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Review

Vitamin D deficiency as a risk factor for thyroid cancer: A meta-analysis of case-control studies

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ABSTRACT

Objective: The association between vitamin D deficiency and thyroid cancer is controversial. Some studies have demonstrated that higher serum vitamin D levels might protect against thyroid cancer, whereas others have not, or have even indicated the opposite to be the case. The aim of this meta-analysis was to investigate the association between vitamin D deficicency and thyroid cancer and propose that vitamin D deficiency is a risk factor for thyroid cancer.
Methods: This was a meta-analysis of 14 articles of the association between vitamin D deficiency and thyroid cancer. Databases including PubMed, Cochrane library, Sinomed, CNKI, Wanfang, and clinical trial register centers, were searched for case-control studies of vitamin D in thyroid cancer.
Results: Fourteen studies were included in this meta-analysis. A fixed-effect model was used to merge the standardized mean difference value of serum 25-hydroxyvitamin D levels. The pooled effect showed that the levels of serum 25-hydroxyvitamin D were lower in patients with thyroid cancer preoperatively than in the controls (−0.22; 95% confidence interval [CI], −0.36 to −0.09; $P = 0.001$). There was no difference after thyroid cancer patients underwent thyroidectomy (−0.19; 95% CI, −0.47 to 0.10; $P = 0.21$). A fixed-effect model was used to pool the odds ratio of thyroid cancer and vitamin D deficiency. It showed that the pooled odds ratio from six studies was 1.30 (95% CI, 1.00–1.69; $P = 0.05$). Subgroup analysis of 25-hydroxyvitamin D levels between different pathologic characteristics in patients with thyroid cancer was summarized, but no statistical differences were determined.
Conclusions: Lower serum 25-hydroxyvitamin D levels were associated with increased risk for thyroid cancer. On the other hand, vitamin D deficiency may act as a risk factor for thyroid cancer.

Introduction

Thyroid cancer is the most common malignant tumor in the endocrine system and is becoming increasingly prevalent worldwide. In the United States, nearly 63 000 new cases of thyroid cancer were diagnosed in 2014 [1] and the yearly incidence nearly tripled from 4.9 per 100 000 to 14.3 per 100 000 in the past three decades [2]. In China, the collection of cancer registration data in 2013 showed that the incidence of thyroid cancer in women reached 16.31 per 100 000 and became the fifth most frequent cancer in women [3]. Currently, the clear risk factors for thyroid cancer include exposure to radiation to the head and neck, sex, age, iodine deficiency or excess, and family history of thyroid cancer [4,5]. Unfortunately, the mechanisms of these known risk factors have not been clearly illuminated and most of them are ineluctable. These known risk factors cannot completely explain this increased prevalence. It is not clear whether the increased incidence of thyroid cancer is caused by the advanced imaging technology and thyroid disease screening or by other unknown reasons. Recently, some scientists proposed that vitamin D deficicency might be a potential risk factor for thyroid cancer [6–19]. The association between vitamin D deficiency and many kinds of cancers such as breast, colon, prostate, and even

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pancreatic has been reported [20]. However, whether vitamin D deficiency is related to thyroid cancer is still inconclusive. Some previous studies found that low levels of serum vitamin D showed a significant relationship with thyroid cancer [9–11,13,15,16,18], whereas other studies showed that there is no association [6–8,12,14,17,19]. The aim of this meta-analysis was to investigate the association between vitamin D deficiency and thyroid cancer. We propose that vitamin D deficiency is a risk factor for thyroid cancer.

Materials and methods

Searching progress

We conducted a search of the following databases for case-control studies of vitamin D in thyroid cancer: PubMed, Cochrane library, Sinomed, CNKI and Wanfang. Additional trials at the clinical trial register centers (http://www.clinicaltrials.gov) also were searched. The literature search for this meta-analysis was restricted to published results. Databases were searched from the earliest data to January1, 2018 with the search terms "25-hydroxyvitamin D" or "vitamin D" or "25(OH)D" or "25 OHD" or "cholecalciferol" and "thyroid cancer*" or "thyroid neoplasm*" or "thyroid tumor" or "thyroid carcinoma*" or "differentiated thyroid carcinoma" or "DTC" or "Papillary thyroid carcinoma" or "Thyroid carcinoma, papillary" or "PTC" or "Thyroid cancer, follicular" or "FTC" or "Thyroid Carcinoma, Anaplastic" or "ATC" or "Thyroid cancer, medullary" or "MTC". Reference lists of all eligible articles and related previous review articles also were hand searched.

Eligible studies met the following criteria:

- Published in English or Chinese language.
- Assessed the association between vitamin D and thyroid cancer.
- Designed as a case-control study.
- Reported at least one outcome, either the serum 25-hydroxyvitamin D (25-OHD) level or the number of patients with vitamin D deficiency.

Study selection and data extraction

Two reviewers independently screened the studies and any disagreements were resolved by consensus. If consensus could not be reached, a third experienced reviewer would make the final decision. From the eligible studies, the following data were extracted:

- Characteristics of populations, including the pathologic type of thyroid cancer, source of controls, mean age, sex, and testing method of vitamin D.
- The main results, including the 25-OHD level and the number of vitamin D deficiency.

Methodological quality assessment

Two reviewers independently assessed the Newcastle-Ottawa Scale (NOS) for case-control studies. A study can be scored one star for each numbered item within the Selection and Exposure categories, and two stars can be given for Comparability. A score of 9 is the highest and shows the highest quality. Disagreements were resolved by evaluating and discussing between two reviewers.

Statistical analysis

The main outcome was the level of serum 25-OHD and the incidence of vitamin D deficiency in patients with thyroid cancer. Other outcomes including the comparison of serum 25-OHD and different tumor node metastasis (TNM) stage or lymph node metastasis also were analyzed. Fixed-model was performed by weighted mean difference, standardized mean difference (SMD), and 95% confidence intervals (CI) for continuous variables. Fixed-model performed by computing odds ratio (OR) and 95% CI for dichotomous variables. The I^2 was calculated as an index of heterogeneity between studies. The analyses were performed by Review Manager 5.3 (Cochrane Collaboration, United Kingdom, http://www.cochrane.org).

Results

Search results and characteristics of included studies

Our research yielded 723 articles of potentially relevant studies. After screening abstracts, 25 were selected for full-text review. Of these 25 articles, 10 were eligible. Three additional articles from the reference lists of eligible articles by hand search and one article from the clinical trial register centers also were included. Fourteen studies were included in this meta-analysis. Search progress is shown in Figure 1. Of these 14 studies, two were published in Chinese [15,16] and the rest in English [6–14,17–19]. With the exception of China and Iran, which had two studies each, the rest of the countries—Brazil, Canada, Finland, Germany, Japan, Korea, Maryland, Poland, Turkey, and the United States—only had one study. In all, there were 1616 thyroid cancer patients in the case group and 6492 controls. The sample size ranged from 8 to 344 in the thyroid cancer group and 17 to 5133 in the control group. All of the cases were histologically and pathologically confirmed as being thyroid cancer. Among them, four studies [8,9,11,18] did not independently report the relationship between vitamin D and a

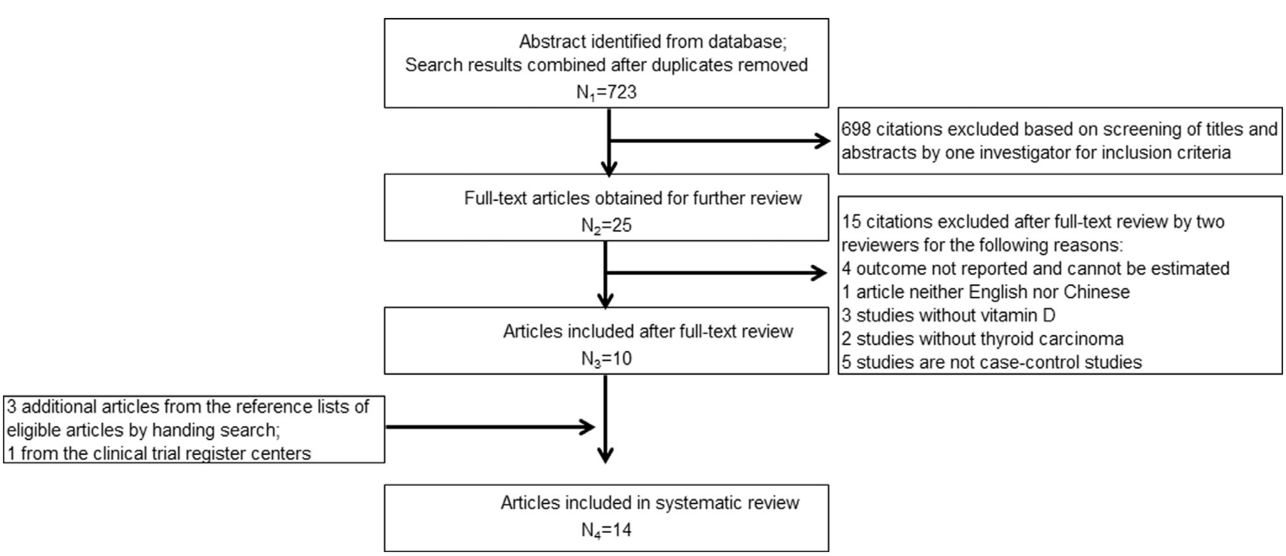

Fig. 1. Flowchart of the systematic search process.

Table 1
Characteristics of the 14 included studies

First author, year of publication	Country	Pathological type of thyroid cancer	Source of controls	Participants (n)		Mean age, y		Female (%)		Testing methods
				Cases	Control	Cases	Control	Cases	Control	
Shoushi Lee, 1982 [6]	Japan	MTC	Normal subjects	8	22	46 (14–68)*	21 to 39†	75	27.3	25-OHD: Competitive binding assay; 1.25-(OH2 D: Radioreceptor assay
Juka Toivonen, 1998 [7]	Finland	DTC	Healthy age- and sex-matched controls who were not using any drugs	29	38	45 (27–71)*	43 (26–65)*	86.2	Sex-matched	Both 25-OHD and 1,25-(OH2 D were determined by saturation analysis using kits
Nathan Laney, 2010 [8]	USA	Papillary, follicular, follicular variant of papillary, or hurthle cell thyroid cancer	Patients with thyroid nodules	69	42	Not mentioned	Not mentioned	81.2	90	25-OHD: DiaSorin or Nichols assay; 1.25-(OH)2 D: tandem mass spectrometry
Tomasz Stepien, 2010 [9]	Poland	PTC, FTC, ATC	Patients with multinodular nontoxic goiter; healthy volunteers	50	34; 26	54.15 ± 11.6‡	56.8 ± 14.3‡ 55.7 ± 9.2‡	66	70.6; 61.5	25-OHD: electrochemiluminescence ECLIA assay; 1.25-(OH2 D: enzyme immunoassay
Marissa Penna-Martinez, 2012 [11]	Germany	DTC	Healthy controls without a family history of thyroid carcinoma	253	302	55	38	66	45.7	25-OHD and 1,25-(OH)2 D were measured by a radioimmunoassay
Michael Roskies, 2012 [10]	Canada	Well-differentiated papillary, follicular, anaplastic, and Hurther cell carcinomas.	Infectious etiologies, benign adenomas, and micropapillary carcinomas	42	58	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Mustafa Sahin, 2013 [13]	Turkey	DTC	Not mentioned	344	116	45.5 ± 11§	44.9 ± 8§	84	85.3	25-OHD: commercially available ELISA kit
Jacqueline Jonklaas, 2013 [12]	Maryland	DTC	Benign thyroid disease.	48	17	45.9 ± 13.5§	52.5 ± 12.8§	Not mentioned	Not mentioned	25-OHD: tandem mass spectrometry
Jiang Yanyan, 2016 [15]	China	PTC	Healthy controls	358	290	44.02 ± 11.79§	43.92 ± 13.98§	77.6	65.5	25-OHD: electrochemiluminescence immunoassay.
Ye Jianbo, 2016 [16]	China	PTC	Healthy controls	31	40	51.44 ± 7.28§	50.29 ± 7.91§	100	Not mentioned	25-OHD: ELISA
Debora Lucia Seguro Danilovic, 2016 [14]	Brazil	DTC	Benign nodular thyroid disease	199	234	51.6 ± 15§	54.6 ± 14.5§	85.9	92.7	25-OHD: commercial chemiluminescent immunoassay
Zahra Heidari, 2017 [18]	Iran	DTC	Healthy euthyroid control participants	85	85	31.24 ± 11.36§	31.94 ± 12.27§	84.7	84.7	25-OHD: enzyme imunoassay.
Yun Mi Choi, 2017 [17]	Korea	PTC, FTC, MTC, and PTC or suspicious for malignancy by FNAC but not undergo surgery	Healthy controls	53	5133	54.44 ± 10.3§	54.1 ± 9.1§	37.7	36.5	25-OHD: DIA source 25 OH -Vit.D3-Ria-CT Kit
Ali Kachui, 2017 [19]	Iran	PTC	Healthy relatives of patients who took no medications were included after sex and age matching	47	55	F: 49.7 ± 38§ M: 65.6 ±7.33§	F: 18.8 ± 2.36§ M: 13.8 ± 2.33§	53.2	50.9	25-OHD: ELISA

25-OHD, 25-hydroxyvitamin D; 1,25-2 D, 1,25-dihydroxyvitamin D; ATC, anaplastic thyroid cancer; DTC, differentiated thyroid cancer; ELISA, enzyme-linked immunosorbent assay; FNAC, fine-needle aspiration cytology; FTC, follicular thyroid cancer; MTC, medullary cancer of thyroid; PTC, papillary thyroid cancer

* Mean (range).
† Range.
‡ Mean ± SEM.
§ Mean ± SD.

Table 2
Quality assessment according to the Newcastle-Ottawa Scale

First author, year of publication	Section	Comparability	Exposure	Total
Shoushi Lee, 1982 [6]	2	1	3	6
Juka Toivonen, 1998 [7]	1	2	3	6
Nathan Laney, 2010 [8]	3	2	3	8
Tomasz Stepien, 2010 [9]	2	2	3	7
Marissa Penna-Martinez, 2012 [11]	4	0	2	6
Michael Roskies, 2012 [10]	4	0	2	6
Mustafa Sagub, 2013	3	1	3	7
Jacqueline Jonklaas, 2013 [12]	4	2	3	9
Jiang Yanyan, 2016 [15]	4	2	3	9
Ye Jianbo, 2016 [16]	4	1	2	7
Debora Lucia Seguro Danilovic, 2016 [14]	4	2	3	9
Zahra Heidari, 2017 [18]	3	2	3	8
Yun Mi Choi, 2017 [17]	4	1	3	8
Ali Kachui, 2017 [19]	4	2	3	9

specific pathologic type. One study clearly divided the type to medullary thyroid cancer [6], three reported papillary thyroid cancer [14,15,19], and six reported differentiated thyroid cancer [7,10,12,13,16,17]. Controls were mainly healthy individuals without thyroid disease in eight studies [6,7,10,14,15,17–19], controls in five studies were patients with benign thyroid disease [8,9,11,13,16], and one was not mentioned [12]. The detailed characteristics of included studies are summarized in Table 1.

Quality of included studies

The quality assessment of the 14 studies is shown in Table 2. Studies that achieved five or more scores on the NOS were considered high quality, and 100% of these included studies were of high quality.

Serum 25-OHD level and thyroid cancer

Of the 14 studies, 11 reported the serum 25-OHD level both in cases and control groups [6,7,9,12–19]. Due to the different units of measurement in different studies, SMD value was used. We use the fixed-effect model to merge the SMD values. The pooled effect size in favor of control was −0.37 (95% CI, −0.45 to −0.28; $P < 0.00001$). Heterogeneity analysis showed a large heterogeneity (heterozygosity test, $\chi^2 = 148.14$; $P < 0.00001$; $I^2 = 93\%$). Studies were sub-grouped to analysis according to the time of blood collection. Studies were divided into preoperation, postoperation, and unknown (those that did not provide detailed messages about blood collection). Fixed-effect model was used to merge the SMD value of serum 25-OHD level and Figure 2 shows that the serum 25-hydroxyvitamin D level was lower in patients with thyroid cancer preoperatively than controls (−0.22; 95% CI, −0.36 to −0.09; $P = 0.001$), which means serum 25-OHD levels in patients with thyroid cancer was statistically significantly decreased. Whereas this difference in serum 25-OHD levels between patients with thyroid cancer and controls disappeared after surgery. The level of serum 25-OHD after surgery in patients with thyroid cancer had no statistical difference with control (−0.19; 95% CI, −0.47 to 0.10; $P = 0.21$). Pooled SMD from the four studies that did not show the detailed messages was −0.52 (95% CI, −0.65 to −0.40; $P < 0.00001$). Due to the large heterogeneity caused by the different pathologic types of thyroid cancer and different source of controls, subgroup by pathologic types of thyroid cancer and source of controls can not be done in the further subgroup analysis. The level of serum 25-OHD in patients with thyroid cancer before surgery is statistically significantly decreased compared with the control group, and there is no difference when these patients underwent thyroidectomy compared with controls.

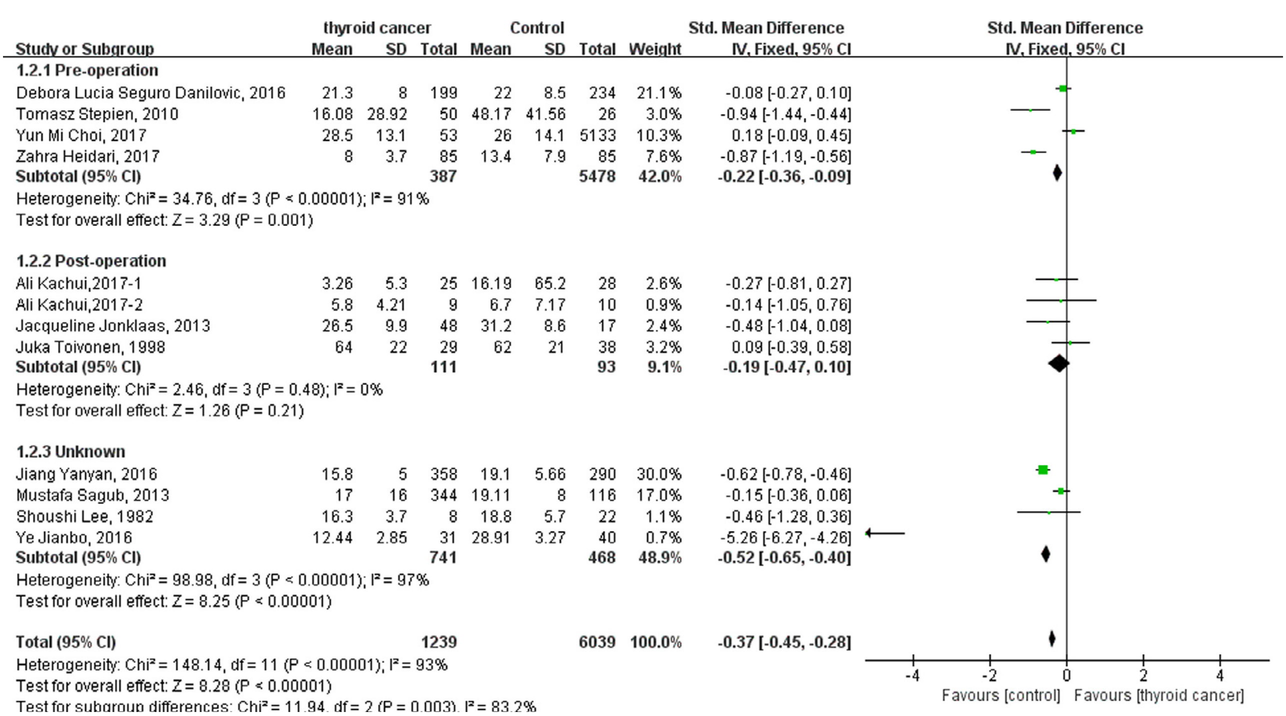

Fig. 2. Forest plot of the serum 25-OHD, 25-hydroxyvitamin D level in patients with thyroid cancer.

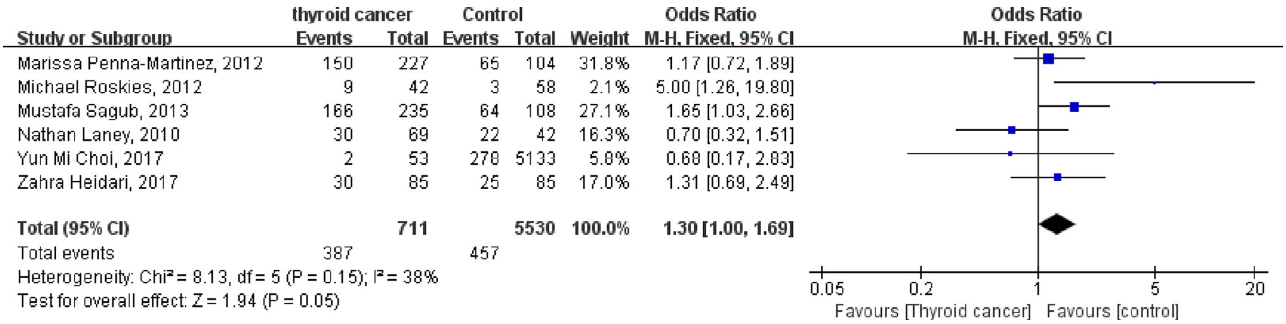

Fig. 3. Forest plot of vitamin D deficiency and risk for thyroid cancer.

Vitamin D deficiency and risk for thyroid cancer

Six studies analyzed the relative risk for vitamin D deficiency-associated thyroid cancer [8,10–12,17,18]. Fixed-effect model was used to estimate pooled OR. Figure 3 shows that the pooled OR from all six studies was 1.30 (95% CI, 1.00–1.69; $P = 0.05$). No significant heterogeneity was detected (heterozygosity test, $\chi^2 = 8.13$; $P = 0.15$; $I^2 = 38\%$). These results indicate that vitamin D deficiency could increase the risk for thyroid cancer by 30% compared with individuals who are not deficient in vitamin D.

Subgroup analysis of 25-OHD between different pathologic characteristics in patient with thyroid cancer

Tables 3 and 4 show the subgroup results according to the different pathologic characteristics (TNM stage and lymph node metastasis) in patients with thyroid cancer. Due to the limited studies and different units of measurement in these studies, further analysis of the association between vitamin D deficiency and thyroid cancer risk cannot be pooled here. According to the data we summarized here, Ye Jianbo et al. [15] reported that higher TNM stage has a higher level of serum 25-OHD and it is statistically different. However, Laney et al. [8] did not find a relationship between different TNM stages. The analysis was grouped by whether lymph node metastasis was done and is shown in Table 4. Two studies conducted in China show a very different conclusion. Yanyan et al. [14] found that patients with thyroid cancer have lower levels of serum 25-OHD than healthy controls. However, data in the study conducted by Ye Jianbo et al. was quite the opposite, showing that healthy controls had lower levels than the thyroid cancer population [15].

Publication bias

Funnel plot is a commonly used method that qualitatively measures publication bias. Through visual observation, we found that all the studies were distributed at the top of the funnel plot (Fig. 4). According to the symmetrical funnel plot, there was no obvious publication bias.

Discussion

The incidence of thyroid cancer has been progressively increasing worldwide [1,3,21]. It is believed by some scientists that the increased incidence of thyroid cancer, especially papillary thyroid cancer, may be caused by improved imaging techniques or universal screening for thyroid diseases, which may cause overdiagnosis or even excessive medical treatment [22]. However, these findings cannot fully explain the increasing incidence of non-microcarcinoma of thyroid. Due to increasing prevalence, researchers have concentrated on the risk factors for thyroid cancer. Most of risk factors we found, such as sex, age, family history of thyroid cancer, or even genetic mutations, cannot be prevented. Therefore, more researchers are focusing on exploring other risk factors that can be prevented by human.

Recently, risk factors such as insulin resistance [13,23], obesity [24,25], nutrition [26], and vitamin D deficiency [11,18] have been found to be associated with thyroid cancer. Serum 25-OHD is the main circulating form of vitamin D that represents the reserve level of vitamin D in human body. In addition to participating in calcium and phosphorus metabolism, it takes part in cell differentiation and proliferation. Davis [27] reported that vitamin D and its metabolites 25-OHD or 1,25-hydroxyvitamin D, as well as vitamin D receptor (VDR) are closely related to the occurrence, development, and prognosis of tumors. Nevertheless, the role of vitamin D deficiency in carcinogenesis remains controversial. Previous studies have suggested that higher serum 25-OHD levels might protect against thyroid cancer [9,10,13,15,16]. However, other studies did not show the same result [6–8,12,14,17,19], and some even indicate that a higher serum vitamin D level was detected in thyroid cancer patients with lymph node metastasis [15]. To reach a conclusion to the controversy, we conducted this meta-analysis of 14

Table 3
Comparison of 25-OHD between thyroid cancer with different TNM stages

First author, year of publication	TNM stage				*P*-value
	I	II	III	IV	
Nathan Laney, 2010 [8]	84 (30–218)*	95 (85–108)*	80 (47–88)*	95 (45–95)*	0.71
	84 (<25–180)*	60 (45–158)*	93 (38–135)*	93 (65–118)*	0.92
Ye Jianbo, 2016 [16]	10.56 ± 2.02†		14.36 ± 2.26†		<0.0001

25-OHD, 25-hydroxyvitamin D
* Data are median (range).
† Data are mean± SD.

Table 4
Comparison of 25-OHD between thyroid with and without lymph node metastasis

First author, year of publication	WMD	95% CI	*P*-value	Heterogeneity	
				I^2	*P*-value
Jiang Yanyan, 2016 [15]	−3.40	−4.53 to −2.27	0.27	99%	<0.00001
Ye Jianbo, 2016 [16]	4.46	2.98 to 5.94			

25-OHD, 25-hydroxyvitamin D; WMD, weighted mean difference

case–control studies and summarized that vitamin D deficiency might be a risk factor for thyroid cancer.

The role of vitamin D deficiency in the pathogenesis of many other cancers has been suggested, such as breast, colon, prostate, and pancreatic cancers [20]. However, little is known about thyroid cancer. Activated vitamin D directly binds to the VDR or indirectly interacts with other transcriptional regulator or cell signaling systems that decrease tumor growth [28,29]. 1,25-hydroxyvitamin D binds to VDR and forms a heterodimer. The heterodimer translocates to the nucleus, binds to vitamin D responsive elements in target genes, and finally alters the transcriptional levels. Cell cycle can be influenced by the activated vitamin D that arrest in the progression from G1 to S phase, thus inhibiting the growth of tumor cells [30]. Moreover, activated vitamin D could induce cell apoptosis through activating proapoptotic proteins and inhibiting antiapoptosis proteins [31–34]. Previous studies have reported that inflammatory cell infiltration was found in thyroid cancer [35,36]. Further experimental research found that inflammatory cells may possess protumorigenic potential [37,38]. Additional findings reported by Passler et al. [39] indicated that the inflammatory response in differentiated thyroid cancer can be reduced by activated vitamin D. On the basis of previous studies, we contend that the potential antineoplastic effects of vitamin D probably based on increased apoptosis, stopped the cell cycle, inhibited proliferation and promoted differentiation, reduced inflammatory response, and decreased invasiveness [8,40,41]. From these findings, the mechanisms by which vitamin D exerts the antineoplastic efficiency are not entirely clear and further study including clinical studies and basic research is needed.

The major limitation of this meta-analysis is that the definition of vitamin D deficiency was based on the level of serum 25-OHD, whereas the cutoff level of 25-OHD was very different between these eligible studies. Meanwhile, the measurement methods and the units of measurement of serum 25-OHD level in different studies were not the same. Some studies have included patients with thyroid cancer in many kinds of pathological types, and subgroup analysis of the association between vitamin D and different pathological types of thyroid cancer cannot be conducted due to the limited data in the published articles. However, we still can conclude that vitamin D deficiency is associated with thyroid cancer.

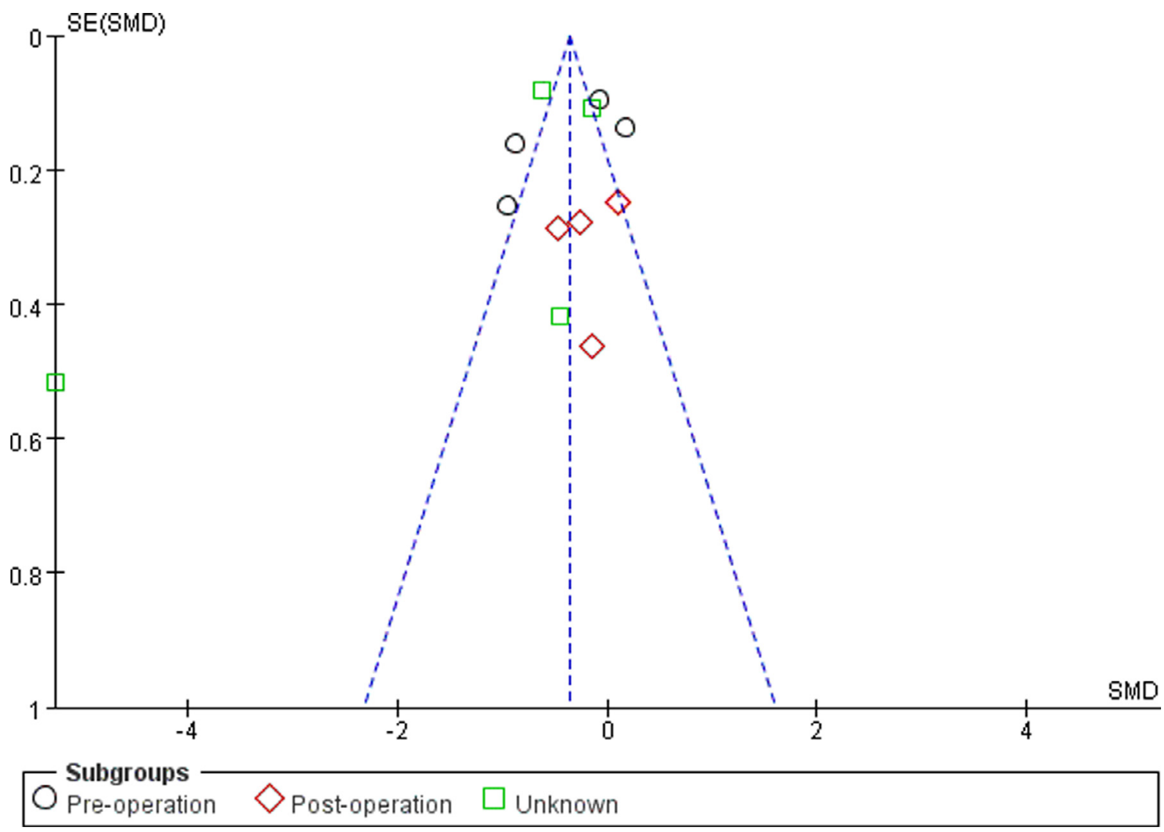

Fig. 4. Funnel plot of publication bias. SMD, standardized mean difference.

Conclusions

The present meta-analysis summarized the association between serum 25-OHD levels and thyroid cancer worldwide. The study suggested that lower serum 25-OHD levels were associated with increased risk for thyroid cancer. Although vitamin D deficiency may act as a risk factor for thyroid cancer, the difference of serum 25-OHD in different pathological characteristics in patients with thyroid cancer cannot be concluded from these limited studies. Therefore, more prospective clinical studies with a larger sample sizes may strengthen the evidence. More experimental studies should be done to elucidate the mechanism of vitamin D deficiency related to thyroid cancer.

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