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# Serum Selenium Level in Thyroid Cancer: A Case-Control Study

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## Abstract

**Background:** Despite the implementation of national iodine supplementation programs, structural thyroid diseases are still highly prevalent in most countries. Thus, the link between trace elements other than iodine, such as selenium, and thyroid diseases should be investigated.

**Methods:** In this case-control study, adult patients with newly diagnosed papillary thyroid carcinoma, benign thyroid nodules, and healthy euthyroid controls without nodules were recruited. Thyroid function tests and serum selenium levels were assessed and compared between groups. The One-way ANOVA test was used to assess the mean difference of numerical variables among the three studied groups (PTC, Benign nodule, and healthy control group). In addition, a post-hoc comparison was conducted based on Bonferroni correction for a pairwise comparison of these three groups.

**Results:** Data from 182 patients with papillary thyroid carcinoma (PTC), 185 patients with benign thyroid nodules, and 180 healthy individuals as a control group were analyzed. The mean serum selenium levels in the PTC, benign thyroid nodules, and control group were 94.9, 121.6, and 134.3 µg/l, respectively ($P < 0.001$). There was a significant relationship between the cancer stage and selenium level in the PTC group. Patients in higher stages of cancer had a lower mean of selenium ($P < 0.001$). In univariate logistic regression, TSH and selenium were significant variables for PTC compared with patients with benign thyroid nodules. Each unit increase in selenium reduces the chance of PTC by about 6%.

**Conclusion:** The low levels of selenium were associated with PTC. Also, serum selenium levels were inversely correlated with the stage of thyroid cancer.

**Keywords:** Selenium, Thyroid Nodule, Thyroid Cancer, Papillary

***Conflicts of Interest:*** *None declared*
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## Introduction

Thyroid nodules are caused by the hyperplasia of thyroid cells and are defined as distinct lesions from thyroid parenchyma in radiological evaluations. Thyroid nodules are recognized as a common clinical problem. According to epidemiological studies, the prevalence of palpable thyroid nodules in regions with iodine sufficiency is about 5% in women and 1% in men. This rate increases to 19-68% if ultrasound is used to detect thyroid nodules. Also, these nodules are more common in the elderly and women. The clinical significance of thyroid nodules lies in the fact that

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***↑What is "already known" in this topic:***
Despite the implementation of national iodine supplementation programs, structural thyroid diseases are still highly prevalent in most countries. Thus, the link between trace elements other than iodine, such as selenium, and thyroid diseases should be investigated. It seems that the available information regarding the effect of low serum selenium levels in patients with benign and malignant thyroid nodules is contradictory.

***→What this article adds:***
According to the present results, the serum selenium level was significantly lower in PTC patients compared to patients with benign nodules and the control group. There was a significant reverse relationship between the cancer stage and selenium level in the PTC group. Each unit increase in selenium reduces the chance of PTC by about 6%.

7-15% of these nodules are malignant. Differentiated thyroid cancers, including papillary and follicular thyroid cancer, constitute more than 90% of thyroid cancers (1-5).

Despite the implementation of national iodine supplementation programs, functional and structural thyroid diseases are still highly prevalent in most countries. Thus, the link between trace elements other than iodine and thyroid diseases should be investigated. One of these trace elements is selenium (6, 7). The association between the incidence of different cancers and selenium deficiency has been established in the literature (8). Also, selenium deficiency can be a risk factor for thyroid cancer; however, the results of previous studies on this subject are contradictory (9-12).

Selenium is an important trace element in human physiology, with anti-inflammatory, anti-cancer, and anti-aging activities, as well as protective effects against oxidative stress (13). Although selenium can be found in the kidneys, liver, and muscles, its highest concentration can be found in the thyroid as selenoprotein (0.2-2 µg/g) (14). This trace element is present in the form of selenocysteine in a number of antioxidant selenoproteins. It also protects thyroid cells against high concentrations of hydrogen peroxide ($H_2O_2$), produced during the biosynthesis of thyroid hormones. Moreover, it is an essential component of iodothyronine deiodinase that catalyzes thyroid hormones by activation or inactivation (6, 15).

It is generally difficult to determine the role of selenium in the etiology of thyroid nodules, considering the significant differences in the selenium level among different populations with different nutritional habits, the bioavailability of selenium compounds, and genetic factors (6). Some clinical studies have been conducted on populations with iodine deficiency (16, 17), while others have not investigated the iodine status (18). The effect of selenium on the goiter and carcinogens in the thyroid gland is still unclear. It seems that the available information regarding the effect of low serum selenium levels in patients with benign and malignant thyroid nodules is contradictory (19). In vitro studies have shown that selenium can reduce the growth of thyroid cancer cells (20). A previous study reported that selenium is inversely associated with the stage of thyroid cancer (12), but in another study, no association between fingernail selenium levels and thyroid cancer was reported (11).

In this case-control study, the association between serum selenium concentration and benign and malignant thyroid nodules was investigated in comparison to the control group in an iodine-sufficient area.

## Methods

This case-control study was conducted between March 2018 and December 2020 on euthyroid patients who were referred to the endocrine clinics in Zahedan, southeastern Iran, with thyroid nodules.

Patients ≥ 18 years who were euthyroid and had a thyroid nodule with a size ≥ 1 centimeter were included in the study.

If subjects had a history of thyroid surgery, received thyroid medication, radiation to the neck, or received contrast in the last 6 months, they were excluded from the study. Other exclusion criteria were renal failure, liver failure, diabetes, and psychiatric disorders. Pregnant women, lactating women, and women receiving estrogen or oral contraceptives were excluded from the study. Also, none of the patients received selenium supplements.

For each participant, a questionnaire that included demographic data, past medical history, and family history of thyroid disease was completed. Thyroid sonography was performed for all participants by a sonologist using a 7.5-MHz linear probe.

All patients with thyroid nodules larger than 1 cm were evaluated by fine-needle aspiration biopsy (FNAB). All FNAB samples were evaluated by an experienced pathologist. The cytology was reported according to the Bethesda system in all cases (21). Patients with a diagnosis of papillary thyroid cancer (PTC) or suspicious of having it were included in the PTC group. In all patients with positive cytology for PTC, total thyroidectomy was done, and permanent pathology confirmed the diagnosis. Patients with benign cytology were included in the benign thyroid nodule group. The control group was selected from hospital staff and non-first-degree relatives of patients who were euthyroid and had no nodules in thyroid ultrasound after applying the inclusion and exclusion criteria. People in the control group were apparently healthy and did not have any findings in favor of acute or chronic disease in the history and physical examination. The subjects of the control group were similar to the case group in terms of socioeconomic level and residential area. Finally, three groups, including the PTC group, benign thyroid nodule group, and control group, were recruited for this study.

The height of participants was measured using a stadiometer, and the weight with minimal clothing was measured using a digital scale. Body Mass Index was determined using this formula: weight in kilograms divided by the square of height in meters. All blood samples were taken after 12 hours of fasting in the morning and were stored at -70 ° C until assay.

Thyroid function tests and serum levels of selenium were evaluated in patients with PTC, as well as in patients with benign thyroid nodules and the control group. FT4, FT3, and TSH using immune-chemo-luminescent assays by an automated analyzer were measured. (normal free thyroxine (FT4:0.8 -1.8 ng/dL); normal free triiodothyronine (FT3:2.3 - 4.2 pg/mL) and normal thyroid stimulating hormone (TSH:0.4 - 4.2 mIU/L) ). Selenium was measured by the atomic absorption spectrometry method in all samples.

All interventions were conducted following the ethical principles of the institutional as well as national research committee and with the 1964 Helsinki Declaration and its later amendments.

### *Statistical analyses*

Mean and standard deviation (SD) were used to describe quantitative variables, and frequency and percentage were used to describe qualitative variables. The normality of the variables was evaluated using the Shapiro–Wilk test. The difference in numerical variables between the three study groups (PTC, Benign nodule, and healthy control group) was measured using the One-way ANOVA test. Also, for a

pairwise comparison of these three groups, a post-hoc comparison was conducted based on Bonferroni correction. Assessment of the relationship between two categorical variables was done by using Chi-square or Fisher's exact test. In addition, the independent t-test and Mann-Whitney U test were used for the assessment of the difference between numerical variables in two groups of tumor size (T1 and >T1), for normality and non-normality distributed variables, respectively. The correlation between two numerical variables was assessed by the Pearson correlation. The multivariate logistic regression was conducted based on the backward stepwise method. P-value < 0.05 was considered statistically significant. Data were analyzed using Stata statistical software: Release 14. College Station, TX: StataCorp LP.

## Results

In this study, the data of 182 patients with PTC, 185 patients with benign thyroid nodules, and 180 healthy individuals were analyzed as a control group. The variables of gender, age, and BMI in the three groups were not significantly different ($P > 0.05$). Clinical and laboratory findings are compared between the three groups in Table 1.

Although patients in all three groups were euthyroid, TSH levels were higher in patients with PTC than in patients with benign thyroid nodules in the control group. The serum selenium level in the control group was higher than the group of patients with PTC and patients with benign thyroid nodules (Figure 1). A comparison of the mean serum selenium in the three study groups showed a significant difference. Based on post-hoc analyses, the difference between the mean serum selenium in a pairwise comparison for all three groups showed a significant difference, too. As shown in Table 1, the difference in the percentage of selenium deficiency in the three groups and also in the comparison between the two groups was statistically significant ($P < 0.05$).

The status of selenium and the clinicopathological characteristics of PTC patients are shown in Table 2. Of all patients with PTC (182 patients), 12.1% had Multifocality, 3.8% Extrathyroid extension, 8.8% Capsular invasion, and 5.5% Vascular Invasion. The mean selenium was not significantly different between patients with and without multifocality. At the same time, the mean of selenium was lower in patients with extrathyroidal extension (66.1 vs 96.1, p <0.001). The mean of selenium in patients with Capsular and Vascular Invasion was higher that the other group. The mean serum selenium level decreased with increasing lymph node involvement. Also, the prevalence of selenium deficiency in patients with N0, N1a, and N1b was 11.7%, 14.3%, and 42.9%, respectively. The patients in higher stages of cancer had a lower mean of selenium ($P < 0.001$). The prevalence of selenium deficiency was also significantly higher in patients with higher stages of cancer ($P < 0.001$). Although the mean of selenium was not significantly different between the histological type of PTC ($P = 0.483$), the prevalence of selenium deficiency in patients with follicular type was (10.4%) and patients with Tall cell variant (29.2%) respectively; that was significantly higher than classic type (10.4%) ($P = 0.024$). Also, as shown in Figure 2, the serum selenium level decreased with increasing tumor size class.

A comparison of anthropometric and biochemical parameters in T1 and >T1 patients in the PTC group is shown in Table 3. The mean of selenium in patients with T1 was significantly higher than in patients with >T1 (99.2 vs 88.3, $P < 0.001$). Also, the prevalence of selenium deficiency in patients with T1 and >T1 was 1.8 and 31.4%, respectively ($P < 0.001$).

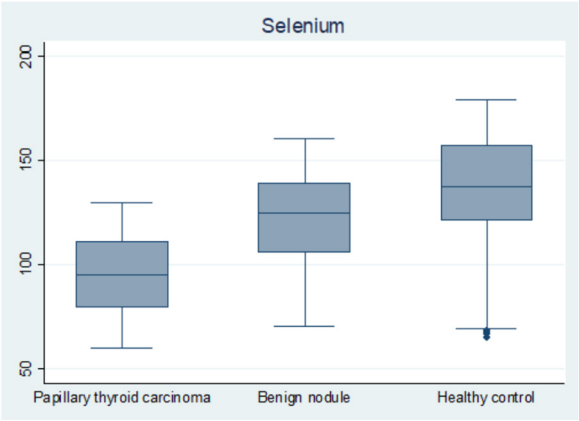


*Figure 1.* Distribution of serum selenium levels by papillary thyroid carcinoma, benign nodule, and healthy control group

*Table 1.* Baseline characteristics of study subjects by study group

| Variable | PTC group (n=182) | Benign nodule group (n=185) | Control group (n=180) | *P*-value |
|---|---|---|---|---|
| Age (years) | 35.53±10.90 | 35.11±13.01 | 34.67±12.96 | 0.917 |
| Sex, female | 145 (79.6) | 148 (80.1) | 145 (80.5) | 0.986 |
| BMI (Kg/m2) | 24.83±2.99 | 24.38±3.75 | 24.27±3.99 | 0.728 |
| FT4 (ng/dl) | 1.26±0.31 | 1.27±0.19 | 1.29±0.36 | 0.683 |
| FT3 (pg/ml) | 3.73±0.59 | 3.86±0.48 | 3.59±0.49 | 0.357 |
| TSH (mIu/L) | 2.49±1.03 [a] | 1.79±1.09 [b] | 2.00±1.11 [b] | <0.001 |
| Selenium (µg/l) | 94.89±19.18 [a] | 121.04±21.07 [b] | 134.00±28.91 [c] | <0.001 |
| Selenium deficiency (<70) | 24 (13.1) [a] | 0 (0.0) [b] | 7 (3.8) [c] | <0.001 |

Data are shown as number (%) or mean±SD. P-values were determined by one-way ANOVA, Pearson $\chi 2$ test, or Fisher's exact test.
BMI: Body mass index, FT4: Free thyroxin, FT3: Free triiodothyronine, PTC: Papillary thyroid carcinoma, TSH: thyroid stimulating hormone.
In numerical variables, mean differences were assessed by the ANOVA test. a, b, c: Post-hoc comparison based on the Bonferroni method. Different superscript letters (a, b, c) in the same row of variables reflect a significant (p < 0.05) difference between the means while the same superscript letters in one row reflect a non-significant difference between the means of three groups.

*Table 2.* The serum selenium level and selenium deficiency prevalence in clinicopathological groups of patients with papillary thyroid carcinoma

| Variable | n (%) | Selenium (µg/l) | | Selenium deficiency (<70) | | |
|---|---|---|---|---|---|---|
| | | Mean±SD | *P*-value | No (%) | Yes (%) | *P*-value |
| Multifocality | | | | | | |
| Absent | 160 (87.9) | 95.11±20.14 | 0.822 | 139 (86.9) | 21 (13.1) | 1.0 |
| Present | 22 (12.1) | 94.09±18.53 | | 19 (86.4) | 3 (13.6) | |
| Extrathyroidal extension | | | | | | |
| Absent | 175 (96.2) | 96.14±19.42 | <0.001 | 157 (89.7) | 18 (10.3) | <0.001 |
| Present | 7 (3.8) | 66.14±3.44 | | 1 (14.3) | 6 (85.7) | |
| Capsular invasion | | | | | | |
| Absent | 166 (91.2) | 95.67±19.66 | 0.138 | 147 (88.6) | 19 (11.4) | 0.042 |
| Present | 16 (8.8) | 87.94±21.71 | | 11 (68.8) | 5 (31.3) | |
| Vascular Invasion | | | | | | |
| Absent | 172 (94.5) | 95.49±19.74 | 0.161 | 152 (88.4) | 20 (11.6) | 0.029 |
| Present | 10 (5.5) | 86.40±21.85 | | 6 (60.0) | 4 (40.0) | |
| Nodal involvement | | | | | | |
| N0 | 154 (84.6) | 95.27±19.55 | 0.741 | 136 (88.3) | 18 (11.7) | 0.060 |
| N1a | 21 (11.5) | 94.86±20.61 | | 18 (85.7) | 3 (14.3) | |
| N1b | 7 (3.8) | 89.29±27.45 | | 4 (57.1) | 3 (42.9) | |
| Cancer stage | | | | | | |
| I | 160 (87.9) | 99.31±17.16 | <0.001 | 158 (98.8) | 2 (1.3) | <0.001 |
| II | 11 (6.0) | 63.09±2.63 | | 0 (0.0) | 11 (100) | |
| III | 4 (2.2) | 62.25±2.63 | | 0 (0.0) | 4 (100) | |
| IVa | 6 (3.3) | 64.67±2.34 | | 0 (0.0) | 6 (100) | |
| IVb | 1 (0.5) | 67.0±NA | | 0 (0.0) | 1 (100) | |
| Histological type | | | | | | |
| Classic | 154 (84.6) | 95.71±19.86 | 0.483 | 138 (89.6) | 16 (10.4) | 0.024 |
| Follicular | 24 (13.2) | 90.42±19.34 | | 17 (70.8) | 7 (29.2) | |
| Tall cell | 4 (2.2) | 94.75±27.06 | | 3 (75.0) | 1 (25.0) | |

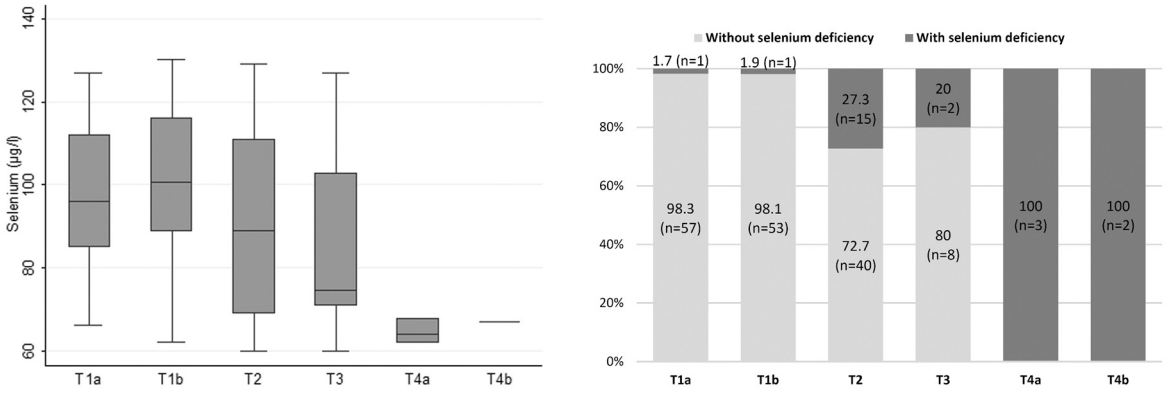


*Figure 2.* Distribution of selenium and prevalence of selenium deficiency by tumor size category in patients with papillary thyroid carcinoma

*Table 3.* Comparison of anthropometric and biochemical parameters in T1 (T1a and T1b) and >T1 (T2, T3, and T4) patients with papillary thyroid carcinoma

| Variable | Tumor size category | | *P*-value |
|---|---|---|---|
| | T1 (n=112) | >T1 (n=70) | |
| Sex, female | 94 (83.9) | 51 (72.9) | 0.071 |
| Age (years) | 34.28±10.92 | 37.33±12.94 | 0.090 |
| BMI (Kg/m2) | 24.48±3.68 | 24.69±4.27 | 0.720 |
| FT4 (ng/dl) | 1.31±0.23 | 1.27±0.28 | 0.317 |
| FT3 (pg/ml) | 3.58±0.63 | 3.59±0.55 | 0.961 |
| TSH (mIu/L) | 2.44±1.10 | 2.64±0.99 | 0.212 |
| Selenium (µg/l) | 99.17±17.10 | 88.30±22.25 | <0.001 |
| Selenium deficiency (<70) | 2 (1.8) | 22 (31.4) | <0.001 |

Data are shown as number (%) or mean±SD. P-values were determined by independent t-test, Pearson $\chi 2$ test or Fisher's exact test.
BMI: Body mass index; FT4: Free thyroxin; FT3: Free triiodothyronine; TSH: thyroid stimulating hormone.

In univariate logistic regression, TSH and selenium variables were significant variables for PTC compared with patients with benign thyroid nodules. These variables also remained significant in the multivariate logistics model. Each unit increase in TSH increases the chance of PTC 1.79 times. Also, the amount of selenium with the highest value of Wald statistic was the most important model variable, and each unit increase in the amount of selenium reduces the chance of PTC by about 6% (Table 4).

## Discussion

According to the present results, the serum selenium

*Table 4.* Univariate and multivariate logistic regression analysis of risk factors of patients with papillary thyroid carcinoma compared to patients with benign thyroid nodules

| Variable | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | Wald | OR (95% CI) | *P*-Value | Wald | OR (95% CI) | *P*-Value |
| FT4 (ng/dl) | 0.153 | 1.19 (0.501, 2.82) | 0.696 | | | |
| FT3 (pg/ml) | 1.96 | 0.787 (0.563, 1.10) | 0.161 | | | |
| TSH (mIu/L) | 30.28 | 1.79 (1.45, 2.20) | <0.001 | 21.74 | 1.79 (1.40, 2.29) | <0.001 |
| Selenium (µg/l) | 81.94 | 0.944 (0.933, 0.956) | <0.001 | 74.16 | 0.945 (0.932, 0.957) | <0.001 |

FT4: Free thyroxin; FT3: Free triiodothyronine; TSH: Thyroid stimulating hormone; OR: Odds ratio; CI: Confidence interval.

level was significantly lower in PTC patients compared to patients with benign nodules and the control group.

These findings are consistent with previous studies, which reported lower serum levels of selenium in thyroid cancer patients compared to the control group (12, 22-24). In this regard, Moncayo et al. found that patients with malignant thyroid nodules had lower serum levels of selenium compared to the control group (22). Also, Kucharzewski et al. showed that the mean level of selenium in the thyroid cancer tissue was significantly lower than in the control group (24). Moreover, in the current study, an inverse association was found between the stage of thyroid cancer and the serum selenium level. This finding is consistent with the results of a study by Jonklass et al. (12), which evaluated the serum selenium level of 65 patients with thyroidectomy and found an association between the lower serum selenium level and higher stages of thyroid cancer.

Conversely, in the current study, no significant difference was found between the serum selenium levels of patients with benign thyroid nodules and the control group, which is in line with previous studies (19, 24-29). It is worth mentioning that the present study was conducted in an iodine-sufficient area (30). Similar to our study, other studies conducted in iodine-sufficient areas did not report an association between the serum selenium level and benign nodules (19). Sakiz and colleagues also reported no significant correlation between the serum selenium level and thyroid nodules (27). On the other hand, some studies conducted in iodine-deficient areas reported lower serum selenium levels in patients with benign thyroid nodules compared to the control group (31-33). Rasmussen et al. conducted a cross-sectional study in an area with iodine deficiency in Denmark and concluded that low serum selenium concentrations were associated with a higher risk of thyroid nodules (31). Also, another study conducted in China reported that low serum selenium levels were risk factors for thyroid nodules (32).

Selenium is a rare mineral element with several biological roles. It is considered the second essential trace element for thyroid function, following iodine, affecting thyroid physiology through at least two mechanisms: antioxidant mechanisms and deiodinase activity. During the synthesis of thyroid hormones, $H_2O_2$ is produced in the thyroid gland, which is converted to $H_2O$ through cellular defense mechanisms; otherwise, thyroid cells are exposed to damage caused by these free radicals. Protection against $H_2O_2$ and its free radicals is supplied by vitamin C, vitamin E, and enzymes, such as selenium-containing enzymes, superoxide dismutase, and catalase. Glutathione peroxidase and other selenium-containing enzymes, produced in the thyroid gland, contribute to defense against antioxidants (34).

The present results showed that low serum selenium levels are associated with thyroid cancer. Although the anticancer mechanism of selenium is not well understood, several mechanisms have been proposed to explain this mechanism, including the reduction of DNA damage, inflammation, and oxidative stress, strengthening of the immune system, induction of cancer cell apoptosis, inhibition of angiogenesis, increased level of tumor-suppressor protein p53, inactivation of kinase C protein, and changes in DNA methylation and cell cycle block. The antioxidant properties of seleno-enzymes in tumor progression and carcinogenesis are significant. Selenium is present in glutathione peroxidase and protects DNA and the main cell components against free radical damage by reducing ROS production. The production of reactive oxygen species in the thyroid tissue leads to carcinogenesis, which can also cause RAS oncogene mutation. In addition, selenium enhances tumor-suppressor protein p53 inhibits proliferation and increases apoptosis and DNA repair (23).

In our study, with regard to benign thyroid nodules and serum selenium levels, a statistically significant correlation was not detected. It should be noted that the current study was performed in an area covered by the national iodine supplementation program, and the population was receiving iodine prophylaxis (they were iodine-sufficient); therefore, the iodine status of the population was not investigated (30).

Overall, no normal serum level has been defined for the prevention of thyroid diseases; however, experimental studies have shown that serum levels above 70 µg/L are essential for producing sufficient amounts of selenoproteins. On the other hand, some studies have shown that serum selenium levels ≥100 µg/dL are necessary for the prevention of goiter and autoimmune thyroid diseases, as well as the induction of anti-cancer activities (35).

The serum selenium levels reported in some studies are significantly different from ours. This discrepancy can be attributed to differences in age, gender, and severity of iodine deficiency in the studied populations, the methodology of the study, differences in statistical analyses, and other confounding factors. Generally, the main source of selenium is soil. The selenium content of the soil affects the selenium levels of all plants and animals. Therefore, various geographical areas have different levels of soil selenium, ranging from very low levels to toxic levels in some other regions (35).

The current study had some limitations. First, this was an observational cross-sectional study that could not confirm

causal relationships. Also, the sample size was relatively low. On the other hand, having a nodule-free control group, evaluation of cytological and histological outcomes of each nodule, and matching the groups are among the strengths of this study.

## Conclusion

According to the present results, low serum selenium levels were associated with papillary thyroid cancer. Also, the serum selenium concentration was inversely associated with the stage of thyroid cancer. Nevertheless, no significant correlation was found between serum selenium and benign thyroid nodules. Therefore, selenium deficiency and its effects on structural thyroid diseases should be examined in future prospective studies with a larger sample size.

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### *Ethical approval*

The Ethics Committee of Zahedan University confirmed the current study (IR.ZAUMS.REC.1399.071). All participants provided informed consent.

### *Conflict of Interests*

The authors declare that they have no competing interests.

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