

Review Article

Vitamin D Deficiency in Smokers: A Major Risk Factor in Lung Carcinogenesis

Subendu Sarkar¹, Manas Kamal Sen², Rajender Pal Singh³, Gorachand Bhattacharya⁴

1. Central Research Laboratory, ESIC Medical College and Hospital, Faridabad, India; 2. Department of Respiratory Medicine, ESIC Medical College and Hospital, Faridabad, India; 3. Department of Experimental Medicine and Biotechnology, Postgraduate Institute of Medical Education and Research (PGIMER), India; 4. Apollo Multispecialty Hospitals, India

Worldwide prevalence and mortality of lung cancer are gradually increasing. Tobacco smoking is the major cause of lung carcinogenesis. Smoking causes a remarkable reduction in vitamin D concentration. Moreover, vitamin D deficiency is associated with lung carcinogenesis. In this context, vitamin D is effective in reducing lung cancer mortality. However, the underlying molecular mechanisms are poorly understood. A comprehensive literature survey has been conducted to search for studies associated with lung cancer, tobacco smoking, vitamin D, and molecular mechanisms. PubMed, Google Scholar, Web of Science, Embase, and Scopus were used to search for articles up to November 2024. Peer-reviewed full articles written only in the English language were taken into consideration. Vitamin D deficiency in smokers is due to VDR gene polymorphism. Smoking increases Ca^{2+} influx in vascular smooth muscle cells, which is correlated with lung carcinogenesis. However, vitamin D reduces Ca^{2+} via decreasing HRC. Smoking enhances genetic/epigenetic alterations, gene mutations, SNPs, inflammation, oxidative stress, and activation of signaling pathways related to lung cancer. Vitamin D reduces gene expressions of HIF-1 α , Ki-67, HTERT, NF1, CYP1A1, EPHX1, and VEGF. Additionally, it increases the survival of lung cancer patients with p53, KRAS, and EGFR mutations. Besides, vitamin D reduces inflammation and increases B and NK-cell counts. It decreases ROS and reactive oxygen. Lung cancer-associated signal transduction of TGF- β , Wnt, Hedgehog, Notch, PI3K/AKT/mTOR, MAPK, ERK1, ERK2, and NF- κ B are also reduced. The present study highlights the therapeutic role of vitamin D to control and prevent the smoking-induced progression of lung cancer.

Corresponding author: Subendu Sarkar, drsubendus@gmail.com

Introduction

As per the World Health Organization, lung cancer is the leading cause of cancer-related death worldwide. Lung cancer is the second most common cancer globally. According to the last update, around 1.8 million deaths have been recorded in the year 2020 ^[1]. According to the Global Cancer Statistics (GLOBOCAN 2020), the lung cancer incidence rate in men is high (37.5 in 100,000) in higher HDI (Human Development Index) countries such as North America, North and West Europe, New Zealand, and Australia, and less (10.3 in 100,000) in lower HDI countries of Africa and South-Central Asia ^[2]. However, the cases of lung cancer are on a steep rise in many countries. Around 14% of lung cancer deaths can be correlated with air pollution with PM_{2.5} (particulate matter). However, most cases of lung cancer deaths (two-thirds) in the worldwide population are due to tobacco smoking.

Two major types of lung cancer are found: non-small cell lung cancer (NSCLC) (85%) and small cell lung cancer (10–15%). NSCLC can be further classified into large cell carcinoma, adenocarcinoma, and squamous cell carcinoma ^[3]. Whereas small cell lung cancer can be sub-divided into lung carcinoid tumor and other lung cancers ^[4]. Lung cancer, or bronchogenic carcinoma, can be characterized by tumor development in lung parenchyma or bronchi. As mentioned earlier, tobacco smoking is the leading cause of lung cancer mortality. Smoking develops dysplasia in the lung epithelium ^[5]. Tobacco smoking activates the PI3K/Akt/mTOR signaling pathway, which in turn initiates tumorigenesis ^[6]. Tobacco smoking contains multiple carcinogenic compounds such as nitrosamines, polycyclic aromatic hydrocarbons, and aldehydes, which may lead to certain mutations in genes such as KRAS, TP53, EGFR, BRAF, MEK, MET, PIK3CA, etc. ^[7]. Besides, the addictive tobacco compound nicotine induces the progression of the cell cycle, epithelial-to-mesenchymal transition, migration, invasion, angiogenesis, and evasion of apoptosis ^[8]. Mutations, including genetic/epigenetic modifications (promoter methylation), transcriptomic changes including inflammation and apoptosis pathways, lead to premalignant alterations such as dysplasia and clonal patches ^[9].

It is extensively studied that vitamin D is less in tobacco smokers ^[10]. Smoking significantly affects vitamin D and calcium metabolism and reduces the serum 25OHD below the normal value and parathyroid hormone ^[11]. As per previous studies, the serum/plasma vitamin D level of <20 ng/ml is considered vitamin D deficiency ^{[12][13]}. However, the exact molecular mechanism behind the reduction of vitamin D in smokers is poorly understood. It is already mentioned that two-thirds of lung cancer deaths are associated with smoking. Besides, lung cancer patients carry remarkably low levels of vitamin

D in their blood ^[14]. Hence, inadequate vitamin D levels may be potentially associated with lung cancer pathophysiology.

Hence, the present study focuses on the molecular targets and pathways related to smoking-induced lung carcinogenesis and vitamin D deficiency in lung cancer. Additionally, molecular targets and biochemical pathways are also explored to understand the therapeutic efficacy of vitamin D in lung cancer.

Data curation

A comprehensive literature survey has been conducted to search for studies associated with lung cancer, tobacco smoking, vitamin D, and molecular mechanisms. PubMed, Google Scholar, Web of Science, Embase, and Scopus were used to search for articles up to November 2024. Peer-reviewed full articles written only in the English language are taken into consideration.

Vitamin D and tobacco smoking

Vitamin D is a potent micronutrient required for various biological functions in the body. Its low level is widely associated with numerous disease pathogenesis and improper molecular functions ^[15]. Vitamin D is synthesized by the epidermis using direct exposure to sunlight on the skin. It is of two types- Vitamin D₂ or ergocalciferol and vitamin D₃ or cholecalciferol. Vitamin D₂ and D₃, after several hydroxylation processes, form intermediates 25-hydroxyvitamin D or 25(OH) D in the liver and 1,25-dihydroxyvitamin D or calcitriol in the kidney (Fig. 1). Serum 25(OH) D is an active hormone and a good parameter for measuring vitamin D in serum.

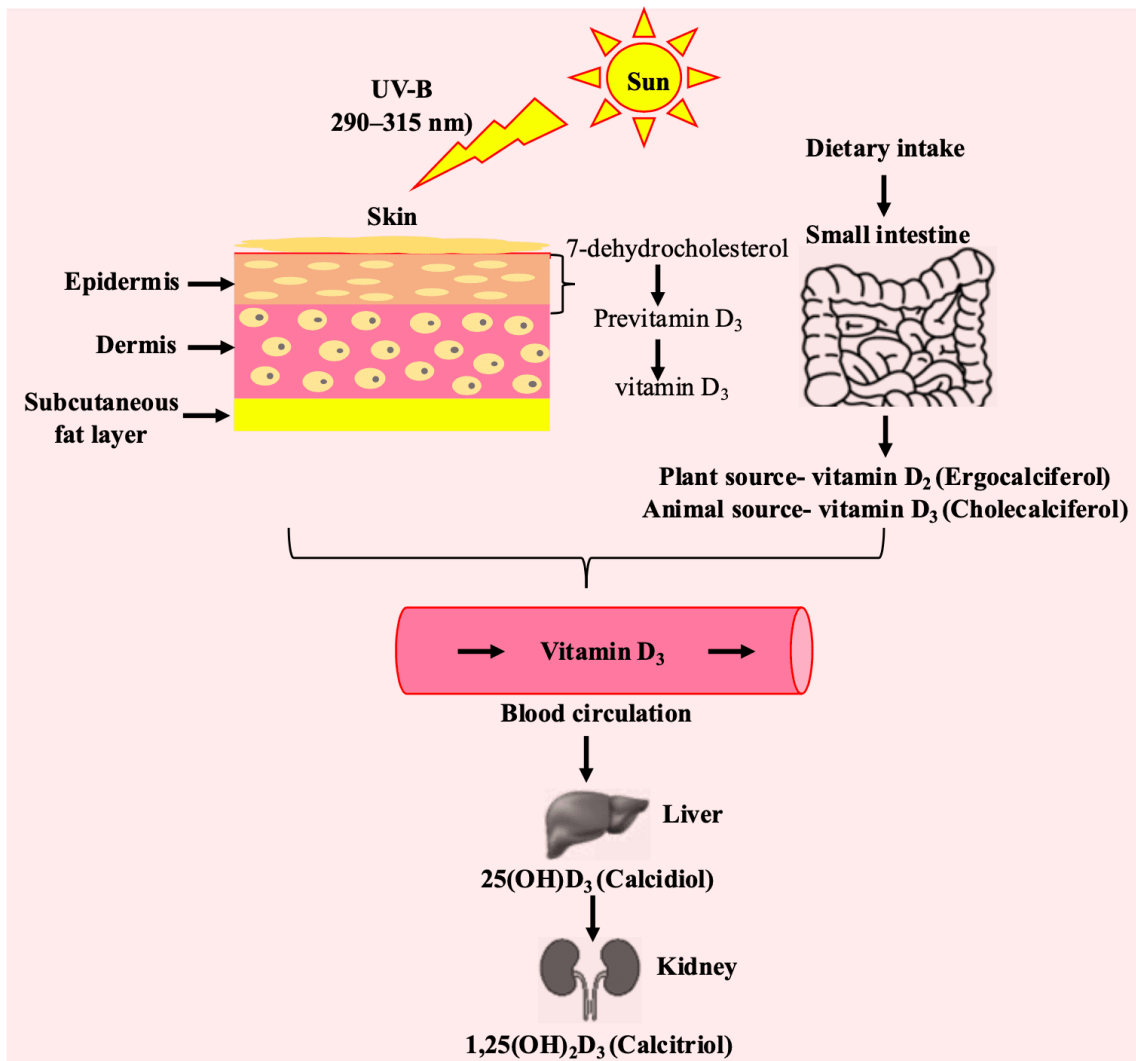


Figure 1. Vitamin D₃ synthesis in the skin using sunlight and vitamin D₂ and D₃ synthesis in the small intestine using dietary intake. Vitamin D₃, after successive hydroxylation, produces 25(OH) D₃ (Calcidiol) in the liver and 1,25(OH)₂D₃ (Calcitriol) in the kidney.

A study conducted on the US population over the period from 2001 to 2014 revealed that both active and passive tobacco smoking are associated with 25(OH) D deficiency [16]. It is reported that the serum concentration of vitamin D in active smokers (54.7 nmol/L) is compared to that in non-smokers (58.3 nmol/L) [17]. An effect of smoking on VDR gene polymorphism is already reported [18]. A previous study on cigarette smoke exposure in a male Wistar rat model has reported lung injury with a reduction of the vitamin D receptor (VDR). Depletion of VDR is associated with activation of the mitogen-activated protein kinase (MAPK) [19]. Activation of the MAPK signaling pathway is observed in lung cancer, especially in

NSCLC [20][21]. VDR has an important role in calcium and inorganic phosphate (Pi) homeostasis [22]. Cigarette smoking significantly increases calcium and Pi [23][24] (Fig. 2). It is reported that nicotine binds to $\alpha 3$ and $\alpha 7$ nAChR (nicotinic acetylcholine receptor) present on vascular smooth muscle cells and promotes intracellular Ca_2^+ influx [25]. It is in this context that increased levels of calcium and Pi are associated with lung cancer [23][26][27]. However, vitamin D supplementation is quite useful in reducing increased calcium and Pi levels. A study on a mice model has revealed that vitamin D maintains calcium homeostasis by downregulating the histidine-rich calcium-binding (HRC) protein and inhibits tumor growth, proliferation, and migration [28]. On the other hand, it is reported that 30% of the Pi absorption in the human intestine is vitamin D-dependent [29]. It is reported that parathyroid hormone (PTH) induces lung cancer in patients having hypercalcemia [30]. However, vitamin D supplementation is effective in reducing serum PTH levels [31]. In addition to the VDR gene polymorphism, various toxic compounds of cigarette smoke may have a potential effect on vitamin D metabolism [32]. Increased levels of carcinogenic polycyclic aromatic hydrocarbons are correlated with decreased levels of vitamin D [33]. Another study shows that a high level of benzene is associated with a low level of vitamin D [34].

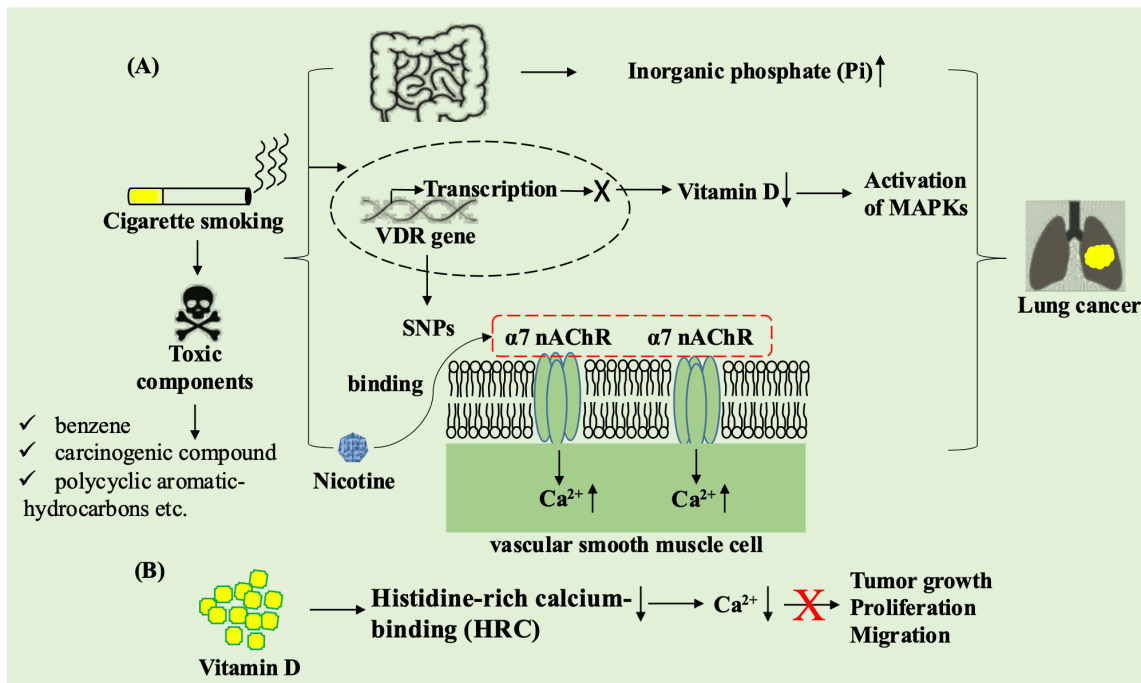


Figure 2. (A) Reduction of vitamin D concentration due to toxic and carcinogenic components of cigarette smoking. Smoking promotes elevation of Ca^{2+} influx in smooth muscle cells, which is associated with lung cancer pathogenesis (B) Supplementation of vitamin D leads to the decrease of Ca^{2+} influx, which may be beneficial to control tumor growth, proliferation, and migration.

Molecular aspects of smoking and lung cancer

It is reported that around 15% of smokers develop lung carcinoma [35]. Whereas, 80% – 90% of cases of lung cancers are caused by smoking [36]. The molecular mechanisms of smoking-induced lung cancer are complex to establish and poorly explored. However, frequent gene mutations, polymorphisms, gene overexpression, inflammation, etc. may explain the disease pathogenesis as described here (Fig. 3).

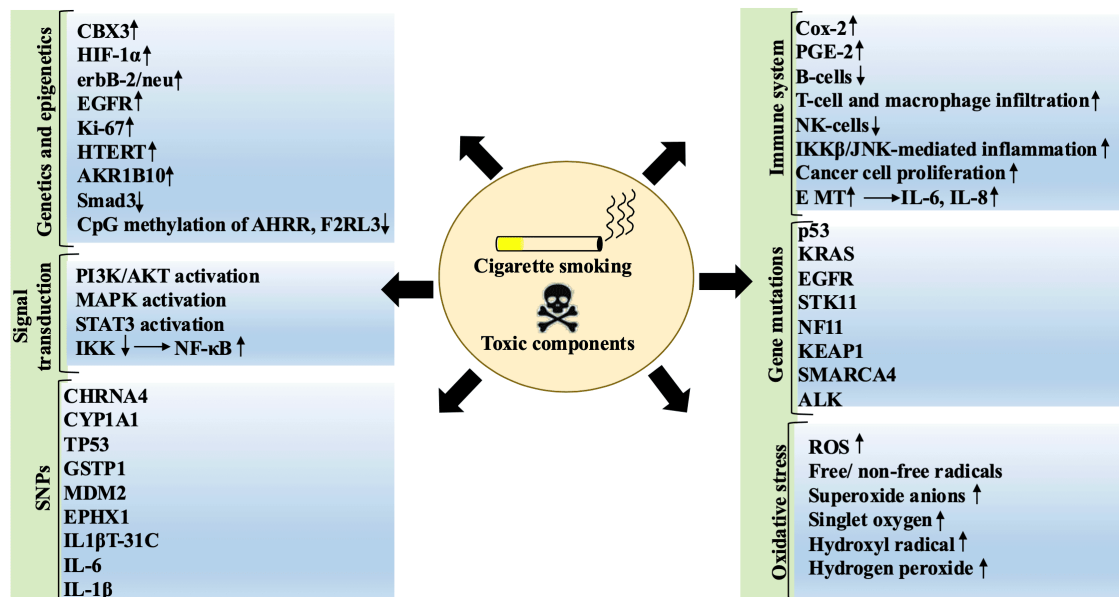


Figure 3. Toxic components of cigarette smoking effects on various biological events such as genetic/epigenetic alterations, gene mutations, SNPs, the immune system, oxidative stress, and signaling pathways related to lung cancer. Symbols “↓” and “↑” represent “low” and “high,” respectively.

It is demonstrated that smoking causes overexpression of the oncogene chromobox homolog 3 (CBX3), which promotes lung cancer progression [37]. A study conducted on NSCLC patients shows that lifetime cigarette smoking is closely associated with p53 tumor suppressor mutation. This study has reported that 47% of the tumor samples represent G:C→T:A transversion [38]. In addition to p53 mutation, cigarette smoking is also associated with K-ras mutation and overexpression of the erbB-2/neu oncogene in lung adenocarcinoma [39]. It is demonstrated that smokers having lung adenocarcinoma exhibit higher expressions of *EGFR*, *Ki-67*, and *HTERT* compared to nonsmokers [40]. Besides, it is reported for lung cancer patients that AKR1B10 (Aldo-Keto Reductase Family 1, Member B10) is overexpressed in smokers than in nonsmokers [41]. AKR1B10 is reported to promote cancer cell survival and the initiation of lung carcinoma [42]. Similarly, overexpression of the epidermal growth factor receptor (EGFR) is associated with NSCLC (40%–80%) [43]. Besides, EGFR mutation is a good biomarker and a potential target in lung cancer [43]. It is reported that EGFR expression is high in current smokers [44]. However, smoking is less associated with EGFR mutation rates and decreased overall survival of NSCLC patients [45]. Current smoking is closely associated with a reduction in the methylation of CpG islands compared to former and never smokers [46]. It is in this context that CpG island promoter methylation is pivotal to regulate gene

expression. Smoking-induced methylation of several genes is already reported [46]. Especially, hypomethylation of CpG sites of *AHRR* and *F2RL3* is associated with lung cancer risk [47]. DNA methylation is catalyzed by DNA methyltransferases (DNMTs). It is shown that DNMT1 gene expression is significantly higher in smokers than in nonsmokers, which depicts the low expression of target genes [48]. An in vitro study using the lung adenocarcinoma cell line A549 shows that cigarette smoking decreases transforming growth factor beta (TGF- β)-mediated suppression of tumors via lowering the expression of SmaD3 (SMAD Family Member 3) [49].

In addition to the epigenetic regulations, tobacco smoking results in 1,000 to 10,000 mutations in a somatic cell [50]. In smokers, 25% of the cells get driver mutations. It is reported for NSCLC that former as well as current smokers show mutations in *KRAS*, *STK11*, *NF1*, *KEAP1*, and *SMARCA4* [51]. Studies conducted on NSCLC patients reveal that 35% of smokers show *EGFR* mutations [52]. Similarly, transversion mutations (G \rightarrow T or G \rightarrow C) can be found in *KRAS* in 25% of lung adenocarcinomas associated with cigarette smoking [53][54]. However, different studies have been conducted, which suggest that *EGFR* and *KRAS* mutations are frequent in smokers having lung cancer [55][56]. It is reported that smokers with advanced lung adenocarcinoma show mutations in the anaplastic lymphoma receptor tyrosine kinase (ALK) gene. Studies conducted on 9,575 patients have shown ALK mutations in 6.8%, out of which 70.9% of lung adenocarcinoma patients are smokers [57].

Similar to gene expressions and mutations, smoking significantly causes gene polymorphisms in lung cancer. Single nucleotide polymorphisms in smokers having lung cancer are documented for nicotinic acetylcholine receptor alpha 4 subunits (CHRNA4) (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6636285/>), cytochrome P450 family 1 subfamily A member 1 (CYP1A1) [58], cytochrome P450 2A6 (CYP2A6) [59], tumor suppressor *TP53* (p53) [60], glutathione S-transferase P1 (GSTP1) [61], murine double minute-2 (MDM2) [62], and epoxide hydrolase 1 (EPHX1) [63].

Smoking-induced SNPs are also documented in inflammatory genes interleukin-1 β T-31C [64], IL-6 [65], IL-1 β [66]. However, IL-6 and IL-1 β polymorphisms are important in the development of lung cancer [67][68]. In addition to the gene expressions, mutations, and SNPs, smoking-induced inflammation causes a tremendous effect to exacerbate lung cancer pathogenesis [69]. In this context, pulmonary disorders such as chronic obstructive pulmonary disease (COPD) can be correlated with an abnormal inflammatory response [70]. Cigarette smoking promotes the overexpression of cyclooxygenase-2 (COX-2) and

prostaglandin (PGE₂) E2 [71]. Elevation of COX-2 and PGE₂ plays an important role in promoting the inflammation-induced development of lung cancer [72]. It is important to mention that smoking reduces B-cell frequency. Depletion of B-cells results in the repression of T-cell and macrophage infiltration towards lung tumors [73]. Besides, smoking impacts the tumor immune environment to induce a subset of Treg cells for immunosuppression in lung cancer [74]. However, the elevation of Treg cells and the reduction of NK-cells in smokers having a high risk of lung cancer are also reported [75]. In vivo studies show that smoking induces lung tumorigenesis through developing IKK β and JNK1-mediated inflammatory responses [76]. Smoking promotes cancer stem cell proliferation, which in turn induces epithelial-mesenchymal transition (EMT) and increases the production of inflammatory cytokines such as IL-6, IL-8 [77].

Hypoxia and angiogenesis are two major factors in lung cancer carcinogenesis. Hypoxia leads to the activation of transcription factors and promotes the high expression of proinflammatory genes, which causes profound inflammation [78]. It is demonstrated that nicotine results in the overexpression of Hypoxia-inducible factor-1 α (HIF-1 α) and vascular endothelial growth factor (VEGF) in NSCLC [79]. HIF-1 α is responsible for antiapoptosis and cancer cell proliferation [80]. Whereas the increased expression of VEGF causes angiogenesis, tumorigenesis, and metastasis [81]. Besides, signal transducer and activator of transcription 3 (STAT3) is shown to be overactivated in tobacco-induced lung tumors with reduced immunosuppression [82]. In vitro studies show that myeloid cell leukemia-1 (Mcl-1) through STAT3 is overexpressed due to nicotine exposure. It suggests that the downregulation of Mcl-1 and inhibition of the STAT3 pathway may be potential targets in lung cancer [83]. Nicotine has been shown to activate phosphoinositide 3-kinases/ protein kinase B (PI3K/AKT), mitogen-activated protein kinases (MAPK), and c-src survival pathways in lung cancer progression [84]. Additionally, PI3K/AKT is also activated by nicotine via α 7-nAChR [85]. In vitro studies show that cigarette smoke condensate phosphorylates and degrades I κ B α kinase (IKK), which in turn activates nuclear factor- κ B (NF- κ B) and enhances lung carcinogenesis [86].

Oxidative damage due to smoking plays an important role in lung cancer pathogenesis. Reactive oxygen species (ROS) can be generated directly from smoke itself and indirectly from other carcinogens or their metabolites [87]. Free radicals and non-free radicals such as superoxide anions, singlet oxygen, hydroxyl radical, and hydrogen peroxide cause significant damage to tissue by the oxidation of nucleic acids, lipids, and proteins. However, the quinone/hydroquinone complex of the tar phase of cigarette smoke induces

ROS generation. Oxidative damage to DNA/RNA results in the breaking of nucleic acid strands followed by improper gap filling, which can lead to gene mutation and lung cancer [88][89]. Oxidative stress can further activate the transcription factor NF- κ B to initiate the inflammatory cascade to trigger lung cancer [90].

Vitamin D in lung cancer

Supplementation of vitamin D is reported to ameliorate lung carcinogenesis in different ways (Fig. 4). It is reported that vitamin D deficiency (<20 ng/mL, 75.9%) is associated with the advanced stage of NSCLC, where smokers (61.1%) show vitamin D concentrations <10 ng/mL [91]. Another study has shown that 46% of the stage-IV lung cancer patients, including NSCLC, have vitamin D deficiency compared to normal [92]. However, supplementation of vitamin D with 30,000 IU/day for 14 days is effective in achieving the target of 25(OH) D level in lung cancer patients (44%) having vitamin D deficiency [93]. A systematic review and meta-analysis including 12 randomized clinical trials with 72,669 participants has revealed the association of vitamin D intake with a reduction in lung cancer mortality [94]. In addition to nicotine, a potential carcinogen nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) promotes the nicotinic acetylcholine receptor (nAChR)/ proto-oncogene tyrosine-protein kinase (Src)/STAT3-mediated lung tumorigenesis and activates the renin-angiotensin system and insulin-like growth factor-1 receptor (IGF-1R) signaling [95].

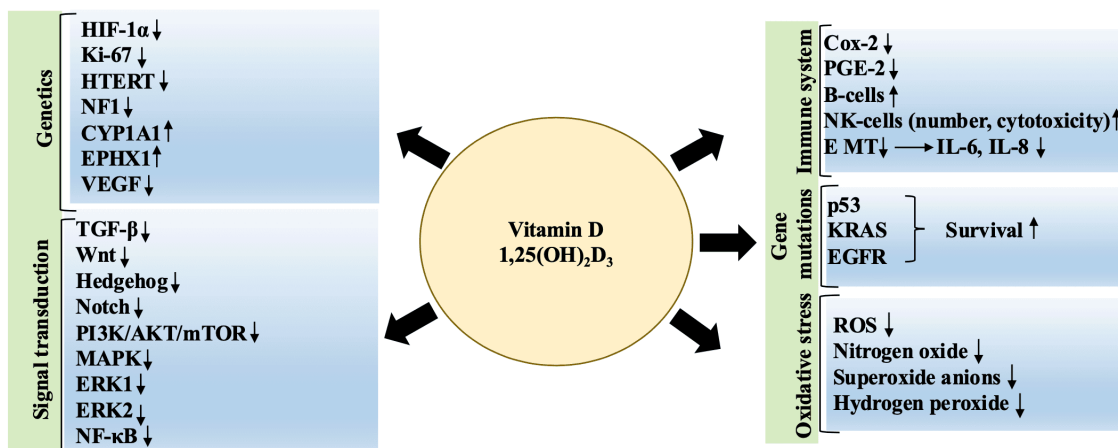


Figure 4. Effect of vitamin D on various biological events such as genetic/epigenetic alterations, survival of gene mutations, immune system, oxidative stress, and signaling pathways related to lung cancer. Symbols “↓” and “↑” represent “low” and “high,” respectively.

It is reported that VDR knockout mice exhibit decreased metastatic growth of lung cancer cells [96]. VDR knockout mice show increased $1\alpha,25(\text{OH})_2\text{D}_3$ levels in serum due to the absence of vitamin D-dependent calcium activity. In this study, wild-type VDR^{+/+} and knockout VDR^{-/-} mice have been injected with cloned metastatic variant LLC cells tagged with GFP. It has been observed after day 18 that VDR^{+/+} mice develop more metastatic nodules and tumors compared to VDR^{-/-} mice. Another study shows that vitamin D downregulates HRC protein and inhibits tumor growth, proliferation, and migration in lung cancer [97]. In this study, H460 lung cancer cells with or without supplementation of calcitriol (2×10^{-8} M) are studied for HRC expression and other cancerous properties. It is noticed that HRC expression, as well as cell migration and proliferation, are inhibited and apoptosis is initiated.

Molecular targets of vitamin D in lung cancer in relation to smoking

As mentioned earlier, mutations in the oncogenic suppressor p53 play a major role in lung cancer progression. However, a study has reported that vitamin D at the dose of 2000 IU/d can reduce the risk of death in p53 immunoreactive patients by increasing the survival rate up to 80.9% in gastrointestinal cancer [98]. Kras mutations are associated with smokers in NSCLC [99]. KRAS itself, or through the RAS/RAF/MEK/ERK canonical pathway, functions in cytoskeleton organization, cell survival, proliferation, and vesicle trafficking [100]. It is reported that Kras mutations are significantly correlated with VDR overexpression [101]. Mutations in EGFR are also reported in smokers (23.4%), however, they are more common in never-smokers (60.3%) [52]. It has been shown that activation of EGFR-tyrosine kinases (TK) plays an important role in lung cancer progression [102]. However, EGFR mutations, such as T790M mutations in EGFR, can resist drugs such as EGFR-TK inhibitors (gefitinib and erlotinib). Reduced levels of vitamin D are associated with EGFR mutations, as reported in pulmonary adenocarcinoma [103]. In this context, vitamin D may be useful for the progression-free survival of lung adenocarcinoma patients having EGFR mutations [104]. Similar to EGFR, Ki-67 is also associated with vitamin D levels. Ki-67 is a prognostic marker, and its staining is useful to measure the tumor proliferative fraction [105]. It is reported that $1,25$ dihydroxyvitamin D concentration in serum is inversely associated with Ki-67 [106]. In this context, vitamin D₃ supplementation in a dose-dependent manner is useful to reduce Ki-67 levels [107]. Additionally, hTERT has been shown to enhance epithelial-mesenchymal transition in lung cancer cells by increasing cMET (receptor tyrosine kinase) [108]. It has been shown that $1,25(\text{OH})_2\text{D}_3$ downregulates hTERT mRNA expression and suppresses cancer growth in ovarian cancer cells [109].

However, the function of vitamin D to suppress lung cancer is yet to be explored. Additionally, hypomethylation of smoking-related genes is already mentioned earlier, which is linked to lung cancer. In this context, a higher concentration of serum 25(OH) D is linked to increased methylation, as reported in breast cancer ^[110]. However, the effect of vitamin D in the regulation of smoking-induced epigenetic modification in lung cancer is yet to be unfurled. Neurofibromatosis 1 (NF1) is a tumor suppressor and is shown to downregulate RAS activity. NF1 mutations are common in lung cancer ^[111]. However, the serum concentration of vitamin D is inversely associated with NF1 ^[112]. It further states the therapeutic efficacy of vitamin D to suppress tumor development in patients with NF1. As mentioned earlier, SNPs in CYP1A1 are reported in smokers having lung cancer ^[113]. In this context, vitamin D-induced expression of CYP1A1 has been reported using *in vitro* studies ^[60]. Besides, mutations and SNPs in epoxide hydrolase 1 (EPHX1) are linked to lung cancer and various diseases ^{[114][115]}. EPHX1 is an enzyme involved in the hydrolysis of epoxides from aromatic hydrocarbons and amines released by cigarette smoke ^[116]. This process leads to the production of carcinogens and enhances the pathogenesis of lung cancer. *In vivo* studies show that 1,25(OH)₂D₃ results in the overexpression of EPHX1 in vitamin D-deficient rats ^[117]. However, this mechanism is not explored in lung cancer. As mentioned earlier, IL-6 and IL-1B polymorphisms are associated with lung cancer pathogenesis ^[118].

Apart from these, vitamin D is known to regulate the immune system. Vitamin D has been shown to downregulate the proinflammatory cytokines IL-6 and IL-8 ^{[119][120]}. Additionally, cyclooxygenase-2 (COX-2) overexpression is associated with cigarette smoking-induced NSCLC ^[121]. However, vitamin D is shown to be effective in reducing COX-2 and prostaglandins (PGs) in a dose-dependent manner ^[122]. Vitamin D is also reported to inhibit PGE2 ^[123]. Moreover, 1,25(OH)₂D₃ has been shown to be involved in activated B-cell proliferation and the improvement of regulatory B-cell function ^{[124][125]}. It is reported that NK cells exhibit the first line of defense against lung tumors. They generally activate both innate and adaptive immune responses. Therefore, NK cells are used as immunotherapy to treat tumors. In this context, 1,25(OH)₂D₃ directly affects the function and cytotoxicity of NK cells, which is supported by *in vivo* studies ^{[126][127]}. Additionally, vitamin D targets cancer stem cell-associated signal transduction pathways such as TGF-β, Wnt, Hedgehog, Notch, and prevents cancer stem cell proliferation ^[128]. As mentioned earlier, EMT is associated with lung cancer progression. Hence, targeting EMT may be a potential therapeutic strategy in lung cancer ^[129]. It is shown that vitamin D 1,25(OH)₂D₃ prevents EMT by inhibiting proliferation ^[130].

It is already mentioned earlier that overexpression of HIF-1 α and VEGF is associated with lung cancer pathogenesis. Besides, vitamin D level is negatively correlated with serum HIF-1 α level in diabetic nephropathy [131]. However, this correlation is not unfurled in the case of lung cancer. It is reported that vitamin D has the potential to reduce VEGF gene expression as well as the serum level of VEGF [132][133]. It is reported that vitamin D inactivates the PI3K/AKT/mTOR signaling pathway and inhibits the progression of NSCLC through suppressing the Warburg effect and stemness of NSCLC cells [134]. It has been shown that vitamin D is capable of suppressing MAPK signaling in colon cancer [135]. However, vitamin D targeting potential signaling pathways related to lung cancer needs to be studied in more detail. As mentioned previously, NF- κ B aggravates lung cancer by promoting lung tumorigenesis and metastasis [136]. Additionally, JAK-STAT signaling also contributes to lung adenocarcinoma, which may be correlated with cigarette smoking [137]. It is reported that inhibition of JAK1/2 may be a therapeutic strategy in K-RAS-mediated lung adenocarcinoma [138]. In this context, an *in vivo* study with *Drosophila melanogaster* reveals significant downregulation of genes associated with NF- κ B and JAK/STAT signaling pathways [139]. Cigarette smoking, especially nicotine, significantly contributes to activating extracellular signal-regulated kinase 1/2 (ERK1/2) through phosphorylation, which can be correlated with lung cancer [140][141]. It is reported that administration of vitamin D can result in the downregulation of the ERK1/2 activation pathway and attenuates chemokine secretion in myocardial injury [142]. However, the correlation between vitamin D and ERK needs to be studied in lung cancer patients.

Vitamin D supplementation is reported to downregulate reactive oxygen species (ROS) [143][144]. Vitamin D plays a central role in modulating mitochondrial oxidative metabolism by lowering fusion/fission and oxidative phosphorylation [145]. Vitamin D upregulates glutathione, which converts hydrogen peroxide (H₂O₂) to water. Additionally, vitamin D activates glucose-6-phosphate dehydrogenase and downregulates nitrogen oxide and converts O²⁻ to H₂O₂ [146]. However, vitamin D increases superoxide dismutase in muscle, which suggests vitamin D as a potential antioxidant [144][147].

Conclusion

The number of lung cancer cases and deaths is increasing. Clinicians are concerned about proper and targeted therapeutics. Tobacco smoking is the leading cause of lung cancer-related mortality. In this context, smoking causes a significant reduction in vitamin D concentration in both active and passive smokers. It is also studied that vitamin D deficiency is associated with lung carcinogenesis in smokers.

Besides, vitamin D supplementation has been shown to be effective in the reduction of lung cancer mortality. However, the underlying molecular mechanisms are poorly understood. The present study has shown the plausible molecular targets and biochemical interactions through which vitamin D can act as a supplementation therapy to control and prevent lung cancer pathogenesis.

Extensive literature study and data compilation have revealed that smoking remarkably decreases the vitamin D level in lung cancer patients. The reasons for reducing vitamin D in lung cancer are VDR gene polymorphism and VDR depletion due to the toxic and carcinogenic components of cigarette smoking, such as nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. Smoking also heightens Ca^{2+} influx in vascular smooth muscle cells, which further aggravates lung cancer pathogenesis. In this context, vitamin D may lower the Ca^{2+} influx through decreasing HRC, which in turn inhibits cancer cell proliferation and migration. Smoking significantly overexpresses genes related to lung cancer pathogenesis. It also results in epigenetic alterations such as hypomethylation and genetic alterations such as gene mutations and polymorphisms. Smoking potentially increases inflammation and reduces vital immune cells such as B-cells and NK-cells. Smoking predominantly increases ROS and activates various signaling pathways related to lung cancer progression. However, existing literature shows the importance of vitamin D in targeting smoking-induced biochemical alterations as mentioned. Vitamin D potentially targets and reduces the gene expressions of HIF-1 α , Ki-67, HTERT, NF1, CYP1A1, EPHX1, and VEGF, which are significantly associated with lung cancer pathogenesis. Additionally, vitamin D increases the survival of lung cancer patients having p53, KRAS, and EGFR gene mutations. Supplementation of vitamin D may reduce lung cancer-related inflammation and increase B and NK-cell counts. Vitamin D has been shown to reduce ROS and reactive oxygen species to control oxidative damage to nucleic acids. Nevertheless, vitamin D targets various signaling pathways such as TGF- β , Wnt, Hedgehog, Notch, PI3K/AKT/mTOR, MAPK, ERK1, ERK2, and NF- κ B, which may control lung cancer progression. Supplementation of vitamin D may be useful as a potential therapeutic to control and prevent the smoking-induced progression of lung cancer. However, extensive research in the concerned field is required for an in-depth understanding of the underlying molecular mechanisms.

Statements and Declarations

Authors' contributions

SS was involved in the literature search, study design, data compilation, conceptualization, interpretation, original draft writing, formatting, editing, and review. MKS performed original draft editing and review. RPS performed the original draft editing and review. GB performed the original draft editing and review.

Conflicts of interest

No potential conflict of interest was reported by the authors.

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Data Availability

No new data were generated in this study. Data sharing is not applicable to this article.

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