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Review Article

VITAMIN D AS A PROMISING ANTICANCER AGENT

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Abstract:

Vitamin D is the steroid vitamin it is a group of fat soluble vitamin it helps in absorption and metabolism of calcium and phosphorous. It is a well-known essential vitamin for bone health it is mainly circulating in blood and regulating the activities of various cell types its main significances is the maintenance of plasma Ca^{2+} concentration. It plays a beneficial role in genesis progression and survival of cancerous growths. It mainly interferes with the various growth factors by inhibiting the proliferation of the cells angiogenesis and facilitation of the cell differentiation and apoptosis. It is not a primary anticancer agent but it poses antitumor and anti metastatic properties it may used in the treatment of cancer as an adjuvant

Key words: vitamin D, cancer, angiogenesis, steroid hormone

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INTRODUCTION

Vitamin D is not only a nutrient, but also a precursor of a steroid hormone with a range of activities that include roles in calcium metabolism and cell differentiation [1]. In contrast to the well-established effects on the regulation of calcium homeostasis, the mechanistic aspects of the induction of differentiation are understood only in a fragmentary fashion. Thus, propelled by the expectation that vitamin D derivatives (deltanoids) can be useful agents for treatment of several forms of cancer, their differentiating and anti proliferative activities are currently undergoing intensive scrutiny [2-7]. Epidemiological studies provide strong evidence that the active form of vitamin D3, its dihydroxylated derivative, 1 α ,25-dihydroxyvitamin D3 (1,25D3), reduces the incidence of common human cancers, including carcinomas of the breast, prostate, and colon [8-11]. In addition, deltanoids have been shown to induce differentiation, apoptosis, and cell cycle arrest of several forms of malignant human cells, including the above-mentioned malignancies and myeloid leukemia's. However, its calcemic actions prevent 1,25D3 from being a clinically useful antineoplastic agent. In the expectation that the anti proliferative activity can be dissociated from the calcemia-inducing activity of deltanoids, many hundreds of deltanoids have been synthesized. Yet in spite of the identification of compounds with superior antineoplastic activities [12-18], an ideal deltanoid has not been found. Thus, the alternative strategy for developing vitamin D-based therapy of cancer by enhancing its activity using other compounds appears to be particularly promising. Combination of anti-cancer agents of different classes has led in various experimental systems and clinical protocols to a higher efficacy compared with the compounds administered as single agents [19-21]. The purpose of this article is to review the findings on cooperative differentiating and anti proliferative effects of deltanoids in combination with the more commonly employed biologically active agents (hormonal, pharmacologic, dietary, herbal, etc.) and to discuss

the possible molecular mechanisms underlying these effects. The co-inducers are discussed here in somewhat overlapping groups of differentiating agents, several plant-derived compounds and antioxidants, and then some examples of compounds which do not belong to these groups, but have potential as co-inducers with vitamin D3 in chemoprevention or chemotherapy of human cancer.

Types of Vitamin D

Vitamin D1: molecular compound of ergocalciferol with lumisterol.

Vitamin D2: ergocalciferol(made from ergosterol)

Vitamin D3: cholecalciferol(made from 7-dehydrocholesterol)

Vitamin D4: 22-dihydroergocalciferol

Vitamin D5: sitocalciferol (made from 7-dehydrositosterol)

From the above 5 forms vitamins D2 and D3 are the major forms. Vitamin D3 is produced in the skin of vertebrate after exposure to ultraviolet B light from sun. Vitamin D2 is made naturally by plants.

Role of Vitamin D

1. Regulation of cell growth.
2. Bone formation.
3. Immune function.
4. Muscle strength.
5. Hair growth.
6. Fighting infections.

Metabolism and effects of Vitamin D. Vitamin D can be obtained from food or from synthesis in the skin under exposure to light. The precursor is hydroxylated cytochrome P450 25-hydroxylase enzymes CYP27A1 and/or CYP2R1 and subsequently by the cytochrome P450 enzyme 25-hydroxyvitamin D-1 α -hydroxylase (CYP27B1) and converted to the bioactive 1,25-(OH) $_2$ D $_3$, which has role in Ca and bone metabolism and, in addition, in several other biological processes. Of note, bioactive 1, 25-(OH) $_2$ D $_3$ can also be generated in lung epithelia cells and monocytes/macrophages.



Fig 1: Source of Vitamin D

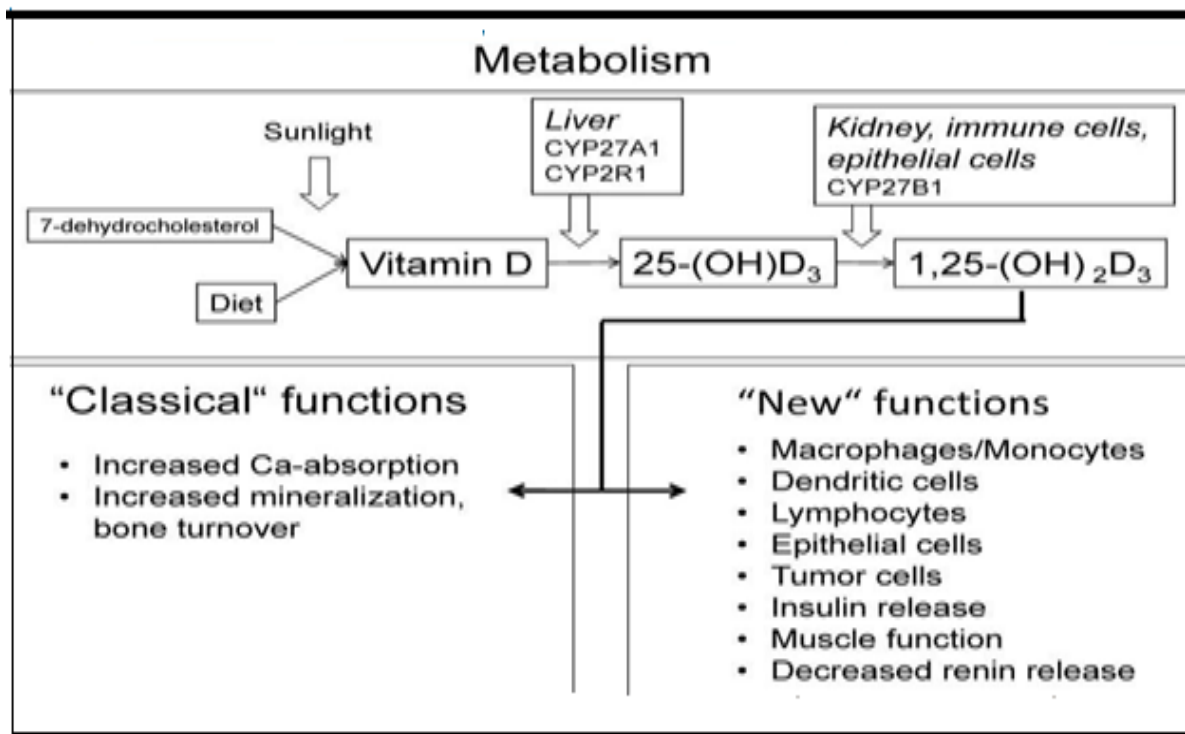


Fig 2: Metabolism and Effects of Vitamin-D

Cancer

Cancer is a generic denomination, which includes different forms of the same illness. All types of cancer have in common, that a group of cells show uncontrolled growth which leads to the formation of tumors threatening the life of the patient. All cancers begin in cells, the body's basic unit of life. The cells grow and divide in a controlled way to produce more cells as they are needed to keep the body healthy. When cells become old or damaged, they die and are replaced with new cells. However, sometimes this orderly process goes wrong. The genetic material (DNA) of a cell can become damaged or changed, producing mutations that affect normal cell growth and division. When this happens, cells do not die when they should and new cells form when the body does not need them. The extra cells may form a mass of tissue called a tumor.

What Causes Cancer

Cancer is a group of diseases that have to do with the overgrowth of cells. Cancer happens when cells in a certain parts of body stop drying in the normal way. Cancer may be caused by:

1. Genetic factors.
2. Life style factors.
3. Smoking
4. Chemicals.
Such as asbestos in the environment
5. Viruses and bacteria

A Natural Cancer Cure

Vitamin D can adjust almost everything in the cancer cell, from its genetic messaging to its cytoskeleton. It can switch genes on and off, and it can reduce cell division, and it can 'calm' the cancer cells so that they settle rather than spread. It seems vitamin D can actually return a cancer cell to a normal and healthy state. One pathway seems to control everything. At cancer active we are very clear about vitamin D [23]. There is more than enough research to be clear that vitamin D can help prevent cancer. And, from the latest studies, it is increasingly clear that every cancer patient should be having a daily half hour in the sunshine, or supplementing [24-26].

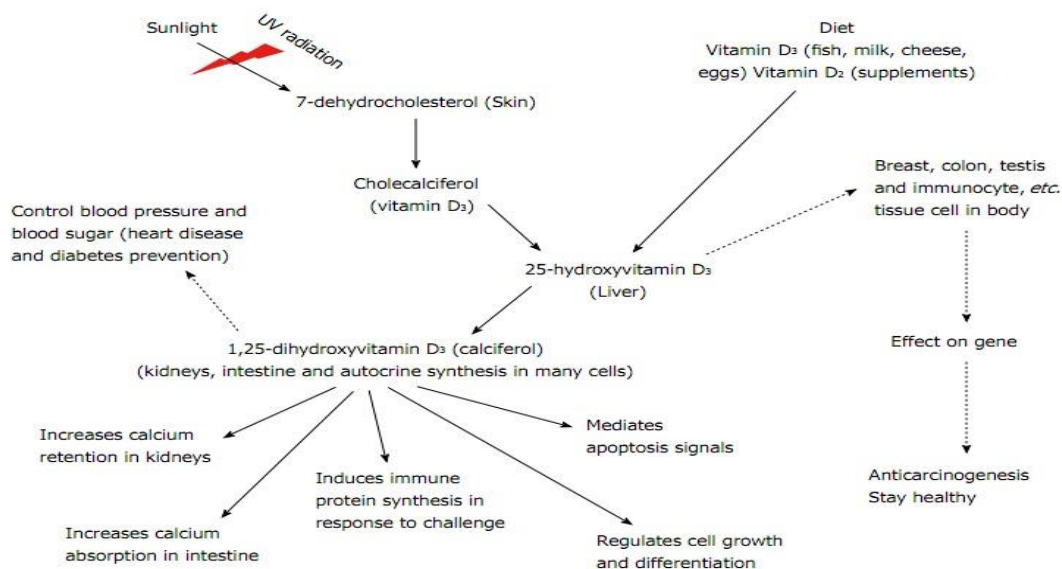


Fig 3: Role of Vitamin D in Cancer Patients

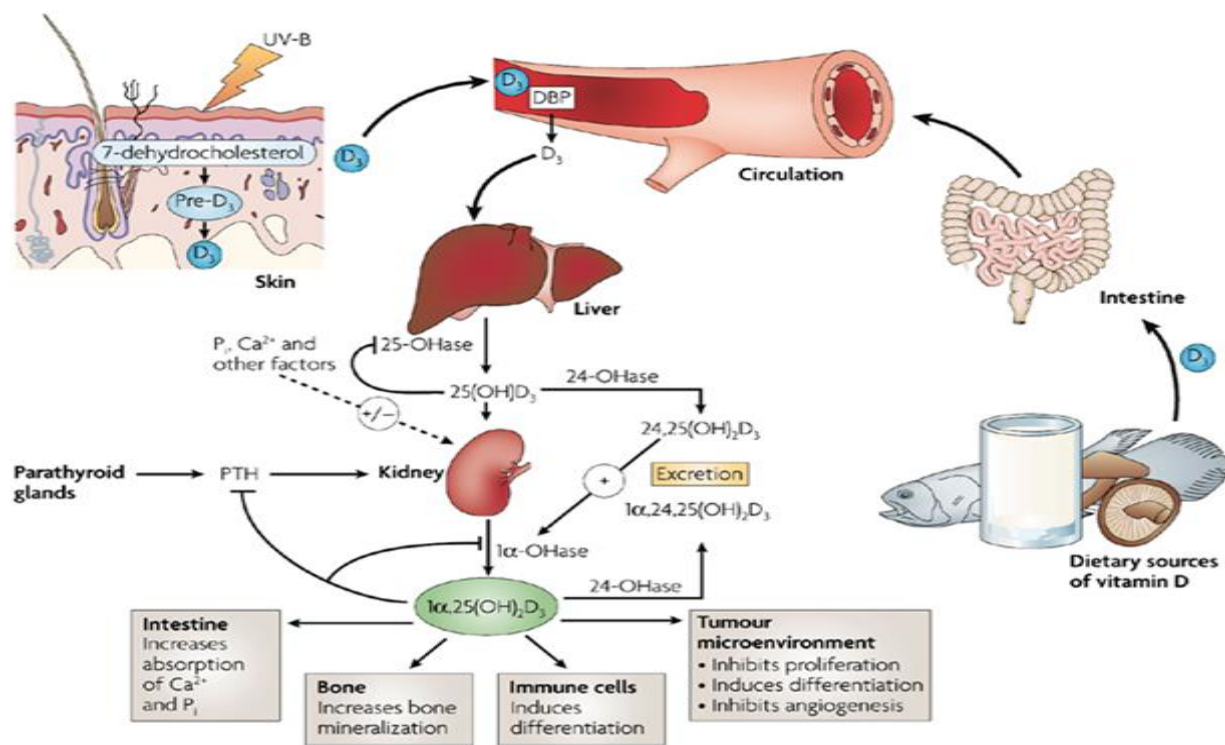


Fig 4: Mechanism of Anticancer Action of Vitamin-D

Is there a role for vitamin-D in Reducing Cancer Risk?

1. A large number of scientific studies have investigated a possible role for Vitamin D in cancer prevention.

2. The first results came from epidemiologic studies known as geographic correlation studies^[24]. In these studies, an inverse relationship was found between sunlight exposure levels in a given geographic area and the rates of incidence and death for certain cancers in that area.

3. Individuals living in southern latitudes were found to have lower rates of incidence and death for these cancers than those living at northern latitudes. Because sunlight/UV exposure is necessary for the production of vitamin D₃, researchers hypothesized that variation in vitamin D levels accounted for the observed relationships.

4. Evidence of a possible cancer-protective role for vitamin D has also been found in laboratory studies of the effect of vitamin D treatment on cancer cells in culture. In these studies, vitamin D promoted the differentiation and death (apoptosis) of cancer cells, and it slowed their proliferation. Randomized clinical trials designed to investigate the effects of vitamin D intake on bone health have suggested that higher vitamin D intakes may reduce the risk of cancer.

5. One study involved nearly 1,200 healthy postmenopausal women who took daily supplements of calcium (1,400 mg or 1,500 mg) and vitamin D (25 µg vitamin D, or 1,100 IU—a relatively large doses) or a placebo for 4 years. The women who took the supplements had a 60 percent lower overall incidence of cancer; however, the study did not include a vitamin D-only group. Moreover, the primary outcome of the study was fracture incidence; it was not designed to measure cancer incidence.

6. This limits the ability to draw conclusions about the effect of vitamin D intake on cancer risk.

7. A number of observational studies have investigated whether people with higher vitamin D levels or intake have lower risks of specific cancers, particularly colorectal cancer and breast cancer.

8. Associations of vitamin D with risks of prostate, pancreatic, and other, rarer cancers have also been examined. These studies have yielded inconsistent results, most likely because of the challenges of conducting observational studies of diet.

9. Information about dietary intakes is obtained from the participants through the use of food frequency questionnaires, diet records, or interviews in which the participants are asked to recall information about their dietary intakes.

10. Information collected in this manner can be inaccurate. In addition, only recently has a

comprehensive food composition database with vitamin D values for the U.S. food supply become available.

11. Other dietary components or energy balance may also modify vitamin D metabolism. Measuring blood levels of 25-hydroxyvitamin D to determine vitamin D status avoids some of the limitations of assessing dietary intake.

12. However, vitamin D levels in the blood vary by race, with the season, and possibly with the activity of genes whose products are involved in vitamin D transport and metabolism. These variations complicate the interpretation of studies that measure the concentration of vitamin D in serum at a single point in time.

13. Finally, it is difficult to separate the effects of vitamin D and calcium because of the complicated biological interactions between these substances. To fully understand the effect of vitamin D on cancer and other health outcomes, new randomized trials will need to be carried out. However, the appropriate dose of vitamin D to use in such trials is still not clear.

Transforming growth factor-beta:

Transforming growth factor-beta (TGF- β) comprises super family of hormone-like polypeptides that affects cell growth, adhesion, and differentiation. Although many cancer cell types show varying degree of resistance to TGF β , this cytokine has been found to markedly potentiate the anti proliferative effect of 1,25D₃ and its analogs in Caco2 and SW480 human colon cancer cells, HL60, AML- 193, HEL/S and U937 myeloid leukemia cells and NCI-H929 multiple myeloma cells.

What Are the Possible Mechanisms by Which Vitamin- D May Modify Cancer Risk

Mechanisms by which vitamin D may modify cancer risk are not fully understood. Laboratory studies have shown that vitamin D promotes cellular differentiation, decreases cancer cell growth, and stimulates apoptosis^[25].

Vitamin D acts on cells by binding to the vitamin D receptor (VDR). The VDR is a regulator of gene transcription that is found in the nucleus of cells. Vitamin D-bound VDR binds to the retinoid-X receptor (RXR), and the resulting complex activates the expression of specific genes. Among the many genes regulated by vitamin D are those that produce the proteins calbindin and TPRV6, both of which are involved in the absorption of calcium by intestinal cells^[26]. Another vitamin D-regulated gene is CYP3A4, whose protein product detoxifies the bile acid lithocholic acid (LCA). LCA is believed to damage the DNA of intestinal cells and may promote colon carcinogenesis. Stimulating the

production of a detoxifying enzyme by vitamin D could explain a protective role for vitamin D against colon cancer [27].

Further insight into the mechanisms by which vitamin D might modify cancer risk could come from study of the vitamin D receptor itself. A large number of variant forms of the VDR gene have been identified, some of which are known to alter the structure or function of the VDR protein. Some of these variants have been linked to risk for certain cancers, including prostate, colorectal, breast, bladder, and melanoma [28]. The association of VDR variants with cancer risk differs by cancer site and appears to be modified by environmental exposures, such as diet and sun exposure.

Vitamin-D Compounds in Cancer Prevention and Treatment

Numerous epidemiological and preclinical studies support a role of vitamin D compounds in cancer prevention and treatment in colorectal, breast, prostate, ovarian, bladder, lung, skin cancers and leukemia [29-31]. Low levels of plasma 25(OH) D₃ are associated with higher cancer incidence and mortality in men in colorectal, breast, lung and prostate cancers [32-35]. The broad spectrum anti-tumor effects of calcitriol and analogs are mostly based on inhibition of cancer cell proliferation and invasiveness, induction of differentiation and apoptosis, and promotion of angiogenesis. Calcitriol has been studied in various combination treatments and shown synergistic or additive antitumor activities. Cisplatin (cis-diammine dichloro-platinum (II)), and its analog carboplatin (Di-ammine cyclobutane dicarboxylatoplatinum, CBDCA) are widely used DNA-damaging agents. It is active in the treatment of testicular, ovarian, cervical, lung, bladder cancer and head and neck squamous cell carcinoma (SCC). Calcitriol enhances both carboplatin and cisplatin-mediated growth inhibition in breast cancer MCF-7 cells and prostate cancer LNCaP and DU145 cells. Calcitriol potentiates cisplatin anti-tumor effect in a Y-79 human retinoblastoma xenograft model and canine breast cancer, osteosarcoma, and mastocytoma cells.

Is Vitamin-D Deficiency May Cause Risk In Cancer Patients

Cancer patients may spend less time in the sun because of their condition. The effect of cancer or its treatment can cause patients to consume less vitamin D in their diet because they are eating less.

Is sufficient vitamin-D Important for Cancer Patients?

Cancer is a disorder which involves uncontrolled cell growth. Vitamin D regulates the production of proteins that are responsible for cell division and growth. Therefore vitamin D deficiency can cause abnormal production of these proteins. Cancer patients who are vitamin D deficient can experience muscle and bone discomfort and fatigue.

Mechanism of Anticancer Action of Vitamin-D

1. Vitamin D is a fat-soluble vitamin that is naturally present in very few foods added to others and available as a dietary supplement. It is also produced endogenously when UV rays from sunlight strike the skin and trigger vitamin D synthesis.
2. Vitamin D obtained from sun exposure, food and supplements is biologically inert and undergo two hydroxylations in the body for activation. The first occurs in the liver and converts vitamin D to 25-hydroxyvitaminD [25(OH) D] also known as calcidiol.
3. The second occurs primarily in the kidney and forms the physiologically active 1, 25-dihydroxyvitaminD [1,25(OH)₂D] also called calcitriol.
4. The principle methods of treatment of cancer include surgery, irradiation and chemotherapy, usually given in combination depending on the type and stage of the disease.
5. Though early treatment is curative in many of the cancers early diagnosis is not possible in majority of cases and the disease still remains incurable in spite of all sincere and rational approaches for treatment.
6. Moreover the after effects of surgery and irradiation along with serious adverse effects of chemotherapy further limit the initiation and continuation of therapy.

Cancer Preventions

1. Medical literature suggests regular sun exposure is associated with substantial decreases in death rates from certain cancers and a decrease in overall cancer death rates [36].
2. Rates for these cancers are two to three times higher than sunnier areas [37].
3. Dark skinned people require more sun exposure to make vitamin D.
4. Vitamin D may also go beyond cancer prevention and provide tumor therapy.
5. Polymorphisms of the vitamin D receptor gene have been associated with an increased risk of breast cancer.

APPLICATIONS

Skin cancer:

The two most relevant effects of vitamin D for skin cancer prevention are its ability to maintain the ordered proliferation and differentiation of the stratified squamous epithelium [38], and its ability to prevent UV induced DNA damage. Vitamin D contributes to skin cancer prevention through protection of keratinocytes from ultraviolet (UV) mediated damage. Since UV radiation stimulates the synthesis of cholecalciferol in the skin, it is tempting to speculate that unique vitamin D compounds might be generated in skin exposed to UV radiation that act through non-genomic mechanisms to confer protection against its damaging effects.

Pancreatic Cancer:

There is experimental evidence for vitamin D having anti-carcinogenic properties, although few studies have examined this with respect to pancreatic cancer. Extra-renal synthesis of hormonally active 1,25-dihydroxy(OH)₂D₃ has been shown to be involved in autocrine and paracrine regulation of cell differentiation, proliferation, and apoptosis, processes involved in carcinogenesis. Expression of 25(OH) vitamin D₃-1α-hydroxylase, the enzyme that catalyzes the synthesis of the active 1,25(OH)₂ vitamin D form, has been observed in pancreatic duct cells, and normal and adenocarcinomatous tissue. Pancreatic cancer cell line growth is inhibited by 25(OH) vitamin D₃ (19;20). 1,25 vitamin D analogs inhibit pancreatic cancer cell proliferation, induce differentiation, promote apoptosis *in vitro*, and inhibit pancreatic xenograft tumor growth in immune deficient mice. In addition, the pancreatic islet cells possess vitamin D receptors and express 25(OH) vitamin D₃-1α-hydroxylase, which has led to the postulation that vitamin D status may be linked to endocrine pancreatic function.

Colon Cancer

The effect of vitamin D on colon carcinogenesis in mice has been studied in spontaneous, chemically induced and genetic models [39,40]. Chronic inflammation in the gut promotes tumorigenesis in mouse models and is a risk factor for colon cancer in humans.

Vitamin D regulates immune responses in many tissues; protection against intestinal tumor genesis by vitamin D may involve anti-inflammatory mechanisms. Both vitamin D₃ and 25D reduce the incidence of colon tumors by approximately 50% without adverse effects such as weight loss.

Breast Cancer

VDR agonists inhibit growth and induce regression of established human breast cancer xenografts in animal models [41, 42]. In estrogen receptor (ER) positive tumors, the effects of vitamin D analogs are comparable to that of standard anti-estrogen therapies such as tamoxifen, and additive effects are observed in combination studies with tamoxifen and ionizing radiation.

Animal studies also support the concept that vitamin D signal introduces initial development of breast cancer. Rodents fed western style diets low in vitamin D and calcium exhibit hyper proliferation in the mammary gland and develop significantly more mammary tumors when treated with 7, 12-dimethylbenzanthracene (DMBA) compared to rats fed adequate calcium and vitamin D.

Prostate Cancer

Similar to breast cancer, syngeneic and immune deficient rodent models have demonstrated that vitamin D analogs inhibit growth of established prostate tumors [43, 44]. Both androgen dependent and androgen independent prostate cells are inhibited by VDR agonists, including metastatic variants. Because of the relative safety of vitamin D therapy compared to available alternatives, we have begun clinical trials to evaluate the role of 1,25(OH)₂D₃ and its analogs in the treatment of patients with cancer of the prostate (CaP). Since others failed to detect any improvement in patients with advanced metastatic CaP in a phase II trial of 1,25(OH)₂D₃ [45]. We chose to recruit patients with early recurrent CaP who had no evidence of metastases. This was a small study using oral calcitriol (Rocaltrol) to treat early recurrent CaP as detected by rising PSA in patients who had prostatectomy or X-ray therapy as primary therapy of their prostate cancer.

Colorectal Cancer:

The anti-cancer activities exerted by 1,25(OH)₂D₃ and its analogs in human colon cancer cells *in vitro*, are mediated by proliferation inhibition and induction of differentiation and apoptosis. The anti-proliferative effect of Vitamin D is attained by inducing G₁ cell-cycle arrest, which is probably mediated by up-regulation of cell-cycle inhibitors, such as p21WAF1/CIP and p27KIP. Vitamin D modulates the activation of these cell cycle related genes by different mechanisms. P21 contains a VDRE in its promoter region, and therefore is susceptible of direct transcriptional control by Vitamin D.

CONCLUSION

Both in vitro in vivo study results arrive at the conclusion that vitamin D not only has got preventive effect on colorectal, prostate and breast cancer but also is capable of causing their regression and death of constitutive cancerous cells up to various degrees.

We can conclude that the anticancer action of vitamin D, it appears that the compound is not suitable for use in cancer as a primary anticancer agent.

It may be used as a adjuvant in combination chemotherapy where it can aid to the actions of other cytotoxic agents by causing tumor regression and inhibition of tumor growth.

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