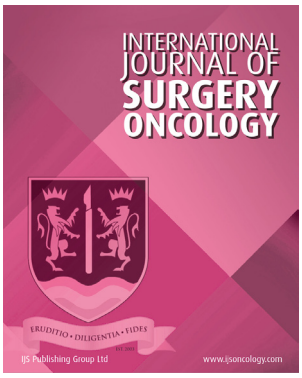

Preclinical Researches of Vitamin D Role in Preventing Malignant Diseased, a Systematic Review

SYSTEMATIC REVIEW AND/OR META-ANALYSIS

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ABSTRACT

Background: In general, the role of vitamin D, [25 (OH)D], is to regulate calcium and phosphate metabolism by bone remodeling but the studies, in the recent decades, shown that low exposure at the sun and vitamin D deficiency are associated with the increased risk of many other extra-skeletal disorders, such as cancer diseases.

Content: Several original studies and meta-analyses have evaluated the role of vitamin D in cancer prevention or the potential to improve cancer treatment outcomes. The broad field of antitumor effects of calcitriol and analogues in the treatment of cancer, as single agents or in combination with other anticancer agents, is mainly based on the mechanisms of inhibition of cancer cell proliferation and invasiveness, induction of differentiation, apoptosis and the promotion of angiogenesis.

Summary and Outlook: The scientific evidence suggests that the provider of health care should consider the increasing of concentrations of 25 (OH) D through sun exposure or by supplementing with vitamin D of people with different ages to reduce the risk ills with Vitamin D deficiency besides the standard treatment of some chronic diseases, inclusive cancer disease beside the specific personalized antineoplastic treatments for every malignant disease.

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1. INTRODUCTION

Vitamin D (VD) is classified as a fat-soluble vitamin, which is obtained from the diet or produced by the skin by ultraviolet B (UVB, 290–320 nm) from sunlight, [1].

Due to vitamin D deficiency and the risk of related diseases, in many countries, there is a legal obligation to enrich certain products (dairy products, especially milk and another dairy drinks, margarine. Vitamin D status must be more precisely defined based on serum 25(OH)D levels. Although there is no general consensus to define optimal values, there is agreement to set vitamin D deficiency on serum calcidiol levels below 20 ng/mL (50 nmol/L). Among others, the International Osteoporosis Foundation (IOF), the Sociedad Española de Investigación Ósea y Metabolismo Mineral (SEIOMM) or the Sociedad Española de Endocrinología y Nutrición (SEEN) assess values >30 ng/mL as optimal, insufficient: 20–29 ng/mL and deficient <20 ng/ml, considering as severe deficiency, [2]. The US Institute of Medicine (IOM) increased the dietary reference intake for vitamin D to 600 IU/day for adults between 18–70 years and 800 IU/d for elder than 70 years, [3].

The classical role of vitamin D is to regulate the metabolism of calcium and phosphate, which is essential for bone remodeling [4] but based on research from recent decades has been shown that low sun exposure, vitamin D limitation and deficiency are associated with an increased risk potential for many other extra-skeletal diseases, such as cancer [5].

Objectives of these studies were to emphasis the recent experimental researches which indicated that the vitamin D has antineoplastic activity via the vitamin D receptor by: transcriptional activation and repression of target genes that have the role of inducing differentiation and apoptosis, inhibition of cancer stem cells and its proliferation, angiogenesis and the metastatic potential.

2. METHODS

Many epidemiological studies have supported and extended the UVB–vitamin D–cancer hypothesis in 18 different types of cancers [6, 7]. Several lines of population-based studies revealed an inverse correlation between serum 25(OH)D levels and high risk of cancers, correlation supported by evidence on cell cultures and animal studies [8]. Many data from epidemiological, clinical, preclinical and in vitro studies support the potential for activating vitamin D signaling as a promising prevention and treatment strategy for many cancers. As such, several therapeutic interventions targeting dysregulated vitamin D metabolism or activity have been investigated and developed for cancer therapy [9].

However, there are some potential limitations of vitamin D or its analogues, based on cancer therapy which should be taken into consideration in therapeutic strategies [10].

2.1. BIOCHEMISTRY AND MOLECULAR BIOLOGY OF VITAMIN D

Vitamin D is a fat-soluble steroid derivative, which plays an important role in calcium homeostasis and bone metabolism through its actions in the intestine, bone, kidney and parathyroid glands [11].

Vitamin D3 (cholecalciferol) is both synthesized in the skin and acquired by the diet from animal sources. Vitamin D2 (ergosterol), produced by irradiated yeast, comes from vegetable intake and both participate in a number of the metabolic pathways in the body:

i) binds to vitamin D-binding protein (VDBP) in circulation and is delivered to the liver where it is metabolized by vitamin D 25 hydroxylase (CYP2R1 and CYP27A1) to 25 (OH) D (calcidiol), which is the major circulating form of vitamin D in serum;
ii) the calcidiol is further metabolized to the kidneys of 25 (OH) D 1α-hydroxylase (CYP27B1) to 1α, 25-dihydroxy vitamin D [1α, 25 (OH)2D, calcitriol], which is the most biologically active form of vitamin D;
iii) the calcitriol produced by the kidneys, after binding to vitamin D binding protein, (VDBP), enters in circulation and is delivered to the target tissues: the intestine, bone and kidneys, where vitamin D regulates the absorption, mobilization and reabsorption of calcium and phosphate [12]. The calcidiol and calcitriol levels are tightly regulated of 25 (OH) D 24-hydroxylase (CYP24A1), the primary enzyme for the inactivation of vitamin D produces bile, in biologically inactive product, [13].

The biological effects of Vitamin D by the active form (1 α, 25-dihydroxy vitamin D3) are determined by the cellular variety of vitamin D receptor (VDR) found in a variety of human cells and which can act through two mechanisms: non-genomic and genomic. By the non-genomic mechanism, active vitamin D produces direct effects by binding VDR to the cell membrane and activating protein kinase C in different organs, [14]. These cells expressing VDR capture circulating calcidiol to synthesized calcitriol and use it within the cell itself in an autocrine manner. So that, it´s important to remark that these autocrine actions are independent of circulating calcitriol and even more, they are not regulated by PTH or FGF23 but by tool-like receptors activation.

In the genomic pathway, calcitriol binds to cytosolic VDR, which promotes phosphorylation of VDR, heterodimerization with the retinoid-X receptor (RXR) causing a conformational change that allows the heterodimer to translocate into the nucleus, where it binds to vitamin D response elements (VDRE) in promoter regions, allowing for transcriptional regulation of target genes: P-21, P-27

and C-myc gene. Through such a synthesis and cellular mechanism, VDR regulates a wide range of central cellular pathways for cancer development, such as apoptosis, cell proliferation, differentiation, angiogenesis and metastasis, [15].

Recently, an alternative pathway of vitamin D metabolism via CYP11A1, known as a cytochrome P450 side-chain cleavage (P450scc) was identified in peripheral tissues such as skin and gastrointestinal (GI) tract, [16].

The enzyme CYP11A1-20 (OH) and its hydroxy-metabolite are characterized by anti-proliferation, differentiation and anti-inflammatory actions in skin cells comparable or better than that of calcitriol and enhance the defence mechanism against UV-induced DNA damage and oxidative stress and provoke anticancer properties dependent on a cell line or function as partial or partial agonists of VDR [17].

The complexities of the genetic variants of the enzymes responsible for D3 metabolism, protein binding, heterodimerization of partners and the multitude of genes modulated by vitamin D hormone systems suggest that, to the analysis of the role of vitamin D in cancer, as well as other diseases, will require much careful and detailed, [18].

2.2. VITAMIN D ANTITUMOR/ANTICANCER PROPERTIES

1. The dysregulation of vitamin D metabolism is a common feature of cancer cells. Calcitriol has a wide range of actions in some different types of cancers as the colon cancer, breast and prostate cancer. Thereby, result a wide range of calcitriol-mediated anticancer actions such example being cyclin-dependent kinase, (CDK), cyclooxygenase 2, (COX2), hypoxia-inducible factor 1α, (HIF1α), interleukin-8, (IL-8), mitogen-activated protein kinase phosphatase 5, (MAPKP5), matrix metalloproteinase 9, (MMP9), nuclear factor-κB, (NF-κB), prostaglandin, (PG), 15-hydroxyprostaglandin dehydrogenase, (15-PGDH), prostaglandin E2; polymerase II, (PEP), prostate-specific antigen, (PSA), tissue inhibitor of metalloproteinases 1, (TIMP1), vascular endothelial growth factor, (VEGF), [19].
2. The broad-spectrum anti-tumor effects of calcitriol and analogues are mostly based on inhibition of cancer cell proliferation and invasiveness, induction of differentiation and apoptosis, and promotion of angiogenesis. Common mechanisms underlying the anticancer effects of the vitamin D system are presented in ***Table 1***, [20].
3. Preclinical and clinical data indicate that maximal anti-tumor effects of vitamin D are seen with pharmacological doses of 1,25 (OH) D. The reference value of pharmacological doses of 1,25 (OH) D is 19.9–79.3 pg/mL, [21]. Moreover 1,25(OH)2D can be involved in the regulation of miRNA expression, so the investigation of the mRNA-miRNA-lncRNA regulatory axis for the gene. Recent studies have suggested that vitamin D/vitamin D (VDR) signaling exerts protective effects on keratinocyte-induced apoptosis by regulating the apoptosis modulator miRNA-802 and protein p-53 and lipopolysaccharide (LPS) is capable of enhancing the production of interferon-gamma

MOLECULAR MECHANISM	ANTINEOPLASTIC ACTION
Proliferation	Increased of pro-apoptosis protein p21 and p27 expression, IGFPB3, EGF, TGF-β Decreased: MYC, ERK, MAPK, PI3K, p38, KCNH1, TERT
Apoptosis	Increased expression of pro-apoptotic proteins Bax, Bak and Bad, Decreased: anti-apoptotic proteins Bcl-2 and Bcl-x-2, Nongenomic actions
Differentiation	Specific pro-differentiation mechanisms: JUN-N terminal kinase, β – catenin, PI3K, C/EBP Decreased: NF-kβ, SNAIL, ZEB 1, Vimentin Increased: E-cadherin
Inflammation	Increased: DUSP 10, MAPK, Phosphatase 5, 15- HPGDH Decreased: p38 stress kinase, NF-kβ, COCS-2, PG-Rs
Invasion and metastasis	Increased: E-cadherin, TIMP 1, MMP 9 Decreased: Tenascin C, β4- Integrin, α6-Integrin, NF-kβ, STAT-3
Angiogenesis	Decreased: HIF1A, IL-8, PG levels

Table 1 Non-specific, transversal anticancer actions of Vit D systems.

Legend: cyclooxygenase 2, (COX2); c-Myc oncogenic protein (Myc); cancer gene DUSP; cancer gene ERK; 15-hydroxyprostaglandin dehydrogenase; extracellular signal-regulated kinase, (HPGD); genes encoding delta protein(C/EBP); E-cadherin repressors genes SNAIL, ZEB1; Insulin-like growth factor binding protein 3, (IGFBP3); hypoxia-inducible factor 1α, (HIF1α); interleukin-8,(IL-8); mitogen-activated protein kinase phosphatase 5, (MAPKP5); matrix metalloproteinase 9, (MMP9); nuclear factor-κB,(NF-κB); prostaglandin,(PG); reverse telomerase transcriptase (TERT); 15-hydroxyprostaglandin dehydrogenase, (15-PGDH); transformin growt factor βTGF-β mitogen actvated protein kinase phosphotase 5, (MAPK phosphotase 5); epithelial growth factor, (EGF); phosphatidylinositol-3-kinase, (PI3K); potassium voltage-gated channel, subfamily protein, (KCNH1); protein p38 (p38).

(IFN γ) and interleukin-1 beta (IL-1β) in human oral keratinocytes (HOKs) dependent on hypoxia-inducible factor-1α (HIF-1α), [22]. Some studies have confirmed that vitamin D/VDR signaling suppresses NF-κB pathway activation in embryonic fibroblasts and intestinal epithelial cells.

Furthermore, it is reported that vitamin D suppresses HIF-1 expression in osteoclasts and tumor necrosis factor-alpha (TNFα) plays a role in regulating VDR levels [23]. Vitamin D-induced apoptosis is mediated mainly by the suppression of anti-apoptotic proteins Bcl-2 and Bcl-XL, as well as by the increased expression of pro-apoptotic proteins Bax, Bak and Bad [31]. Also, apoptosis induction has been reported by upregulation of other pro-apoptotic proteins, such as switch G0-G1 fazes of cellular division, death-associated protein (DAP-3), death domain associated with Fas (FADD), and caspases family, [24].

Vitamin D may also inhibit the AKT-mediated anti-apoptotic signaling pathway by increasing phosphatase and tensin homolog, (PTEN) expression [25]. Moreover, vitamin D can also initiate apoptotic events by recruiting Ca2 + -dependent apoptotic effectors, such as μ2-calpain-dependent Ca2 + and calpain-12-dependent Ca2 +/caspase [26].

3. RESULTS

3.1. THE CLINICAL EVALUATION OF SERUM 25 (OH) D AND 1,25(OH)2D3

Clinical trials to assess whether vitamin D reduces the risk of cancer are largely based on the pharmaceutical drug model. Because the source of vitamin D is exposure to UVB, diet and supplements, the dose-response relationship is not linear: serum 25 (OH) D concentrations for the same amount of vitamin D supplement vary with patients [27], due to body mass differences and different base concentrations 25(OH) or dose administration deficiencies, [28].

Vitamin D clinical trials could be conducted, including the following key points:

a) Start with an understanding of the 25(OH)D concentration–health outcome relationship;
b) Measure 25(OH)D concentration of prospective participants and try to enroll hose with concentrations near the low end of the relationship;
c) Give vitamin D3 doses high enough to raise 25(OH)D concentrations to the upper part of the relationship;
d) Measure 25(OH)D concentration again during the trial to determine the success of the dosing and assess compliance, [29].

Guidelines for designing vitamin D trials more likely to find beneficial effects were outlined in two recent papers. It was suggested that all trial outcomes be related to 25(OH)D concentrations, measured several times during the rial, with adjustments in dosing to produce desired achieved concentrations. Thus, according to a study on the administration of vitamin D (≥400 IU/daily), the risk of lung cancer among smokers was significantly lower compared to non-smokers [30].

The relationship between vitamin D levels, serum concentrations 25 (OH) D3 and the risk of different cancer diseases, measured in healthy patients and with colorectal, lung, prostate and pre/postmenopausal cancer, revealed two aspects: levels of vitamin D were significantly lower in cancer patients compared to the control group and 64% of lung cancer patients, 35% of breast cancer patients, 29% of colorectal cancer patients and 18% of prostate cancer patients had concentrations of 25 (OH) D3 below the limit value of 47.5 nmol/L, [31].

3.2. COMBINED D3 ANTICANCER DRUGS

To achieve higher serum concentrations and maximum antitumor effects, clinical studies have used 1,25 (OH) 2D3 plus other anticancer drugs. Some of the studies reported promising antitumor activity, while others did not. Was reported that the application of high doses (20 IU/kg) of 1.25 OH) 2D3 combined with docetaxel and carboplatin was safe and well-tolerated [32].

A phase II study, recurrent prostate cancer, combined therapy with 1,25 (OH) 2D3 weekly (DN-101, 1800 IU) and daily naproxen, indicated the encouraging benefits with doubling the duration of PSA, [33]. On the contrary, in another phase II trial 1,25 (OH) 2 D3 intravenously applied at a dose of 2960 IU in combination with dexamethasone for castration-resistant prostate cancer, no positive results were reported, [34].

To reduce the side effects, increasing the therapeutic effect of 1,25 (OH) 2D3 for cancer, a series of vitamin D analogues have been researched and developed for therapeutic use: EB1089, 19-nor-1α,25-(OH)2D2 (paricalcitol), BXL-628 (ergocalciferol), calcipotriol, PRI-2191 (tacalcitol, 1,24-dihydroxy-vitamin D3), PRI2205 (5,6-trans-isomer of calcipotriol), (***Table 2***).

For example, oral paricalcitol is associated with a low level of serum iPTH in patients with metastatic breast cancer and a VDR antagonist activates VDR the expression more effectively than 1.25 (OH) 2D3, exerting a much inhibitory effect. stronger on prostate cancer, [35].

Although there is still limited usefulness of vitamin D and 1,25 (OH) 2D3 for clinical use by administering high doses and consequently of the hypercalcemia induced by them, they rely on fewer calcium analogues of vitamin D and/or on new vitamin D treatments combined with other anticancer drugs, [36]. In breast cancer, a dose-response meta-analysis of plasma levels 25 (OH) D, identified an inverse association above a threshold of

SUBJECT	DOSAGE REGIMEN	MAIN FINDING
128.779 participants	Oral 400 IU vitamin D plus 1 g calcium per day	Among non-smokers, vitamin D intake significantly benefited for decreasing risks of lung cancer when compared with control.
25 patients	Oral 1,25(OH)2D3 0.5 μg/kg on day 1, followed by docetaxel 36 mg/m2 i.v. on day 2 per week for three consecutive weeks, followed by 1-week non-treatment	Weekly oral intake of 1,25(OH)2D3 and docetaxel might prevent. Pancreatic cancer progression.
19 patients	Oral DN-101 180 μg on day 1 and i.v. mitoxantrone 12 mg/m2 on day 2 every 21 days with daily prednisone 10 mg orally for a maximum of 12 cycles	The addition of DN-101 does not appear to increase the toxicity of mitoxantrone in AIPC.
18 patients	i.v. 1,25(OH)2D3 weekly at a dose of 74 μg and dexamethasone in patients with CRPC	1,25(OH)2D3 supplement did not achieve favorable clinical outcomes. CRPC treatment and prevention
953 patients	ASCENT plus control (5 mg prednisone twice daily with 75 mg/m2 docetaxel and 24 mg dexamethasone every 3 weeks)	ASCENT treatment decreased prostate cancer survival compared with control.
54 patients	Inecalcitol at eight dose levels (40–8.000 μg) daily combined with docetaxel	Inecalcitol in combination with docetaxel encouraged PSA response of prostate cancer.
1.107 patients	0.5 μg 1,25(OH)2D3 plus 75 mg acetylsalicylic acid and 1,250 mg calcium carbonate (n = 209), or placebo (n = 218)	Supplement with 1,25(OH)2D3 did not reduce the risk of CRC recurrence
64 cases and 64 controls	Diclofenac sodium 3% gel, 1,25(OH)2D3 3 μg/g ointment	Combination of diclofenac and 1,25(OH)2D3 treatment inhibited BCC proliferation
104 CRC patients	Calcium (1.200 mg daily)) alone, vitamin D (1.000 IU daily) alone and in combination or placebo,	Vitamin D intake significantly suppressed AIPC/β-catenin pathway. colorectal mucosa
2.259 participants colon adenoma	Daily oral 1.000 IU vitamin D or 1.200 mg calcium carbonate, or both or placebo.	Vitamin D prevented colon cancer recurrence among individuals with AA genotype in VDR rs7969585 polymorphism. Colon adenoma recurrence

Table 2 Representative clinical trials of vitamin D intake for cancer prevention or treatment; the effects of combined D3 anticancer drugs.

Legend: Androgen-independent prostate cancer, AIPC; ASCENT treatment schedule of docetaxel + calcitriol (Oral, DN-101); castration-resistant prostate cancer, CRPC; basal cell carcinoma, BCC; Calcitriol, (1,25-dihydroxyvitamin D3); prostate-specific antigen, PSA; vitamin D receptor, VDR.

27 ng/ml, flattening over 35 ng/mL and observed only in postmenopausal women [37].

In breast cancer, the lowest level of vitamin D is associated with triple-negative breast cancer. In a recent meta-analysis, performed for women and was shown that patients with the highest circulating 25 (OH) D at diagnosis showed a 37% reduced risk for all causes of death, compared to the lowest quartile. For patients with breast cancer with the highest quartile of 25% (OH) D, reduced risk of 35% for cancer-specific mortality was reported, and 58% had a better disease-free survival (DFS) compared to those with the lowest 25 (OH) D quarters level, [38].

Recent findings from a case study have shown that elevated plasma levels of 25 (OH)D is negatively correlated with the incidence or mortality of several cancers. There was a direct correlation between vitamin D intake and the risk of gastrointestinal cancer: the daily intake of vitamin D over 1000 IU reduces the risk of colorectal cancer by approximately 50% compared to people receiving less than 100 IU daily of vitamin D; high-dose vitamin D intake and high levels of serum 25(OH) D reduce the risk of colorectal cancer by 12% and 33%, respectively [39].

4. OBSERVATIONAL STUDIES REGARDING 25-HYDROXYVITAMIN D[25(OH)D] RELATED TO SOME CANCER DISEASES IN METANALYSES AND CLINICAL TRIALS

The results of a study based on 120,000 men and women, including 365 confirmed cases of pancreatic cancer, regarding the relationship of vitamin D intake to pancreatic cancer, showed that respondents with a higher level of vitamin D in their diet had a lower incidence of cancer pancreatic than those with lower vitamin D intake, [40].

4.1. COLORECTAL CANCER

Colorectal cancer (CRC) is the neoplasm that is most commonly associated with vitamin D deficiency in epidemiological and observational studies regarding incidence and mortality. Many mechanical studies show that the active vitamin metabolite, vitamin D3 or calcitriol, inhibits the proliferation and promotes epithelial differentiation of human colon carcinoma cell

lines that express vitamin D receptor (VDR) by regulating a large number of genes. A key action that underlines this fact is the inhibition of multilevel Wnt/β-catenin signaling pathway, whose abnormal activation in colonic epithelial cells initiates and promotes CRC, [41]. Micro RNAs (miRs) are involved in the antineoplastic influence of vitamin D. The miR-22 expression is associated with VDR expression in human colorectal cancer probes, suggesting that miR-22 plays a role in R-mediated anti-tumor effect of vitamin D, [42].

Oncogenic-MYC is also regulated, by binding to vitamin D, response element by increasing expression and binding of intermediate proteins to regions. gene regulators, [43, 44]. Recently, calcitriol has been shown to modulate gene expression and inhibit the pro-tumor properties of fibroblasts associated with colon cancer (CAF). As a result, high expression of VDR in stromal tumor fibroblasts is associated with the survival of patients with CRC. Given the role attributed to the gut microbiota in CRC and the finding that it is altered by vitamin D deficiency, an indirect antitumor effect of calcitriol is also plausible at this level. So, calcitriol has many potential protective effects against CRC, acting on carcinoma cells, CAFs, immune cells and probably also the gut microbiota, [45].

Health International (WHI) provided the information on the action of vitamin D in colorectal cancer, further clinical studies are needed before vitamin D becomes mainstream in colorectal cancer therapy, [46]. Vitamin D and its analogues are potent inhibitors of colorectal cancer growth and metastasis. Some recent studies have defined the intersections between the βcatenin-TCF pathway (a known contributor to colorectal cancer progression) and the vitamin D receptor (VDR) pathway, shedding light on the basic mechanisms, [46, 47, 48].

4.2. PROSTATE CANCER

Findings for prostate cancer in terms of solar UVB doses and serum 25 (OH) D concentration differs from those for many other cancers, such as breast and colon. Geographic variation in the U.S.A prostate cancer mortality rate indicates the highest rates in the northwest, regions exposed to the sun during the year, and the lowest in the southeast, while most cancers have higher rates in the northeast and the lowest in the south. west. A meta-analysis of 21 studies supported this finding. Vitamin D increases calcium uptake, and people with genetically reduced calcium uptake have a higher risk of prostate cancer, [49]. So, the persons which intake more coffee (>3–4 cups/day) must assess the level of D Vitamin in peripheral blood.

4.3. LUNG CANCER

Lung cancer is one of the most serious malignancies for the health and life of the population. Compared to many other types of cancer, there are several identified risk factors for lung cancer, including asthma, chronic obstructive emphysema, pneumonia, tuberculosis, and air pollution.

The previous study found that 25(OH) D plays the role of inhibiting the growth of lung cancer cells in the formation of epidermal cells in guinea pigs. Also, 25(OH0 can induce the expression of the major antioxidant protein – superoxide dismutase SOD1 and SOD2, thereby inhibiting the formation of lung cancer to some extent and can regulate the immune function of lung epithelial cells and inhibit cell proliferation, angiogenesis, while promoting cell differentiation and apoptosis, [50].

Serum levels higher than 25 (OH) D are thought to be associated with better survival in early-stage lung cancer (NSCLC). Therefore, whether supplementation with vitamin D can improve the prognosis of patients with NSCLC was examined in the clinical trial. It was concluded that in patients with NSCLC, vitamin D supplementation may improve the survival of patients with early-stage pulmonary adenocarcinoma with levels below 25 (OH) D, [51].

4.4. BREAST CANCER WITH DEFICIENT OF VITAMIN D

Four meta-analyses were published that included both case-control and prospective studies of the relationship between circulating 25 (OH) D concentrations and breast cancer risk. When presenting the point estimates for both types of combined epidemiological studies, the results showed, in general, a statistically significant inverse relationship between 25 (OH) D and breast cancer. Vitamin D has been shown to inhibit telomerase activity by reducing the expression of reverse telomerase transcriptase (TERT) by microRNA-49 and that Vitamin D induces expression of transforming growth factor β (TGFβ) as well as its receptors, which results in cell growth inhibition, [52]. Taken together, the results for prognosis and survival generally provide a more consistent picture than for vitamin D and the incidence of breast cancer, [53].

4.5. VITAMIN D DEFICIENCY IN HODGKIN LYMPHOMA

Vitamin D deficiency is described as a modifiable risk factor for the incidence and mortality in many cancers including Hodgkin's lymphoma (HL). A study was conducted that measurement of pretreatment vitamin D levels in patients treated with HL and has correlated this with clinical outcomes. A total of 351 patients from the clinical trials of the German Hodgkin study group (HD7, HD8 and HD9) were included. Fifty per cent of patients had vitamin D deficiency (<30 nmol/L) before planned chemotherapy. Pretreatment vitamin D deficiency was more common in relapsed/refractory patients than appropriate non-relapsed controls (mean baseline vitamin D, 21.4 nmol/L v 35.5 nmol/L; the proportion of vitamin D deficiency, 68% v 41%; $P < 0.001$)). Patients with vitamin D deficiency had poor prognostic in survival and it was hypothesized that vitamin D status might be important in the progression of HL [54].

CONCLUSIONS

Recent experimental evidence indicated that vitamin D has a antineoplastic activity via the vitamin D receptor with the transcriptional activation and repression of target genes and has the role of inducing differentiation and apoptosis, inhibition of cancer stem cells and decrease proliferation, angiogenesis and metastatic potential.

The beneficial effect of Vitamin D, administered in malignancies, has been demonstrated experimentally by clinical trials in phase 1 and II, concluding that the vitamin D have an anti-inflammatory and antitumor effects, by modulating the immune response.

ABBREVIATIONS

CDK-cyclin-dependent kinase
COX2-cyclooxygenase 2
CAF-fibroblasts associated with colon cancer;
HIF1α- hypoxia-inducible factor 1α
15-PGDH-15-hydroxyprostaglandin dehydrogenase,
IL-8-interleukin-8;
MMP9- matrix metalloproteinase 9
MAPKP5-mitogen-activated protein kinase phosphatase 5
NF-κB-nuclear factor-κB
PG-prostaglandin
PTEN-phosphatase and tensin homolog;
TERT- reverse telomerase transcriptase
TIMP1-tissue inhibitor of metalloproteinases
1-TGFβtransforming growth factor
VEGF-vascular endothelial growth factor

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COMPETING INTERESTS

The authors have no competing interests to declare.

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