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Can vitamin D deficiency affect the development of cancer? - review of the literature

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ABSTRACT:

Introduction and purpose:

Over recent years, there has been a noticeable increase in cases of cancer around the world. At the same time, there is the problem of vitamin D deficiency, which may affect up to one-quarter of the population. The aim of this article is to link these two epidemics and organize knowledge about vitamin D and its multidirectional effects related to many diseases, especially cancer.

State of knowledge:

Many scientific works have proven that vitamin D has a beneficial effect not only on the known calcium-phosphate metabolism. Researchers emphasize its pleiotropic effect on many organs and systems in the human body, and thus on many diseases, including cancer. Studies show that vitamin D modulates the expression of many different miRNAs specific to various types of cancer. The results of in vitro and in vivo studies showed the effect of calcitriol on cell growth and development. It influences processes such as differentiation, proliferation, apoptosis, strengthens the immune system, and reduces oxidative stress.

Summary:

Based on accumulated research, we can conclude that vitamin D presumably regulates the entire process of tumorigenesis, from initiation to metastasis and cell-microenvironment interactions. However, some studies do not confirm these data or provide contradictory results. For this reason, it is necessary to deepen research on this topic in order to establish specific recommendations, therapeutic and preventive plans. However, vitamin D and its role in the pathogenesis of many diseases should not be underestimated. In cases of low vitamin D concentration in the body, its supplementation will be reasonable, considering the functional identity of this source compared to sun exposure or diet.

Key words: vitamin D; vitamin D deficiency; cancer;

INTRODUCTION

Over recent years, there has been a noticeable increase in cancer diagnoses in both Poland and around the world. Despite the enormous progress in medical technologies, the creation of screening programs, better access to tests, and improvement of research methods, the mortality rate caused by these diseases is constantly increasing. [1] In this work, we want to analyze one of the numerous factors that may be involved in the pathogenesis of cancer, which in this context is not yet appreciated - vitamin D. It is mainly associated with exposure to the sun but is also provided in the diet and dietary supplements [2].

However, research shows that its deficiency is very common. It may affect as much as one quarter of the population [3].

There are a lot studies about vitamin D, and emphasis is placed on its use to prevent diseases of the skeletal system, including rickets in infants and children, but based on current medical knowledge, we must emphasize the need to maintain the correct level of vitamin D3 in the body not only during childhood, but also throughout life. It should be noted that older people have an increased demand for this vitamin. Research shows that in old age, even despite regular exposure to sunlight, 75% less vitamin D is produced than in a young person [4,5]. This leads to the occurrence of osteoporosis, and with it increased bone fragility.

Many scientific works have proven that vitamin D affects not only the well-known calcium-phosphate metabolism. Researchers emphasize its pleiotropic effect on many organs and systems in the human body, and thus on many diseases, including cancer. Therefore, it is worth delving deeper into learning and understanding its effects, role, and impact on the human body. This will open up new preventive and even therapeutic possibilities [6].

SOURCES OF VITAMIN D

Vitamin D consists of two forms: ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3). The main source of vitamin D is skin synthesis, which produces approximately 90-95% of the demand for vitamin D [7]. Diet is the second source of vitamin D for the human body. Ergocalciferol is found in products of plant origin, and cholecalciferol in products of animal origin [2]. However, despite a balanced diet, proper eating habits and the correct composition of food, there is no guarantee of ensuring the appropriate level of vitamin D in the body, which is why its supplementation plays a very important role [8].

PLEIOTROPIC EFFECTS OF VITAMIN D

Ergocalciferol is produced from ergosterol, which occurs, among others, in yeast, under the influence of ultraviolet radiation. Cholecalciferol is formed from 7-dehydrocholesterol is under the influence of ultraviolet radiation in keratinocytes, and is also absorbed in the small intestine into the lymphatic system. It is a biologically

inactive form. To gain full hormonal activity, it must undergo a two-stage hydroxylation process. Its first stage takes place via D3 25-hydroxylase (CYP2R1, cytochrome P450 family 2 subfamily R member 1) in the liver, where it is transported after attaching vitamin D-binding globulin (DBP, vitamin D-binding protein). As a result, the main metabolite of vitamin D is formed - 25-hydroxyvitamin D (25(OH)D3, calcidiol). Its concentration is the main indicator of the body's resources, used in clinical practice. Calcitriol (1,25(OH)2D3), the hormonally active form is produced in the kidneys thanks to the action of 25-hydroxyvitamin D 1-a-hydroxylase (CYP27B1) [6].

25-hydroxylase (CYP24A1) leads to the inactivation of active forms and their excretion, regulating the level of vitamin D [9-11]. However, the action of 1,25(OH) 2D is mediated by intracellular vitamin D receptors (VDR, vitamin D receptor). Various sources state that these receptors, together with coreceptors, are responsible for the expression of 2,000 to even 3,000 genes [10, 12]. VDR receptors are particularly important in the context of vitamin D pleiotropism because it was with their discovery in various body tissues that its concept appeared in 1985. [13] Today, with the presence of VDR and 25(OH)D-1a-hydroxylase (CYP27B1) in many tissues (which allows for the extrarenal synthesis of active 1,25(OH)2D), its pleiotropic effect is noticed [6].

The presence of VDR was demonstrated among others in the brain and spinal cord, in areas responsible for regulating behavior and motor activity [14, 15]. It has been proven that vitamin D metabolites can penetrate the blood-brain barrier, inhibit oxidative stress in the central nervous system, reduce the feeling of pain in postoperative patients, and improve postural stability in patients after spine surgery [16, 17, 18, 19, 20]. It is also believed to have an impact on the reduction of pro-inflammatory cytokines [18].

Research shows that 25(OH)D reduces the risk of osteoporosis and fractures, rickets, and osteomalacia, reduces the cases of recurrent infections, including tuberculosis, and reduces the risk of perinatal complications. [10, 21, 22]. Other studies show its anabolic effect on skeletal muscles [11, 23] and neuroprotective effects, including improvement of verbal functions in patients with Parkinson's disease [11, 24]. A relationship has also been demonstrated between vitamin D deficiency and cardiovascular diseases - hypertension, coronary artery disease, left ventricular hypertrophy, and systolic heart failure. It seems that the presence of 25(OH)D in endocrine, autocrine, and paracrine pathways may be crucial for reducing the risk of developing autoimmune diseases such as multiple sclerosis

or type 1 diabetes, bronchial asthma, strokes, type 2 diabetes, systemic lupus erythematosus, atopic dermatitis, neurocognitive disorders, and cancers [10, 22, 25]. In the further part of this work, we will focus on the impact of its deficiency on the pathogenesis of various cancers.

ANTI-CANCER ACTION OF VITAMIN D - MECHANISMS

Studies show that vitamin D modulates the expression of many different miRNAs specific to various types of cancer [26]. The results of in vitro and in vivo studies showed the effect of calcitriol on cell growth and development.

Vitamin D has antiproliferative effects in many tissues, significantly slowing down the carcinogenesis process [27]. To understand this action, it is necessary to recall the process that determines the transition of cells from the G1 phase to the S phase of the cell cycle. This is the phosphorylation of the retinoblastoma protein (Rb), catalyzed by G1 cyclins and cyclin-dependent kinases (CKD), which leads to the release of transcription factors that activate the progression of the cell cycle. The activity of CKD kinases is inhibited by p21 and p27 proteins, to which Vitamin D, linked to its VDR receptor, binds through regulatory sites in gene promoters. Through this combination, vitamin D increases the expression of these proteins, leading to inhibition of CDK kinases, lack of Rb phosphorylation and inhibition of the cell cycle in the G phase [28].

Other mechanisms of cell cycle regulation by 1,25(OH)2 D3 include stimulation of the transforming growth factor b (TGF-b) and insulin-like growth factor binding proteins (IGF-BP), for example IGF-BP3 [29], and inhibition of mitogenic signals transmitted by growth factors, including the receptor for epithelial growth factor (EGF) [30], as well as inhibition of the activity of prostaglandins, well-known as cell growth stimulators [28].

It turns out that, in addition to inhibiting the proliferation of 1,25(OH) 2D3, it also has the ability to stimulate apoptosis in various cancer cells, including colon, prostate and breast cancer, but its mechanism is not fully understood [31]. One of the apoptosis activation pathways stimulated by vitamin D derivatives has been found in breast cancer and chronic lymphocytic leukemia cells - inhibition of the expression of the bcl-2

proto-oncogene [32,33]. However, in invasive breast cancer cells exposed to 1,25(OH)2D3, an increase in the expression of the pro-apoptotic protein Bax was observed [34].

In vitro and in vivo studies have shown that 1,25(OH)2D3, by inhibiting the activity of metalloproteases and serine proteases, increasing the expression of E-cadherin and decreasing the expression of α6 and B4 integrins reduces the invasiveness of tumors [35-37]. Inhibition of angiogenesis by 1,25(OH)2D3 has also been described. This happens by inactivating interleukin 8, which is responsible for stimulating angiogenesis. In prostate cancer, 1,25(OH)2 D3 inhibits the activation of interleukin 8 (IL-8, interleukin-8) gene transcription through interaction with the p65 subunit of nuclear factor kB (NF-kB) [38].

Mentioned earlier the VDR receptor, the presence of which, as well as an increase in expression compared to healthy tissues (for example normal keratinocytes), was found in various cancer cells [39, 40]. In the VDR locus the presence of over 200 polymorphisms was discovered, which proves that this gene is evolutionarily "young" and "dynamic" [28,41]. The association of these polymorphisms with the development of human cancers, including prostate and breast cancer, has been described [42,43]. It was also found that individual polymorphisms may affect the stability of the VDR transcript, the gene's transcriptional activity, and even the response to treatment with cholecalciferol derivatives, bisphosphonates, and calcium preparations [45-47]. It has not yet been clarified which of the above-mentioned mechanisms plays a key role in the development of cancer. Most likely, such a mechanism depends on the type of cell and the type of cancer. Based on accumulated research, we can conclude that vitamin D probably regulates the entire process of tumorigenesis, from initiation to metastasis and cell-microenvironment interactions [48]. Therefore, it affects processes such as differentiation, proliferation, apoptosis, it also strengthens the immune system and reduces oxidative stress [49].

SKIN CANCERS AND VITAMIN D

Let's start with the group of cancers that may be the first to be associated with vitamin D - skin cancer. Although we naturally associate their formation with excessive exposure to solar radiation, which could also be associated with a higher level of vitamin D in the body, in reality, this is not always the case. The increase in skin cancer cases goes

simultaneously with the increase in vitamin D deficiency in the population [50], but the exact relationship between these two epidemics remains to be discovered.

There is a lot of talk about the need to expose the skin to sunlight, especially in the summer, to ensure the appropriate level of vitamin D in the body. However, a study conducted on Polish children during the holidays showed that the increased concentration of 25(OH)D3 was accompanied by a much greater increase in DNA damage associated with carcinogenic potential [51]. This shows that special care should be taken in selecting the source of vitamin D, limiting sun exposure and increasing its supply through diet and supplementation. This is especially true since it has been shown that vitamin D obtained from diet and dietary supplements is functionally identical to the vitamin produced after exposure to UV radiation [52]. Because it is difficult to separate high levels of vitamin D from excessive sun exposure, the results of some studies on the relationship between vitamin D deficiency and skin cancers that are associated with excessive sun exposure are contradictory.

The three main cancers associated with UV radiation are cutaneous malignant melanoma (CMM), squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) [53]. Cutaneous melanoma accounts for approximately 1.7% of cancer diagnoses worldwide [54]. Age-standardized the incidence rate is 3.8/100,000 for men and 3.0/100,000 for women. [55] The average age at diagnosis is 65 years, with 65.7% of diagnoses made between the ages of 55 and 84 years [56]. VDR expression is detected in melanoma cells, which indicates a significant role of vitamin D in this cancer. Studies in animal models have shown that calcitriol inhibits invasion and angiogenesis in melanoma cell lines [57], and normal vitamin D levels are associated with a reduced risk of melanoma [58], although there are also other research results that do not confirm this [59]. One study showed that lower serum vitamin D3 concentrations are significantly associated with worse prognostic features and poorer treatment outcomes, even after taking into account the effect of vitamin D3 on inflammatory markers [60]. Another study found an association between vitamin D levels at diagnosis and the rate of tumor division and ulceration [61]. It has also been observed that low vitamin D level is an independent prognostic factor for overall survival in melanoma patients, associated with histological ulceration [53]. Additionally, a different investigation revealed that changes in the gene encoding vitamin D binding protein, predisposing to reduced serum vitamin D level was associated with poor melanoma-specific

survival [62]. Its low level has even been shown to be associated with increased susceptibility to the disease and shorter survival due to this cancer [63]. However, some studies failed to confirm the above data [64].

Regarding the effectiveness of vitamin D3 supplementation in patients with melanoma, one study confirmed its safety and good tolerability. The response to supplementation was dependent on Breslow thickness - greater thickness was associated with a worse response to supplementation and greater susceptibility to future relapses, compared to people with a low Breslow score at diagnosis [65]. It is also reported that the incidence of melanoma is lower in people who follow a diet rich in vitamin D. However, there are no case-control studies on this subject [64]. Additionally, there are also research results that are contradictory to the above. One study demonstrated the protective effect of vitamin D against invasive melanoma in women, but this effect was not observed in men [66]. It should be emphasized that regular testing of vitamin D levels in patients with melanoma or at risk of developing melanoma is important [67]. However, it would be worth conducting more research to finally determine whether vitamin D supplementation can help patients suffering from or at risk of developing melanoma [68] and to be able to make specific recommendations on this basis.

Other skin cancers are even less studied than malignant melanoma. When it comes to squamous cell carcinoma (SCC), there are emerging studies confirming that vitamin D supplementation may be useful in preventing its formation [69]. It also proved helpful in enhancing photodynamic therapy in the treatment of SCC [70]. It should also be noted that there are studies in which an increase in the incidence of SCC was observed in people with higher levels of vitamin D in serum, but it was probably caused by excessive photodamage from sun exposure [71]. However, it has been proven that vitamin D inhibits the hedgehog pathway which is the key tumor pathway in the development of Basal-Cell Carcinoma (BCC) [53]. Another study showed that maintaining the 25-OH vitamin D3 level > 25 ng/ml in patients with a preliminary diagnosis of BCC could significantly reduce the incidence of recurrence after BCC [72]. It is also worth mentioning one of the precancerous skin conditions. In a study conducted on patients with Xeroderma pigmentosum (XP), a disease characterized by defective repair of DNA damage caused by ultraviolet (UV) radiation and a high risk of skin cancer, vitamin D deficiency was found. [73].

PROSTATE CANCER AND VITAMIN D

Prostate cancer is the most common cancer occurring in men. In 2015, 1.6 million cases of the disease and 366,000 deaths were recorded worldwide. The odds of developing prostate cancer between the ages of 0 and 79 years were 1 in 14 at the global level, ranging from 1 in 47 men in countries with low and medium sociodemographic indexes to 1 in 6 men in countries with high sociodemographic indexes [74].

Many preclinical studies have been performed indicating the protective effect of vitamin D in the development of prostate cancer. Prostate cancer cells contain receptors for vitamin D and androgens. 1,25-dihydroxyvitamin D3 increases the expression and enhances the action of androgens connecting both receptor systems. 1,25-dihydroxyvitamin D3 has antiproliferative effects in both androgen-positive and androgen-negative prostate cancer cells. In androgen-sensitive human prostate adenocarcinoma cells, 1,25(OH)2D3 and its analogues exert antiproliferative effects mainly through cell cycle arrest and, to a lesser extent, induce apoptosis [75].

A study conducted to investigate the mechanism of vitamin D deficiency on the development of prostate cancer in nude mice found that vitamin D deficiency promotes the development of prostate cancer. In individuals fed with a vitamin D-deficient diet, tumor growth rate, weight, and size were greater. In transgenic prostate adenocarcinoma-bearing mice fed a vitamin D-deficient diet, prostate cancer invasion and metastasis were exacerbated. The results of the study showed that vitamin D deficiency promotes the growth and metastasis of prostate cancer in two classic mouse models. The study provided new evidence that vitamin D deficiency worsens prostate cancer growth and metastasis, possibly by promoting EMT through two β-catenin-related mechanisms [76].

Plasma vitamin D concentrations were examined to determine the correlation between prediagnostic vitamin D concentrations and mortality in prostate cancer. Men in the lowest quartile of vitamin D levels were more likely to die from cancer compared to men in the highest quartile. Higher pre-diagnostic vitamin D concentration in plasma may be associated with improved prognosis in prostate cancer [77].

According to the results of Mendel's randomized trials conducted on a large population, the causal effect of vitamin D concentrations on the development of prostate cancer [78] and other cancers [79] cannot be confirmed. However, a modest or non-linear effect of vitamin D still cannot be ruled out. Preclinical studies indicate the preventive effect of vitamin D in prostate cancer, but this phenomenon requires more randomized studies to provide a clear answer.

ORAL CANCER AND VITAMIN D

When it comes to the relationship between vitamin D and oral cancer, the number of studies is unfortunately insufficient to draw any specific conclusions. Many preclinical studies indicate the need to deepen the study of this topic [80, 81]. However, vitamin D deficiency has been shown to be more common in patients with oral cancer [81] and has also been associated with an increased risk of oral cavity, pharynx and esophageal squamous cell carcinoma, which were more common in heavy smokers and severe alcoholism [82]. One study found increased expression of vitamin D receptors in precancerous lesions and oral cancer. It also proved that vitamin D supplementation reduces the toxicity associated with therapy, especially in advanced cancer, thereby improving the quality of life of patients [83]. Therefore, it is worth further research and explaining the role of vitamin D deficiency in the development and treatment of oral cavity cancer [84].

BREAST CANCER AND VITAMIN D

Breast cancer is the most frequently diagnosed cancer in women worldwide. Breast cancer patients constitute as many as 36% of women living with cancer. It is estimated that 1.7 million women are diagnosed with breast cancer every year, and over 500,000 die from it [85].

One study showed that low serum vitamin D levels are a risk factor for breast cancer. As serum vitamin D levels decrease, the odds for breast cancer increases. Moreover, the study showed a positive effect of supplementation with weekly high doses of vitamin D. Vitamin D deficiency in patients treated for breast cancer is associated with numerous side

effects, especially those related to low bone mineral density. The study indicates the positive effect of vitamin D supplementation as a factor supporting the treatment of side effects of breast cancer [86].

In order to determine whether the blood concentration of 25-hydroxyvitamin D or its active metabolite, 1,25-dihydroxyvitamin D, is lower in women at the time of their first diagnosis of breast cancer than in comparable women without breast cancer, a case-control study was performed with a frequency-matched control study to cases by race, age, clinic, and month of blood collection. There were significant mean differences in 1,25-dihydroxyvitamin D levels between breast cancer cases and controls; Caucasian cases had lower 1,25-dihydroxyvitamin D levels than white controls, and black cases had higher 1,25-dihydroxyvitamin D levels than black controls. After adjusting for age, test batch, month of blood collection, clinic, and sample storage time, the odds ratio for the lowest versus highest quartile was 5.2 for white cases and controls. The association in white women was stronger in women over the median age of 54 than in younger women, 4.7 vs. 1.5. There were no differences in case control in 25-D levels in either group [87].

Another study found a significant inverse relationship between serum 25(OH)D concentration and the risk of postmenopausal breast cancer. Additionally, the relationship was non-linear, suggesting a stronger effect in women with low 25(OH)D concentrations compared to women with higher concentrations. It was found that the use of menopausal hormone therapy and the number of pregnancies moderate the relationship between serum 25(OH)D concentration and the risk of breast cancer. This association was stronger in women who had never used menopausal hormone therapy compared with women who had used it in the past or currently, and in women with an increasing number of pregnancies; however, these findings require confirmation in further studies. These findings strongly suggest a protective effect on postmenopausal breast cancer risk through vitamin D intake, as characterized by measurement of serum 25(OH)D concentration [88].

In women in Pakistan, where vitamin D deficiency is common, increasing and maintaining serum vitamin D levels is a safe and inexpensive strategy. It may play a role in reducing the incidence of breast cancer, particularly among women in socioeconomically disadvantaged groups where breast cancer mortality is highest due to limited resources for early detection, diagnosis and treatment. Serum vitamin D deficiency was associated with an increased risk of breast cancer, whereas vitamin D supplementation was associated with

a decreased risk of breast cancer. Compared to patients with sufficient serum vitamin D (>30 ng/ml), women with serum vitamin D deficiency (<20 ng/ml) had a higher risk of breast cancer. Women who took vitamin D for a year before entering the study had a significant protective effect against breast cancer. In order to clearly determine the impact, more detailed studies should be performed [89].

COLON CANCER AND VITAMIN D

Colorectal cancer (CRC) accounts for approximately 10% of all cancer types worldwide. Colorectal cancer is a problem occurring all over the world, but it particularly affects highly developed communities. It is the second most common cancer in women and the third most common in men, and the fourth most common cause of cancer death in the world. Incidence varies by country, being more common in men. [90,91]

Numerous studies indicate the protective effect of 1α,25-dihydroxyvitamin D3 (1,25(OH) 2D3) against colorectal cancer. 1,25(OH) 2D3 is a hormone with a pleiotropic effect that binds to the vitamin D receptor with high affinity, which leads to the possibility of regulating gene transcription. 1,25(OH) 2D3 inhibits the proliferation, induces differentiation, and sometimes apoptosis of human colon cancer cells [92].

The most active metabolite of vitamin D, 1α,25-dihydroxyvitamin D3, induces differentiation, controls detoxification metabolism and cell phenotype, sensitizes cells to apoptosis, and inhibits the proliferation of cultured human colon cancer cells. 1α,25-dihydroxyvitamin D3 and its analogues reduce the formation of intestinal tumors in animal models [93].

In another study serum 25-hydroxyvitamin D (25(OH)D) has been shown to be associated with the risk of colorectal cancer (CRC). Higher serum 25(OH)D concentrations were significantly associated with a lower incidence of CRC in a dose-dependent manner. We observed a significant association between higher 25(OH)D concentrations and lower cases of colon cancer. These findings suggest the potential benefits of maintaining adequate vitamin D in preventing CRC, particularly in colorectal cancers [94].

According to recent studies, colorectal cancer stem cells (CCSCs) are responsible for chemotherapy failure and tumor recurrence [95], so targeting them may improve the therapeutic effect of CRC [96]. Ferroptosis is a form of non-apoptotic cell death [97].

It may play an important role in the fight against chemotherapy resistance and even in achieving complete cancer eradication [98]. Solute carrier family 7 member 11 (SLC7A11) is involved in the induction of ferroptosis. According to research, vitamin D regulates iron metabolism and the hepcidin-ferroportin axis in humans and mammals [99]. The described study sought to understand the effect of vitamin D on ferroptosis in colorectal cancer stem cells. The results showed that vitamin D treatment significantly inhibited stem cell proliferation and reduced the number of tumor spheroids in vitro. Vitamin D treatment has been shown to induce ferroptosis in CCSCs by downregulating SLC7A11 in vitro and in vivo. [100] This provides interesting data on the relationship between vitamin D and colorectal cancer, as well as leaving a lot of room for further research.

SUMMARY

Although many research results confirm the impact of vitamin D deficiency on the development of cancer and its supportive effect in their treatment, there are also studies with contradictory and unclear results, leaving this topic controversial. There are still no large randomized trials that would provide definitive results and management guidelines. However, vitamin D and its role in the pathogenesis of many diseases, including the most serious ones, should not be underestimated. Vitamin D deficiency may affect up to a quarter of the population, which gives us an idea of the scale of this problem. This also means that ensuring the proper level and control of vitamin D in the body will be the responsibility of doctors in almost every specialization. Due to the increased incidence of cancer in the elderly population, it is worth focusing, especially on this group in the context of the relationship between vitamin D deficiency and cancer. Solar radiation should not be treated as the only source of vitamin D, remembering its harmful effects. It is worth checking the vitamin D level in people at risk of its deficiency. In cases of low vitamin D concentration in the body, its supplementation will be reasonable, considering the functional identity of this source compared to sun exposure or diet.

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