Original Article

Relationships between serum levels of vitamins and papillary thyroid cancer: a single center case-control study

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Background: Vitamins are involved in various human physiological and biochemical mechanisms due to their antioxidant properties and their ability to enhance the immune response. Deficiency of some serum vitamins has been reported to be associated with an increased risk of developing cancer, including thyroid cancer. However, medical literature dealing with cholecalciferol supplementation was not able to show the potential of this intervention in cancer prevention. The aim of this paper is to highlight the association between lower serum vitamins levels and papillary thyroid cancer occurrence.

Methods: This case-control study was conducted between September 2018 and October 2019. Cases were defined as patients with histologically diagnosed papillary thyroid cancer who underwent thyroidectomy were retrospectively recruited and serum levels of various vitamins were assessed by examining their relationships with clinical, pathological and molecular data (n=51). Controls matched on sex and thyroid surgery were randomly selected from the same population (n=49).

Results: In this study, serum concentrations of vitamins A and E in neoplastic patients were significantly lower than in controls (1.40 *vs.* 1.78, P<0.003 and 23.9 *vs.* 29.1, P<0.003, respectively). Serum concentrations of vitamin D and methylmalonic acid were borderline significantly low (15.6 *vs.* 17.9, P=0.06 and 100.3 *vs.* 110.4, P=0.055, respectively), while homocysteine was statistically similar in the two groups. Furthermore, serum vitamin levels were compared with the pathological characteristics of cancer patients, and vitamin D concentrations were significantly lower in BRAF-positive than in BRAF-negative neoplastic patients (8.2 *vs.* 16.0, P=0.021). On the other hand, no significant differences were observed in the correlation between serum levels of vitamins and other pathological characteristics, in particular with regard to lymph node metastases.

Conclusions: In conclusion, albeit with the analysis of a limited sample, this study highlighted the

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phenomenon that deficiencies in vitamins A and E can be associated with a higher frequency of occurrence of papillary thyroid cancer.

Keywords: Vitamins; cancer; thyroid cancer (TC); papillary thyroid cancer (PTC)

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Introduction

Epidemiological studies have indicated the role of nutrients, particularly a deficiency in their antioxidant properties, in carcinogenesis (1-3). Some nutrients are involved in DNA repair, inflammation, endogenous hormones and growth factors levels through regulation of gene expression (4,5). Vitamins are required for various functions of the body through mechanisms that include their antioxidant properties and enhancement of the immune response (6-8).

Papillary thyroid carcinoma (PTC) is an epithelial malignancy harboring follicular cell differentiation and particular nuclear features. It is the most frequent thyroid neoplasm (9). Known risk factors for PTC include radiation exposure especially childhood exposure (environmental or medical reasons), genetics, high dietary iodine intake and preexisting thyroid disease (9). Moreover, an association has been controversially suggested between inflammation in chronic lymphocytic thyroiditis (CLT) and PTC. Fiore *et al.* reported a higher frequency of PTC in nodular-CLT patients than in patients with non-CLT nodular goiter and a significant correlation with thyroid-stimulating hormone (TSH) levels. They hypothesized that higher TSH levels increase the probability that mutated oncogenes may cause clinically detectable cancer (10,11).

There is literature that evaluated the role of vitamin D in the development of thyroid disease (12-15), particularly of vitamin D deficiency (5,7,8,16-18) associated with thyroid cancer (TC), with one study also evaluating the serum concentrations of vitamin E, calcium, zinc which were lower in medullary TC patients than in healthy controls and that their integration can reduce the neoplastic risk (19). However, only a few studies suggested that low intake/low serum levels of vitamin D are associated with higher risk of TC (5,7,16). Knowledge gaps exist in the clinical significance of serum vitamin levels in PTC. The study of Kuang *et al.* (20) evaluated the impact of preoperative serum vitamin D levels and local vitamin D metabolism on PTC development and prognosis. The authors concluded that serum 25(OH)D levels may not contribute to risk assessment workup of thyroid nodules and that lower preoperative levels of vitamin D were not associated with poor prognosis of PTC. Moreover, a recent case-control study and meta-analysis found that a high level of circulating 25(OH)D was associated with a decreased TC risk (8).

Possible reasons for the inconsistencies between studies include differences in the analytical methods to measure vitamin D and its metabolites, differences in the histotypes of TC evaluated, and differences in the ethnicity and inclusion criteria of participants (7,14,16).

On the ground that certain nutrients and vitamins may be particularly associated with promoting or protecting against certain types of TC, their stratification for specific tumor characteristics is important (18,21-23).

In this study, the serum levels of various vitamins in patients with PTC and their relationships with clinical, pathological, and molecular parameters were investigated

Highlight box

Key findings
- Vitamin D deficiency may play a role in papillary thyroid cancer development.
- Vitamin A and E deficiencies tend to increase the risk of papillary thyroid cancer occurrence.

What is known and what is new?
- Vitamins are involved in various mechanisms due to their antioxidant effects and their ability to enhance the immune response.
- Deficiency of some serum vitamins can be associated with an increased risk of developing cancer, including thyroid cancer.
- This study highlights possible associations between lower serum vitamins levels and papillary thyroid cancer occurrence.

What is the implication, and what should change now?
- Vitamins deficiency can be reduced by five major interventions: dietary modification, supplementation, promotion of both public health interventions and breastfeeding.

Table 1 Indication for surgery in control group (benign multinodular goiter, n=49)

Mnemonic	N*
Symptoms of pressure	29
Tracheal compression^	16
Substernal extension§	12
Toxic multinodular goiter^{c}	11
Suspicious cytologic findings°	5
Cosmetic deformity	4
Recent enlargement°	3

*, some patients had more than one surgical indication. ^, noticeable on clinical examination, or radiological imaging. §, this includes a goiter extending 3 cm below the sternal notch or extension of the gland below the fourth thoracic vertebra. ^{c}, patients were euthyroid at the time of surgery. °, the definitive histological examination excluded malignant pathology.

and examined. This PTC group was compared with a control group consisting of patients operated for benign nodular goiter. The aim of this paper is to highlight the association between lower serum vitamins levels and PTC occurrence. We present this article in accordance with the STROBE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-520/rc).

Methods

Study design

This was a retrospective cohort study of patients undergoing thyroid surgery. Data were progressively collected from a clinical medical record database. Quality assurance of the database was maintained by an informatics specialist.

Study setting and period

Academic Asiatic tertiary medical center for thyroid surgery. Recruitment of participants between September 2018 and October 2019. Patient recruitment was subsequently stopped due to the Covid-19 pandemic.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the China-Japan Union Hospital Institutional Review Board (No. JL.UNI.251), and informed consent was obtained from all individual participants. Data were collected and stored digitally. Data did not include personal identifiers and were kept confidential.

Study population

Consecutive patients with histologically diagnosed PTC who underwent thyroidectomy.

Inclusion criteria: Patients with PTC and planned surgical treatment. Euthyroidism. Age >18 years old. Exclusion criteria: Patients with tumors other than PTC. Age <18 years old. Patients with malabsorption, recurrent infections, inflammatory diseases, or patients with impaired kidney or liver function (serum creatinine >1.8 mg/dL, total bilirubin >2.5 mg/dL, alkaline phosphatase (ALP) >5 times above the interval limit reference, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times above the interval limit reference) were excluded. Patients with other TC subtypes (follicular, anaplastic, medullary, lymphoma), Graves' disease, and/or parathyroid disease were also excluded.

Control group

Each case detected was matched to one control randomly selected from people undergoing thyroid surgery at the same center. Control subjects, that is patients without PTC, were recruited from individuals who had undergone thyroidectomy in the same time interval and whose histologic examination revealed no tumor (final diagnosis: benign multinodular goiter). The reasons for thyroidectomy are illustrated in *Table 1*. Patients with malabsorption, recurrent infections, inflammatory diseases, or patients with impaired renal or hepatic function were also excluded. Patients with concurrent Graves' disease and/or parathyroid disease were excluded.

Figure 1 shows the flowchart of patient recruitment in the said two groups of patients.

Analytical tools

Serum levels of vitamins A and E were measured by high-performance liquid chromatography (HPLC). Liquid chromatography with tandem mass spectrometry (LC-MS/MS) was used to measure serum levels of 25-hydroxyvitamin D2 [25(OH)D2] and 25-hydroxyvitamin D3 [25(OH)D3]. Serum levels of vitamin D [25(OH)D] were determined as

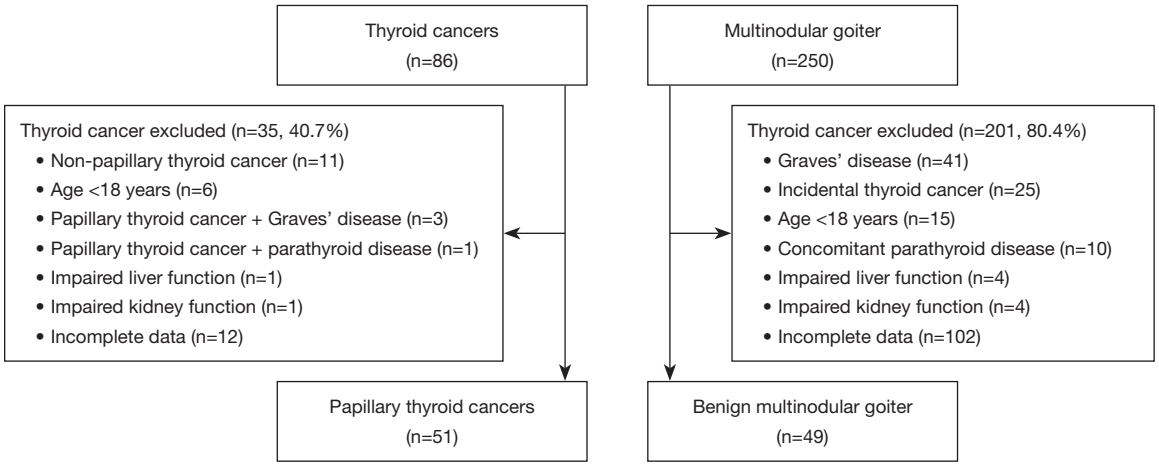

Figure 1 Flowchart of patient recruitment.

the sum of serum levels of 25(OH)D2 and 25(OH)D3. Serum homocysteine and methylmalonic acid levels, as indicators of vitamin B12 or folate status, were measured using LC-MS/MS. Serum chemical parameters such as total protein, albumin, ALP, ALT, AST, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol were measured to assess biochemical status as well.

Definitions

Vitamin deficiencies for specific vitamins were defined as follows: vitamin A <1.05 μmol/L, vitamin E <11.6 μmol/L, vitamin B12 as a methylmalonic acid concentration >300 μmol/L or a homocysteine concentration >15 μmol/L (24). Vitamin D deficiency was defined as a serum concentration of 25(OH)D <20 ng/mL, while severe lack was defined as <10 ng/mL (20).

Measured outcomes

Vitamin deficiency was measured as the primary endpoint. Demographic and clinical characteristics such as age, body mass index (BMI), and serum biochemical test results (total protein, albumin, ALP, ALT, AST, LDL, HDL, total cholesterol) were collected from electronic medical records. In accordance with World Health Organization guidelines for the Asian population (25), the subjects were classified according to the increased risk of developing the metabolic syndrome, in particular if the BMI (kg/m^2) was between 18.5 and 23 as low to moderate risk, if between 23 and 27.5 as moderate to high risk, and above 27.5 as high to very high risk. Information from surgery and pathology was stored in electronic medical records.

Statistical analysis

To estimate the number of participants necessary for this study, a sample size calculation was performed using the STATA statistical package (version 13, College Station, TX, USA). A target sample size of 47 participants per group was selected to ensure adequate power. Descriptive statistics were calculated for participant characteristics. Continuous variables were expressed as medians (interquartile ranges), means (± standard deviation) or numbers (%) and categorical variables as percentages. Differences between means and medians were assessed by *t*-test and Kruskal-Wallis test, respectively, while the percentages of categorical variables were evaluated by the χ^2 test. Regardless of the test, a P value of <0.05 was considered statistically significant, while a P value between 0.05 and 0.10 was considered borderline significant. A normality test was used to assess the distribution of variables. Statistical analyses were performed using the SPSS® v. 22 for Windows® software package (IBM, Armonk, NY, USA).

Results

Baseline demographic and clinical characteristics of the study cohort

The general characteristics of the study participants are summarized in *Table 2*. This study included 51 PTC patients and 49 control subjects. Patients with TC were

Table 2 General characteristics of the study population

Characteristics	PTC group (n=51)	Control group (n=49)	P value
Gender			0.49
Female	39	30	
Male	12	19	
Age at surgery (years)	41 [35–50]	49 [44–55]	0.001
BMI*	25 [21–25]	22 [20–24]	
18.5–23	27 (53%)	31 (63%)	0.02
23–27.5	24 (47%)	18 (37%)	0.03
Thyroid gland volume (mL)	29 [18–39]	45 [39–87]	0.001
Mean dominant nodule size (mm)	20 [7–42]	38 [30–62]	0.001
Number of nodules			0.0021
Solitary	42 (82%)	49 (100%)	
Multiple	9 (18%)	0	
Thyroid function test			
TSH (μIU/mL)	1.85±0.86	1.65±0.66	0.24
Free T4 (pmol/L)	1.20±0.43	1.23±0.49	0.28
Free T3 (pmol/L)	1.12±0.56	1.32±0.64	0.6
Tg (μg/L)	18.81±14.12	19.12±17.13	0.1
Extent of Surgery			0.21
Total thyroidectomy	6 (12%)	40 (82%)	
Near-total thyroidectomy	5 (10%)	5 (10%)	
Subtotal thyroidectomy	–	4 (8%)	
Hemithyroidectomy	–	–	
Total thyroidectomy + CCLND	35 (69%)	–	
Total thyroidectomy + CCLND + LCLND	5 (10%)	–	
Laboratory tests			
Total protein (g/dL)	7.2 [6.8–7.4]	7.3 [6.8–7.6]	0.91
Albumin (g/dL)	4.3 [4.1–4.3]	4.4 [4.1–4.5]	0.74
AST (U/L)	18 [15–23]	16 [14–20]	0.78
ALT (U/L)	14 [12–22]	14 [12–18]	0.54
ALP (U/L)	56 [45–69]	55 [47–69]	0.38
HDL (mg/dL)	62 [51–76]	65 [51–73]	0.18
LDL (mg/dL)	115 [98–140]	109 [92–139]	0.23
Total cholesterol (mg/dL)	178 [159–205]	191 [175–225]	0.002

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	PTC group (n=51)	Control group (n=49)	P value
Morbidity			0.23
RLN palsy transient	2	2	
RLN palsy permanent	–	–	
RLN palsy all	2	2	
Hypocalcemia transient	7	5	
Hypocalcemia permanent	1	–	
Hypocalcemia all	8	5	
Bleeding	–	–	
Seroma	1	1	

Data were expressed as median [interquartile range], mean ± standard deviation, numbers (%), or numbers. P values <0.05 were considered statistically significant. *, appropriate BMI for Asian population (Lancet 2004). PTC, papillary thyroid cancer; BMI, body mass index; TSH, thyroid-stimulating hormone; Tg, thyroglobulin; CCLND, central compartment lymph nodes dissection; LCLND, lateral compartment lymph nodes dissection; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; HDL, high density lipoprotein; LDL, low density lipoprotein; RLN, recurrent laryngeal nerve.

younger (P=0.001), had a smaller thyroid gland and nodal size (P=0.001), and had more frequently multiple nodules (χ^2=9.502, P=0.0021), (*Table 2*). Furthermore, TC patients had a higher BMI and a lower concentration of total cholesterol than the control group (P=0.02 and P=0.03, respectively), both statistically significant (*Table 2*). Of the 51 PTC patients, 7 (13.7%) had microPTC (maximum diameter <10 mm), 22% had BRAF mutations, 30% had lymph node metastases, and only 2% had distant (bone) metastases (*Table 3*).

Vitamin status

Serum levels of vitamins status in the study populations are presented in *Table 4*. Serum concentrations of vitamins A and E in patients with PTC were significantly lower than in controls (P<0.003). However, serum concentrations of vitamin D and methylmalonic acid were borderline significantly low (P=0.06 and P=0.055, respectively), while homocysteine was statistically similar (P=0.45) in the two groups. In detail, vitamin A deficiency was observed in 9 patients with PTC (17.6%) and in 3 patients with benign disease (6.1%) a borderline significant difference (χ^2=3.14, P=0.076). Vitamin D deficiency was observed in 4 patients with PTC (7.8%) and in 3 patients with benign disease (6.1%). Vitamin B12 deficiency was observed in 2 patients with PTC (3.9%) and in 2 patients with benign thyroid disease (4%). Vitamin E deficiency was observed in 9 patients with PTC (17.6%), and in 2 patients with benign disease (4%) a significant difference (χ^2=4.0, P=0.030).

Serum levels of vitamins were compared among subgroups of PTC patients (*Table 5*). The sole statistically relevant results concern the concentrations of vitamin D that were significantly lower in BRAF-positive PTC than in BRAF-negative PTC patients (P=0.021). Methylmalonic acid concentrations were only borderline significantly lower (P=0.09) in PTC patients with extrathyroidal extension compared to PTC patients without extrathyroidal extension (*Table 5*).

Discussion

Serum vitamin D deficiency has been associated with an increased risk of developing chronic obstructive pulmonary disease and, most topically in an interesting meta-analysis, also with increased severity and mortality of SARS-CoV-2 infection (26,27). Vitamin D supplementation has also shown positive effects on the outcome of patients suffering from head trauma and stroke, and it is likely that it can also counteract the neurotoxicity induced by anesthetic drugs (28-30). A recent study supports the hypothesis that normal levels of vitamin D, due to its anti-inflammatory and immunomodulatory properties, reduce the risk of developing chronic inflammatory diseases and cancer of the

Table 3 Characteristics of PTC patients (n=51)

PTC group	N [%]
Multifocal tumor	11 [22]
Extrathyroidal extension	6 [12]
Vascular invasion	7 [14]
T status	
T1	17 [33]
T2	25 [49]
T3	8 [16]
T4	1 [2]
Positive surgical margin	1 [2]
LN status	
NX	11 [22]
N0	24 [47]
N1a	11 [22]
N1b	5 [10]
Mean dominant tumor size in mm [range]	20 [7–42]
Tumor size <10 mm	7 [14]
PTC variants (dominant tumor)	
Classic	41 [80]
Follicular	8 [16]
Tall cell	1 [2]
Diffuse sclerosing	1 [2]
BRAF mutations	11 [22]

LN, lymph node; PTC, papillary thyroid cancer.

gastrointestinal tract (31).

In a meta-analysis, it was also highlighted that this vitamin deficiency and its relative supplementation, affects with inverse associations the general neoplastic mortality but not the incidence of cancer, in particular colorectal one (32).

In an interesting Chinese case-control study, 276 subjects were recruited to investigate the association between serum vitamin D and the development of PTC (8). A meta-analysis was also performed, which included 11 articles, showed that serum vitamin D concentration was inversely associated with the risk of developing cancer. This association was independent on the BMI and physical activity performance (8).

Abuduwaili *et al.* evaluated retrospectively the inverse relationship between pre-operative vitamin D levels and poor prognostic factors for PTC in a large series of patients (n=1,161) and found a statistical significance concerning larger tumor diameter (P=0.049) and occurrence of lymph node metastasis (P=0.00) (33).

The literature on vitamin A and E deficiency and their interactions with the endocrine system, and in particular with the thyroid, is quite limited.

Brossaud *et al.* hypothesized that vitamin A (retinol), a micronutrient with known metabolic functions in the eye and brain, could play less important roles at the endocrine level, in particular adrenal and gonadal with prevailing effects on spermatogenesis (34). Regarding thyroid, authors reported that in iodine-deficient areas, vitamin A deficiency increases the TSH-stimulation and consequently the goiter size in children, and its supplementation improves

Table 4 Serum levels of vitamins

Serum vitamin concentrations	PTC group (n=51)	Control group (n=49)	P value
Vitamin A (μmol/L)	1.40 (1.10–1.59)	1.78 (1.52–2.16)	<0.003
Vitamin D (ng/mL)	15.6 (9.3–22.1)	17.9 (12.3–23.3)	0.06
Vitamin E (μmol/L)	23.9 (20.3–32.5)	29.1 (26.1–38.6)	<0.003
Methylmalonic acid (nmol/L)	100.3 (79.5–129.3)	110.4 (79.5–170.1)	0.055
Homocysteine (μmol/L)	7.8 (6.4–9.3)	8.2 (6.8–9.6)	0.45

Results are presented as median (interquartile range). P values <0.05 were considered statistically significant. PTC, papillary thyroid carcinoma.

Table 5 Subgroup analyses of vitamin levels in PTC patients

	Vitamin A (μmol/L)	Vitamin D (ng/mL)	Vitamin E (μmol/L)	Methylmalonic Acid (μmol/L)	Homocysteine (μmol/L)
BRAF					
Negative (n=40)	1.44 (1.15–1.67)	16.0 (11.1–23.8)	26.4 (21.0–28.4)	103.0 (82.8–161.4)	7.9 (7.1–9.6)
Positive (n=11)	1.39 (1.18–1.77)	8.2 (7.0–15.9)	26.7 (21.6–33.0)	96.9 (79.0–129.5)	8.2 (6.9–9.6)
P value	0.65	0.021	0.59	0.65	0.9
N status					
NX (n=11)	1.44 (1.10–1.88)	13.6 (8.1–21.9)	26.2 (21.7–29.0)	95.6 (85.0–172.4)	8.5 (7.1–10.0)
N0 (n=24)	1.44 (1.10–1.73)	14.5 (9.7–22.0)	26.6 (21.5–31.1)	94.6 (74.1–125.0)	7.6 (7.0–10.3)
N1a (n=11)	1.46 (1.14–1.76)	13.4 (8.1–22.1)	26.1 (22.0–30.1)	95.8 (85.0–172.1)	8.5 (7.0–10.5)
N1b (n=5)	1.44 (1.11–1.70)	13.9 (9.6–22.1)	27.6 (21.4–32.9)	95.0 (74.1–120.0)	7.5 (6.6–11.3)
P value	0.81	0.46	0.60	0.77	0.81
Multifocal tumor					
Positive (n=11)	1.39 (1.10–1.71)	15.2 (9.0–22.0)	26.1 (21.5–32.5)	95.4 (73.1–130.5)	7.5 (6.3–9.0)
Negative (n=40)	1.41 (1.10–1.74)	16.1 (10.1–23.5)	25.9 (21.1–31.0)	97.5 (75.3–133.9)	8.5 (7.3–10.9)
P value	0.74	0.49	0.65	0.42	0.09
Extrathyroidal extension					
Positive (n=6)	1.45 (1.17–1.69)	12.8 (9.5–22.5)	26.0 (21.6–31.7)	97.3 (80.1–124.4)	7.9 (6.6–9.4)
Negative (n=45)	1.30 (1.18–1.71)	9.5 (7.2–11.3)	25.7 (21.9–29.1)	112.2 (109.4–177.7)	7.5 (6.5–8.3)
P value	0.6011	0.6	0.775	0.09	0.4641
T status					
T1 (n=17)	1.45 (1.19–1.68)	15.0 (9.3–22.6)	25.8 (21.7–31.5)	94.3 (73.3–126.0)	7.8 (6.7–9.3)
T2 (n=25)	1.38 (1.14–1.93)	13.4 (9.7–20.3)	26.6 (20.5–31.7)	108.3 (80.7–134.5)	8.8 (6.5–10.3)
T3 (n=8)	1.45 (1.19–1.68)	15.0 (9.3–22.6)	25.8 (21.7–31.5)	94.3 (73.3–126.0)	7.8 (6.7–9.3)
T4 (n=1)	1.38 (1.14–1.93)	13.4 (9.7–20.3)	26.6 (20.5–31.7)	108.3 (80.7–134.5)	8.8 (6.5–10.3)
P value	0.8429	0.6654	0.9139	0.3605	0.502
PTC subtypes					
MicroPTC (n=7)	1.45 (1.19–1.70)	14.3 (9.1–21.9)	26.0 (21.7–31.6)	94.7 (73.0–125.7)	7.7 (6.5–9.2)
MacroPTC (n=44)	1.46 (1.14–1.73)	16.3 (10.2–24.6)	26.2 (20.8–31.2)	96.4 (75.3–135.4)	8.4 (7.2–10.2)
P value	0.9357	0.5001	0.6788	0.8032	0.0946
PTC variants (dominant tumor)					
Classic (n=41)	1.44 (1.18–1.67)	14.7 (9.0–22.3)	25.6 (21.6–31.3)	94.6 (73.4–127.6)	7.8 (6.6–9.2)
Follicular (n=8)	1.48 (1.28–1.86)	16.0 (9.3–22.8)	25.1 (21.6–30.2)	103.3 (82.5–131.0)	8.7 (6.8–10.2)
Tall cell (n=1)	1.19 (1.04–1.89)	14.0 (11.3–18.5)	31.7 (22.9–35.8)	94.3 (75.0–110.5)	7.9 (6.5–9.6)
Diffuse sclerosing (n=1)	1.17 (1.02–1.86)	13.9 (11.1–18.3)	30.9 (23.0–35.9)	94.1 (74.2–111.1)	7.8 (6.5–9.4)
P value	0.5472	0.8976	0.447	0.6803	0.5515

P values <0.05 were considered statistically significant. PTC, papillary thyroid carcinoma.

the efficiency of iodine uptake reducing the risk of hypothyroidism. Previously, Zimmermann *et al.* had come to the same conclusions, hypothesizing a suppression of the TSH-beta pituitary gene as a possible cause (35).

Few articles on the possible effects of vitamin E deficiency on thyroid function exist, and the first study is very old (36) and the most recent concerns the risk of medullary TC (19).

Overall, a systematic review of Zhang *et al.* (37), evaluated the association between dietary supplements of vitamins and minerals and TC development. They found conflicting results about TC development and common antioxidants such as vitamins A, C, E and β-carotene. Moreover, dietary supplement combinations or other specific minerals and/or vitamins interventions (calcium, iodine, iron, magnesium, zinc, vitamins B and/or D) are largely inconsistent across studies. They concluded that scientific evidence about eventual protective or hazardous effect of mineral or vitamins supplementation on TC development is inconclusive and further studies are necessary to elucidate possible associations.

Despite the numerous studies that show how vitamin D has protective effects on development of cancer, the results of this study come to different conclusions.

In this study serum levels of vitamins (A, E, and D) in patients with PTC or benign thyroid disease were measured. Possible relationships between serum levels of vitamins and molecular subtypes of PTC and tumor stages were also analyzed.

This study has several strengths and limitations. First, various biases could have affected the study, mainly the retrospective nature of the study and the fact that only patients undergoing thyroid surgery were included. On the other hand, enrolling patients from a single center can ensure that patients belong to the same population with the same environmental living risk factors.

Conclusions

In conclusion, albeit with the analysis of a limited sample, it is worth noting that not only vitamin D but also vitamin A and E deficiencies tend to increase the risk of developing a PTC. Further verification of these observations on larger case series is however necessary. Vitamin deficiency can be reduced by five major interventions: supplementation, dietary modification, fortification, promotion of both public health, and breastfeeding.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the China-Japan Union Hospital Institutional Review Board (No. JL.UNI.251), and informed consent was obtained from all individual participants. Data were collected and stored digitally. Data did not include personal identifiers and were kept confidential.

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