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# Anti-Inflammatory and Anti-Angiogenic Properties of VitD3 in Ovarian Cancer

**Nafiseh Saghafi[1], Elham Abdollahi[1,2]*, Mahsa Khajouee[1]**

[1]Department of Gynecology and Obstetrics, Mashhad University of Medical Sciences, Mashhad, Iran

[2]Immunology Research Center, Inflammation and Inflammatory Disease Research Centre, Mashhad University of Medical Sciences, Mashhad, Iran

***Corresponding author:** Elham Abdollahi, ea6112@gmail.com



**Abstract:** Ovarian malignancies are the most complicated type among all gynecological cancers. Their etiology is yet unknown; however, they are a heterogeneous, rapidly growing, and very fatal group of cancers. Chronic inflammation and angiogenesis appear to have major contributions in the development and progression of ovarian malignancies. Angiogenesis and inflammation are involved in the pathogenesis of ovarian cancer. Vitamin D3 (VitD3) has shown to have anti-inflammatory and anti-angiogenic properties in different types of cancers. The anti-inflammatory and anti-angiogenesis effects of VitD3 on ovarian cancer are investigated in this review.

**Keywords:** VitD3, Ovarian cancer, Inflammation, Angiogenesis

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## 1. Introduction

Ovarian cancer is a malignant neoplasm of the ovaries that mainly affects postmenopausal women. Unfortunately, among all gynecological malignancies, it has the worst prognosis and the highest mortality rate [1]. As ovarian cancer is related to the rupture of the ovarian epithelium and the sensitivity impact of the follicular fluid with a high content of estrogens, research has suggested that the number and frequency of ovulations in a woman's lifetime are linked to her risk of developing ovarian cancer [2,3].

Ovarian malignancies are separated into two types. Type I cancers include low-grade endometrioid, mucinous, and clear-cell cancers, whereas type II cancers include serous cancers, which can originate de novo from the tubal and/or ovarian surface epithelium [2]. Surgery, as well as chemotherapy, are important in the treatment of ovarian cancer [2]. Unfortunately, due to its unknown cause, it may not be averted. Natural components have the potential to play a role in prophylactic or supportive treatment. According to existing evidence, there may be a relationship between ovarian cancer and nutrition. Chronic inflammation, for example, has been suggested as a contributing factor to ovarian carcinogenesis [4]. It has been found that women who are exposed to pro-inflammatory products have higher risk of ovarian cancer [5].

VitD3 is a hormone that has multiple targets [6], and it is involved in calcium and phosphate homeostasis [7]. In addition to its traditional function, it has been found that VitD3 controls the function and development of immune cells, including, dendritic cells, macrophages, B cells, and T cells, by binding to vitamin D receptors [8]. The anti-inflammatory property of 1,25VitD3 has been recognized as an important part of the "non-classical activities" of VitD3 [9-11]. Vitamin D modulates inflammatory responses by downregulating T helper 1 (Th1) cells, inhibiting the production of several pro-inflammatory cytokines, upregulating Th2

cells and regulatory T (Treg) cells, downregulating Th17 cells, and modulating antigen-presenting dendritic cells into a "tolerogenic state" [12-14].

Low vitamin D levels have therefore been linked to an increased propensity to infections and a higher chance of developing autoimmune disorders [15]. Higher levels of vitamin D have been found related to a decreased risk of developing malignancies, including ovarian cancer [16,17]. Based on a comprehensive analysis on ecologic and case-control studies, it has been proposed that increasing geographic latitude, more exposure to sun, or vitamin D supplementation can reduce the incidence or death of ovarian cancer.

A meta-analysis of four cohort studies showed an inverse association between the incidence of ovarian cancer and circulating 25(OH)D levels [18]. According to the new evidence regarding the anti-cancer effects of VitD3, this review examines the anti-inflammatory and anti-angiogenesis effects of VitD3 on ovarian cancer.

## 2. Anti-inflammatory property of VitD3 in ovarian cancer

Inflammatory reactions contribute to the development and progression of ovarian cancer and other cancers [19,20]. Cyclooxygenase 1 and 2 (COX-1 and COX-2) are enzymes that are involved in the production of prostaglandin and therefore regulate inflammatory response [21] (**Figure 1**). However, COX-1 is expressed permanently, differing from the expression of COX-2, which is controlled by growth factors, prostaglandins, and cytokines [21]. The increased expression of COX-2 is associated with the development of ovarian cancer, a reduction in apoptosis, increased cell expansion, and neoangiogenesis [22]. It has been suggested that stable inflammatory environments may lead to reduced levels of VitD3, which may explain why cancer is associated with low levels of circulating VitD3 [23]. Vitamin D combined with COX-2 inhibitor (celecoxib) has shown to decrease the growth rates of ovarian cancer significantly when compared to celecoxib alone [24]. The correlation between vitamin D activities and prostaglandin metabolism in ovarian carcinomas has also been discussed [24].

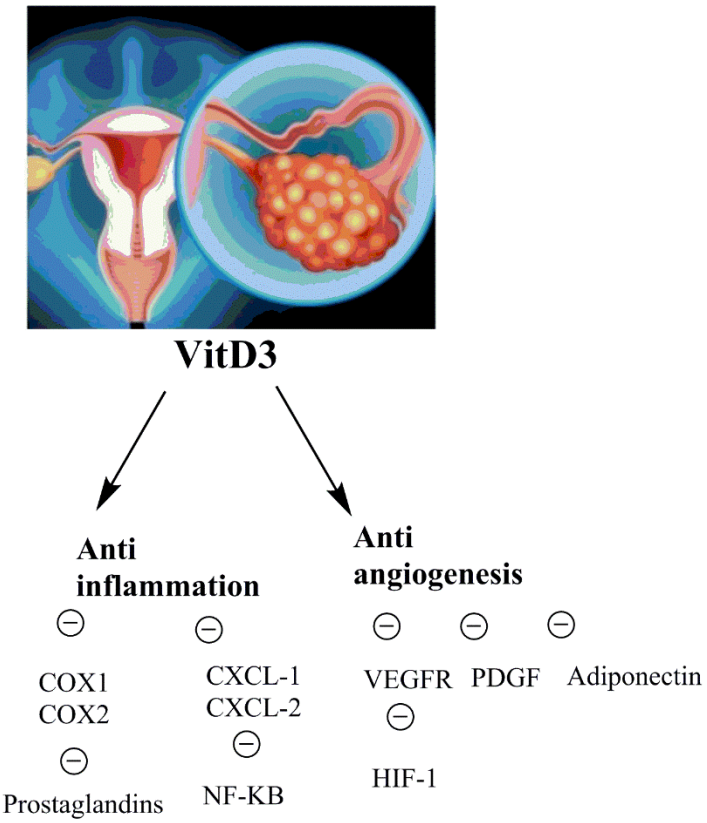


**Figure 1.** Anti-inflammatory and anti-angiogenic effects of VitD3 in ovarian cancer

A study that was conducted on ovarian and endometrial cancer cell lines revealed that VitD3 and progesterone can reduce the expression of CXCL1 and CXCL2 as pro-inflammatory chemokines in ovarian cells. This, in turn, leads to the downregulation of nuclear factor-kappa B (NF-kβ), which is the one of the most important transcription factors involved in tumor metastasis and inflammation [25]. The increased expression of CXCL1 and CXCL2 is associated with metastasis, angiogenesis, and tumor growth in breast and squamous cell cancers [25].

## 3. Anti-angiogenic property of VitD3 in ovarian cancer

Growing evidence indicates that vitamin D has a potential role in inhibiting tumor angiogenesis [29-33]. The presence of hypoxic regions within most solid tumors is a major pathophysiologic factor that regulates angiogenesis. Increased angiogenesis occurs as a cellular adaptation to hypoxia, which is regulated by hypoxia-inducible factor 1 (HIF-1). HIF-1 target genes, such as vascular endothelial growth factor (VEGF), are inhibited by $1,25(OH)_2D_3$, and this molecular inhibition is mediated via a HIF-dependent pathway [34]. In a study, VitD3 decreased the growth inhibition of tumor-derived endothelial cells from vitamin D receptor (VDR) knockout mice [34]. Moreover, the loss of VDR resulted in an increase in HIF-1α, VEGF, angiopoietin 1, and platelet-derived growth factor [34] (**Figure 1**).

## 4. Conclusion

The role of vitamin D in ovarian cancer has been studied, in which it has been suggested that vitamin D plays a protective and anti-cancer role. Based on relevant studies, this review suggests that vitamin D may serve as an anti-inflammatory and anti-angiogenic agent in ovarian cancer. Vitamin D may enhance anti-tumor effects, allowing for potential clinical application. Combined vitamin D and calcium supplement could be the therapeutic approach for preventing and treating ovarian cancer.

## Disclosure statement

The authors declare no conflict of interest.

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