating the role of vitamin D in men with prostate cancer	Vitamin D has an inhibitory effect on the progression of prostate tumors in early-stage	[11]
Evaluating the effect of vitamin D on prostate cancer, metastasis, and cell invasion	Metastasis of prostate tumors can be prevented by dietary vitamin D	[12, 93]
Determining the Effect of 25-Hydroxyvitamin D3 on the proliferation of primary prostatic epithelial cells	Inhibitory effects of 25(OH)2D3 and 1,25(OH)2D3 were observed regarding the in vitro growth of prostate cancer cells	[15]
Breast cancer		
Evaluation of VDR as a possible target in metaplastic carcinomas and the effect of 1α,25(OH)(2)D(3) In triple-negative breast cancer cells	Vitamin D reduces EMT by inducing E-cadherin synthesis	[23]
Determining the role of 1α,25-dihydroxyvitamin D in preventing breast cancer cell metastasis using rMET		[24]
Colorectal cancer		
This study aims to examine the potential involvement of MED28 in the progression of EMT, and explore the probable inhibitory impact of calcitriol on both MED28, as well as EMT in colorectal cancer cells of human origin	MED28 is a critical component in the pathogenesis of colorectal cancer, suggesting a potential therapeutic target for this malignancy. Furthermore, calcitriol may have translational implications as an adjuvant in the treatment of colorectal cancer	[61]
This study investigated the effect of vitamin D3 supplementation on NF-κB and Caspase 3 in the HCT116 cell line	Vitamin D3 positively affected caspase 3 while displaying no significant effect on NF-κB	[62]
This study proposes a novel molecular mechanism that explains how 1,25(OH)2D3-VDR interacts with the NF-κB pathway to suppress its activation	The VDR is believed to exert its inhibitory effect on NF-κB activation through direct interaction with IKKβ	[94]
Hepatocellular cancer		
Investigating the effect of 1,25$(OH)_2$Vitamin D treatment on mTOR inhibitor, everolimus, sensitivity in established models of HCC cell lines resistant to everolimus	Vitamin D is capable of enhancing sensitivity to everolimus treatment in HCC cells that have developed resistance. This effect is accomplished via up-regulation of miR-375, which in turn down-regulates various oncogenes responsible for EMT	[82]
This study explores the impact of 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] on the expression levels of HDAC2 and p21(WAF1/Cip1)	The research showed that 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] displayed anti-tumorigenic characteristics by Downregulating the expression levels of HDAC2 and upregulating p21(WAF1/Cip1) expression. These effects prevented the progression of HCC and may point to a possible underlying mechanism	[83]
This study aims to investigate the impact of vitamin D3-induced TXNIP stimulation on cell lines derived from HCC	The findings of this study indicate that stimulation of TXNIP by vitamin D3 leads to a reduction in cell proliferation and an increase in apoptosis in cell lines derived from HCC	[84]
This study aimed to investigate the correlation between expression levels of vitamin D-related genes and the TGF-β superfamily in liver cancer in humans	The research findings suggest that vitamin D deficiency can promote tumor growth in Smad3-deficient contexts, possibly by modulating TLR7 expression and activating β-catenin. This observation may position Vitamin D as a viable option for preventing liver cancer in the presence of disrupted Smad3 signaling	[85]
Leukemia		
Investigating the effect of vitamin D3 on autophagic death in human myeloid leukemia cells	Vitamin D can stimulate both apoptosis and autophagy in myeloid leukemia cells, thereby promoting recovery	[89]

VDR Vitamin D receptor, *EMT* epithelial-mesenchymal transition, *TXNIP* Thioredoxin-interacting protein, *HDAC2* Histone deacetylase 2

Table 2 Some of the available clinical, epidemiological, and review studies regarding the association between vitamin D and various cancers, that are mentioned throughout the text are summarized below

Objective	Result	Reference(s)
Prostate cancer		
Studying the link between Circulating vitamin D levels and mortality in prostate cancer	Vitamin D decreases cancer mortality and protects against prostate cancer	[10]
Determining the effect of vitamin D on prostate cancer risk	UVB radiation and sunlight exposure are inversely related to the risk of prostate cancer. Dietary vitamin D can be beneficial in high doses	[16]
Establishing a relationship between vitamin D levels and the risk of prostate cancer	There is a U-shaped relation between 25-hydroxyvitamin D levels and the risk of cancer	[17, 95]
Evaluating the role of 25-hydroxy vitamin D in diseases and traits	There is no significant relationship between vitamin D levels and Prostate cancer	[96]
Studying Circulating vitamin D levels and the risk of prostate cancer	Higher vitamin D levels are correlated with an elevated risk of prostate cancer	[18, 97]
Breast cancer		
Reviewing the role of vitamin D in EMT, underlying Genes, and mechanisms	Vitamin D reduces EMT by inducing E-cadherin synthesis	[22]
Determination of the effect of 25(OH)D, 1,25(OH)2D, and vitamin D intake on breast cancer risk	25(OH)D had a protective effect on breast cancer development in premenopausal women	[38]
Determining the relationship between dietary, serum 25(OH)D, and breast cancer occurrence	Vitamin D deficiency had an inverse association with breast cancer occurrence in African women. No association between higher 25(OH)D and breast cancer occurrence was found	[41]
Evaluation of the relation between serum 25-hydroxy vitamin D, menopause, and breast cancer risk	25-hydroxy vitamin D had no association with breast cancer risk in premenopausal women an inverse nonlinear relationship was observed between 25-hydroxy vitamin D levels and the risk of breast cancer	[56]
Colorectal cancer		
This study aims to investigate the impact of a Western-style diet, oral supplementation of calcium, and/or 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] on the mucosal layer of the human colon	The addition of 1,25-dihydroxyvitamin D3 [1,25(OH)2D3] to the Western-style diet led to a remarkable increase in the expression of genes involved in inflammation, immune response, extracellular matrix, and cell adhesion	[98]
Melanoma		
Examining the relationship between serum levels of 1,25-dihydroxy vitamin D and melanoma. (With the MR method)	The researchers did not find any evidence to support a causal relationship between genetically determined levels of vitamin D and the risk of melanoma	[71]
Examining the correlation between the dietary intake of vitamin D and its potential role in reducing the risk of melanoma	It has been observed that a higher intake of vitamin D through the human diet is associated with a 50% decrease in the risk of melanoma	[72]
Studying the serum level of vitamin D and the development of melanoma	Elevated levels of vitamin D in the body have been associated with an increased risk of melanoma progression	[73]
Investigating the efficacy of vitamin D on melanoma cancer	High levels of vitamin D can be both beneficial and harmful for subjects with cancer, including melanoma	[99]
Leukemia		
Investigating the relation between vitamin D and survival rate in children with AML	Scant levels of vitamin D in these patients were associated with AML and decreased survival	[88]
The objective of the study was to examine the correlation between vitamin D levels, patient survival, as well as time to treatment in individuals with CLL	Vitamin D deficiency is associated with a decrease in time to treatment and overall survival. The supplemental use of vitamin D needs more research	[91]

Table 2 (continued)

Objective	Result	Reference(s)
The study aimed to identify a potential relationship between serum vitamin D levels and molecular response in chronic myeloid leukemia (CML)	Severe vitamin D deficiency is associated with molecular unresponsiveness in individuals with CML	[92]

UVB ultraviolet blue, *EMT* epithelial-mesenchymal transition, *AML* acute myeloid leukemia, *CML* chronic myeloid leukemia, *CLL* chronic lymphoid leukemia

age of mice [29]. This conclusion is further backed up by Filip-Psurska et al., indicating that the effect of vitamin D3 on breast cancer development is correlated with a variety of factors such as age, menopausal status, and obesity [30].

Furthermore, vitamin D 1,25(OH)2D3 reduces aromatase expression in MCF7 tumor xenografts and surrounding adipose tissue [31]. The use of Vitamin D with several inhibitors including 1,25(OH)2D3/aromatase inhibitors [32], 1,25(OH)2D3/tamoxifen [33], 1,25(OH)2D3/ruxolitinib [34]., and 1,25(OH)2D3/celecoxib [35], as well as 1,25(OH)2D3 in combination with lapatinib and neratinib [36], suggests an essential role for vitamin D in enhancing molecularly targeted therapies [29]. Also, the administration of 1,25(OH)2D3 with chloroquine inhibited MCF7 cell proliferation in vitro and in vivo more than in groups receiving only one of the treatments [37].

A study by Estebanez et al. [38] reported 25(OH)D to have a protective effect against breast cancer development in premenopausal women. In addition, in a dose–response meta-analysis by Song et al. [39], a 6% decrease in breast cancer risk by a 5 nmol/l increase in serum vitamin D levels in premenopausal and postmenopausal women was reported. Vaughan-Shaw et al. proposed an association between higher 25(OH)D levels and reduced risk of breast cancer mortality and progression [40]. In contrast, Hossain et al. [41] reported an inverse association between vitamin D deficiency and breast cancer occurrence in African women. However, no association between higher 25(OH)D levels and breast cancer occurrence or mortality was found. Furthermore, Crew et al. reported an inverse relationship between plasma 25(OH)D levels and breast cancer risk [42]. In another study, serum levels of plasma 25-hydroxyvitamin D above 40 ng/mL were linked to decreased breast cancer risk. Also, the risk reduction was more significant among postmenopausal women [43]. Increased sun exposure was found to have an inverse relationship with ER+, ER−, and TNBC breast cancer subtypes in black women [44]. Moderate supplementation of vitamin D was inversely associated with TNBC risk.

The Vitamin D and OmegA-3 Trial did not report any difference in vitamin D3 and placebo groups regarding breast cancer incidence [45]. In contrast, in secondary analysis, the BMI-corrected supplemented group had a remarkable reduction in breast cancer risk in comparison to the placebo group [46]. In an RCT study by Lappe et al., combined supplementation of vitamin D (2000 IU/day) with calcium (1500mg/day) did not decrease breast cancer risk in postmenopausal women [47]. In addition, the ViDa study [48] did not find any effect of vitamin D3 supplementation on overall cancer incidence. A study by Arnaout et al. randomized breast cancer patients to receive either 40,000 IU of vitamin D3 per day or a placebo for 2 to 6 weeks before breast surgery. Despite notably higher levels of serum 25(OH)D in the supplemented group, no significant signs of tumor proliferation

or apoptosis were observed [49]. Furthermore, meta-analyses could not find any relationship between vitamin D3 supplementation and breast cancer risk [50]. In another study, vitamin D deficiency was common in recently diagnosed breast cancer patients [51].

A study by O'Brien et al. concluded that methylation of CpGs in various vitamin D-related genes was directly associated with 25-hydroxy vitamin D concentration. Higher serum 25-hydroxy vitamin D concentrations were associated with a higher methylation-breast cancer hazard ratio [52]. Simmons et al. found CYP24A1, CLMN, EFTUD1, SERPINB1, and KLK6 to be regulated by 1,25-hydroxy vitamin D [53]. In another study, recent use of vitamin D supplementation was inversely associated with breast cancer in comparison to non-recent use [54]. In another study by Sheng et al., it was concluded that the downregulation of the vitamin D3 pathway via the elevation of CYP24A1 weakens its anti-tumor effect [55]. Also, a step-wise inverse relation between plasma 25-hydroxy vitamin D levels and the risk of breast cancer was reported between the concentrations of 27 ng/ml and 35 ng/ml [56].

A summary of the findings is listed in Tables 1 and 2. As a result, vitamin D may play a role in breast cancer risk and development. Further research is needed to settle the exact link between vitamin D levels and breast cancer's overall occurrence and progression.

Colorectal cancer

Colorectal cancer, a malignant disease that develops in the colon or rectum, is globally recognized as the third most commonly diagnosed cancer in men and the second most in women. Tragically, this cancer is one of the leading causes of cancer-associated mortality [57].

According to studies, a lack of vitamin D in patients with colorectal cancer has been found to decrease their overall quality of life and lifespan [58]. Calcitriol is known to reduce cell proliferation through various mechanisms, including the downregulation of cyclin-dependent kinases, intervention in the IGF-II pathway, and intervention in the EGF pathway. It is worth noting that calcitriol has been demonstrated to disrupt the Wnt/β-catenin pathway, which plays an integral role in the initiation of colorectal cancer. As a result, it can impede the onset of this malignancy [59]. The Wnt signaling pathway can be disrupted by SFRP proteins. Studies have shown that elevated levels of vitamin D result in a decline in promoter methylation of SFRP genes. The reduction of gene promoter methylation prompts an intensified production of SFRP proteins, thus leading to the disruption of the Wnt pathway [60]. On the contrary, when cell adhesion damage occurs, free cytosolic β-catenin can be transferred to the nucleus, triggering the Wnt/β-catenin pathway. This pathway plays a crucial role in developing and advancing colorectal cancer. However, through its suppression of MED28, calcitriol improves the expression of E-cadherin, thereby preventing EMT and Wnt/β-catenin pathway activation [61].

Studies have indicated that inflammation and inflammatory diseases, such as inflammatory bowel disease, are linked to an escalated possibility of developing colorectal cancer. In animal studies, it has been observed that eliminating VDR triggers inflammation and increases the activity of NF-κB and Wnt/ β-catenin [59]. However, a cell study in the HCT116 cell line has demonstrated vitamin D3 to affect caspase3 positively, but not NF- κB [62]. Additionally, it is possible that calcitriol can stimulate apoptosis, which is a mechanism of programmed cell death, by increasing the expression of pro-apoptotic proteins, such as BAX, and diminishing that of anti-apoptotic proteins, such as BCL2 [63].

The available literature regarding the link between vitamin D and colorectal cancer is summarized in Tables 1 and 2. Although the exact mechanism by which vitamin D impacts EMT and metastasis is not entirely understood, several studies have indicated that calcitriol may have a suppressive effect on the progression of colorectal cancer by influencing various signaling pathways.

Melanoma

Melanoma is among the most dangerous and invasive forms of cancer. In melanoma, the cells that typically produce skin pigment are affected. Although various drugs and treatments have been proposed and used for this cancer, melanoma scarcely responds positively to treatments. This cancer is one of the ten most common forms of malignancies in Europe [64]. Although certain factors such as age, gender (especially men), as well as hair, and skin color are correlated with the risk of melanoma [65], Primarily, melanoma is greatly influenced by two significant risk factors: prolonged exposure to the sun's ultraviolet rays and a family history of skin cancer [66]. UV radiation has a dual role: Firstly, it is one of the most essential factors in melanoma. Secondly, it has a notable impact on the production of vitamin D within the skin [1, 67].

The significance of the Wnt/β-catenin pathway lies in its crucial involvement in the maintenance of cellular function and homeostasis. Among the main factors in the occurrence of melanoma is the incorrect signaling of the Wnt pathway, which can lead to uncontrolled proliferation, cell invasion, and, eventually resistance against the immune system [68]. By employing various mechanisms, the activated state of vitamin D can hinder or dampen this signaling pathway across distinct regions [69]. The presence of elevated levels of vitamin D in the bloodstream of individuals is associated

with a favorable impact on melanoma, including a decrease in its severity and an enhancement of its benign characteristics. However, the mechanism of this issue has not yet been fully clarified. Studies have shown that mortality from primary melanoma, as well as its metastatic state, is reduced by increasing gene expression and thus increasing the number of VDR receptors [69]. Melanoma tumor cells typically exhibit low expression of this receptor; nonetheless, tumor cells that express normal or high levels of VDR demonstrate an enhanced ability to suppress the Wnt/β-catenin pathway.

In addition to binding to VDR inside the cell and its related reactions, vitamin D can also use other intracellular signaling pathways. Vitamin D can exert its anti-oxidative effect by acting on Nrf2. Interestingly, through its interaction with the ROR receptor located on the cellular nucleus membrane, it governs the synthesis of inflammatory factors like TNF-alpha, triggering an adaptive immune response. It can also affect the p53 protein gene and cause its transcription, thus exerting its anti-cancer properties [70].

A recent study [71], used a Mendelian Randomization method to investigate the relationship between serum levels of 1,25-dihydroxy vitamin D and melanoma. The study evaluated five types of SNP mutations that were specifically located in genes related to critical enzymes and proteins involved in vitamin D metabolism. The authors examined the changes in these essential enzymes or proteins' structure or function as a result of SNPs to determine the connection between these changes and the occurrence of melanoma. The study found that all five SNPs, even in combination, did not reveal compelling evidence indicating a causal link between genetically determined vitamin D levels and the risk of melanoma. The study selected SNPs that had not been reported to be related to skin pigmentation and UV radiation, which represents a significant risk factor for melanoma. The study also took into consideration a group of potential confounding factors, including phenotypic traits such as hair color, facial aging, and skin color, concerning melanoma. Therefore, based on the authors' conclusions, it is not possible to definitively establish a correlation between vitamin D levels and the risk of melanoma. Furthermore, the results of the study do not support the use of vitamin D supplements as a means of reducing the risk of melanoma.

In a case–control study conducted by Millen et al., it was found that a higher intake of vitamin D through diet was associated with a 50% decrease in melanoma incidence [72]. Similarly, another study reported a correlation between elevated levels of vitamin D in the body and the risk of developing melanoma. The researchers suggested that the variation in vitamin D levels among individuals is linked to their sun exposure, which in turn leads to increased synthesis of vitamin D and a higher likelihood of melanoma development due to the damaging effects of ultraviolet rays on the skin [73].

Numerous studies have documented a relationship between elevated serum levels of vitamin D and the diagnosis of melanoma, as well as an improved prognosis [74]. Furthermore, a study revealed that high levels of vitamin D do not provide a protective function against melanoma. Instead, a concentration of less than 25 nmol/liter in serum may increase the severity of the disease and improve the mortality rate in melanoma patients [75]. In addition, 20-hydroxy D3 has been shown to deter melanoma cell migration and toxicity. Also, in mice lacking a functioning immune system, this form of vitamin D reduced melanoma tumor growth [76].

A study was conducted on a cohort of 36,282 postmenopausal women for seven years. The objective was to investigate the potential impact of vitamin D and calcium levels on the risk of skin cancer. Subjects received calcium and vitamin D complex [77]. In this study, consisting of experimental and placebo control groups, upon analyzing the obtained results, no significant difference in the occurrence of melanoma and non-melanoma cancers was observed between the two groups.

Various studies have been conducted to discover or investigate the types of VDR polymorphisms. The VDR gene is located on chromosome 12, and it consists of 11 exons. Approximately 600 single nucleotide polymorphisms (SNPs) have been identified in the VDR gene, including variants such as FokI, BsmI, and ApaI. These polymorphisms have been extensively studied in melanoma [78]. A meta-analysis study conducted in 2020 evaluated the odds ratio of melanoma according to these three polymorphisms [79]. For example, concerning Bsml, FokI, and ApaI polymorphisms, melanoma susceptibility is different in individuals having the dominant allele compared to those carrying the rare allele. In the second and third cases, rarer alleles predispose to melanoma. But for other VDR polymorphisms, such as Taql. no significant relationship with melanoma was observed.

The studies regarding vitamin D and melanoma are summarized in Table 1 and 2. While some cases show the effective task of vitamin D in reducing the possibility of melanoma, In certain studies an association has been observed between elevated concentrations of vitamin D and a higher incidence of melanoma in individuals. Considering that ultraviolet rays have a dual role, On the one hand, it causes vitamin D to be created in the human skin, and on the other hand, it causes the person to be susceptible to melanoma. These results should be considered as confounding factors, and based on the provided studies, it is not conclusive to assert a strong relationship between high levels of vitamin D and melanoma.

Hepatocellular cancer

Hepatocellular carcinoma HCC ranks as the sixth most common cancer worldwide and is the fourth primary cause of cancer-related deaths, making it a worrisome matter. Furthermore, the incidence rate of Hepatocellular carcinoma is on the rise, suggesting that it may contribute to over 1 million deaths worldwide by 2030 [80]. The factors that increase the chances of developing this fatal illness are varied. These include inheriting genetic tendencies, getting infected with viruses such as hepatitis B and C, maintaining an unhealthy diet that consists of the intake of alcohol and unhealthy weight gain due to obesity, as well as coming into contact with harmful toxins such as tobacco and aflatoxin B1 [81].

Notwithstanding the challenges of resistance to presently available treatments, Provvisiero et al. determined that vitamin D had the potential to bolster susceptibility in resistant cells. Furthermore, their research indicates that miR-375 can potentially act as a tumor suppressor in vitamin D-receiving cells. The insufficiency of vitamin D might trigger the depletion of miR-375, which might, in turn, lead to escalated cell proliferation and increased metastatic activity. In summary, vitamin D could significantly contribute to the fight against HCC and augment the vulnerability of resistant cells to treatment [82].

Vitamin D is beneficial in two ways. First, it can increase the responsiveness of cells to crucial therapeutics. Second, it has a significant capacity to limit the spread of HCC in a dose-dependent manner. Studies discovered that administering high quantities of vitamin D decreases the levels of Histone deacetylase 2 (HDAC2). This, in turn, leads to a rise in the creation of p21 (WAF1/Cip1), which ultimately suppresses the development of HCC [83].

Hamilton et al. made a fascinating finding related to the impact of vitamin treatment on cells. They discovered that vitamin treatment resulted in the upregulation of CDKN1A and p21 (WAF1/CIP1), tumor suppressors that regulate the cell cycle by inhibiting cyclin-dependent kinases. Although CDKN1A expression increased, it did not account for the reduction in cell proliferation. Instead, vitamin D treatment increased Thioredoxin-interacting protein (TXNIP) expression, which led to P27kip1 stabilization and a subsequent decrease in cell proliferation. Furthermore, investigators established that elevated levels of TXNIP prompted heightened activity of caspase 3, which led to apoptosis. Notably, vitamin D treatment increased malignant cells' sensitivity to oxidative stress damage, which requires further examination [84].

Chen et al. conducted a study that shed light on the anti-tumor effects of vitamin D, which operates through the Smad3/TGF-β signaling pathway. Their results suggest a plausible association between vitamin D insufficiency and elevated susceptibility to liver fibrosis and EMT. Furthermore, the study's findings indicate that vitamin D's anti-inflammatory properties are inversely correlated with TLR7. Intriguingly, when TLR7 was silenced, it resulted in suppressed cell proliferation and mobility. These insights illustrate the complex nature of vitamin D and its prospects for further investigation [85].

A brief summarization of the findings is listed in Table 1 and 2. Overall, studies suggest that vitamin D supplementation could prove useful in restoring sensitivity to medication-resistant cells and suppressing HCC development. Additionally, vitamin D has been shown to have anti-tumor properties through various pathways and could potentially reduce the risk of liver fibrosis and EMT. These findings warrant further investigation into the potential benefits of vitamin D in combating HCC.

Leukemia

Leukemias are cancers that originate from the bone marrow, which is the place where blood cells are produced, eventually leading to the production of a large number of abnormal blood cells. In general, leukemias are classified based on the cell types involved and the rate of progression and deterioration of the disease and are generally divided into two categories: acute and chronic. If not treated, acute leukemias have a more severe clinical course. Nowadays, the treatment of acute leukemias is somewhat possible with chemotherapy, but the treatment of chronic leukemias is challenging. In general, blood cancer or leukemia, like many other cancers, is caused by mutations in the genetic material or DNA, which can also be influenced by environmental factors [86].

As mentioned in various cancers earlier, vitamin D can play a significant role in fighting cancer as well as modulating and regulating inflammation. It has been reported that low levels of this vitamin are associated with disease recurrence and reduced ailing durability in adult acute myeloid leukemia (AML) patients [87]. A study conducted on several Swedish children with various types of leukemia concluded that in preschool children, low levels of 25-hydroxyvitamin D were associated with AML. Also, levels of 25-hydroxy vitamin D less than 50 nmol/lit are associated with decreased patient survival. According to the researchers of this study, a definitive conclusion can't be reached on whether the use of vitamin D supplements in children with leukemia will improve the outcome [88].

A study conducted by Wang et al. examined the effectiveness of vitamin D3 on autophagic cell death in human myeloid leukemia cells. According to the obtained results, inhibiting the differentiation of leukemia cells does not prevent the suppressive efficacy of vitamin D3 on leukemia

cells. One of the mechanisms is that vitamin D3 regulates Beclin1, and it connects to phosphatidyl 3-kinase class III, ultimately leading to autophagy in leukemia cells. Also, vitamin D phosphorylates the molecule from its second BH3 region and further causes Bcl-xL to connect with Beclin1, resulting in suppression of apoptosis. If we remove Beclin1 from the cell; As a result, differentiation and autophagy caused by vitamin D will be suppressed in leukemia cells, but it will activate apoptosis in these cells [89].

The analysis and investigation carried out in more than ten different studies show that receiving a large amount of sunlight, which subsequently increases the level of vitamin D, is associated with a significant diminution in the risk of non-Hodgkin's lymphoma [90]. In the study conducted by Shanafelt et al., vitamin D deficiency in people with Chronic lymphoid leukemia (CLL) is associated with a decrease in TTT and OS, where TTT is the time defined as the interval between the initial diagnosis of cancer and the start of the patient's treatment, and OS is considered as the overall survival of the patient. According to the researchers, further tests and studies are demanded to confirm the use of vitamin D supplements in the treatment of CLL [91].

In another study conducted by Gediz et al., the presence of a correlation between serum levels of 25-hydroxyvitamin D and molecular response in chronic myeloid leukemia (CML) was investigated. By examining 61 patients with this disease, positive results were obtained. The analysis of the study findings conducted by this group revealed that elevated levels of vitamin D were independently linked to molecular response in individuals diagnosed with CML. For the first time, the results from this group demonstrated that severe vitamin D deficiency is correlated with molecular unresponsiveness in individuals diagnosed with CML. Therefore, the therapeutic use of vitamin D and 25-hydroxyvitamin D can be effective in these patients [92].

The available literature regarding the link between vitamin D and leukemias is summarized in Table 1 and 2. Overall, the results indicate a positive role of vitamin D in Leukemia patient's survival rate and overall disease progression. Nevertheless, further research is required to elucidate the underlying mechanisms in greater detail.

Conclusions

Genetic and environmental factors, as well as immune responses, play an essential role in the pathogenesis of cancers. Among these is vitamin D which is found to correlate with cancer.

The outcome of our research summarized the recent findings and analyses regarding the relationship between vitamin D and Cancer. Our paper summarizes the available research conducted on this particular topic and contributes a clearer understanding of the association between vitamin D and cancers. However, our article also has limitations. While, a comprehensive world map of the available literature on the topic of vitamin D and cancers was provided, nevertheless, in a handful of these studies, some of the confounding factors, such as lifestyle and genetic background that could influence the association between vitamin D and cancers were not fully accounted for. In addition, most of the results reviewed were obtained from relatively short periods of research duration. Future studies should focus on investigating the long-term effect of vitamin D uptake on the occurrence and progression of cancers.

Although vitamin D is suspected of having a positive effect on breast cancer, colorectal cancer, hepatocellular cancer, and leukemia, the results regarding the relation between vitamin D and prostate cancer, as well as melanoma, are contradictory. It is important to note that a definitive conclusion cannot be reached currently with existing research; Thus, more sensitive studies with targeted groups are needed to determine the exact mechanism by which vitamin D can affect cancer cells.

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