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*Original Article*

# Significance of serum phosphorus, and vitamin D in papillary thyroid cancer patients in the eastern coastal China

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**Abstract:** Vitamin D deficiency is closely related with various cancers, while the clinical studies about serum vitamin D concentrations and thyroid cancer are few and inconsistent. Besides, the relationship between vitamin D concentrations and Chinese patients with thyroid cancer was not available. Therefore, we try to find whether there are differences in serum vitamin D levels and other test items of thyroid cancer compared with controls. We also want to assess their association with clinical characteristics and prognostic factors in papillary thyroid cancer (PTC) individuals. We investigated vitamin D levels and other test items, including 25-hydroxyvitamin D (25(OH)D), calcium, phosphorus, triiodothyronine (T3), free triiodothyronine (FT3), tetraiodothyronine (T4), free tetraiodothyronine (FT4), thyrotropin (TSH) and C-reaction protein (CRP), in 62 pre-operation thyroid cancer patients, 25 benign controls, and 53 healthy controls. Increased serum phosphorus concentrations, decreased vitamin D levels, and increased TSH levels in thyroid cancer than control. Serum phosphorus levels were inversely related with calcification and collagen, and vitamin D levels were negatively correlated with smoking status. The percentage of vitamin D deficiency was greatest among PTC patients. Serum phosphorus and vitamin D levels are associated with increased risk of PTC, and vitamin D could serve as a potential biomarker of thyroid cancer. Further studies with larger sample size need to be conducted to confirm.

**Keywords:** Phosphorus, vitamin D, papillary thyroid cancer

## Introduction

In most countries, the incidence of thyroid cancer (mainly papillary thyroid cancer, PTC) has increased rapidly over the past few decades [1]. Although the incidence rates vary widely in different countries, the incidence data show an upward trend such as the Republic of Korea [2], Italy [3], France [4] and the United States [5]. In China, the incidence of thyroid cancer increases at the rate of 14.51% annually [6]. The incidence has been appreciably increasing in the eastern coastal China because of the excessive iodine intake [7, 8].

As we known, the main function of vitamin D is to preserve bone health by maintaining calcium and phosphorus homeostasis. Vitamin D contributes to reabsorb calcium and phosphorus in kidney, also has a positive effect on the active transport of calcium and absorption of phosphorus in small intestine [9]. However, researches have founded that vitamin D is also related with non-skeletal system diseases in recent years, for instance, diabetes [10], adrenal diseases [11] and cancers [12, 13]. In vitro experiments, suboptimal vitamin D concentrations might lead to carcinogenesis by influencing the cancer cell proliferation [14], differentiation [15], apoptosis [16], and angiogenesis [17]. Interestingly, vitamin D deficiency has been correlated with the incidence and prognosis of breast cancer [18], colon cancer [19] and prostate cancer [20]. Nevertheless, the relationship between vitamin D and PTC is few and inconsistent [21].

**Table 1.** Clinical and laboratory characteristics of healthy controls, benign, and thyroid cancer patients

| | Healthy (n=53) | Benign (n=25) | Thyroid cancer (n=62) | *P* value |
|---|---|---|---|---|
| Age (years) | 47.6±8.1 | 52.2±8.2 | 47.8±11.7 | 0.123 |
| Sex | | | | |
| Male | 17 (32.1%) | 5 (20.0%) | 16 (25.8%) | 0.511 |
| Female | 36 (67.9%) | 20 (80.0%) | 46 (74.2%) | |
| BMI (kg/m$^2$) | 22.9±3.4 | 23.5±3.2 | 23.7±3.5 | 0.819 |
| Smoking | | | | |
| NO | 46 (86.8%) | 22 (88.0%) | 53 (85.5%) | 0.984 |
| Yes | 7 (13.2%) | 3 (12.0%) | 9 (14.5%) | |
| Drinking | | | | |
| NO | 49 (92.5%) | 23 (92.0%) | 57 (91.9%) | 0.994 |
| Yes | 4 (7.5%) | 2 (8.0%) | 5 (8.1%) | |
| Family history of cancer | | | | |
| NO | 44 (83.0%) | 21 (84.0%) | 45 (72.6%) | 0.304 |
| Yes | 9 (17.0%) | 4 (16.0%) | 17 (27.4%) | |
| Calcium (mmol/L) | 2.3±0.1 | 2.3±0.1 | 2.3±0.1 | 0.538 |
| Phosphorus (mmol/L) | 1.0±0.2 | 1.0±0.2 | 1.1±0.1 | 0.012 |
| 25(OH)D (ng/mL) | 22.5±14.8 | 18.1±8.4 | 16.8±8.1 | 0.025 |
| T3 (ng/mL) | 1.1±0.2 | 1.1±0.2 | 1.0±0.3 | 0.295 |
| FT3 (pg/mL) | 3.5±0.3 | 3.5±0.4 | 3.6±0.5 | 0.947 |
| T4 (μg/dL) | 8.6±1.4 | 8.6±1.4 | 8.5±1.4 | 0.952 |
| FT4 (ng/dL) | 13.1±0.1 | 1.3±0.2 | 1.3±0.2 | 0.333 |
| TSH (μIU/mL) | 1.7±0.9 | 2.3±1.3 | 2.6±0.2 | 0.009 |
| CRP (mg/L) | 1.7±2.3 | 2.4±4.6 | 2.7±5.2 | 0.425 |

**Table 2.** Odds ratio of thyroid cancer according to serum phosphorus, 25(OH)D and TSH level usinglogistic regression model

| | Adjusted OR | 95% CI | *P* value |
|---|---|---|---|
| Phosphorus | 20.7 | [1.328, 324.009] | 0.031 |
| 25(OH)D | 0.965 | [0.928, 1.004] | 0.078 |
| TSH | 1.589 | [1.062, 2.378] | 0.024 |

The most bioactive form of vitamin D is 1, 25-dihydroxyvitamin D3 [1,25-$(OH)_2D_3$], with a half-life of 4 hours only. Whereas, the primary circulating form of vitamin D is serum 25(OH)D and its half-life is 2-3 weeks [22]. So serum 25(OH)D level is the most suitable to reflect vitamin D status. 25(OH)D level <20 ng/mL is considered vitamin D deficiency, with 20-40 ng/ml defined as suboptimal vitamin D by WHO [23].

An epidemiology study has shown that high calcium and phosphorus intake has been related with an incremental risk of advanced prostate cancer [24]. While the relationship between calcium intake and risk of colon cancer is controversial [25]. Meanwhile, phosphorus plays a vital role in cell metabolism by participating in the synthesis of nucleic acids, high energy metabolites, and phospholipids [26]. Calcium is an important intracellular messenger, involving in cell signaling, proliferation, and apoptosis [27].

This study aims to explore whether there have abnormal serum vitamin D, phosphorus and calcium levels in PTC compared with benign and healthy controls. Meanwhile, their association with clinical characteristics and prognosis factors will be evaluated in the future.

## Materials and methods

### *Subjects*

In our study, there are 75 cases specimens obtained from PTC patients who were newly diagnosed and without any treatment in Zhejiang Cancer Hospital from June 2014 to August 2014. Exclusion criteria consisted of hypothyroidism, hyperthyroidism, diabetes, and non-thyroid malignancies. Two of the 75 patients had hypothyroidism, four had hyperthyroidism, and five had diabetes, and two had other cancers for the past. Thus only 62 cases specimens met the inclusion criteria from these individuals in our study. In accordance with the AJCC/UICC stage classification (7th edition), PTC staging was carried out. Benign controls include 25 benign patients who had non-malignant thyroid disorders such as follicular adenomas, cysts and goiter. Meanwhile, 53 healthy individuals who came to do physical examinations were selected to be healthy controls. This research was approved by the ethics committee in Zhejiang Cancer hospital. The requirement of informed consent was acquired from all individuals.

### *Measurements*

Blood samples were centrifuged at 4°C at 3000 rpm for 5 min, and serum was collected.

**Table 3.** Association of serum phosphorus, and 25(OH)D levels with prognostic factors and thyroid cancer stage

| | Cases | Serum phosphorus | | 25(OH)D | |
|---|---|---|---|---|---|
| | | Mean ± SD | *P* value | Mean ± SD | *P* value |
| Age (years) | | | | | |
| <45 | 23 (37.0%) | 1.1±0.1 | 0.557 | 19.0±8.9 | 0.110 |
| ≥45 | 39 (63.0%) | 1.1±0.1 | | 15.6±7.4 | |
| Sex | | | | | |
| Male | 16 (25.8%) | 1.05±0.13 | 0.011 | 17.7±11.0 | 0.682 |
| Female | 46 (74.2%) | 1.15±0.13 | | 16.5±7.4 | |
| BMI (kg/m$^2$) | | | | | |
| <25 | 43 (69.4%) | 1.1±0.1 | 0.402 | 17.2±8.1 | 0.646 |
| ≥25 | 19 (30.6%) | 1.1±0.2 | | 16.1±8.3 | |
| Smoking | | | | | |
| NO | 53 (85.5%) | 1.1±0.1 | 0.147 | 17.8±8.0 | 0.025 |
| Yes | 9 (14.5%) | 1.1±0.1 | | 11.3±7.1 | |
| Drinking | | | | | |
| NO | 57 (91.9%) | 1.1±0.1 | 0.223 | 17.0±8.2 | 0.548 |
| Yes | 5 (8.1%) | 1.1±0.1 | | 14.7±7.8 | |
| Family history of cancer | | | | | |
| NO | 45 (72.6%) | 1.1±0.1 | 0.909 | 16.4±8.4 | 0.471 |
| Yes | 17 (27.4%) | 1.1±0.1 | | 18.1±7.5 | |
| Tumor diameter (cm) | | | | | |
| <2 | 53 (85.5%) | 1.1±0.1 | 0.155 | 16.9±8.0 | 0.871 |
| ≥2 | 9 (14.5%) | 1.1±0.1 | | 16.4±9.3 | |
| Stage | | | | | |
| I-II | 50 (80.6%) | 1.1±0.1 | 0.925 | 16.7±8.1 | 0.878 |
| III-IV | 12 (19.4%) | 1.1±0.2 | | 17.1±8.4 | |
| Number of positive lymph nodes | | | | | |
| NO | 41 (66.1%) | 1.1±0.1 | 0.899 | 16.5±8.4 | 0.660 |
| Yes | 21 (33.9%) | 1.1±0.1 | | 17.5±7.7 | |
| Calcification | | | | | |
| NO | 43 (69.4%) | 1.15±0.13 | 0.046 | 16.0±7.7 | 0.196 |
| Yes | 19 (30.6%) | 1.07±0.14 | | 18.9±8.9 | |
| Collagen | | | | | |
| NO | 46 (74.2%) | 1.15±0.13 | 0.012 | 17.0±8.5 | 0.859 |
| Yes | 16 (25.8%) | 1.05±0.14 | | 16.5±7.2 | |

Serum 25(OH)D concentrations were measured on the Cobas e602 (Roche, Switzerland) by electrical chemiluminescence immunoassay (ECLIA). Serum levels of phosphorus, calcium, C-reaction protein (CRP) were checked on the Hitachi-7600 automated chemistry analyzer (Hitachi, Japan). The other analyses including triiodothyronine (T3), free triiodothyronine (FT-3), tetraiodothyronine (T4), free tetraiodothyronine (FT4), and thyrotropin (TSH) were analyzed on ADVIA Centaur XP (Siemens, Germany). The reference ranges for the thyroid assays were T3 0.66-1.92 ng/mL, FT3 1.80-4.10 pg/mL, T4 4.3-12.5 μg/dL, FT4 0.81–1.89 ng/dL, and TSH 0.38-4.34 μIU/mL. All analyses were checked in the clinical laboratory of Zhejiang Cancer Hospital.

*Statistical analysis*

All statistical analysis was performed by the software SPSS 16.0 software (SPSS, Inc., Chicago, IL, USA). Normality of distribution of variables was conducted using Kolmogorov-Smirnov tests. Means (standard deviation) were described for continuous variables and frequency (proportion) was assessed for categorical variables in this study. The comparisons of all analyses values among healthy controls, benign, and thyroid cancer were estimated by One-Way ANOVA. Odds ratio of thyroid cancer according to serum phosphorus, 25-(OH)D and TSH levels using logistic regression model. Individuals were compared for differences in phosphorus, and 25(OH)D values by a Wilcoxon rank sum test according to the baseline characteristics, such as age, sex, BMI, smoking status, drinking status, family history of cancer, tumor diameter, stage, number of positive lymph nodes, calcification, and collagen. The association between variables and thyroid cancer prognostic factors was evaluated by spearman correlation. P<0.05 (two-tailed) was defined as statistically significant.

**Table 4.** Correlation between serum phosphorus, 25(OH)D level and tumor clinical characteristics

| Factors | Spearman correlation coefficient (*P* value) | |
|---|---|---|
| | Phosphorus | 25(OH)D |
| Age (years) | 0.038 (0.769) | -0.141 (0.275) |
| BMI (kg/m$^2$) | 0.086 (0.505) | -0.049 (0.708) |
| Smoking | -0.188 (0.143) | -0.285 (0.025) |
| Drinking | -0.126 (0.330) | -0.055 (0.673) |
| Family history of cancer | 0.028 (0.827) | 0.080 (0.538) |
| Tumor diameter (cm) | -0.018 (0.889) | -0.045 (0.730) |
| Stage | -0.021 (0.871) | 0.008 (0.952) |
| Number of positive lymph nodes | 0.003 (0.982) | 0.096 (0.457) |
| Calcification | -0.267 (0.036) | 0.152 (0.240) |
| Collagen | -0.500 (0.003) | -0.006 (0.972) |

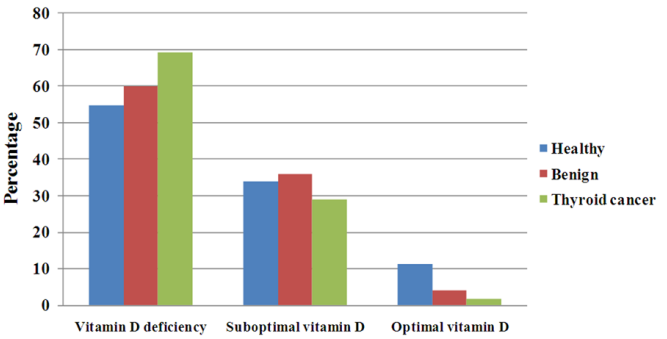


**Figure 1.** Percentage of vitamin D deficiency (<20 ng/ml), suboptimal vitamin D (20-40 ng/ml) and optimal vitamin D (>40 ng/ml) among the healthy, benign and thyroid cancer patients.

## Results

*Elevated phosphorus, lower 25(OH)D, increased TSH levels in PTC*

The 62 remaining thyroid cancer individuals were 74% female and their ages ranged from 18 to 77 years, with an average age of 48 years. The distribution of TNM staging systems was as follows: 71% (44 patients) in stage 1, 10% (6 patients) in stage 2, 13% (8 patients) in stage 3, and 6% (4 patients) in stage 4. The clinical and laboratory characteristics of PTC, benign and healthy controls were shown in **Table 1**. Elevated phosphorus (P=0.006), lower 25(OH)D (P=0.008), increased TSH levels (P=0.002) were significantly related to thyroid cancer individuals compared with healthy controls. Meanwhile, there was significantly higher phosphorus concentration in PTC than benign (P=0.039). The odds ratios (ORs) and 95% confidence intervals (CIs) for having PTC based on serum phosphorus, 25(OH)D, and TSH levels were displayed in **Table 2**. Serum phosphorus (OR 20.7 [95% CI 1.3-324.0]) and TSH (OR 1.6 [95% CI 1.1-2.4]) were related with an elevated risk of PTC.

*Association of phosphorus, and 25(OH)D with clinical characteristics and prognostic factors*

**Table 3** shows the relationship of serum phosphorus, and 25(OH)D concentrations with age, sex, BMI, smoking status, drinking status, family history of cancer, tumor diameter, stage, number of positive lymph nodes, calcification, and collagen. Serum phosphorus in female patients were higher than in male (P=0.011), and phosphorus in patients with calcification or collagen were lower than without. While smoking status was negatively associated with 25(OH)D level (P=0.025). **Table 4** shows Spearman correlation coefficient between serum phosphorus, 25(OH)D level and tumor clinical characteristics and prognostic factors. There were negatively correlations between phosphorus and calcification (r=-0.267, P=0.036). Also, there was same inversely correlation between phosphorus and collagen (r=-0.5, P=0.003). Meanwhile, 25(OH)D level was negatively correlated with smoking status (r=-0.285, P=0.025).

*Vitamin D deficiency in three groups*

The percentages of vitamin D deficiency (<20 ng/ml), suboptimal vitamin D (20-40 ng/ml) and optimal vitamin D (>40 ng/ml) among the healthy, benign and thyroid cancer patients are displayed in **Figure 1**. Vitamin D deficiency was found in 55% (29/53) healthy control, 60% (15/25) of benign, while 68% (42/62) of PTC patients were deficient. Suboptimal vitamin D was seen in 34% (18/53) controls, 36% (10/25) of benign, and 29% (18/62) of thyroid cancer group (P=0.165). Association of vitamin D tertiles with thyroid cancer prognosis factors was listed in **Table 5** and no relationship was found.

## Discussion

In vitamin D deficiency individuals, serum phosphorus and calcium concentrations usually low. Vitamin D deficiency was closely associated with cancer such as breast cancer, lung cancer,

**Table 5.** Association of vitamin D tertiles with thyroid cancer prognosis factors

| Factors | Vitamin D deficiency | Suboptimal vitamin D | *P* value |
|---|---|---|---|
| Cases | 42 | 19 | |
| Age (years) | 49.1±11.1 | 45.2±12.8 | 0.231 |
| BMI (kg/m$^2$) | 23.8±3.8 | 23.4±2.7 | 0.669 |
| Smoking | 7 (16.7%) | 2 (10.5%) | 0.535 |
| Drinking | 3 (7.1%) | 2 (10.5%) | 0.658 |
| Family history of cancer | 13 (31.0%) | 3 (15.8%) | 0.216 |
| Tumor diameter (cm) | 1.0±0.5 | 1.4±1.3 | 0.277 |
| Stage | | | |
| I-II | 35 (83.3%) | 14 (73.7%) | 0.384 |
| III-IV | 7 (16.7%) | 5 (26.3%) | |
| Number of positive lymph nodes | 12 (28.6%) | 9 (47.3%) | 0.156 |
| Calcification | 12 (28.6%) | 6 (31.6%) | 0.813 |
| Collagen | 11 (26.2%) | 5 (26.3%) | 0.992 |

and prostate cancer [12, 13]. However, the previous study indicated that in lung cancer pretreatment serum phosphorus levels were higher than the normal range [28]. The epidemiology study has found that high calcium and phosphorus intake was associated with an elevated risk of advanced-stage and high-grade prostate cancer [24]. And high-phosphorus intake may contribute to abnormal cell metabolic and the development of chronic disease such as cancer, hypertension, and obesity [29]. Another study showed there was no significant difference in calcium levels between Hashimoto's thyroiditis patients with vitamin D deficiency and healthy controls [30]. Based on this research, we found there was significantly higher serum phosphorus in PTC group than benign and healthy controls. No significant difference in calcium level was found among the three groups. What's more, serum phosphorus was positively associated with an elevated risk of thyroid cancer and negatively related with calcification and collagen.

The early research showed that higher preoperative TSH concentrations compared with healthy controls and higher TSH levels were associated with an increased risk of thyroid cancer [31]. We found the consistent result, but TSH levels were not found to be related with prognostic factors.

The report about relationship between vitamin D deficiency and thyroid cancer is few and ambiguous. A recent research demonstrated the negative relationship between 25(OH)D deficiency and well-differentiated thyroid cancer in Canada. The malignancy rate increased from 37.5% to 75%, when comparing the vitamin D sufficiency with vitamin D deficiency [32]. Another study showed reduced serum 25(OH)D concentrations and increased rate of 25(OH)D deficiency in PTC compared with healthy controls [33]. A different group from Egypt showed prevalence of vitamin D deficiency in thyroid cancer was similar with the thyroid nodules group, and vitamin D deficiency was only associated with BMI [34]. Another report demonstrated the decreased serum 1,25-$(OH)_2D_3$ of Poland patients, but no differences in serum 25(OH)D concentrations [35]. Other studies did not show any relationships between 25(OH)D levels or the rate of 25(OH)D deficiency and the risk or the clinical characteristics of thyroid cancer [36, 37].

On this study, we found decreased 25(OH)D levels and higher percentage of 25(OH)D deficiency in PTC compared with healthy controls. No significant difference in 25(OH)D levels were found between thyroid cancer and benign or between benign and healthy controls. We demonstrated the smoking status was the only predictor of 25(OH)D levels and was inversely related with 25(OH)D concentrations. We did not find any related reports about smoking status and 25(OH)D concentrations because smoking status of thyroid cancer patients may not be included in their consideration. Vitamin D levels were known to be negatively related with BMI [38]. But we did not find the similar result between vitamin D status and BMI. Other clinical characteristics and prognostic factors such as family history of cancer, drinking status were not associated with 25(OH)D levels or the percentage of 25(OH)D deficiency.

Our research has a few limitations: first due to the small amount of thyroid cancer, the case of optimal vitamin D (>40 ng/ml) was too small. So the vitamin D tertiles were only included two groups in **Table 5**. Besides, small samples in this study leads to the fact that the upper bound of 95% CI of serum phosphorus was too high. Second, all the thyroid patients in this study were PTC. We did not analysis the association

between vitamin D levels and other types of thyroid cancer. Third, vitamin D intake was not available, so we couldn't take this potential confounder into account. We were not matched other confounding factors such as sex, age. Finally, different vitamin D analytical methods may cause different vitamin D concentrations. We did not choose different assays to compare the results.

As vitamin D levels were influenced by many kinds of factors, such as season, diet, race, regions. To account for the season confounder, we only collect serum of PTC in summer from June to August. All the serum was obtained from the pre-operation patients without any treatment. Because excess of iodine intake is a reputed predisposing factor for thyroid factor, we only choose individuals resident in the eastern coastal China.

In summary, based on the results in our research, high serum phosphorus levels and low levels of vitamin D in PTC individuals compared to controls. Increased serum phosphorus concentrations were positively associated with the risk of PTC and negatively related with calcification and collagen. No relationship between serum vitamin D levels and risk of PTC. The only predictor of vitamin D is smoking status and inversely correlated. The percentage of vitamin D deficiency is the greatest in PTC patients and lowest in healthy controls but no statistical difference was found. No relationship was found between the rate of vitamin D deficiency and clinical characteristics or prognostic factors. Our sample size was too low, and the association of phosphorus levels and vitamin D levels with clinical characteristics of thyroid cancer individuals should be confirmed by further researches with bigger sample size. What's more, the association between serum vitamin D concentrations and vitamin D receptor in thyroid cancer is unknown. Further studies need to explore in this area.

## Disclosure of conflict of interest

None.

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## References

[1] La Vecchia C, Malvezzi M, Bosetti C. Thyroid cancer mortality and incidence: a global overview. Int J Cancer 2015; 136: 2187-2195.

[2] Ahn HS, Kim HJ, Welch HG. Korea's thyroid-cancer "epidemic"--screening and overdiagnosis. N Engl J Med 2014; 371: 1765-1767.

[3] Dal Maso L, Lise M, Zambon P. Incidence of thyroid cancer in Italy, 1991-2005: time trends and age-period-cohort effects. Ann Oncol 2011; 22: 957-963.

[4] Binder-Foucard F, Bossard N, Delafosse P. Cancer incidence and mortality in France over the 1980-2012 period: solid tumors. Rev Epidemiol Sante Publique 2014; 62: 95-108.

[5] Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg 2014; 140: 317-322.

[6] Liu YQ, Zhang SQ, Chen WQ. [Trend of incidence and mortality on thyroid cancer in China during 2003 - 2007]. Zhonghua Liu Xing Bing Xue Za Zhi 2012; 33: 1044-1048.

[7] Wang Y, Wang W. Increasing incidence of thyroid cancer in Shanghai, China, 1983-2007. Asia Pac J Public Health 2015; 27: NP223-229.

[8] Teng W, Shan Z, Teng X. Effect of iodine intake on thyroid diseases in China. N Engl J Med 2006; 354: 2783-2793.

[9] Basit S. Vitamin D in health and disease: a literature review. Br J Biomed Sci 2013; 70: 161-172.

[10] Song Y, Wang L, Pittas AG. Blood 25-hydroxy vitamin D levels and incident type 2 diabetes: a meta-analysis of prospective studies. Diabetes Care 2013; 36: 1422-1428.

[11] Pani MA, Seissler J, Usadel KH, Badenhoop K. Vitamin D receptor genotype is associated with Addison's disease. Eur J Endocrinol 2002; 147: 635-640.

[12] Giammanco M, Di Majo D, La Guardia M. Vitamin D in cancer chemoprevention. Pharm Biol 2015; 53: 1399-1434.

[13] Watanabe R, Inoue D. [Current Topics on Vitamin D. Anti-cancer effects of vitamin D]. Clin Calcium 2015; 25: 373-380.

[14] Thill M, Woeste A, Reichert K. Vitamin D inhibits ovarian cancer cell line proliferation in combination with celecoxib and suppresses cyclooxygenase-2 expression. Anticancer Res 2015; 35: 1197-1203.

[15] Ribiczey P, Papp B, Homolya L. Selective upregulation of the expression of plasma membrane calcium ATPase isoforms upon differentiation and 1,25$(OH)_2D_3$-vitamin treatment of

colon cancer cells. Biochem Biophys Res Commun 2015; 464: 189-194.
[16] Sergeev IN. Vitamin D-mediated apoptosis in cancer and obesity. Horm Mol Biol Clin Investig 2014; 20: 43-49.
[17] Xu J, Li W, Ma J. Vitamin D-pivotal nutraceutical in the regulation of cancer metastasis and angiogenesis. Curr Med Chem 2013; 20: 4109-4120.
[18] Rose AA, Elser C, Ennis M, Goodwin PJ. Blood levels of vitamin D and early stage breast cancer prognosis: a systematic review and meta-analysis. Breast Cancer Res Treat 2013; 141: 331-339.
[19] Robsahm TE, Tretli S, Dahlback A, Moan J. Vitamin D3 from sunlight may improve the prognosis of breast-, colon- and prostate cancer (Norway). Cancer Causes Control 2004; 15: 149-158.
[20] Trummer O, Langsenlehner U, Krenn-Pilko S, Pieber TR, Obermayer-Pietsch B, Gerger A, Renner W, Langsenlehner T. Vitamin D and prostate cancer prognosis: a Mendelian randomization study. World J Urol 2016; 34: 607-11.
[21] Muscogiuri G, Tirabassi G, Bizzaro G. Vitamin D and thyroid disease: to D or not to D? Eur J Clin Nutr 2015; 69: 291-296.
[22] Holick MF, Binkley NC, Bischoff-Ferrari HA. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96: 1911-1930.
[23] Abdelgawad IA, El-Mously RH, Saber MM. Significance of serum levels of vitamin D and some related minerals in breast cancer patients. Int J Clin Exp Pathol 2015; 8: 4074-4082.
[24] Wilson KM, Shui IM, Mucci LA, Giovannucci E. Calcium and phosphorus intake and prostate cancer risk: a 24-y follow-up study. Am J Clin Nutr 2015; 101: 173-183.
[25] Heilbrun LK, Hankin JH, Nomura AM, Stemmermann GN. Colon cancer and dietary fat, phosphorus, and calcium in Hawaiian-Japanese men. Am J Clin Nutr 1986; 43: 306-309.
[26] Anghileri LJ. The metabolism of calcium and phosphorus and the cellular lipoproteins of the Ehrlich's ascites tumor cell. Int J Clin Pharmacol 1974; 10: 23-29.
[27] Rasmussen H, Rasmussen JE. Calcium as intracellular messenger: from simplicity to complexity. Curr Top Cell Regul 1990; 31: 1-109.
[28] Kouloulias V, Tolia M, Tsoukalas N. Is there any potential clinical impact of serum phosphorus and magnesium in patients with lung cancer at first diagnosis? A multi-institutional study. Asian Pac J Cancer Prev 2015; 16: 77-81.
[29] Anderson JJ. Potential health concerns of dietary phosphorus: cancer, obesity, and hypertension. Ann N Y Acad Sci 2013; 1301: 1-8.
[30] Tamer G, Arik S, Tamer I, Coksert D. Relative vitamin D insufficiency in Hashimoto's thyroiditis. Thyroid 2011; 21: 891-896.
[31] Boi F, Minerba L, Lai ML. Both thyroid autoimmunity and increased serum TSH are independent risk factors for malignancy in patients with thyroid nodules. J Endocrinol Invest 2013; 36: 313-320.
[32] Roskies M, Dolev Y, Caglar D. Vitamin D deficiency as a potentially modifiable risk factor for thyroid cancer. J Otolaryngol Head Neck Surg 2012; 41: 160-163.
[33] Sahin M, Ucan B, Ginis Z. Vitamin D3 levels and insulin resistance in papillary thyroid cancer patients. Med Oncol 2013; 30: 589.
[34] Laney N, Meza J, Lyden E. The prevalence of vitamin D Deficiency is similar between thyroid nodule and thyroid cancer patients. Int J Endocrinol 2010; 2010: 805716.
[35] Stepien T, Krupinski R, Sopinski J. Decreased 1-25 dihydroxyvitamin D3 concentration in peripheral blood serum of patients with thyroid cancer. Arch Med Res 2010; 41: 190-194.
[36] Jonklaas J, Danielsen M, Wang H. A pilot study of serum selenium, vitamin D, and thyrotropin concentrations in patients with thyroid cancer. Thyroid 2013; 23: 1079-1086.
[37] Mack WJ, Preston-Martin S, Bernstein L, Qian D. Lifestyle and other risk factors for thyroid cancer in Los Angeles County females. Ann Epidemiol 2002; 12: 395-401.
[38] Wortsman J, Matsuoka LY, Chen TC. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000; 72: 690-693.