VITAMIN D AND LUNG CANCER: A NARRATIVE REVIEW

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ABSTRACT

Lung cancer is one of the most common malignancies worldwide. The aim of the present review was to describe the role of vitamin D in the pathophysiology, prevention, treatment and prognosis of lung cancer, based on the current scientific evidence. Although there is evidence supporting the hypothesis of an anticancer effect of vitamin D, the current scientific literature does not allow definitive conclusions on the ability of vitamin D intake and 25(OH)D3 serum levels to reduce lung cancer risk. Some encouraging results were obtained with respect to the clinical utility of vitamin D-based medications as potential boosters of lung cancer therapies. Future steps in this field could lead to the design of novel pharmacological strategies with the intent to enhance the curative effects of modern targeted therapeutic agents against lung cancer.

Keywords: *lung cancer, NSCLC, vitamin D, 25(OH)D3, targeted therapy.*

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Introduction

Lung cancer is one of the most common malignancies worldwide, with more than two million cases and more than 1.8 million deaths estimated by GLOBOCAN 2018[(1)]. Lung cancer incidence is rising especially in developing countries and among women, as a consequence of the evolving tobacco epidemic among these specific subpopulations. Mortality rates remain high and tightly close to incidence rates, despite recent advances in all fields of research and in the clinical management of the disease[(2)]. These figures are particularly factual for patients with unresectable tumors, and for those affected by small-cell variants of lung cancer (SCLC). The molecular mechanisms of non-small-cell lung cancer (NSCLC) subtypes have been better elucidated over the past two decades, allowing the introduction of novel therapies that target specific molecular alterations, such as epidermal growth factor receptor (EGFR) gene mutations, anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 (ROS1) rearrangements, and the expression of particular proteins like the programmed-death 1 (PD1) protein[(3-7)]. Even though the advancements in target therapy and immunotherapy have improved survival time for patients with NSCLC, the overall disease-specific survival is still disappointing.

It is for this reason that global strategies have long been focused on primary prevention of lung cancer, rather than its treatment. In fact, results from previous awareness campaigns were particularly effective in preventing malignancies that are traditionally linked to environmental causative agents, such as malignant mesothelioma and asbestos exposure, thyroid cancer and radiations, and others[(8-11)]. With regard to lung cancer and tobacco smoking, which are associated in 80 to 90% of cases, anti-smoking campaigns have indeed reduced the risk among males

in western countries, and hold promising projections for the future[2]. Measures for the reduction of atmospheric pollution, another prominent risk factor for lung cancer, may have additional positive effects in the future; unfortunately, urban air levels of pollution are estimated to deteriorate globally, and air particulate matter will be the leading cause of pollution-related deaths worldwide by 2050[12].

In recent years, nutrition became a subject of fervent research in the perspective of primary cancer prevention, including that of lung cancer. Numerous studies have demonstrated strong associations between dietary habits and specific types of malignancies, such as the consumption of red meat and colorectal cancer, spicy foods and gastrointestinal cancer, and the reduction of gastric cancer incidence rates in Asian immigrants who moved to the USA thus adopting local nutritional habits[13-14].

In 2018, The World Cancer Research Fund published a comprehensive report on the effects of numerous dietary compounds on several types of cancers[16]. The report includes information on nutrition and lung cancer, but no specific data regarding the role of vitamin D are provided. Numerous epidemiological, laboratory and clinical studies suggest that this vitamin may have a protective role against cancer, even if some discrepancies in methodology and conflicting results encumber conclusive evidences. Despite this, there are convincing results arising from a few pharmaceutical clinical trials that support the vitamin D cancer prevention hypothesis[17]. The aim of the present review is to describe the role of vitamin D in the pathophysiology, prevention, treatment and prognosis of lung cancer, based on the current scientific evidence.

Main pathophysiological mechanisms of vitamin D involvement in cancer

Vitamin D3 (cholecalciferol), the natural form of vitamin D, is produced in the skin from 7-dehydrocholesterol. Upon irradiation, 7-dehydrocholesterol transforms into pre-vitamin D3 which then undergoes a temperature-sensitive rearrangement of three double bonds to form vitamin D3[18]. Vitamin D can also be taken with diet, but there are scarce food sources (salmon, sardines and other fishes, cod liver oil, egg yolk etc.). Vitamin D3 itself does not have a significant biological activity; once absorbed, the major proportion binds to the vitamin D binding protein (DBP) and is thus carried to the liver. In the hepatocytes, vitamin D is hydroxylated at C-25 by CYP27A1 to produce 25-hydroxyvitamin D3 (25(OH)D), which is the metabolically active protein. Vitamin D can also be produced in extrahepatic tissues; indeed, CYP27B1 is widely expressed in multiple organs and it works by encoding 25-hydroxy vitamin D 1-α hydroxylase to catalyze 1,25(OH)D to active 1α,25(OH)2D3; other cytochrome P-450 enzymes (CYPs) including CYP2R1 and CYP2D25 are believed to contribute (19); as opposed, CYP24A1 encodes 25-hydroxy vitamin D3-24-hydroxylase, that in turn converts active metabolites to inactive 24,25-dihydroxy vitamin D[20]. The underlying genomic mechanism of action of 25(OH)D involves the interaction of the vitamin with its receptor (VDR) complexed with RXR, and subsequently the direct binding of 25(OH)D activated VDR/RXR to specific DNA sequences (vitamin D response elements) in and around target genes, resulting in either activation or repression of transcription (18). A large number of regulators of this process have been identified, such as p160 coactivators, steroid receptor activator 1, 2, and 3 (SRC-1, SRC-2, and SRC-3), and acetylation or methylation of specific histones[21]. Any alteration of this finely regulated process can lead to overexpression or suppression of genes, contributing to carcinogenesis.

Decreased circulating serum levels of 25(OH)D in mice on a vitamin D-deficient diet and inoculated with cancer cells were associated with an increased tumor growth[22]. The cancerogenic effects of vitamin D deficiency involve several molecular mechanisms. Among the best described cell-type dependent effects are the interactions with Wnt/β-catenin, ERK/mitogen-activated protein kinase pathway, c-myc, FOXM1 and other signalling pathways that inhibit growth and promote differentiation[23,24]. In addition, 25(OH)D induces apoptosis in specific types of cancer cells by suppression of the antiapoptotic B-cell lymphoma 2 (Bcl2) proteins and B-cell lymphoma extra large (Bcl-xl), activation of the proapoptotic protein Bax, or interference with other signaling pathways such as tumor-necrosis factor (TNF)-α[25,26]. The induction of PDZ-LIM domain-containing protein 2 (PDLIM2) and tissue inhibitor of metalloproteinase 1(TIMP1), the reduced expression and secretion of metalloproteinase (MMP) 2 and 9, the reduced activity of cathepsin K and the regulation of various components of the plasminogen activator system by 25(OH)D are the main molecular mechanisms that promote pro-adhesion, anti-migration, and anti-invasion[27,28].

Moreover, interactions with chronic inflammation molecular networks and regulation of several miRNAs by 25(OH)D have been observed within the

signaling cascade that is responsible for the effects of 25(OH)D on cell proliferation, differentiation, apoptosis, and gene regulation[18]. Furthermore, several studies in VDR knockout mice pointed out that the absence of VDR leads to enhanced proliferation and higher susceptibility to carcinogenesis, both in genetic models and upon exposure to carcinogenic products[29]. Nevertheless, studies on humans have described an inverse association between 25(OH) D levels and risk of cancer which was consistent for colorectal neoplasms, as opposed to inconsistent results for other types of malignancies like melanoma[30,31]. Recent meta-analyses support an inverse association between circulating 25(OH)D levels and cancer-related deaths, suggesting that the effects of vitamin D may have a less incisive impact on cancer risk than on mortality rates. In addition, underexpression of VDR has only been observed sporadically in human cancers[32]; on the other hand, VDR overexpression has been associated to better prognosis in breast cancer[33].

With regard to lung cancer, a few data are available on the molecular implications of vitamin D. Recent studies have speculated that some alterations in the expression of the main enzymes involved in the metabolism of vitamin D could be implicated in lung cancerogenesis. In particular, Ge et al.[20] showed that CYP24A1 expression was associated with histologic subtype, differentiation and prognosis of lung cancer, while CYP27B1 expression was significantly associated with TNM stage, differentiation and prognosis, but not age, sex, smoking or any histologic subtype. In other studies, high CYP24A1 expression significantly correlated with poor survival in lung cancer cohorts, while high CYP27B1 was associated with better overall survival[34,35]. VDR polymorphism were conversely associated with NSCLC survival, while DBP polymorphisms were linked to protein variants with different affinity for 25(OH)D (36). Further studies are necessary to better elucidate the implications of vitamin D and its metabolic pathways in the genesis of lung cancer.

Vitamin D and lung cancer risk

Several studies investigated on the impact of vitamin D dietary intake and serum levels in lung cancer risk; from 2015 to 2018 five systematic reviews and meta-analyses were conducted including published studies. The first meta-analysis, published by Zhang et al., enrolled twelve studies (9 prospective cohort and 3 nested case-control studies) with a total of 288,778 individuals[37]. The global analysis showed that high vitamin D status was associated with decreased risk of lung cancer; subgroup analysis showed that a high serum vitamin D level was associated with reduced risk of lung cancer, but high vitamin D intake was not associated with decreased risk of lung cancer. The main limit of this meta-analysis in assessing the correlation between vitamin D levels and lung cancer risk was the small number of articles enrolled.

A further dose-response meta-analysis published the same year by Chen et al.[38] including 13 reports from ten prospective studies with a total of 2,227 lung cancer events. The results showed a significant 5% reduction in the risk of lung cancer for each 10 nmol/L increment in 25(OH)D concentrations. This inverse association was not significantly modified by area, study duration, sex, methods for 25(OH)D measurement, baseline 25(OH)D levels, or quality score of included studies. It must be kept in mind that most of the randomized control trials (RCTs) analysed in this study were not designed to test cancer as a primary end point, supplemented with a combination of vitamin D and calcium, and potential effect modification by smoking status was not addressed due to a limited number of studies. Two years later, Feng et al. performed a new meta-analysis focusing on the circulating levels of 25(OH)D; they included 17 eligible studies with a total of 138,858 participants, and 4,368 incident cases[39]. The authors found a statistically significant association between 25-hydroxyvitamin D and lung cancer risk and mortality.

However, circulating 25-hydroxyvitamin D was not associated with overall lung cancer survival. Furthermore, results were quantified and the authors reported that an increase of 10 nmol/L dose of circulating 25-hydroxyvitamin D was associated with a 8% reduction in lung cancer risk, and a 7% reduction in lung cancer mortality. Some limitations must be considered in this meta-analysis. First, the authors only select literature written in English, which may have resulted in a language or cultural bias, other languages should be chosen in the further. Second, they only selected literature from PubMed and Embase databases.

A further meta-analysis was published in the same year by Liu et al. investigating the association between vitamin D levels and lung carcinoma risk and outcomes[40]. The meta-analysis included 22 clinical studies with 813,801 participants, who were divided into the following 4 categories based on serum

25(OH)D levels: 1) sufficient levels, ≥ 20 ng/ml(50 nmol/L); 2) insufficient levels, 10-19.9 ng/ml (25-49.9 nmol/L); 3) deficient levels, 5-9.9 ng/ml (12.5-24.9 nmol/L); 4)severe deficient levels, < 5 ng/ml (12.5 nmol/L). Also this meta-analysis demonstrated an inverse association between serum 25(OH)D, Vitamin D and calcium levels and lung cancer risk.

Subgroup analysis showed that vitamin D intake reduced lung cancer risk, especially in non-smokers. A positive trend in serum vitamin D levels was also linked to longer survival rates. In relation to annual sun exposure and latitude, vitamin D levels positively correlated with extent of sun exposure, but negatively correlated with latitude. Nevertheless, some potential limitations of this meta-analysis should be considered, in particular the fact that the selected studies evaluated circulating 25(OH)D levels with different measurements, and the time (time quantum, season) of collecting blood sample was not always consistent. It must also be considered that a meta-analysis of observational studies cannot fully explain the causative relation between vitamin D and lung cancer.

Finally, in 2018 Wei et al.[41] enrolled 16 studies including 7,823 lung cancer patients and 272,304 control subjects. Comprehensive meta-analysis, dose-response analysis, and subgroup analysis revealed that an increase in the vitamin D intake was associated with a decrease in the risk of lung cancer. Moreover, the serum 25 (OH)D level was not associated with risk of lung cancer in overall statistics and in most subgroup analyses except for women, baseline 25(OH)D level >50nM, SCLC, and squamous carcinoma. The latter finding is in contrast with those of previous meta-analyses, (the meta-analysis of Wei et al. included more case-control and cohort studies). Nevertheless, in this meta-analysis the number of included studies in some subgroup analysis was small, and the original studies did not provide individual data, therefore results were evaluated by pooled RR and the associated 95% CI which limited the analyses. Taken together, the results of these meta-analyses suggest that an inverse relationship between vitamin D intake and 25(OH)D serum levels with lung cancer risk may exist. However, this statement cannot be considered fully conclusive in consideration of the aforementioned inconsistent results observed within these studies.

Vitamin D in lung cancer treatment

A few studies investigating the use of vitamin D supplementation in lung cancer patients have been published to date. Ma et al.[42] designed a study to examine the prognostic role of plasma 25(OH) D levels in advanced NSCLC patients treated with platinum-based doublet first-line chemotherapy. The authors included 195 patients whose 25(OH)D level was measured at the time of diagnosis. Both univariate and multivariate analyses showed that having a plasma 25(OH)D level <10 ng/mL was associated with a significantly shorter overall survival (OS), while the baseline plasma 25(OH)D level was not significantly associated with progression free survival (PFS)[42]. This suggests that in this specific subset of patients, vitamin D supplements could produce favourable therapeutic effects.

Akiba et al.[36] performed a randomized, double-blind, placebo-controlled trial in 155 patients with NSCLC, randomly assigned to receive vitamin D supplements (n=77) or placebo (n=78). Relapse and death occurred in 40 (28%) and 24 (17%) patients, respectively. In the total study population, no significant differences in either relapse free survival (RFS) or OS was seen with vitamin D compared to the placebo group. When the analysis was restricted to a subgroup with early-stage adenocarcinoma and low 25(OH)D, the cluster receiving vitamin D supplementation showed significantly better 5-year RFS and OS than the placebo group. The authors additionally examined associations with DBP, VDR, CDX and other polymorphisms: DBP1 (rs7041) TT and CDX2 (rs11568820) AA/AG genotypes stood as markers of better prognosis, even with multivariate adjustment (36).

Shin et al.[43] explored the potential association between serum 25(OH)D levels and EGFR gene mutations in 135 patients with pulmonary adenocarcinoma, an area of particular interest considering that this subset of tumors responds to targeted therapies with tyrosine kinase inhibitors (TKIs). Multivariate analysis revealed an association between low 25(OH)D levels and high incidence of EGFR mutations. This finding was investigated in some subsequent studies. Verone-Boyle et al.[44] determined vitamin D receptor (VDR) expression in human lung tumors using a tissue microarray comprised of cancer specimens in never-smokers (where EGFR gene mutations are prevalent). EGFR-mutant lung cancer cells were treated with 25(OH)D to study anti-proliferative activity, while mice were fed diets containing 100 or 10,000 IU vitamin D3/kg to determine the effects of modulated serum 25(OH)D levels on growth of EGFR mutant lung tumor xenografts. The authors established that EGFR mutant lung cancer is indeed a

vitamin D-responsive disease, and that diet-derived 25(OH)D might be a therapeutic agent[44].

A possible application of vitamin D-derived drugs in patients treated with EGFR-TKIs was recently proposed by Liu et al[45]. TKIs are initially effective in treating EGFR mutant NSCLC, but drug resistance may develop rapidly due to several mechanisms, including induction of the epithelial-mesenchymal transition (EMT). 25(OH)D promotes epithelial differentiation and inhibits growth of NSCLC cells, and the authors postulated that this could be a promising agent to treat EMT-associated resistance to EGFR TKIs. CTA091, a potent and selective 24-hydrosylase inhibitor, was co-delivered together with 25(OH)D through EGFR-targeted liposomal nanoparticles (EGFR-LP) in an EMT-associated model of EGFR TKI resistance; the nanoparticles improved the cellular uptake of 1,25D3 and CTA091, drove pro-epithelial signaling by upregulating E-cadherin (CDH1), and significantly inhibited the growth of EGFR TKI resistant cells[45].

This represents an encouraging approach which could be applied to explore other types of resistance to both lung cancer targeted therapies and immunotherapy, and which could possibly be translated into clinical practice. The main limitation of these studies consist in heterogeneity in properly measure values of vitamin D, because the level varies according to numerous factors, including sun exposure, diet, and supplementation. Furthermore, the definitions of vitamin D status including sufficiency, insufficiency and deficiency are not universally accepted. These aspects the main methodological challenges for future studies on the role of vitamin D in lung cancer treatment.

Future perspectives

The current evidence obtained from meta-analyses on the role of vitamin D and its metabolites on reducing lung cancer risk is not conclusive; the power of serum levels of 25(OH)D3 and calcium in predicting clinical outcomes is also not clear. In this regard, more general approaches such as umbrella or network meta-analysis may be useful. Most importantly, we feel that there is a need for well designed prospective epidemiological and clinical studies with high methodological standards in order to produce valuable scientific evidence on the topic, overcoming the methodological limitations mentioned before.

The introduction of targeted therapies brought significant improvements in lung cancer survival rates. Nevertheless, these medications are weighted by several side effects and limitations, like the early development of resistance. It would be noteworthy to further assess the role of vitamin D intake in the attenuation of these effects, and in the outcomes of precision oncology therapies. For example, administration with modern vehicles such as nanoparticles should be investigated, as it could consistently implement the pharmacologic kinetics of vitamin D supplements and related medications. Furthermore, the identification of patient subsets holding specific molecular, pathological and/or clinical features that may benefit from vitamin D supplements would be a further step in optimizing future pharmacological approaches.

Conclusions

Numerous in vivo and in vitro studies have elucidated some of the mechanisms involving vitamin D metabolites, receptors, regulators and enzymatic biochemical pathway components in the genesis of human cancer. Although there is evidence supporting the hypothesis of an anticancer effect of vitamin D, the current scientific literature does not allow definitive conclusions on the ability of vitamin D intake and 25(OH)D3 serum levels to reduce lung cancer risk. Some encouraging results were obtained with respect to the clinical utility of vitamin D-based medications as potential boosters of lung cancer therapies. Future steps in this field could lead to novel pharmacological strategies able to enhance the curative effects of modern targeted therapies against lung cancer.

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