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*Review Article*

# Research Progress on the Relationship between Vitamin D and Lung Cancer

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**Abstract**

Vitamin D is a common steroid hormone in the human body, which is closely related to the occurrence and development of various tumors, including lung cancer. At present, a large number of in vivo and in vitro studies have confirmed that vitamin D and its analogs have a positive role in the prevention, treatment and prolongation of survival of lung cancer. Therefore this article provides a comprehensive review of research on the relationship between vitamin D and lung cancer, examining possible reasons for the discrepancies in results, particularly in clinical studies.

**Keywords:** Vitamin D; Lung cancer; Inhibition.

## Introduction

Lung cancer is one of the common malignant tumors in the human body, and its incidence and mortality rates are among the highest in the world [1]. Despite being the second most common cancer in males, it remains the leading cause of cancer-related deaths [2]. Vitamin D, a steroid hormone, plays a crucial role in maintaining calcium and phosphorus homeostasis [3]. In addition, previous research has highlighted the significance of vitamin D and its impact on tumor development. Numerous studies have demonstrated the involvement of Vitamin D and its receptor (VDR) in the growth, invasion, and metastasis of various common cancers, including breast cancer, colon cancer, and thyroid cancer, with some studies yielding positive outcomes [4-8]. So, numerous studies have also attempted to explore the potential of vitamin D in the prevention and treatment of lung cancer. This article provides a comprehensive review of the recent advancements in understanding the role of vitamin D in the development and progression of lung cancer.

Research on cellular evidence of the relationship between vitamin D and lung cancer.

Research indicates that lung tumors primarily originate from mutations and proliferation of lung epithelial cells. While lung epithelial cells typically have the ability to resist external environmental stimuli, prolonged exposure to cancer-promoting factors can increase the accumulation of gene mutations, resulting in the differentiation of lung epithelial cells into tumor cells [9]. In vitro studies have demonstrated that vitamin D suppresses the growth and proliferation of lung cancer cells through interaction with the Vitamin D Receptor (VDR) located on the surface of these cells [10]. In a study by Y Higashimoto et al., the response of five lung cancer cell lines to calcitriol was evaluated, revealing that only cell lines expressing high levels of VDR exhibited the inhibitory effects of vitamin D on lung cancer cells [11]. In addition, several studies have demonstrated that vitamin D plays a significant role in inhibiting the growth and proliferation of small cell lung cancer cell lines such as NCI-H82 and NCI-H209, as well as non-small cell cancer cell lines like EBC-1 and H520 [11,12]. Furthermore, research has shown that vitamin D analogs also exhibit inhibitory effects on lung cancer cell growth. For instance, a study by Tsuyako Saito et al. revealed that the vitamin D analog BXL-01-0120 is more than 200

times as effective as 1,25-dihydroxyvitamin D3 in inhibiting lung cancer cell proliferation [13]. The inhibitory effect of vitamin D on lung cancer cells is also reflected in its regulation of cell cycle and apoptosis. Moffatt et al.'s research has demonstrated that vitamin D and its analogs lead to an increase in the production of p21waf1 and p27kip1 (Cyclin-dependent kinase inhibitors), thereby halting the cell cycle transition from the G0/1 phase to the S phase. And in the later stages of the cell cycle, vitamin D and its analogs can induce a decrease in the production of GADD45α, leading to cell cycle arrest in the G2/M phase[14]. In addition, studies by Diaz et al. have shown that vitamin D biases the cell balance toward apoptosis by affecting the levels of pro-apoptotic and/or anti-apoptotic proteins[15]. Recent research has indicated that $1,25(OH)_2D_3$ in combination with sunitinib and docetaxel can enhance the anti-cancer activity of individual drugs [16]. Moreover, Yiyan Songyang et al. have verified that vitamin D can inhibit the proliferation, invasion, and metastasis of non-small cell lung cancer cells A549 and NCI-H1975, promote cell apoptosis, and boost the anti-cancer effects of chemotherapy drugs when combined with cisplatin [17]. In conclusion, the aforementioned studies offer a solid foundation for revealing the anti-growth and anti-proliferation properties of vitamin D and its analogues in lung cancer cells.

Research on animal model evidence of the relationship between vitamin D and lung cancer.

In addition to demonstrating the inhibitory impact of vitamin D on lung cancer through in vitro cell experiments, a significant number of in vivo animal studies have also yielded consistent results. These findings primarily highlight the ability of vitamin D to inhibit tumor growth, angiogenesis, invasion, metastasis, and enhance immunity. The Lewis Lung Cancer (LLC) model is commonly used in animal experiments. Its formation principle is to transplant lung cancer tissue into cancer-free mice, and then gradually form cancer-bearing mice [23]. Previous studies have demonstrated that $1,25(OH)_2D_3$ can effectively reduce tumor volume in mouse Squamous Cell Carcinoma (SCC) models by inhibiting cell proliferation cycle through vitamin D, rather than promoting tumor cell apoptosis, and further research indicates that the combination of vitamin D and dexamethasone can enhance the inhibitory effect on tumors [19]. In addition, a randomized controlled trial based on Squamous Cell Carcinoma (SCC) demonstrated that the tumor volume of mice in the vitamin D single-drug group was smaller than that of the unadministered group. Furthermore, the tumor volume of the group receiving vitamin D combined with cisplatin treatment showed a more significant reduction. These result are achieved by promoting tumor cell apoptosis through vitamin D [17]. In a study by Kimie Nakagawa et al., it was found that the vitamin D analog 22-oxa-1alpha, 25-D(3) can decrease angiogenesis induced by tumor cells or fibroblast growth factors in Lewis (LLC) mice. Additionally, this vitamin D analogue was observed to directly decrease the metastatic activity of lung cancer cells in a dose-dependent manner [18]. These findings suggest a potential role for vitamin D in inhibiting tumor angiogenesis and metastasis. Furthermore, Vitamin D also plays a crucial role in tumor immunity. Studies have indicated that 25(OH) D can decrease the activity of rapamycin in mammalian lung cancer cells and enhance the expression levels of related proteins, ultimately facilitating the autophagy of tumor cells [22]. 25(OH) D can also inhibit the proliferation and metastasis of lung cancer cells by increasing the expression level of the antioxidant protein superoxide dismutase [21]. Of course, in addition to LLC mice being used as animal models, the A/J mouse model induced by carcinogens is also used for vitamin D research, and relevant research results have also revealed the significant anti-tumor properties of vitamin D [24].

## Clinical evidence study on the relationship between vitamin D and lung cancer

Numerous clinical observational studies have investigated the association between vitamin D and lung cancer. Findings suggest a strong correlation between serum vitamin D levels and lung cancer risk. Some studies indicate that low serum vitamin D concentrations may increase the likelihood of developing lung cancer by over threefold, while no such association was observed with breast cancer, thyroid cancer, and other types [25]. A study on Chinese individuals revealed a correlation between low serum vitamin D levels and a higher incidence of lung cancer, particularly advanced non-small cell lung cancer [26]. Additionally, a Finnish prospective cohort study found that while serum vitamin D levels were not linked to overall lung cancer risk, subgroup analysis indicated that higher vitamin D levels were associated with reduced lung cancer incidence in women and younger age groups [27]. What's more, some studies have reported that vitamin D can also significantly affect the survival and mortality rates of lung cancer patients [27-30]. For instance, Ting-Yuan et al. conducted a study on Americans which revealed that higher levels of vitamin D could potentially reduce lung cancer mortality by 58% [30]. Other research has shown that elevated vitamin D levels can extend the Overall Survival (OS) and Progression-Free Survival (PFS) of lung cancer patients [28]. However, conflicting findings exist as some studies have suggested that vitamin D may not have a direct impact on the incidence and survival of lung cancer. A cohort study utilizing the Norwegian HUNT database found that 25-hydroxyvitamin D levels did not show a significant correlation with the overall incidence and histological type of lung cancer, and even Low levels of vitamin D were found to be associated with a lower risk of lung cancer [31]. A study conducted by the Lung Cancer Cohort Consortium (LC3), which included 5313 case groups and 5313 control groups, found no significant association between 25(OH) $D_3$ and lung cancer risk [29]. Clinical trials have also reported the positive impact of vitamin D supplementation on lung cancer outcomes. For instance, In a randomized, double-blind, placebo-controlled trial, researchers found that vitamin D supplementation (1,200 IU/day) in lung cancer patients 1 year after surgery improved survival rates in patients with early-stage lung adenocarcinoma who had low 25(OH) D levels [32]. Furthermore, a study by Ting-Yuan et al., it was found that while total vitamin D intake was not significantly associated with lung cancer overall, Among former smokers, total vitamin D intake ≥600 IU/day was associated with a significantly lower risk of non-small cell lung cancer compared with <200 IU/day [33]. Meta-analyses are known for their extensive data analysis and high level of evidential value. However, the conclusions obtained are also different. A meta-analysis conducted in 2017 revealed an inverse relationship between vitamin D levels and lung cancer risk among non-smokers. It also suggested that high vitamin D intake could potentially enhance the prognosis

of lung cancer patients. Furthermore, the study indicated that factors such as sunlight exposure intensity and geographical latitude might influence lung cancer development by impacting vitamin D levels [34]. In a separate study by Qianqian Feng et al., it was found that a 10 nmol/L increase in circulating vitamin D could potentially reduce the risk of lung cancer by 8% and decrease lung cancer mortality risk by 7% [35]. A recent meta-analysis found that vitamin D can improve the long-term survival rate of lung cancer patients and also has a positive impact on the incidence of lung cancer [36]. However, there are conflicting conclusions from other related meta-analyses. For instance, Hu Wei et al.'s study suggested that high levels of vitamin D are not associated with lung cancer risk. Nonetheless, a daily intake of 100 IU of vitamin D may decrease the risk of lung cancer by 2.4%, while excessive intake has limited effect on reducing this risk [37]. So, The findings of clinical studies regarding the link between vitamin D and lung cancer are inconsistent, the inconsistency may be attributed to factors such as sample size, potential confounders, and statistical methodologies influencing clinical data research. Future investigations should aim to increase sample sizes and account for variables such as smoking, alcohol consumption, diet, vitamin D supplementation, prior cancer diagnoses, light exposure, among others, to validate current findings. Genetic evidence of the relationship between vitamin D and lung cancer.

With the completion of the whole human genome sequencing, research on the relationship between vitamin D and lung cancer has advanced to the genetic level. Previous studies have demonstrated that Single Nucleotide Polymorphisms (SNPs) associated with vitamin D metabolism are strongly linked to lung cancer. Specifically, variations in the Vitamin D Receptor (VDR) and cytochrome P450 (CYP24A1) genes have shown significant associations with lung cancer [40]. Research has demonstrated that the enzyme produced by CYP24A1 can diminish the activity of vitamin D, and CYP24A1 is found to be overexpressed in various malignant tumors, such as lung cancer, thus contributing to the development of lung cancer [41,42]. Additionally, CYP24A1 is utilized as a standalone prognostic indicator for the survival of lung cancer patients [43]. Vitamin D exerts biological effects through the Vitamin D Receptor (VDR). A study by Mark G Anderson found that VDR mRNA expression in lung tumors was significantly lower compared to non-tumor tissues [42]. Studies have found that 27 SNPs related to vitamin D metabolism may be linked to the risk of lung cancer through their influence on serum vitamin D levels. It is noteworthy that 80% of these 27 SNPs are found within the CYP24A1 and VDR genotypes [44]. Mendelian randomization studies have gained popularity as a research tool in recent years, utilizing large-scale Genome-Wide Association Study (GWAS) databases to explore causal relationships between variables and specific diseases. Despite the lack of significant causal relationship between 25(OH) D and lung cancer morbidity or mortality in several Mendelian randomization studies [45-47], this does not rule out the potential role of vitamin D in suppressing lung cancer. Because in the Mendelian randomization study, although we used genetic instrumental variables to assess vitamin D levels, other undiscovered potential factors may interfere with the actual serum vitamin D levels during lung tumor development, resulting in false negative results. While the research on the genetic link between vitamin D and lung cancer has yielded positive outcomes, we cannot ignore the results of Mendelian randomization, and further research is needed to improve them.

## Summary and Outlook

Lung cancer is one of the most malignant tumors that threatens human life and health. Recent in vitro cell and in vivo animal experiments have demonstrated the beneficial effects of vitamin D in inhibiting the growth, proliferation, and differentiation of lung cancer. While findings from clinical observational studies, randomized controlled trials, and meta-analyses may vary, a large number of clinical researches indicate that serum vitamin D plays a positive role in the prevention and treatment of lung cancer, as well as in extending the survival of patients with this disease, and genetic studies also support these findings. The discrepancy in findings between laboratory and clinical studies may be attributed to varying levels of control over confounding variables. As a result, it is imperative for future clinical studies to meticulously manage the inclusion and exclusion criteria of variables and employ suitable statistical methods to control for confounding factors. Although a large number of clinical studies have revealed the potential role of vitamin D in both preventing and treating lung cancer, determining the ideal dosage of this vitamin remains a challenge. Future research endeavors should focus on conducting more extensive clinical studies with larger sample sizes to ascertain the most effective level of vitamin D for the prevention and treatment of lung cancer in the general population.

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