

Original Article

Examining the association of circulating 25-hydroxyvitamin D with kidney cancer risk: a meta-analysis

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Abstract: Objective: To examine the relationship between circulating 25-hydroxy-vitamin D (25 (OH) D) and risk of kidney cancer. Methods: We searched PubMed, EMBASE, and Web of Science databases through August 31, 2015 for eligible studies. Pooled ORs with 95% confidence interval were calculated using fixed effect models. All data analyses were performed with STATA version 12.0. Results: The final analysis included 2 prospective cohort studies and 7 nested case-control studies, with a total of 130, 609 participants and 1, 815 cases of kidney cancer. No obvious heterogeneity was observed between individual studies. The results of this study revealed that higher circulating 25-hydroxyvitamin D levels were associated with lower risk of kidney cancer (OR=0.79, 95% CI 0.69-0.91; *P* value for heterogeneity: 0.61, *I*²=0%). After stratified by geographical region, the similar association was detected in European studies (OR=0.81, 95% CI 0.69-0.94; *P* value for heterogeneity: 0.38, *I*²=0%), though no significant association was observed in the USA studies (OR=0.73, 95% CI 0.51-1.04; *P* value for heterogeneity: 0.44, *I*²=0%). Conclusion: Our present findings suggest that higher levels of circulating 25-hydroxyvitamin D could reduce the risk of kidney cancer by 21%. Further well-designed large-scaled prospective studies and randomized controlled trials are warranted to provide more conclusive evidence.

Keywords: Kidney cancer, renal cell carcinoma, 25-hydroxyvitamin D, risk, meta-analysis

Introduction

Kidney cancer is the 13th most common malignancy, with approximately 338,000 new cases diagnosed worldwide in 2012 [1]. Kidney cancer is a serious threat to public health-the American Cancer Society estimated that, in 2014, 63,920 new kidney cancer cases would be diagnosed, and 13,860 people would die of the disease in the United States [2]. The incidence of kidney cancer has increased at a rate of approximately 1.6% per year over the last 10 years [2]. Mounting epidemiologic evidence has identified several well-established risk factors for kidney cancer, such as tobacco smoking, overweight and obesity, hypertension and family history of the disease [3-6]. However, preventive measures for kidney cancer are limited.

In recent studies, vitamin D, the sunshine vitamin, has received increased attention. Vitamin D is well known for its role in facilitating calcium absorption, which is essential for bone health [7]. New studies have shown that vitamin D has a positive effect on the immune system and is likely to be an anti-carcinogenic agent [8-10]. Further evidence-based studies suggest that vitamin D can reduce the incidence of several cancers, including colorectal, breast, prostate and kidney cancers [11-15]. Vitamin D from diet, dietary supplements and skin production is first metabolized into circulating 25-hydroxyvitamin D in the liver [16]. Circulating 25-hydroxyvitamin D is the major circulating metabolite of vitamin D with a half-life of 2-3 weeks [17]. Furthermore, circulating 25-hydroxyvitamin D is generally considered as the best blood biomarker of vitamin D [18]. In recent years, inc-

25-hydroxyvitamin and kidney cancer

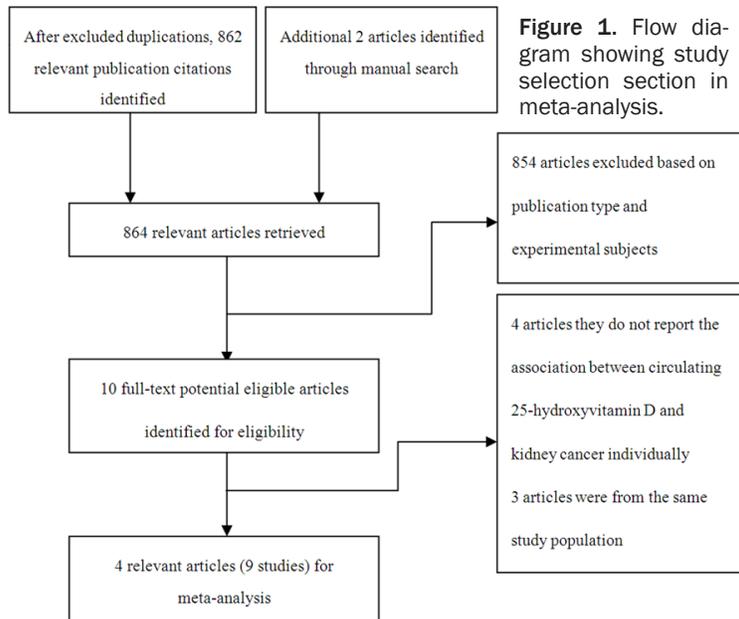


Figure 1. Flow diagram showing study selection section in meta-analysis.

Hydroxylase or 1, 25-dihydroxyvitamin D or vitamin D) and (kidney or renal cell) and (tumor or cancer or carcinoma or neoplasm). In addition, we manually searched the references of all retrieved publications to find additional related researches. In light of the recent increased incidence of kidney cancer in China, we also searched CNKI, CBM and Wan-fang databases to find more eligible studies.

Inclusion and exclusion criteria

A study was eligible for inclusion if it met the following criteria: (1) an original study that conducted on humans only; (2) it evaluated the correlation between circulating 25-hydroxyvi-

itamin D and kidney cancer risk and (3) the studies reported point estimates (i.e., relative risks RR or odds ratios OR) and measures of variability (i.e., 95% confidence intervals CIs) for higher versus non/lower level of circulating 25-hydroxyvitamin D or the study provided enough information (e.g.: raw data and *p* value) to estimate the effect sizes and their CIs. If more than one article examined the same study population, only the article with the larger dataset was included. The following criteria applied to exclude studies: (1) review articles, case reports or mechanistic analyses and (2) studies that reported irrelevant data.

Data extraction

Two independent reviewers extracted the data in a standardized data collection form; any disagreement was resolved by discussion and consensus. The following information was extracted from each included study: first author, year of publication, study design, country, characteristics of the study population, duration of follow-up, number of kidney cancer cases, number of participants and adjusted ORs with 95% CI for kidney cancer according to circulating 25-hydroxyvitamin D levels, as well as covariates that were adjusted in the analysis.

Statistical analysis

The cut-off points for circulating 25 (OH) D levels were different across the included studies. However, we used the ORs with 95% CI of the

reasing studies have discussed the relationship between circulating 25-hydroxyvitamin D and kidney cancer, but results have been equivocal. A comprehensive quantitative analysis of the association between circulating 25-hydroxyvitamin D and kidney cancer risk is still missing from the current research.

To date, 2 prospective cohort and 7 nested case-control studies have been conducted. These studies are inconsistent in terms of establishing the relationship between circulating 25-hydroxyvitamin D and kidney cancer risk [19-24]. In the present study, a meta-analysis is performed to investigate the potential correlation between circulating 25-hydroxyvitamin D and kidney cancer.

Materials and methods

Literature search strategy

This meta-analysis was conducted in accordance with the meta-analysis of observational studies in epidemiology [25]. A literature search was performed to explore the potential correlation between circulating 25-hydroxyvitamin D and kidney cancer. PubMed, EMBASE, and Web of Science databases were searched through August 31, 2015 for eligible studies. Our research focused on human cases, without any limitation on language. Our search items were: (25-OH-D or cholecalciferol or calcidiol or calcitriol or 25-hydroxyvitamin D or Hydroxycholecalciferols or 25-Hydroxyvitamin D3 1-alpha-

25-hydroxyvitamin and kidney cancer

Table 1. Characteristics of nine included studies in the meta-analysis

Author (s), (year)	Study design	Study population*Country (time of recruitment)	No. of cases/cohort size or no. controls	Setting	Pooled RR (95% CI)	Adjustment factors
Gallicchio et al. 2010 [23]	N	ATBC*Finland (1985-2005) [23]	286/286	Smoking Men	1.66 (0.54, 5.12)	Education, BMI, height, season, smoking status, hypertension, diabetes, and alcohol consumption
		CLUE*USA (1974-2007) [23]	102/102	General	0.74 (0.30, 1.79)	
		CPS-II*USA (1998-2004) [23]	58/58	General	0.57 (0.19, 1.70)	
		MEC*USA (2001-2006) [23]	64/64	General	2.09 (0.47, 9.28)	
		PLCO*USA (1993-2005) [23]	161/161	General	1.08 (0.47, 2.46)	
		MHS/SWHS*CHINA (1997-2008) [23]	69/69	General	1.40 (0.20, 9.63)	
		OVERALL	740/740	General	1.01 (0.65, 1.58)	
Joh et al. 2013 [20]	P	NHS*USA (1986-2008)	201/72051	Women	0.70 (0.45, 1.07)	Age, smoking status, hypertension, diabetes, BMI, error correction in predicted 25 (OH) D score
		HPFS*USA (1986-2000)	207/46380	Men	0.61 (0.35, 1.04)	
		OVERALL	408/118431	General	0.58 (0.35, 0.96)	
Afzal et al. 2013 [21]	P	CCHS*Denmark (1981-2008)	112/9791	General	0.75 (0.58, 0.96)	Age, sex, education, smoking status, BMI, alcohol consumption, leisure time and work-related physical activity
Muller et al. 2014 [33]	N	EPIC*European (1992-2000)	555/1647	General	0.82 (0.68,0.99)	Smoking status, circulating cotinine, BMI, and alcohol consumption

Abbreviations: ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CPS-II, Cancer Prevention Study II Nutrition Cohort; HPFS, Health Professionals Follow-up Study; MEC, Multiethnic Cohort Study; NDI, National Death Index; NHS, Nurses' Health Study; NYU-WHS, New York University Women's Health Study; 25 (OH) D, 25-hydroxyvitamin D; PLCO, Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; SEER, Surveillance, Epidemiology, and End Results; SMHS, Shanghai Men's Health Study; SWHS, Shanghai Women's Health Study; N, nested case-control; P, prospective cohort. BMI, Body Mass Index.

25-hydroxyvitamin and kidney cancer

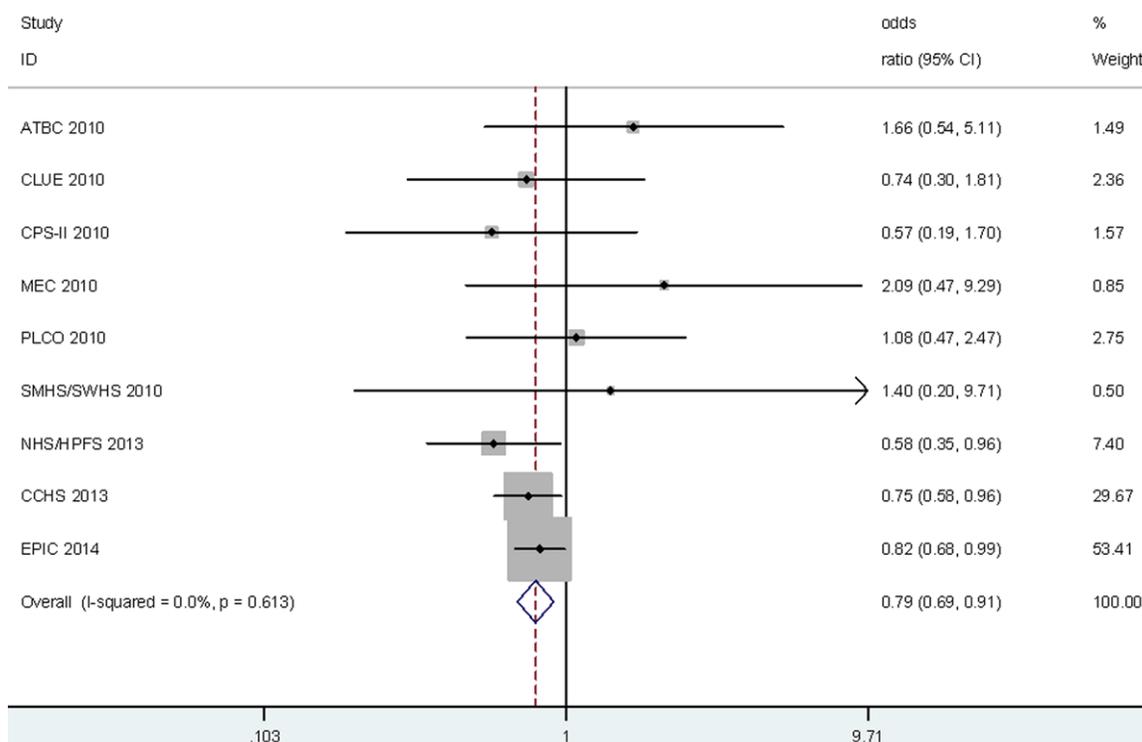


Figure 2. Forest plot for the association of highest versus lowest circulating 25-Hydroxyvitamin D levels with risk of kidney cancer.

highest level versus the lowest level of circulating 25-hydroxyvitamin D to keep uniformity in the meta-analysis. We used I^2 and Cochran's Q to assess possible heterogeneity in results across studies. An I^2 value below 50% or a P value over 0.10 indicated no statistically significant heterogeneity between studies [26, 27]. When there was no obvious between-study heterogeneity, fixed effects estimates were used to calculate the pooled ORs with 95% CIs [28]. Z-test was used to calculate the significance of the pooled ORs. Fixed effect models were performed using the Mantel-Haenszel method for homogeneous studies [29, 30]. Forest plots were also applied to assess the relationship between circulating 25-hydroxyvitamin D and kidney cancer. Subgroup analyses were conducted on the basis of study design and geographical region. In the sensitivity analysis, the influence of each individual study on the pooled ORs was examined by excluding any single study at one time. Risk of publication bias was assessed in funnel plots. Furthermore, Egger's test (linear regression method) [31] and Begg's test (rank correlation method) [32] were also employed to assess indications of publication bias. A P value <0.05 for Egger's or Begg's tes-

ts indicated significant statistical publication bias.

All data analyses were conducted by STATA version 12.0.

Results

Our literature search yielded 864 abstracts and 2 additional articles through manual search (Figure 1). Two duplications were excluded, and 864 relevant publication citations were identified. After screening by titles and abstracts, 854 articles were excluded and 10 full-text articles were identified for potential eligibility [19-24, 33-36]. After full-text review, 6 articles [19, 22, 24, 34-36] were further excluded because they either did not report the association between circulating 25-hydroxyvitamin D and kidney cancer individually [22, 34-36] or were from the same study population [19, 24]. Finally, 4 articles were included in our meta-analysis [20, 21, 23, 33]. The 4 included articles contained 10 studies, including 2 prospective cohort studies and 8 nested case-control studies. In the 4 articles, the Vitamin D Pooling Project, which comprised seven nested case-control studies, was conducted in differ-

25-hydroxyvitamin and kidney cancer

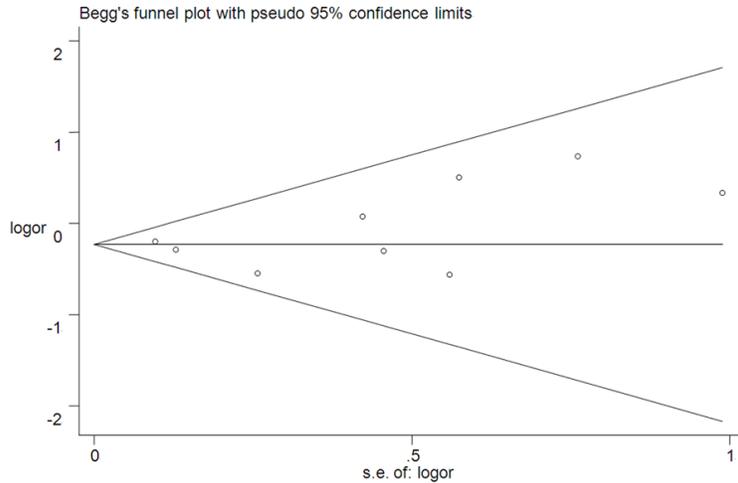


Figure 3. Funnel plot shows no obvious evidence of asymmetry.

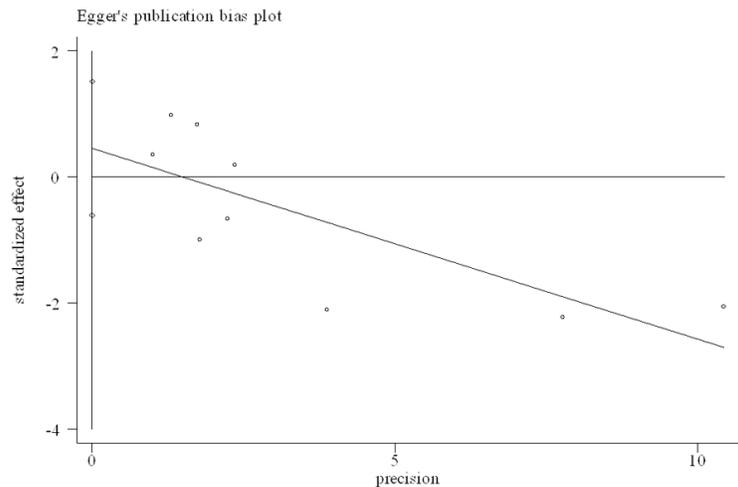


Figure 4. Egger's publication bias plot shows no evidence of asymmetry in the meta-analysis.

ent countries-China, Finland, and the United States, including a study center in Hawaii. Six studies were included from the abovementioned seven nested case-control studies. The NYU-WHS was excluded because it didn't report the association between circulating 25-hydroxyvitamin D and kidney cancer. Therefore, the remaining nine studies were included in the present meta-analysis. **Table 1** provides descriptive data for the studies. The meta-analysis included 2 prospective cohort studies and 7 nested case-control studies with a total of 130,609 participants and 1,815 cases of kidney cancer. Of those nine studies, five were conducted in the USA, three in Europe and one in China. All studies provided the adjusted ORs,

though the adjusted confounders were different.

The combined result of 9 studies revealed that a higher level of circulating 25-hydroxyvitamin D could reduce the risk of kidney cancer by 21% (OR=0.79, 95% CI: 0.69-0.91, *p*-value for heterogeneity =0.61, $I^2=0$) (**Figure 2**). No obvious heterogeneity was observed between individual studies (Heterogeneity: $P=0.613$, $I^2=0\%$; $P=0.001$, $Z=3.26$). In the subgroup meta-analysis of the nested case-control studies [23, 33], no association was detected (OR=0.85, 95% CI: 0.71-1.01, *p*-value for heterogeneity=0.67, $I^2=0$). However, a statistically significant inverse association was observed in the subgroup analysis of prospective cohort studies [20, 21] (OR=0.71, 95% CI: 0.57-0.89, *p*-value for heterogeneity=0.37, $I^2=0$). When stratified by geographical region, a statistically significant inverse association between circulating 25-hydroxyvitamin D and kidney cancer was found in studies in Europe [21, 23, 33] (OR=0.81, 95% CI: 0.69-0.94, *p*-value for heterogeneity=0.38, $I^2=0$), but not in the USA [20, 23b-23e] (OR=0.73, 95% CI: 0.51-1.03, *p*-value for heterogeneity=0.44, $I^2=0$). We recalculated the

result by excluding any single study at one time and did not observe any significant modification of results. There was no obvious evidence of publication bias in the funnel plot. Furthermore, the results of Begg's ($P=0.348$) (**Figure 3**) and Egger's test ($P=0.342$) did not indicate a publication bias (**Figure 4**).

Discussion

While the relationship between circulating 25-hydroxyvitamin D and kidney cancer risk has received increased attention, there has no uniform clarification of the association. To further clarify the association of circulating 25-hydroxyvitamin D with kidney cancer, a meta-

analysis of studies was performed. We pooled 2 prospective cohort studies and 7 nested case-control studies with a huge sample size of 130,609 to obtain a more conclusive result. Among the nine studies, ambiguous results were observed on the association between circulating 25-hydroxyvitamin D and kidney cancer. Findings from the current meta-analysis indicate that circulating 25-hydroxyvitamin D was associated with a 21% reduction in risk of kidney cancer when comparing the highest level with the lowest level. Significant inverse associations between circulating 25 (OH) D and kidney cancer risk were observed in the prospective cohort studies and in European studies. Furthermore, no obvious heterogeneity was observed between all studies, which suggested a consistent estimation of the relationship between circulating 25-hydroxyvitamin D and kidney cancer risk. In addition, no obvious evidence of publication bias was detected with the Egger's or Begg's tests. Moreover, the combined estimate was robust across sensitivity analyses.

The mechanisms of vitamin D on kidney cancer are still unknown. Several plausible biological links might support the association of circulating 25-hydroxyvitamin D with kidney cancer. The anti-cancer effects of vitamin D were clearly demonstrated in vitro and animal studies [10], and the mechanism might be that vitamin D decreased the expression of aromatase and suppressed tumor angiogenesis, invasion and metastasis [37]. Recent studies showed that vitamin D could reduce the incidence of colorectal, breast and prostate cancers [11, 14, 15]. Vitamin D may also interact with several risk factors for kidney cancer, such as hypertension and diabetes. Furthermore, there is increasing evidence that vitamin D might be beneficial in controlling blood pressure [38] and optimizing glucose metabolism [39]. Finally, some unknown effects of vitamin D may be from cancer.

Subgroup analyses were performed, with groups assigned according to study design and geographical region; no obvious heterogeneity was detected. In the subgroup analysis of study design, the magnitude of risk reduction reported in prospective cohort studies was stronger than that reported in nested case-control studies (a 29% risk reduction compared with 15% reduction), which indicates that the association may have been diluted by study methodologies.

The possible explanation might be that prospective cohort studies are more relevant for identifying the associations between the disease and risk factors because the cohort studies were conducted in a larger population with a wider range of the circulating 25-hydroxyvitamin D concentrations and a longer period of follow up. Compared with nested case-control studies, prospective studies could reduce a variety of biases such as selection bias. In the meta-analysis of model on geographical region, a significant protective effect of circulating 25-hydroxyvitamin D was observed in European studies but not in the USA studies. Though limited, these studies may suggest that different races or geographical latitudes influence the potential association between circulating 25-hydroxyvitamin D and kidney cancer risk.

There were several limitations to our meta-analysis. First, the number of included articles was small and limited to developed countries. However, all nine studies were prospective studies with large populations; these studies were of high quality and thus, could provide reliable estimation on the association between circulating 25-hydroxyvitamin D and kidney cancer. Second, most included studies in the meta-analysis were from developed countries, including the USA and Europe. Further research should be conducted in African, Asian and other populations. Third, different studies used different methodological tools for measurement, including chemiluminescent immunoassay, liquid chromatography coupled with tandem mass spectrometry and predicted 25 (OH) D score. While these differences could affect comparability of studies and introduce heterogeneity between studies, we compared the highest level with the lowest level of circulating 25-hydroxyvitamin D in order to maintain uniformity. Fourth, though some studies had been adjusted for some relevant potential factors, such as age, sex and smoking status, the possibility of residual and unknown confounding cannot be excluded. Finally, the different pathological classifications of kidney cancer might have an influence on results. More well-designed studies are needed to further evaluate the association between circulating 25-hydroxyvitamin D and kidney cancer.

A prominent strength of our meta-analysis is the application of advanced techniques of statistical analysis that allowed for the explora-

tion of the relationship between circulating 25-hydroxyvitamin D and kidney cancer. To our best knowledge, it is the first meta-analysis on the potential relationship between circulating 25-hydroxyvitamin D and kidney cancer. Furthermore, all the included studies are longitudinal prospective studies which could provide reliable estimation. Finally, as there is no significant heterogeneity between individual studies, the results are robust and reliable.

Conclusion

Our present findings suggest that higher levels of circulating 25-hydroxyvitamin D could reduce the risk of kidney cancer by 21%. Further well-designed, large-scaled prospective studies and randomized controlled trials are warranted to provide more conclusive evidence.

Disclosure of conflict of interest

None.

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25-hydroxyvitamin and kidney cancer

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