The Role of Vitamin D Intake on the Prognosis and Incidence of Lung Cancer: A Systematic Review and Meta-Analysis

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Summary The correlation between vitamin D intake and lung cancer development is controversial. This meta-analysis aims to evaluate the relationship between vitamin D and the prognosis and incidence of lung cancer. A comprehensive database search on PubMed, Web of Science, EBSCO, and Cochrane Library was carried out from the beginning to November 2020. Long-term survival and the incidence rate of patients with lung cancer were the primary outcomes of the study. Ten eligible studies were selected for the meta-analysis following specific inclusion and exclusion criteria. Four included studies, covering 5,007 patients, compared the overall survival (OS) and relapse-free survival (RFS) of lung cancer patients among total vitamin D users with non-users. Significantly, the estimated pooled hazard ratio (HR) revealed that vitamin D could improve OS and RFS of lung cancer patients [HR = 0.83, 95% CI (0.72–0.95); HR = 0.79, 95% CI (0.61–0.97), respectively]. Vitamin D intake was inversely associated with lung cancer incidence in six studies [OR = 0.90, 95% CI (0.83–0.97)]. The present meta-analysis shows vitamin D not only improves the long-term survival of lung cancer patients but has a beneficial effect on the incidence of lung cancer. Notwithstanding, more studies are needed to confirm the study results.

Key Words vitamin D, lung cancer, risk, prognosis, meta-analysis

Lung cancer, with distinct subtypes, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (1), is a leading cause of cancer incidence and death (2). In 2018, GLOBOCAN estimated 2.09 million new cases (11.6% of total cancer cases) and 1.76 million deaths (18.4% of total cancer deaths), much higher than reported rates in 2012 (1.8 million new cases and 1.6 million deaths) (1). Hence, early prevention and diagnosis are incredibly vital to reduce the morbidity and mortality of the disease. Presently, the role of vitamin D has been recognized in several cancers (3, 4), including lung cancer (5).

Vitamin D is principally obtained from three pathways in humans (diet, supplements, and ultraviolet radiation from the sun synthesized on the skin). Additionally, vitamin D supplements usually contain a much higher dose of vitamin D compared to foods (6). Vitamin D is metabolized to 25-hydroxy vitamin D (25(OH)D) in the liver and further activated by 1-hydroxylase to 1,25-dihydroxvitamin D (1,25(OH)2D) in the kidneys. It also accelerates calcium absorption and is connected tightly with bone health (7). More specifically, the vitamin D receptor (VDR) is a steroid hormone nuclear receptor that regulates a variety of genes within a cell (8). Vitamin D is hypothesized to prevent cancer relapse by inhibiting cell proliferation, angiogenesis, and metastasis while inducing apoptosis and differentiation (9–13). Previous studies have reported that vitamin D intake is associated with a decreased risk of different cancers, including prostate (14) and breast (3) cancers, whereas there is no association between vitamin D and cancer types such as esophageal (15), pancreatic (16), skin (17), and gastric (18) cancers. Several observational studies (5, 19) have also investigated the correlation between vitamin D and lung cancer prognosis, but results are not conclusive. However, the effect of vitamin D intake on the incidence of lung cancer remains...
elusive. For instance, vitamin D was inversely associated with lung cancer incidence in the Carotene and Retinol Efficacy Trial (CARET) (20), but not in the Shanghai Women’s Health Study (SWHS) (21).

Therefore, to address these issues and guide physicians, we conducted a comprehensive meta-analysis using the available data to evaluate the relationship between vitamin D and the prognosis and incidence of lung cancer.

METHODS

Search strategy. This meta-analysis was conducted per the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement (22). Two investigators independently assessed the observational studies and the quality of the randomized controlled trials (RCTs) via the Newcastle-Ottawa Quality Assessment Scale (NOS) checklist and the Cochrane Collaborations tool, respectively. In the meta-analysis, systematic retrieval of databases (PubMed, Web of Science, EBSCO, and Cochrane Library) was conducted from the beginning to November 2020. The subject search was bonded with free text terms and medical subject headings, including ((‘lung’ OR ‘pulmonary’) AND (‘cancer’ OR ‘carcinoma’ OR ‘adenocarcinoma’ OR ‘squamous carcinoma’ OR ‘neoplasms’)) OR (‘non-small cell lung cancer’ OR ‘small cell lung cancer’ OR ‘NSCLC’ OR ‘SCLC’) AND (‘vitamin D’ OR ‘dietary vitamin D intake’ OR ‘vitamin D supplementation’). Also, literature references were manually retrieved to avoid omitting relevant studies.

Selection criteria. Each study retrieved for inclusion was independently assessed by two authors. The inclusion criteria included: (1) studies conducted on human populations, (2) studies including RCTs, cohort, or case-control studies, and (3) reports on the correlation between vitamin D and the prognosis and incidence of lung cancer. Exclusion criteria included: (1) non-original articles, (2) articles with insufficient detailed data and irrelevant outcomes, (3) non-cancer diseases such as lung nodule, and (4) overlapping publications. Significantly, only the most recent, relevant, and compre-
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A comprehensive study was included to avoid duplicates or studies reporting data from the same population in the analysis.

Data extraction and study quality assessment. Two authors independently completed data extraction and study quality assessment. Uncertainties encountered between the two authors were resolved by consensus or by a third author. Two databases were used to record available information of the literature: a database of the correlation between vitamin D and the prognosis of lung cancer and a database of the correlation between vitamin D and the incidence of lung cancer. These indicators included primarily author(s), year of publication, country, cohort characteristics, sample size, time to recruit, age, follow-up time, vitamin D dose, study design, and adjustment factors.

Statistical analysis. Hazard ratio (HR), including a 95% confidence interval (CI), was used to evaluate the relationship between vitamin D and lung cancer prognosis. Odds ratio (OR), including 95% CI was used to evaluate the correlation between vitamin D and lung cancer incidence. Statistical analyses were conducted via STATA 12.0 Software (Stata, College Station). Cochran’s Q statistic and I² statistics were applied to evaluate heterogeneity in the included studies. Considering that in the RCTs, they were assessed actual amount of vitamin D intake, whereas it is difficult to assess actual amount of vitamin D intake in observational studies because of an estimated value calculated by food frequency questionnaire (FFQ). Additionally, there are the diversities in study populations, lung cancer types, and dosage of vitamin D intake. Hence, we adopted random effects model in this meta-analysis in order to improve the reliability. Publication bias was evaluated by Begg’s and Egger’s test, and p < 0.05 was considered statistically significant. Publication bias and sensitivity analysis were not performed on analysis subgroup with less than ten studies because of the low sensitivity of qualitative and quantitative tests (23).

RESULTS

Eligible studies and characteristics

A total of 1,086 studies were screened after a database search. Additionally, four studies were identified via other sources. After deleting 329 duplicates, 761 records were browsed through reading article titles and abstracts. Also, 25 studies were evaluated via full-text articles. Finally, ten eligible articles were included in the quantitative synthesis (four studies (5, 19, 24, 25) included the correlation between vitamin D and lung cancer prognosis, while six studies (20, 21, 26–29) included the correlation between vitamin D and the incidence of lung cancer) (Fig. 1). The quality of ten studies was assessed, as shown in Table S1 (Supplemental Online Material).

The characteristics of four studies on the correlation between vitamin D and lung cancer prognosis conducted on lung cancer patients are shown in Table 1. Vitamin D intake was from dietary vitamin D and vitamin D supplementation. Adjustment factors were pri-
Table 2. Characteristics of all the studies included in the meta-analysis (the correlation between vitamin D and the incidence of lung cancer).

| Author        | Year | Country | Cohort characteristics                                      | Time to recruit | Length of follow-up (y) | Age, year median (range) | Follow-up number | Vit D type                | Total Vit D dose | Study          | Adjustment                        |
|---------------|------|---------|-------------------------------------------------------------|-----------------|-------------------------|--------------------------|------------------|--------------------------|-----------------|----------------|----------------------------------|
| Cheng 2013    | US   | Women’s Health Initiative                                 | 1993            | 17.8                    | 50–79                    | 128,779                  | Dietary Vit D     | >100                     | <100            | POBS           | age, region, race, education, hormone, calcium, BMI, smoking, walking, vitamin A, energy |
| Takata 2013   | China| The Shanghai Women’s Health Study                        | 1997            | 13                      | 40–70                    | 74,941                   | Dietary Vit D     | users                    | non-users       | POBS           | age, caloric, income, occupation, smoking, history of asthma, BMI |
| Redaniel 2014 | UK   | The UK Clinical Practice Research Datalink                | 2002            | 8                       | ≥ 55                     | 484                      | Supplementary Vit D| >2 prescriptions | 1–2 prescriptions | ROBS           | NA                                      |
| Cheng 2014    | NA   | The Carotene and Retinol Efficacy Trial                   | 1988            | 17.8                    | 50–69 (women) 45–69 (men)| 14,254                   | Dietary Vit D     | >200                     | <200            | ROBS           | age, study center, race, education, asbestos exposure worker, trade, smoking, BMI, energy, vitamin A |
| Lappe 2017    | US   | A double-blind, placebo-controlled, population-based randomized clinical trial | 2009            | 6                       | 65.2                     | 1,102 (vitamin D+Ca) 1,095 (placebo) | Supplementary Vit D | vitamin D+Ca | placebo | RCT | NA                                      |
| Lappe 2007    | US   | A double-blind, placebo-controlled, population-based randomized clinical trial | 2003            | 4                       | ≥ 55                     | 1,179                    | Supplementary Vit D | vitamin D+Ca | Ca | RCT | NA                                      |

NA, not available; RCT, randomized controlled trial; ROBS, retrospective observational study; POBS, prospective observational study; Vit D, vitamin D; BMI, body mass index.
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Marily gender, age, alcohol, body mass index, and smoking. Similarly, the characteristics of six studies investigating the correlation between vitamin D and the incidence of lung cancer based on human populations are indicated in Table 2. Total vitamin D intake was from dietary or supplement or both. Adjustment factors were primarily age, education, energy, body mass index, and smoking.

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Four studies, covering 5,007 people, were included in the analysis to compare the overall survival (OS) of lung cancer patients between vitamin D users and non-vitamin D users (high intake and low intake). The estimated pooled HR revealed that the use of vitamin D could improve the OS of lung cancer patients [HR = 0.83, (0.72–0.95)] (Fig. 2). Only two studies were utilized to compare the relapse-free survival (RFS) of lung cancer between vitamin D users and non-vitamin D users (high intake and low intake). According to the estimated pooled HR, vitamin D intake significantly improved the RFS of lung cancer patients [HR = 0.79, (0.61–0.97)] (Fig. 3).

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Six studies, covering 225,894 people, reported OR of lung cancer among vitamin D high intake compared with low intake. Additionally, there was no heterogene-
ity ($I^2=0\%$). Due to the variability of vitamin D type and dose, a random-effects model was applied to the meta-analysis. The estimated pooled OR of lung cancer for high intake versus low intake of total vitamin D was 0.90 (95% CI: 0.83–0.97), indicating an association between increased total vitamin D intake and a small reduction in the risk of lung cancer (Fig. 4).

Publication bias and sensitivity analysis

Considering that these studies selected were less than ten, Begg’s and Egger’s tests for publication bias and sensitivity analysis were not used for the meta-analysis due to the low efficiency of qualitative and quantitative tests.

**DISCUSSION**

In the study, we conducted a comprehensive meta-analysis on ten articles. Four articles evaluated the correlation between vitamin D and lung cancer prognosis, while six articles examined the correlation between vitamin D and lung cancer risk. Significantly, vitamin D intake was related to a decline in lung cancer risk and an improved long-term prognosis in lung cancer patients. The relatively few relevant studies that observed the relationship between vitamin D intake and lung cancer prognosis and lung cancer incidence limited our ability to conduct subgroup analyses.

Vitamin D intake is derived from diet, supplements, and ultraviolet radiation from the sun synthesized on the skin. 1,25(OH)$_2$D may exert its anticarcinogenic effects via stimulating the secretion of protein glues, such as E-cadherin and catenin, which make cells more adherent to each other (19). It reduces the possible mobilization of several malignant cells into the lymphatic or blood circulation, invariably delaying lung cancer progression. Besides, 1,25(OH)$_2$D inhibits the expression of cyclooxygenase-2 and prostaglandin synthesis, which can contribute to cancer cell growth and angiogenesis (30).

Vitamin D enhances the transcription of cathelicidin antimicrobial peptide genes, and the translation of CD14, a co-receptor for recognizing bacterial lipopolysaccharides. Both immensely improve the host body defense and are essential for congenital immunity (31). The anticarcinogenic role of 1,25(OH)$_2$D in regulating cell proliferation and angiogenesis are relevant to lung tumorigenesis. 1,25(OH)$_2$D inhibits lung cancer signaling pathways, including mutations in epidermal growth factor receptor, Wnt-$\beta$-catenin dysregulation, and vascular endothelial growth factor (9, 32).

Moreover, vitamin D promotes G1 cell-cycle arrest through signaling cyclin-dependent kinase inhibitors p21 and p27 (33). Both p21 and p27 proteins closely co-function with the ras oncogene family (34, 35), and K-ras often mutate in adenocarcinoma (36). Further, human lung tumor cell lines and animal experiments have demonstrated that the active metabolite of 25(OH)D–1,25(OH)$_2$D suppresses angiogenesis and cancer cell growth by inhibiting the response to vascular endothelial growth factor (37).

The meta-analysis indicated that vitamin D intake could improve the long-term survival of lung cancer patients. A previous meta-analysis reported no significant association between blood vitamin D levels and lung cancer survival (38). The study results above might be related to the vitamin D concentrations, which were too low (average value=17.7 ng/mL) to observe
any significant impact on the prognosis. Clinically, vitamin D levels below 20 ng/mL are considered deficient (39). Besides, the disease stage was likely too advanced among patients selected for vitamin D levels to influence prognosis.

It is worth noting that these studies focusing on serum levels of vitamin D on lung cancer progression might not be directly comparable to vitamin D intake. Vitamin D intake might not correlate with vitamin D levels, since sun exposure, dietary vitamin D, and supplementation source affect vitamin D serum levels. Nevertheless, vitamin D from sun exposure is limited in some countries situated above the latitude. Moreover, older patients have reduced dermal capacity to synthesize vitamin D and spend relatively large amounts of time indoors, while younger adults are more likely to use sun creams outdoors. In comparison, the present meta-analysis is the first to investigate the correlation between vitamin D and lung cancer prognosis.

Notably, two cohort studies (5, 19) reported that vitamin D intake could significantly improve lung cancer patients’ OS. However, the Women’s Health Initiative indicated that vitamin D has little effort on the OS of lung cancer patients (24). Indeed, there is evidence that estrogens might play a role in lung adenocarcinoma in women (40). Findings suggesting that estrogen receptors are present in lung tumors; however, playing a role in the activation of vitamin D and its receptor expression are provocative and warrant further exploration (41).

Simultaneously, two studies by Zhou et al. (19) and Akiba et al. (25) were conflicting because the former highlighted that vitamin D intake could significantly improve the RFS of lung cancer patients, whereas the latter did not corroborate the result. Collectively, the present meta-analysis concludes that increased vitamin D intake could improve the prognosis of lung cancer patients. Thus, further research and more evidence are needed to prove if vitamin D intake can influence lung cancer prognosis. A meta-analysis showed the inverse correlation between dietary vitamin D intake and lung cancer hazard, which was not investigated further if total vitamin D intake has a protective effect on lung cancer hazard (42). Although another meta-analysis, which included only three RCTs, suggested that vitamin D intake cannot play a significant role in lung cancer (43). In contrast, the present study showed that total vitamin D intake can protect against lung cancer occurrence. Therefore, it is pertinent to investigate further the correlation between total vitamin D intake and lung cancer risk.

Based on the strata of cohort studies, a study by Cheng et al. (20) compared high and low vitamin D intake found a negative association between vitamin D intake and lung cancer. However, it was discrepant with a report (28) by Redaniel et al. The contradicting results between Redaniel et al. (28) and other studies (20, 27) probably could be due to the different vitamin D intake sources, with the latter studies, including the dietary intake of vitamin D (20, 27).

Moreover, the present trial showed that the total vitamin D intake has no protective effect on lung cancer incidence, which was likely because the present trial did not separate calcium from vitamin D influence on lung cancer, as these agents were simultaneously used in the study (29). An RCT by Lappe et al. comparing Calcium (Ca) plus vitamin D supplementation and Ca supplementation suggested that vitamin D intake was associated with a decreased lung cancer risk. Herein, the present study result demonstrated that vitamin D intake protects against the risk of lung cancer (26).

Dietary supplements should be supplemented with foods containing vitamin D, such as deep-sea fish and animal liver. However, it is not enough for individuals vulnerable to vitamin D deficiency to only get vitamin D from their daily diet. Therefore, it is recommended to consider vitamin D nutritional supplementation. The Institute of Medicine (IOM) recommended 400 IU daily for children under one year of age, 600 IU daily for children one year and older and older adults between the ages of 70 y, and 800 IU daily for adults over 70 y of age, to achieve a blood level of at least 20 ng/mL. The Endocrine Society recommends a daily dose of 400–1,000 IU for children under one year of age, 600–1,000 IU for children one year and older, and a 1,500–2,000 IU daily dose for all adults to sustain a circulating serum level of 25(OH)D>30 ng/mL (39). Nonetheless, more studies are needed to confirm these suggestions to regulate the safety range better. Though the safe dose range of vitamin D is vast, intoxication, or other harmful events following vitamin D intake must be considered. Notably, the dose-response relation was not consistent. Thus, the optimal dose of vitamin D usage still needs to be evaluated further via large-scale studies. Therefore, to delay cancer progression and reduce lung cancer risk, individuals are advised to take vitamin D supplements in conjunction with a healthy lifestyle.

In addition to supplementation and diet, factors that affect vitamin D intake including race, sex, age. Different racial/ethnic groups have different dietary patterns. Previous studies showed that African Americans (AAs) prefer different foods than European Americans (EAs), and dairy consumption is lower in AAs than other ethnic groups (44). Notably, a study has explained the protective effect of milk may be attributed to its relatively high content of vitamin D and calcium to delay cancer progression (45). Along with low dietary supplement usage, parathyroid hormone (PTH) concentrations in serum are also different between AAs and EAs (44). These factors partly contributed to lower vitamin D intake in the participants of studies (46). In addition, there are differences in genetic variations that affect vitamin D metabolism and signaling in different ethnic groups (47, 48). Vitamin D metabolism is different in different age groups. Adults aged 75 y and over have lower 1,25(OH)2D levels compared with youngsters (49). The finding may, at least in part, be due to an age-dependent decline in kidney function. Experimental studies demonstrate that circulating 25(OH)D levels are reduced in case of high circulating 1,25(OH)2D levels.
(50). Therefore, it can be assumed that age-dependent differences in vitamin D physiology can in part explain the age-related effects of vitamin D supplements on circulating 25(OH)D (51). Above all, these factors that may potentially affect vitamin D intake, absorption and metabolism should be considered. However, the number of studies concerning about the link between vitamin D intake and incidence and prognosis of lung cancer was still limited, we could not conduct subgroup analyses to detect the role of these factors on vitamin D intake and absorption. And there is a need to consider further these factors that may have interaction effects with vitamin D intake in the observational studies. Therefore, there is a need to further investigate.

Study strengths: To our knowledge, the study herein is the first comprehensive meta-analysis investigating the role between vitamin D intake and the prognosis of lung cancer patients. Besides, the present meta-analysis contains relatively more comprehensive studies for investigating vitamin D’s effect on the hazard of lung cancer, thereby updating and extending previous results to provide more robust support.

Significantly, the meta-analysis herein has few inherent potential limitations that should be taken into account. Firstly, in the RCTs, they were assessed actual amount of vitamin D intake, while vitamin D intake is assessed by FFQ in observational studies. Additionally, there are the diversities in study populations, lung cancer types, and dosage of vitamin D intake, which may yield an inherent bias in the quantitative assessment. For some of the observational studies, the covariates and confounders may exert the influence on the results, which should be taken into consideration. Secondly, even though we attempted to carry out a literature search as comprehensively as possible, we could not acquire unpublished articles, and the language was merely confined to English. Finally, the studies included are limited. Hence, it is difficult to make further subgroup analysis on RCTs and observational studies. We could not carry out sensitivity analysis on possible publication bias, which might have influenced the study conclusions. Therefore, the present study results should be interpreted with caution.

CONCLUSION

The meta-analysis herein shows that vitamin D intake can improve the prognosis of lung cancer patients. Additionally, vitamin D intake is inversely linked with the incidence of lung cancer. Notwithstanding, the meta-analysis herein still requires well-designed large-scale observational studies and RCTs to confirm the study results. Meanwhile, there is a need to lengthen the duration of follow-up and evaluate the optimal dosing of vitamin D usage.

Authorship

Research conception and design: LLQ; collection of the data: JL, MXQ and SPQ; interpretation of the data: RRF and XJF; writing of the manuscript: LLY, JL and MXQ.

Disclosure of state of COI

No conflicts of interest to be declared.

Supporting information

Supplemental online material is available on J-STAGE.

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