

## Original Paper

# Vitamin D and Lung Cancer Risk: A Comprehensive Review and Meta-Analysis

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Vitamin D • Lung cancer • Risk

**Abstract**

**Background/Aim:** Vitamin D has been suggested to have important roles against cancer development. There were several published studies on the association between vitamin D and lung cancer risk, but not conclusive results were available. **Methods:** To clarify the role of vitamin D in lung carcinogenesis, we performed a comprehensive review of the literature and a meta-analysis to evaluate the association of serum vitamin D levels and dietary vitamin D intake with lung cancer risk. Twelve studies (9 prospective cohort and 3 nested case-control studies) with a total of 288,778 individuals were included. The summary relative risk (RR) with 95% confidence interval (CI) was used to assess lung cancer risk. **Results:** Meta-analysis of total 12 studies showed that RR for the association of high vitamin D status with lung cancer was 0.84 (95%CI 0.78-0.90,  $P < 0.001$ ). The RR of lung cancer for the highest versus lowest quintile of serum vitamin D levels was 0.83 (95%CI 0.77-0.90,  $P < 0.001$ ). The RR of lung cancer for the highest versus lowest quintile of vitamin D intake was 0.89 (95%CI 0.74-1.06,  $P = 0.184$ ). **Conclusion:** Current data suggest an inverse association between serum vitamin D and lung cancer risk. Further studies are needed to investigate the effect of vitamin D intake on lung cancer risk and to evaluate whether vitamin D supplementation can prevent lung cancer.

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**Introduction**

The role of vitamin D in the bone health has been well known [1]. Recent studies have shown that vitamin D is an important pro-hormone and has many biological roles in human body [2, 3]. Vitamin D insufficiency is a global health problem and is associated with a number of illnesses [4, 5]. Vitamin D also has been suggested to have important roles against cancer development, and it has anti-tumor effects [6, 7]. Previous epidemiological

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studies have suggested that vitamin D is associated with decreased risks of colorectal cancer, and breast cancer [4, 8]. Findings from *in vitro* studies showed that vitamin D could result in an additive decrease in cell proliferation and the induction of apoptosis in small cell lung carcinoma cell lines [7, 9]. Other studies found that vitamin D could inhibit the metastatic growth of lung cancer cells in animal models [6, 10]. Thus, findings from previous studies showed the possible preventive role of vitamin D against lung cancer. There were also several epidemiological studies assessing the association between vitamin D and lung cancer risk [11-19]. However, there were not conclusive results available from previous studies. To clarify the role of vitamin D in lung carcinogenesis, we performed a review of the literature and meta-analysis of cohort studies to evaluate the association of serum vitamin D levels and dietary vitamin D intake with lung cancer risk.

## Materials and Methods

### *Search of papers and inclusion criteria*

A systematic literature search was conducted in PUBMED, EMBASE and Web of Knowledge. We searched all studies published before 20 October, 2014. We used the following combinations of searching terms: (vitamin D, or 25-hydroxyvitamin D) AND (lung cancer, pulmonary cancer, lung carcinoma, or pulmonary carcinoma). There was no language in the literature search. After reviewing the abstracts, studies potentially eligible for inclusion were further assessed by reading full-texts. The reference lists of all eligible studies and relevant reviews were also retrieved to find other eligible studies. Two investigators independently assessed all the retrieved papers, and decided on the inclusion of studies according to the inclusion and exclusion criteria listed below.

The inclusion criteria in the meta-analysis were as following: a). Cohort studies or nested case-control studies; b). Assessing the association between serum vitamin D levels and lung cancer risk or the association between vitamin D intake and lung cancer risk; c) The outcomes were lung cancer incidence or mortality; d). Reporting relative risk (RR) with 95% confidence intervals (95% CI) or other data to calculate risk estimates. Case-control studies, reviews, case-only studies, case reports, and editorials were all excluded. When several articles reported the results from the same participants, only the study with the largest sample of subjects was used into the meta-analysis.

### *Data extraction*

A standardized protocol for data collection was used for data extraction. For each study we extracted information on first author, publication year, study design, country of participants, number of participants, gender distribution, mean age at enrolment, exact definition of dietary intake of vitamin D, types of serum vitamin D levels, duration of follow-up, cases of incident lung cancer, risk estimates for lung cancer risk, and variables used for adjustment. Two authors performed the data extraction independently, and any initial disagreement was resolved by consensus after further review of the studies. The quality assessment of the included studies was conducted using the Newcastle-Ottawa Scale [20]. By the Newcastle-Ottawa Scale, there were four stars for participants' selection, two stars for study comparability, and three stars for outcomes. Studies with 6 or more stars were high quality studies.

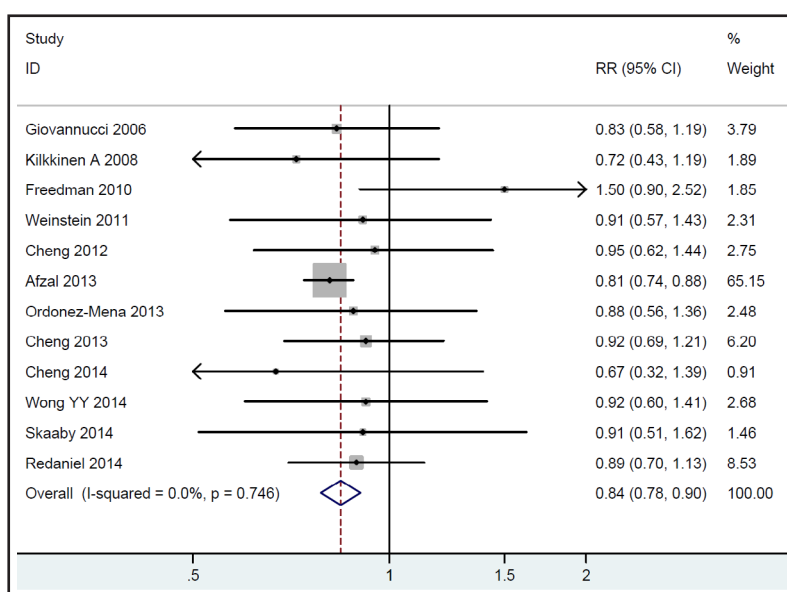
### *Statistical analysis*

The summary RR with 95% CI was used to assess lung cancer risk. The Z test was used to estimate the statistical significance of pooled RR. The RR comparing high levels of vitamin D with low levels of vitamin D was used in the meta-analysis. For RRs comparing low levels of vitamin D with high levels of vitamin D provided in some studies, we transformed them into RRs comparing high levels of vitamin D with low levels of vitamin D. Between-study heterogeneity was assessed using Cochrane's Q test, and P value less than 0.05 indicated that there was obvious heterogeneity in the included studies [21]. A further measure of heterogeneity was assessed by I<sup>2</sup> statistic method, and an I<sup>2</sup> less than 50% was generally considered an acceptable level of variability [22]. When there was obvious heterogeneity, a random effect model was used to calculate the pooled RR [23]. When there was no obvious heterogeneity in the included studies, a fixed effect model was used to calculate the pooled RR [24]. Subgroup analysis was performed by the type

**Table 1.** Main features of included studies on the association between vitamin D and lung cancer risk

Study	Study design	Participants number	Gender	Cases	Vitamin D	Data type
Giovannucci 2006 [19]	Prospective cohort	47800 individuals	Men	418	Serum	Increment per 25 nmol/L
Kilkkinen A 2008 [18]	Prospective cohort	6937 individuals	Mixed	122	Serum	H vs L
Freedman 2010 [17]	Prospective cohort	16819 individuals	Mixed	252	Serum	H vs L
Weinstein SJ 2011 [16]	Nested case-control	29133 individuals	Men	500	Serum	H vs L
Cheng 2012 [15]	Prospective cohort	16693 individuals	Mixed	258	Serum	H vs L
Afzal 2013 [14]	Prospective cohort	9791 individuals	Mixed	507	Serum	50% increment
Ordonez-Mena 2013 [13]	Prospective cohort	9949 individuals	Mixed	136	Serum	H vs L
Cheng 2013 [26]	Prospective cohort	128779 individuals	Women	1771	Intake	H vs L
Cheng 2014 [12]	Nested case-control	1428 individuals	Mixed	749	Intake	H vs L
Wong YY 2014 [28]	Prospective cohort	4208 individuals	Men	101	Serum	H vs L
Skaaby 2014 [11]	Prospective cohort	12204 individuals	Mixed	110	Serum	H vs L
Redaniel 2014 [27]	Nested case-control	5037 individuals	Women	484	Intake	H vs L

**Fig. 1.** Forest plot showing an inverse association between vitamin D status and lung cancer risk.



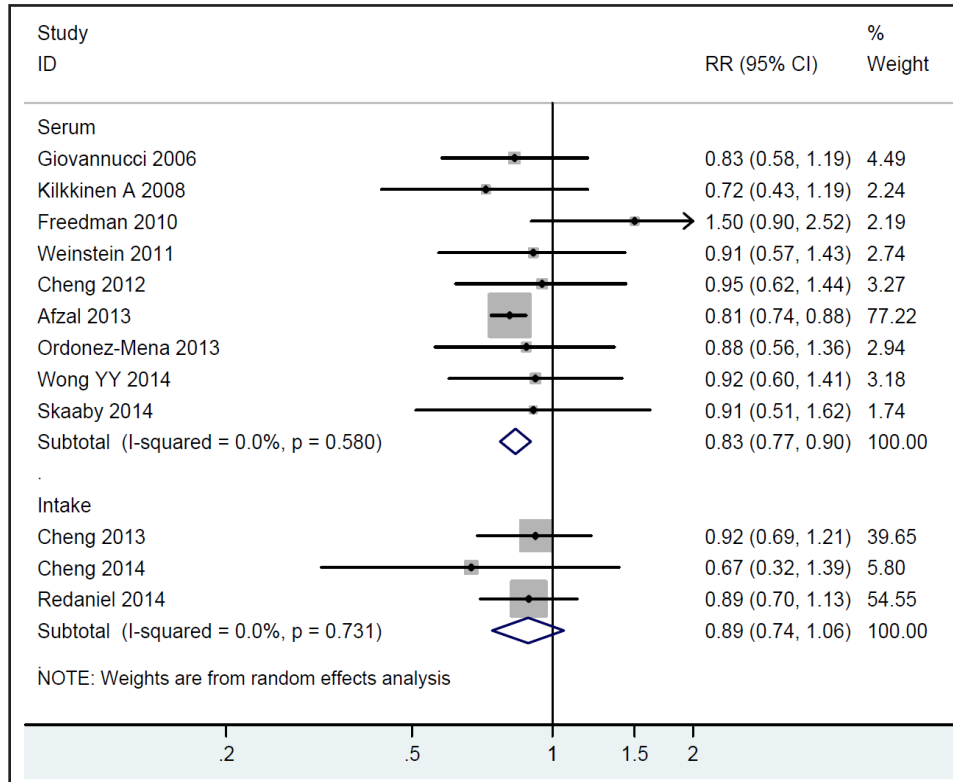
of vitamin D status (Serum vitamin D levels, or vitamin D intake). Sensitivity analysis was conducted by omitting one study by turns to evaluate the validity and reliability of the pooled RRs. Publication bias was evaluated graphically with the funnel plot, and asymmetry in the funnel plot suggested possible risk of publication bias. Egger's test was also employed to assess risk of publication bias in the meta-analysis [25]. All the statistical analyses were performed using STATA software (version 12.0).

## Results

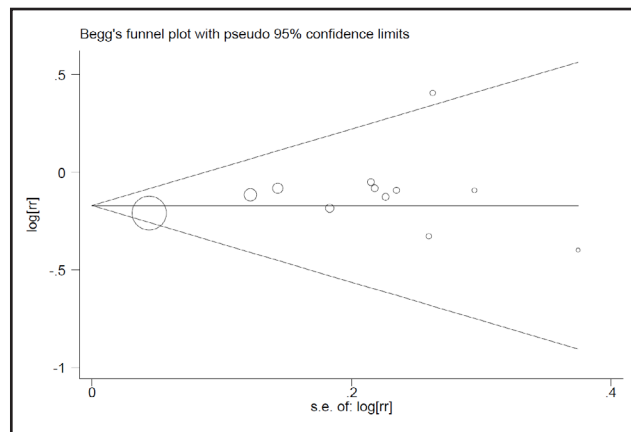
### Study selection and features

A total of 453 abstracts of possible studies were identified from online databases. After an initial screening of retrieved abstracts, 14 papers were preliminarily considered for inclusion in the meta-analysis [11-19, 26-30]. After applying inclusion criteria, two papers were further excluded [29, 30], and 12 studies were finally included into the meta-analysis [11-19, 26-28]. Among those 12 studies, 9 studies were prospective cohort studies [11, 13-15, 17-19, 26, 28], and 3 were nested case-control studies [12, 16, 27]. The main features of those 12 studies were shown in the Table 1 (Table 1). Those 12 studies were published from 2006 to 2014 (Table 1). All studies provided adjusted risk estimates of lung cancer according to the levels of vitamin D. Nine studies assessed the association between serum vitamin D levels and lung cancer risk, and three studies assessed the association between vitamin D intake and lung cancer risk (Table 1). According to the quality scale, all 12 studies had 6 or more stars and had high quality.

**Fig. 2.** Forest plot showing the association of serum vitamin D levels and dietary vitamin D intake with lung cancer risk.



**Fig. 3.** Forest plot for the assessment of publication bias in the meta-analysis.



### Meta-analysis

There was no between-study heterogeneity among those 12 studies ( $I^2 = 0.0\%$ ). Meta-analysis of total 12 studies showed that RR for the association of high vitamin D status with lung cancer was 0.84 (95%CI 0.78-0.90,  $P < 0.001$ ) (Fig. 1). Sensitivity analyses showed that no study had significant influence on the summary results. The RR of lung cancer for the highest versus lowest quintile of serum vitamin D levels was 0.83 (95%CI 0.77-0.90,  $P < 0.001$ ) (Fig. 2). The RR of lung cancer for the highest versus lowest quintile of vitamin D intake was 0.89 (95%CI 0.74-1.06,  $P = 0.184$ ) (Fig. 2).

The funnel plot in the meta-analysis was symmetric, which suggested no obvious risk of publication bias. In addition, there was also no indication for publication bias in the Egger's test ( $P = 0.12$ ).

## Discussion

Vitamin D has been suggested to be associated with risks of many diseases, such as diabetes [31-33]. Vitamin D has been suggested to have important roles against cancer development, and it has anti-tumor effects. Previous studies have provided strong evidence for the preventive effects of vitamin D against colorectal cancer and breast cancer [34]. However, there was no evidence for the preventive effects of vitamin D against other types of cancers, such as lung cancer. In present meta-analysis, we performed a meta-analysis of 12 studies involving a total of 288,778 individuals, which provided a comprehensive assessment of the role of vitamin D against lung cancer. Meta-analysis of total 12 studies showed that high vitamin D status was associated with decreased risk of lung cancer (Fig. 1). Subgroup analysis showed that high serum vitamin D level was associated with decreased risk of lung cancer, but high vitamin D intake was not associated with decreased risk of lung cancer (Fig. 2). Thus, current data suggest an inverse association between serum vitamin D and lung cancer risk, and vitamin D has preventive effects against lung cancer.

Vitamin D also has been suggested to have important roles in cancer development, and it has anti-tumor effects [6, 7]. Findings from previous studies have showed that vitamin D can result in an additive decrease in cell proliferation and the induction of apoptosis in small cell lung carcinoma cell lines [7, 9]. Vitamin D can also inhibit the metastatic growth of lung cancer cells in animal models [6, 10]. In addition, vitamin D also has the ability to prevent angiogenesis and migration in malignant cells. Thus, there are experimental explanations for the preventive role of vitamin D against lung cancer, and vitamin D could play an important role in several common pathways of cancer.

There are also many studies assessing the association between circulating levels of vitamin D and the prognosis of cancer patients [35, 36]. Previous studies also provided some evidence for the prognostic roles of serum vitamin D levels in colorectal cancer and breast cancer [35, 37]. Several studies were also published to assess the association between serum vitamin D levels and prognosis of lung cancer patients, but they failed to identify a consistent conclusion [38-42]. More future studies are needed to further assess the association between serum vitamin D levels and prognosis of lung cancer patients.

In present meta-analysis, there were only three studies assessing the association between vitamin D intake and lung cancer risk. The RR for the highest versus lowest quintile of vitamin D intake was 0.89 (95%CI 0.74-1.06,  $P = 0.184$ ) in present meta-analysis. Though there was not a statistically significant association found in the meta-analysis, there was a tendency of low risk of lung cancer in individuals with high levels of vitamin D intake. Thus, more studies are needed to investigate the effect of vitamin D intake on lung cancer risk.

Previous studies showed that vitamin D supplementation could decrease cancer mortality [43]. However, there is still no evidence for the lung cancer prevention by vitamin D supplementation from clinical trials. In addition, the adequate dosages and duration of vitamin D supplementation are also still unclear. Therefore, further clinical trials were needed to evaluate whether vitamin D supplementation can prevent lung cancer. In addition, more trials on vitamin D supplementation are also needed to assess the benefits and harms among people with low vitamin D status, and assess the benefits and harms of longer duration of treatments or higher dosages of vitamin D.

In conclusion, current data suggest an inverse association between serum vitamin D and lung cancer risk. Further studies are needed to investigate the effect of vitamin D intake on lung cancer risk and to evaluate whether vitamin D supplementation can prevent lung cancer. In addition, more future studies are needed to further assess the association between serum vitamin D levels and prognosis of lung cancer patients.

## Disclosure Statement

None declared.

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