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Review Article

Circulating 25-hydroxyvitamin D levels and Risk of Lung Cancer: A Meta-epidedmiological Meta-analysis

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Abstract

Background: Five previous systematic reviews (SR) evaluating the hypothesis that serum vitamin D deficiency was associated with risk of lung cancer showed unstable and uncertain results. Especially antipathic relative risks (RR) of selected articles as well as missed articles were found among them.

Objective: The aim of this SR was to conduct a meta-epidemiolgical meta-analysis (MEMA) based on them.

Methods: Using citation discovery tools, additional articles were selected from cited lists based on 16 selected articles. Fixed effect model was applied if I2 value was less than 50%. A publication bias was evaluated using Egger's test.

Results: Of 13 articles, the summary RRs (and their 95% confidence intervals) (I2 value) were 1.17 (1.09, 1.26) (18.3%). The sRR from 10 articles adjusted for sex and 12 articles adjusted for smoking habits showed stable RRs with keeping the statistical significance. Egger's test showed no publication bias.

Conclusion: This MEMA supported the lower level of serum vitamin D was associated with an increased risk of lung cancer.

Impact: This might be an evidence for conducting some public health programs against vitamin D deficiency status in order to prevent lung cancer.

Keywords: Vitamin D; Lung neoplasms; Risk factors; Systematic Review; Meta-analysis

1. Introduction

In the last several decades, vitamin D has been shown to be involved in processes such as cell differentiation, proliferation, and apoptosis [1]. And low vitamin D levels have been reported to be associated with risk of breast cancer [2], colorectal cancer [3], and prostate cancer [4]. Meanwhile, lung cancer is known to be the most common cancer worldwide, while also being fatal [5]. Accordingly, in addition to early diagnosis, prevention of lung cancer is of the utmost importance. Among previous 5 meta-analyses on the lung cancer risk associated with reduced plasma 25-hydroxyvitamin D [25(OH)D] [6-10], in the most recent study, by Wei et al. [10], the summary relative risk (sRR) reversed direction to 0.95 and lost its statistical significance. In other words, the meta-analysis results reported to date are unstable and uncertain (Table 1).

FA (RF)			**Zhang (6)**	**Chen (7)**	**Feng (8)**	**Liu (9)**	**Wei (10)**
PY			2015	2015	2017	2017	2018
Search upto			Oct 2014	May 2015	Aug 2017	NA	Dec 2017
sRR			1.19	1.05	1.19	1.39	0.95
(95% CI)			1.11-1.28	1.01-1.10	1.05-1.35	1.18-1.64	086-1.06
I-squared (%)			0	51.3	50.3	61.3	37.9
Lists of PAS	RF	PY					
	(18)	2006	√	√	√		
	(11)	2008	√	√	√	√	√
	(16)	2010	√				
	(12)	2011	√	√	√	√	√
	(17)	2012	√	√			√
	(13)	2013	√	√	√	√	√
	(19)	2013	√				
	(14)	2014	√	√	√	√	√
	(15)	2014	√	√	√	√	√
	(20)	2014		√	√	√	
	(21)	2015		√	√		
	(22)	2015			√	√	
	(23)	2016				√	√
	(24)	2017					√
	(25)	2017					√
	(26)	2017					√

*CI: confidence intervals; FA: First author; NA: not available; PY: publication year; RF: reference number; sRR: summary relative risks

Table 1: Summary table of prospective studies selected (PAS) from five systematic reviews.

Table 1 highlights several issues with the processes of these 5 systematic reviews. First, there is no consistency in the studies selected for meta-analysis. If the selection criteria were the same, more recent searches should obviously include studies selected by the authors of previous meta-analyses. However, there were only 5 studies that were included in all 5 meta-analyses [11-15]. Second, the selection criteria differed between meta-analyses studies. If the endpoint in the hypothesis is lung cancer risk, the two studies dealing with lung cancer mortality [16, 17] should be excluded. Third, the results extracted from the selected studies show differences between the meta-analyses. These differences in the extracted values can be found in the forest plots presented as the results of each meta-analysis. Fourth, there was a lack of subgroup analysis or sensitivity analysis for lung cancer-related variables. It is important to examine the effects of plasma vitamin D depending on gender, smoking history, and histological type of lung cancer.

Accordingly, the list of studies selected in the previous 5 meta-analyses [6-10] needs to be reorganized, and the information extracted from those studies needs to be re-examined. In this study, we aimed to investigate hypothesis that decreased plasma 25(OH)D levels increase the risk of lung cancer. To this end, we performed a meta-epidemiological meta-analysis (MEMA) aiming to utilize and update the 5 previous meta-analyses.

2. Materials and Methods

In accordance with the aims of this study to update the previous 5 meta-analyses [6-10], it was necessary to add relevant studies that were published after the meta-analyses were performed. Utilizing the list of 16 studies [11-26] selected by the authors of the previous meta-analyses (Table 1), we made a search list using the 'cited by' option as citation discovery tools (CDT) provided by PubMed [27]. We set the end of the search period as the end of March 2019. To select relevant studies from the search list, we applied the same selection criteria as the systematic reviews in Table 1. Specifically, we selected analytic epidemiological studies of lung cancer risk that obtained plasma 25(OH)D levels at constructing a cohort and used a prospective observational design.

From the studies selected according to the criteria, we extracted the RR and 95% confidence intervals (CI) using the 'highest versus lowest' method (HLM), only extracting data for the group with the lowest plasma 25(OH)D compared to the highest plasma 25(OH)D. In cases using the lowest 25(OH)D group as the reference, we obtained the inverse values, such that the highest 25(OH)D group would become the reference. This was to reflect the aim of our study, examining the risk associated with low plasma 25(OH)D levels. Since Giovannucci et al. [18] presented their results in the form of a graph, we used the values suggested by Zhang et al [6]. Wu et al. [23] presented results separately for the smoking group and the non-smoking group; therefore, we took values derived from a meta-analysis of the results from these two groups and used these as the results for that study. From the RR and 95%CIs of each study, we calculated the logarithm RR (logRR) and standard error of logRR (SElogRR).

Study heterogeneity was assessed using the I-squared value (%); a random effect model was applied for $I^2 \geq 50\%$, and a fixed effect model was applied for $I^2 < 50\%$ [28]. Subgroup analysis was performed by histological type of lung cancer (total *vs.* non-small cell lung cancer (NSCLC)), sex (men *vs.* women), and smoking status, as well as by study design (cohort (CO) *vs.* case-control (CC)). We constructed a funnel plot and performed Egger's test to

examine publication bias. If a publication bias was detected, we limited SElogRR and performed a sensitivity analysis. The statistical significance level was set to 0.05.

3. Results

Using PubMed's CDT, we retrieved a total of 389 studies citing the 16 studies in Table 1. Of these we selected 3 studies that satisfied the selection criteria [29-31]. All studies had been published after January 2018. Notably, Muller et al. [31] derived their results from a CC study using cases obtained from internationally famous cohorts. In order to exclude duplicate data in the meta-analysis, this study was only included in the meta-analysis of CC studies.

Of the 16 studies in Table 1, we excluded 2 studies that used lung cancer deaths as outcomes [16, 17]. Ananthakrishnan et al. [20] was also excluded because the subject were patients with inflammatory bowel diseases. And, of the 3 studies using results from the ESATER cohort [19, 21, 26], we selected Ordóñez-Mena et al. [21] as the representative study, since they presented their results in the most detail. Therefore, we selected 14 studies finally to include in the meta-analysis [11-15, 18, 21-25, 29-31]. Table 2 shows the logRR and SElogRR calculated by applying the HLM to these studies.

RN	First Author	Year	Design	Sex	logRR	SElogRR	Study or Nation
18	Giovannucci	2006	CO	M	0.19	0.18	HPF
11	Kilkkinen	2008	CO	B	0.33	0.26	Mini-Finland Health Survey
12	Weinstein	2011	CC	M	0.19	0.23	ATBC
13	Afzal	2013	CO	B	0.17	0.05	Copenhagen City Heart
14	Wong	2014	CO	M	0.32	0.27	HIMS
15	Skaaby	2014	CC	B	0.09	0.29	Monica10, Inter99, Health2006
22	Wang	2015	CC	B	0.89	0.4	China
21	Ordóñez-Mena	2016	CO	B	0.33	0.29	CHANCES
23	Wu	2016	CC	B	0.12	0.14	HongKong
24	Gromowski	2017	CC	B	0.48	0.25	Poland
25	Cheng	2017	CC	W	-0.06	0.14	WHI CTs & OS
29	Budhathoki	2018	CO	B	0.33	0.17	HPHC
30	Sun	2018	CO	B	-0.15	0.14	HUNT
31	Muller	2018	CC	B	0.01	0.07	LC3

* CC: case-control study; CI: confidence interval; CO: cohort study logRR: logarithm relative risk; RN: reference number; Sex: B(men and women) M(men) W(women); SElogRR: standard error of logarithm relative risk

Table 2: Summary of the extracted information of 14 selected articles.

When we performed meta-analysis of the 13 selected studies excluding Muller et al. [31], the sRR (95% CI) (I^2 value, %) was 1.17 (1.09-1.26) (18.3%) (Table 3). When we analyzed the 7 CO studies and 7 CC studies separately,

the sRRs were 1.18 (1.08-1.28) (15.3%) and 1.07 (0.96-1.18) (32.4%), respectively (Table 3, Figure 1).

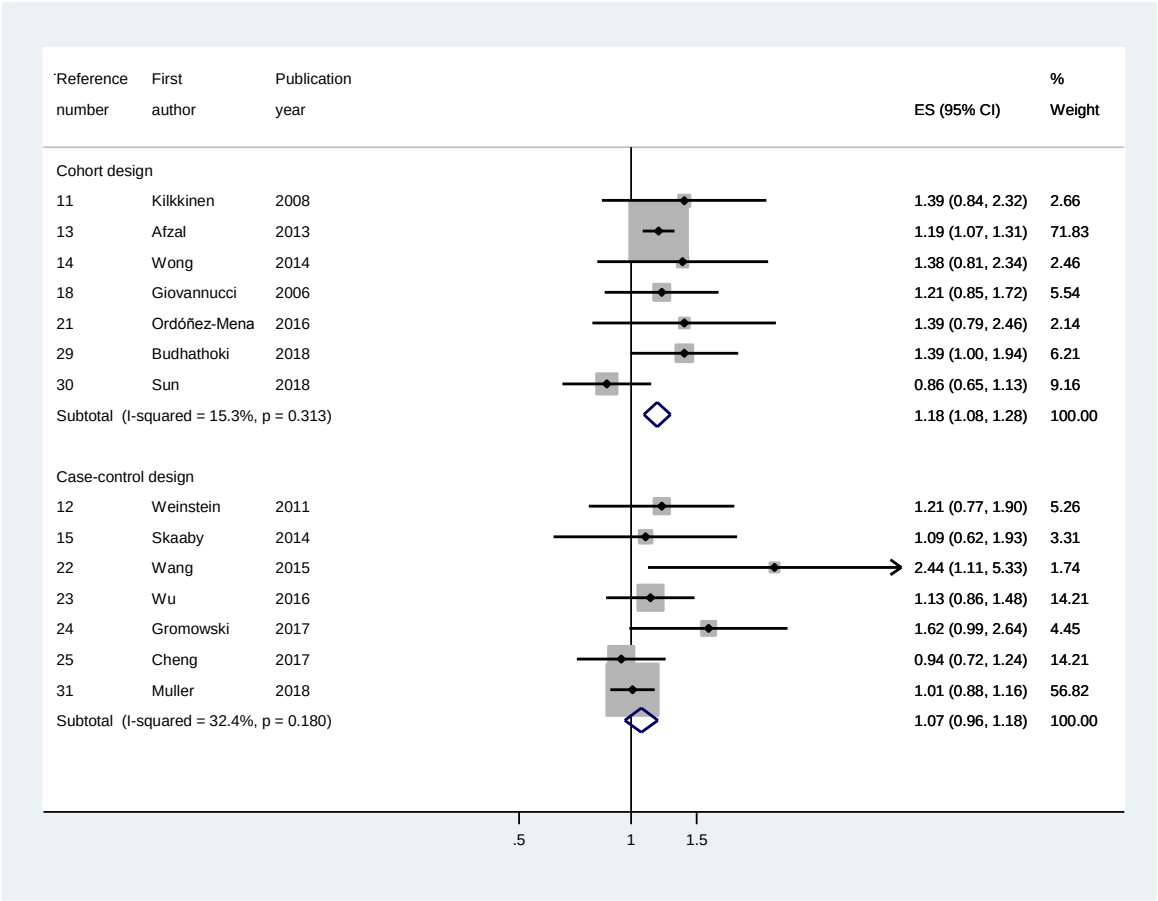

Figure 1: Forest plot for estimating the summary effect size (ES) by study design.

Subgroup	All	Cohort Design	Case-control design
Histological type			
All histological	1.17 (1.09-1.26) (18.3) {13}	1.18 (1.08-1.28) (15.3) {7}	1.07 (0.96-1.18) (32.4) {7}
Non-small cell	1.17 (0.92-1.49) (27.7) {3}	-	1.17 (0.92-1.49) (27.7) {3}
Sex			
Adjusted	1.14 (1.06-1.22) (42.4) {10}	1.17 (1.07-1.28) (40.4) {5}	1.08 (0.96-1.21) (48.3) {5}
Men	1.21 (0.96-1.51) (0.0) {4}	1.21 (0.93-1.57) (0.0) (3)	1.21 (0.76-1.89) (-) {1}
Women	0.44 (0.08-2.46) (84.2) {2}	0.16 (0.14-0.59) (-) {1}	0.94 (0.54-0.94) (-) {1}
Smoking habit			
Adjusted	1.15 (1.07-1.23) (32.4) {12}	1.18 (1.08-1.28) (15.3) {7}	1.08 (0.96-1.22) (49.3) {5}
Non-smokers	0.97 (0.77-1.23) (0.0) {2}	-	0.97 (0.77-1.23) (0.0) {2}

*Summary relative risks (95% confidence intervals) (I-squared value, %) of {number} selected cohorts

Table 3: Subgroup analyses by study design.

The 10 studies adjusting for sex and the 12 studies adjusting for smoking history each showed similar, significant risk. However, in studies restricted to NSCLC, men, women, or non-smokers, we no longer observed statistical significance. Egger's test on the results of the 14 studies showed that there was publication bias (*P*=0.332) (Figure 2).

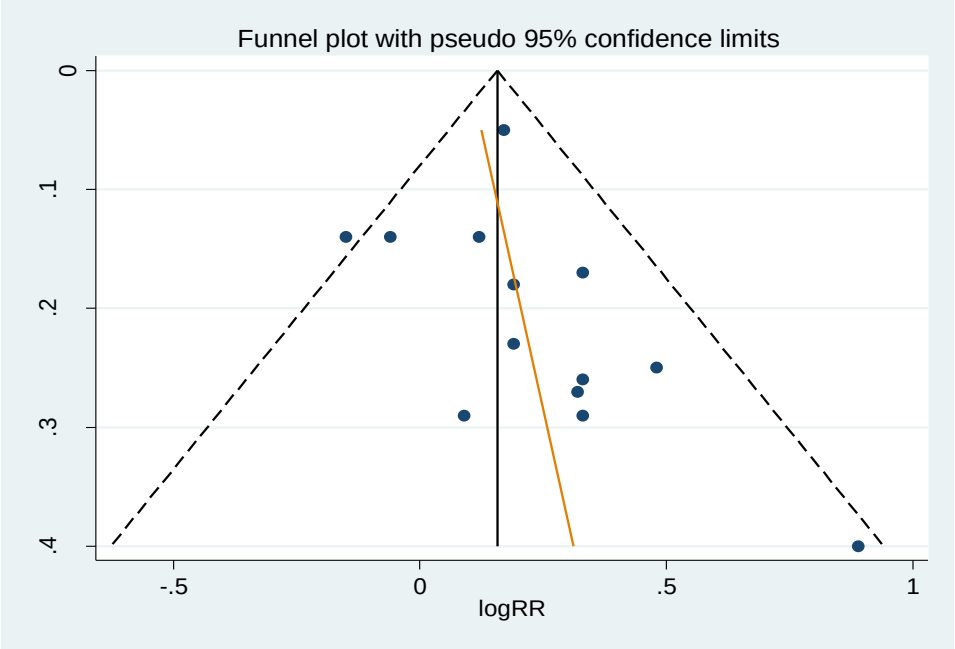

Figure 2: Funnel plot for 13 articles (P-value of Egger's test=0.332).

4. Discussion

The above results show that low plasma 25(OH)D was associated with a significant, 1.17-fold (95% CI: 1.09-1.26) increase in lung cancer risk. In subgroup analysis, statistical significance was maintained in studies adjusting for sex and smoking history. In subgroup analyses, significances were also maintained in cohort design, sex-adjusted, or smoking habit-adjusted group. When the sRR from this MEMA was compared with the 5 previous meta-analyses in Table 1, the results were similar to 3 of the previous meta-analyses [6-8]. Meanwhile, the direction and significance of the sRR differed from the 2 more recently published meta-analyses [9, 10]. These facts demonstrates the importance of strict selection criteria, accurate data extraction, and selecting appropriate studies in order to obtain a valid sRR.

In order to fit the study objectives, this MEMA excluded 3 studies that had been selected in related meta-analyses [16, 17, 20], and selected only the study by Ordóñez-Mena et al. [21] to represent 3 studies presenting results from the same cohort [19, 21, 26]. In addition, we used PubMed's CDT to search studies based on the list of studies selected in the previous 5 meta-analyses (Table 1), and we added 3 studies that had been published between January 2018 and March 2019 [29-31]. When we performed subgroup analyses for studies adjusting for sex and smoking history, we obtained more stable sRR values, and statistical significance was maintained.

On the other hand, as shown in Table 3, when the number of studies analyzed was 5 or lower, or when analyzing only CC studies, statistical significance was lost and sRR was unstable. This can be interpreted as showing that the meta-analysis results are affected by the number of subjects. Given that a CC analysis by Muller et al. [31] found plasma 25(OH)D to be unrelated to lung cancer incidence, it will be necessary to perform a cohort analysis using individual patient data. It will also be necessary to perform a MEMA that adds further relevant studies by extending the range of publication dates in the selection criteria [32].

Meanwhile, author did not evaluate the quality of selected articles using the NewcastleOttawa Scale (NOS) or Grading of recommendation, assessment, development and evaluation. Instead, author did conduct subgroup analyses by study design for observational studies in nutritional epidemiology. The reason was based on the suggestion by Bae JM [33], which concluded that 'it is more reasonable to control for quality level by performing subgroup analysis according to study design rather than by using high quality based on the NOS quality assessment tool.

Until new MEMA results are published, this MEMA is evidence that increasing circulating vitamin D levels could be a measure to help prevent lung cancer. Amidst recent environmental changes such as the spread of electronic cigarettes and increased levels of particulate matter, these results can be utilized in planning and promoting public health projects for lung cancer prevention.

Conflicts of Interest

The author declares no potential conflicts of interest.

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