American Journal of Health Research
2024; 12(1): 1-7
http://www.sciencepublishinggroup.com/j/ajhr
doi: 10.11648/j.ajhr.20241201.11
ISSN: 2330-8788 (Print); ISSN: 2330-8796 (Online)

Research Progress and Controversy on the Relationship Between Iodine Excess and Thyroid Cancer Occurrence

Zhou Feng[1], Liu Na[2], Yang Guiran[1, *]

[1]Office of Biochemistry, Department of Medical Technology, Cangzhou Medical College, Cangzhou, China

[2]Department of Public Courses, Cangzhou Medical College, Cangzhou, China

Email address:

yangguiran2006@126.com (Yang Guiran)

[*]Corresponding author

To cite this article:

Zhou Feng, Liu Na, Yang Guiran. (2024). Research Progress and Controversy on the Relationship Between Iodine Excess and Thyroid Cancer Occurrence. *American Journal of Health Research*, *12*(1), 1-7. https://doi.org/10.11648/j.ajhr.20241201.11

Received: December 11, 2023; **Accepted**: January 8, 2024; **Published**: January 11, 2024

Abstract: Thyroid cancer is the most common thyroid malignant tumor, and its incidence rate is on the rise in most countries. Iodine is an essential trace element for the synthesis of thyroid hormones in the human body. Long term excessive iodine can induce thyroid diseases such as hyperthyroidism and thyroid nodules, but its relationship with the occurrence of thyroid cancer is uncertain. There may be regional differences and some confusing or interfering factors, due to the influence of iodine intake and dietary habits on the final iodine nutritional status of the human body, and the influence of water iodine content on the iodine nutritional status of the human body. In recent years, researchers have revealed the relationship between iodine excess and thyroid cancer through ecological studies of regional water iodine distribution, dietary iodine and thyroid cancer, but the results are controversial. In the epidemiological studies on the correlation between urinary iodine concentration and thyroid cancer in residents, there is no conclusion on the correlation between urinary iodine concentration and iodine level of thyroid cancer patients and whether MUI can truly reflect the iodine nutrition level of thyroid cancer patients. This article reviews the research progress and controversies on the relationship between iodine excess and thyroid cancer, and comments on the possible reasons for the controversies, providing reference for future research.

Keywords: Iodine, Thyroid Cancer, TSH, BRAF

1. Introduction

Thyroid cancer is the most common malignant tumor of the thyroid gland, with the vast majority originating from thyroid follicular epithelial cells. Thyroid carcinoma of follicular cell origin is further divided into papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), Hurthle cell carcinoma (HCC), poorly differentiated thyroid carcinoma (PDTC) and anaplastic thyroid carcinoma (ATC), among which PTC accounts for about 90% of the total number of thyroid cancers [1, 2]. According to statistics, from 1990 to 2017, global thyroid cancer events increased by 169%, and the standardized incidence rate showed an upward trend throughout the entire time period [3]. There are research reports that factors such as environment and nutrition play an important role in the occurrence of thyroid cancer [4]. In recent years, researchers have begun to pay attention to the relationship between iodine, which is closely related to thyroid hormone metabolism, and the occurrence of thyroid cancer.

Iodine mainly comes from seawater and can be dispersed through the air in a gaseous or foggy form to crops near land and sea areas. The human body mainly obtains physiological iodine requirements through drinking water and food (including iodine fortified foods). About 99% of the iodine in the body is excreted from the body through urine, so urine iodine levels can effectively reflect the iodine nutritional status of the population. The World Health Organization (WHO) recommends the use of median urinary iodine (MUI) to reflect the iodine nutritional status of the population, and has issued evaluation standards for iodine nutritional status of various populations [5]. Iodine is an essential trace element for the synthesis of thyroid hormones in the human body. Adequate iodine intake is beneficial for maintaining the homeostasis of the human body's internal environment.

However, long-term iodine excess or iodine deficiency can lead to various thyroid diseases [6]. Some studies have reported that excessive iodine is associated with the occurrence of thyroid cancer, but the relationship between the two is still controversial [7-9]. This article reviews the research progress and controversies on the relationship between iodine excess and thyroid cancer, explores the possible reasons for the controversies, and provides a reference basis for subsequent research.

2. Ecological Research on Water Iodine Distribution, High Iodine Diet, and Thyroid Cancer Occurrence

The iodine required by the human body is mainly obtained from drinking water and food. Researchers have attempted to reveal the relationship between excessive iodine and the occurrence of thyroid cancer from an ecological perspective, but the conclusion is controversial. For example, sea fish and shellfish are iodine rich foods, and some studies have pointed out that these iodine rich foods are risk factors for thyroid cancer [10, 11]. On the contrary, large-scale prospective studies conducted in iodine suitable European populations have shown that long-term consumption of marine fish or shellfish is not associated with changes in thyroid cancer risk [12]. Some reports even suggest that sea fish and shellfish can reduce the risk of thyroid cancer and play a protective role [6, 13, 14]. A retrospective study on the relationship between iodine and thyroid diseases indicated that there is a correlation between water induced high iodine and the high incidence of thyroid cancer [15]; However, a 10-year retrospective study based on the relationship between water iodine and thyroid cancer in different regions suggests that the increase in thyroid cancer incidence may be due to advances in diagnostic technology and improved living standards, rather than the role of water iodine [16].

The results of ecological research should be interpreted with caution. Firstly, some researchers overlooked the impact of changes in iodine intake patterns, lifestyle habits, and other factors on the final iodine nutritional status of the human body when exploring the iodine nutritional status of people in high iodine areas. Iceland is a region with a high incidence of thyroid cancer in northern Europe. The residents of the island have a traditional habit of consuming fish with high iodine content. Theoretically, iodine nutrition should be in an adequate state. However, a recent report on iodine nutrition assessment of the Icelandic population pointed out that residents, especially pregnant women, have already suffered from iodine deficiency [17]. In fact, the dietary habits of the younger generation in Iceland are no longer significantly different from those of other Nordic populations, and even young women and adolescents on the island receive less than two-thirds of the WHO recommended iodine levels from their food [18]. Daishan County, under the jurisdiction of Zhoushan City, Zhejiang Province, belongs to the coastal area, where sea salt is abundant and residents like to eat seafood. However, the population urinary iodine monitoring results show that the iodine nutrition level of permanent residents in Daishan County is lower than that of surrounding counties and cities, and children and women of childbearing age are in iodine deficiency state [19]. Therefore, the impact of factors such as the intake of iodine and changes in dietary habits on the final iodine nutritional status of the human body cannot be ignored. Secondly, there is controversy over the correlation between water iodine and the iodine nutritional status of the population in various regions. According to the report of the third national iodine deficiency Disorders survey in Sri Lanka, the average water iodine in the country was only 7 μg/L, but the residents' MUI was as high as 457 μg/L [20]. A survey on the iodine nutritional status of pregnant women in different iodine rich areas in Tianjin (water iodine levels of 150-300 and>300 μg/L) showed a correlation between the iodine content in drinking water and the urine iodine of pregnant women, and with the increase of water iodine content, the impact of drinking water iodine intake on the iodine nutritional status of pregnant women is gradually increasing [21]. A survey conducted by Zhang Xiangdong et al. in areas with different water iodine levels in Shanxi Province pointed out that only when water iodine>100 μg/L can it significantly affect the iodine nutrition level of residents [22]. Therefore, there may be regional differences in the impact of water iodine content on human iodine nutritional status. Once again, there are various ways for the human body to obtain water and food, and researchers cannot control the confusion or interference of certain suspicious or unknown risk factors with the target factors. The above may be the main reason for the controversy surrounding the relationship between iodine and thyroid cancer based on ecological research.

3. Epidemiological Studies Based on Urinary Iodine

Several reports have indicated that urinary iodine in patients with thyroid cancer, especially PTC, is at a high level, and increased urinary iodine may be a risk factor for the occurrence of PTC [23-26]. Teng et al. [15] found that from 1999 to 2004, no thyroid cancer occurred in Panshan County of Tianjin (MUI was 97 μg/L) and Zhangwu County of Liaoning Province (MUI was 375 μg/L), while 13 cases of PTC occurred in Huanghua City of Hebei Province (MUI was 615 μg/L) during the same period. In contrast, data from the National Health and Nutrition Examination Survey (NHMC) showed that thyroid cancer continued to increase at an annualized rate of 6.6 percent from 1988 to 2010 in the United States, all of whom were in iodine adequacy [27]. Since 2000, the prevalence of thyroid cancer has increased dramatically among Shanghai residents, with an annualized rate of 14.4% [28]. However, the iodine nutrition survey of Shanghai residents showed that from 2002 to 2014, all residents in Shanghai were in an appropriate state of iodine [29]. Huang et al. [30] found that high urinary iodine was a

risk factor for PTC, and changes in its concentration were significantly related to PTC invasion and migration. On the contrary, a meta-analysis of the association between urinary iodine and thyroid cancer suggested that high urinary iodine may be a clinical feature of patients with thyroid cancer and is not related to iodine intake in the resident population [31]. Therefore, there is still controversy about the relationship between urinary iodine and the occurrence of thyroid cancer, and urinary iodine may not be an independent risk factor for the development of thyroid cancer. In addition to the role of iodine, the influence of other factors such as environmental pollution, biological clock imbalance, and increased body fat on the occurrence of thyroid cancer should be comprehensively considered.

Thyroid nodules are a common clinical symptom before the occurrence of thyroid cancer, and 3%-17% of thyroid nodules are malignant, which is a risk factor for the occurrence of thyroid cancer [32, 33]. There is a U-shaped relationship between urinary iodine and the prevalence of thyroid nodules [34], with low or too high iodine leading to the development of thyroid nodules [35-37]. For example, Kim et al. [38] found that the prevalence of thyroid cancer and the level of MUI in the range of <300 μg/L and >2500 μg/L) were significantly higher than those of thyroid nodules. The authors suggest that iodine excess may be related to the high incidence of thyroid cancer.

It is worth considering whether MUI can truly reflect the iodine nutrition level of thyroid cancer patients. 70%-80% of human iodine is stored in thyroid cells, and iodine in blood is mainly transported to thyroid cells through the sodium iodide symporter (NIS) on thyroid basement membrane cells against the concentration gradient. Therefore, NIS is also referred to as the "portal" to regulate the iodine concentration inside and outside thyroid cells [39]. Thyroid stimulating hormone (TSH) is a key regulator of NIS expression, which can up-regulate NIS transcription through cyclic adenosine phosphate (cAMP), thereby enhancing iodide uptake by the thyroid [40]. Most studies have shown that thyroid cancer tissues have low levels of NIS protein expression compared with normal tissues [41-43]. Mechanistic studies have shown that mutated murine sarcoma virus oncogene homolog B1 (BRAF) protein in thyroid cancer cells can inhibit NIS protein expression through the mitogen-activated protein kinase (MAPK) pathway [44]. Theoretically, when the expression of NIS gene or protein is suppressed, it will affect the iodine uptake capacity of the thyroid gland to a certain extent. However, the correlation between urine iodine concentration and iodine levels in the thyroid gland has not been clearly described in many studies.

4. Studies Based on the Molecular Characteristics of Thyroid Cancer

4.1. Iodine Overdose, BRAF Gene Mutation and the Occurrence of Thyroid Cancer

In the evolution of human thyroid cancer, gene mutation plays an important role. The most common one is the substitution of thymine and adenine at 1799 position of BRAF gene, which causes valine at position 600 to be replaced by glutamic acid, and the post-translational mutated BRAFV600E protein is highly expressed [45]. According to statistics [46, 47], BRAF gene mutations account for 30%-40% of all PTC, of which 71% are V600E replacement mutations. BRAFV600E protein can cause the activation of serine/threonine kinases in the body structure, leading to constitutive activation of downstream kinases of the MAPK pathway, which plays an important role in the occurrence of thyroid cancer, especially PTC, leading to changes in downstream gene expression and abnormal proliferation of cancer cells. Animal and cellular experiments have also shown [48, 49] that high BRAFV600E expression alone can cause a malignant appearance of the thyroid gland in the absence of any mutagen, with a preference for papillary pathological features.

For the controversial factor of iodine excess, researchers have also tried to reveal the relationship between iodine excess and PTC by changing the BRAFV600E mutation rate. Studies have found [50] that the BRAFV600E mutation rate of PTC in the population in iodine excess areas is significantly higher than that in iodine adequate areas, and high iodine exposure may be the driving factor for changing the BRAF gene into an active state. However, some recent studies [51, 52] have shown that BRAFV600E mutation rate of PTC in both iodine excess and iodine deficiency areas has no significant change compared with iodine adequate areas, and BRAFV600E is more like the clinical manifestation of PTC. Although in theory, the long-term continuous stimulation of mutagens will amplify this accumulation effect of thyroid follicular cells and eventually induce gene mutations. However, animal studies have shown that only thyroid adenoma occurs in rats fed with high-iodine diet alone at the end of the experiment, and even when co-exposed with carcinogen diisopropanol nitrosamine, the rat thyroid does not show a malignant phenotype, indicating that high-iodine alone may not be the initiating factor inducing thyroid cancer [53].

Under normal circumstances, thyroid follicular epithelial cells grow very slowly, which makes it able to withstand the invasion of various adverse factors from the outside world, and at the same time, they will accumulate the consequences of these damage. High iodine can mediate the apoptosis of thyroid cancer cells by increasing the activities of extracellular signal-regulated kinase 1/2 (ERK1/2) and mission-activated protein kinase 1/2 (JNK1/2) in MAPK and nuclear factor-κb (NF-κB) pathways [54]. In addition, it has been reported that when high iodine induces apoptosis in BRAF-mutated papillary human thyroid cancer cells (BCPAP), BRAF can protect against apoptosis by increasing the level of autophagosomes in BCPAP cells. At the same time, high iodine can also promote the expression of BRAF gene, activate the MAPK pathway, and up-regulate the level of BRAF kinase, thereby promoting the proliferation and migration of BCPAP cells [55]. In

conclusion, whether high iodine can induce BRAF gene mutation needs further study.

4.2. Iodine Excess, TSH, and the Development of Thyroid Cancer

Under the condition of iodine deficiency, the low level of thyroid hormone promotes the synthesis and secretion of TSH by the pituitary gland through negative feedback regulation. It should be noted that long-term high iodine intake can also lead to an increase in the body's TSH level. Data from the National Health and Nutrition Examination Survey of Korea [56] showed that TSH levels of residents in iodine excess areas were significantly increased. Animal experiments have also shown that there is a time and measurement effect relationship between serum TSH level and iodine intake in rats [57].

In physiological state, TSH binds to thyroid stimulating hormone receptor (TSHR) on thyroid cell membrane and activates it. Through coupling signaling pathways, it promotes the expression of downstream effector genes, thereby controlling the proliferation and differentiation of thyroid cells and the secretion and release of thyroid hormones. Clinical cohort studies and meta-analyses have shown that the serum TSH level of patients with thyroid cancer is mostly within the physiological range, but beyond the quartile of the median, the TSH level of patients with thyroid nodules is positively correlated with the prevalence of thyroid cancer [58-61]. However, the association between serum TSH levels and thyroid cancer is controversial. A clinical cohort study showed that serum TSH level was not associated with the rate of thyroid nodule deterioration and was not a risk factor for thyroid cancer [62]. In addition, retrospective studies based on data from the Israeli National Cancer Registry have shown an inverse relationship between elevated serum TSH levels and the prevalence of thyroid cancer when within the physiological range [63].

Relevant animal and cell experiments provide some information about this controversy. Franco et al. [64] found that the serum TSH level of BRAFV600E/TPO-Cre mice established by gene knock-in technology was significantly higher than that of wild-type mice, and all of them developed highly aggressive PTC at the 5th week of birth. Shimamura et al. [65] found that BRAFV600E/TPO-Cre mice did not develop thyroid cancer when serum TSH levels were within the physiological range, while BrafCA/+ mice with higher thyroid cancer transformation rates all showed a malignant phenotype after 1 year. During the study of TSH/TSHR signaling pathway, Wu et al. [66] found that appropriate concentrations of TSH promoted the proliferation of thyroid cancer cells by activating TSHR, while high concentrations of TSH had an inactivating effect on these cells. Therefore, there are two possibilities of TSH/TSHR signaling in the process of thyroid cancer: (1) TSHR is not the initiator of thyroid cancer, but an important factor in promoting thyroid cancer: a large number of clinical cohort studies have shown that TSHR promotes the occurrence and development of thyroid cancer [67-69]; (2) The activation of TSHR is not only dependent on the binding mode of the ligand receptor of TSH: researchers have found in patients with thyroid cancer that TSHR with germline or tumor-specific mutations can self-activate and start downstream cascades to promote the proliferation of cancer cells [70].

Over the past few decades, the incidence of thyroid cancer has continued to increase in most countries, especially after the implementation of the strategy of iodized salt to correct iodine deficiency [71], but the role of iodine intake in the development of thyroid cancer remains uncertain. The greatest challenge is the lack of biomarkers that can accurately reflect individual iodine nutritional status over a long period of time. A large number of studies have reported that long-term high iodine intake can cause an increase in serum TSH levels in humans [15, 56]. At the same time, it has been widely reported that the activation of TSH/TSHR signaling cascade promotes the occurrence and development of thyroid cancer [70]. This makes serum TSH level potential in studying the association between iodine excess and thyroid cancer. However, the self-activation of TSHR expressed by thyroid cancer cells may affect the judgment of the association between TSH and thyroid cancer. Therefore, when exploring the relationship between iodine excess and thyroid cancer, researchers should bring both TSH and TSHR into the research system at the same time. In conclusion, the relationship between iodine excess and thyroid cancer may be as follows: (1) Iodine excess may not be the mutagenic factor of thyroid cancer gene mutation; (2) Iodine excess plays both an inhibitory and a promoting role in BRAF-induced PTC development; (3) Iodine excess can increase the secretion level of TSH in human body, and the promotion effect of TSH on BRAF-induced PTC is affected by the activation status of TSHR. In conclusion, at present, the research on the relationship and mechanism between iodine excess and TSH/TSHR signaling in the development of thyroid cancer is limited, and researchers need to conduct extensive and in-depth exploration.

ORCID

Zhou Feng: 0009-0001-1743-7183
Liu Na: 0009-0008-1393-4992
Yang Guiran: 0009-0009-0480-1781

Acknowledgments

Project Introduction: Science and Technology Project of Hebei Province (182777168).

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Haroon Al Rasheed MR, Xu B. Molecular Alterations in Thyroid Carcinoma [J]. Surg Pathol Clin, 2019, 12(4): 921-930. DOI: 10.1016/j.path.2019.08.002.

[2] Pitoia F, Smulever A. Active surveillance in low risk papillary thyroid carcinoma [J]. World J Clin Oncol, 2020, 11(6): 320-336. DOI: 10.5306/wjco.v11.i6.320.

[3] Deng Y, Li H, Wang M, et al. Global Burden of Thyroid Cancer From 1990 to 2017 [J]. JAMA Netw Open, 2020, 3(6): 1-14. DOI: 10.5306/wjco.v11.i6.320.

[4] Barrea L, Gallo M, Ruggeri RM, et al. Nutritional status and follicular-derived thyroid cancer: An update [J]. Crit Rev Food Sci Nutr, 2021, 61(1): 25-59. DOI: 10.1080/10408398.

[5] Zhao H, Li H, Huang T. High Urinary Iodine, Thyroid Autoantibodies, and Thyroid-Stimulating Hormone for Papillary Thyroid Cancer Risk [J]. Biol Trace Elem Res, 2018, 184(2): 317-324. DOI: 10.1007/s12011-017-1209-6.

[6] Li Y, Ba J, Chen B, et al. Efficacy and Safety of Long-Term Universal Salt Iodiztion on Thyroid Disorders: Epidemiological Evidence from 31 Provinces of Mainland China. [J]. Thyroid, 2019, 30(4): 568-579. DOI: 10.1089/thy.2019.0067.

[7] Ivanova LB, Vukov MI, et al. Thyroid Cancer Incidence in Bulgaria before and after the Introduction of Universal Salt Iodization: An Analysis of the National Cancer Registry Date [J]. Balkan Med J, 2020, 37(6): 330-335. DOI: 10.4274/balkanmedj.galenos.2020.2019.10.5.

[8] Kim K, Cho SW, Park YJ, et al. Association between Iodine Intake, Thyroid Function, and Papillary Thyroid Cancer: A Case-Control Study [J]. Endocrinol Metab, 2021, 36(4): 790-799. DOI: 10.3803/EnM.2021.1034.

[9] Winder M, Kosztyła Z, Boral A, et al. The Impact of Iodine Concentration Disorders on Health and Cancer [J]. Nutrients, 2022, 14(11): 2209-2209. DOI: 10.3390/nu14112209.

[10] Memon A, Varghese A, Suresh A. Benign thyroid disease and dietary factors in thyroid cancer: a case-control study in Kuwait [J]. Br J Cancer, 2002, 86(11): 1745-1750. DOI: 10.1038/sj.bjc.6600303.

[11] Asif F, Noor-Ul-Amin M, Jabeen R. Identification of thyroid cancer risk factors incidence in urban and rural areas, Pakistan [J]. Pak J Pharm Sci, 2020, 33(6): 2607-2610. DOI: 10.36721/PJPS.2020.33.6.REG.2607-2610.1.

[12] Zamora-Ros R, Castañeda J, Rinaldi S, et al. Consumption of Fish Is Not Associated with Risk of Differentiated Thyroid Carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study [J]. The Journal of Nutrition, 2017, 147(7): 1366-1373. DOI: 10.3945/jn.117.247874.

[13] Cléro É, Doyon F, Chungue V, et al. Dietary iodine and thyroid cancer risk in French Polynesia: a case-control study [J]. Thyroid, 2012, 22(4): 422-429. DOI: 10.1089/thy.2011.0173.

[14] Cao LZ, Peng XD, Xie JP, et al. The relationship between iodine intake and the risk of thyroid cancer: meta-analysis [J]. Medicine, 2017, 96(20): 1-5. DOI: 10.1097/MD.0000000000006734.

[15] Teng W, Shan Z, Teng X, et al. Effect of iodine intake on thyroid diseases in China [J]. N Engl J Med, 2006, 354(26): 2783-2793. DOI: 10.1056/NEJMoa054022.

[16] Lv C, Yang Y, Jiang L, et al. Association between chronic exposure to different water iodine and thyroid cancer: A retrospective study from 1995 to 2014 [J]. Sci Total Environ, 2017; 609(12): 735-741. DOI: 10.1016/j.scitotenv.2017.07.101.

[17] Adalsteinsdottir S, Tryggvadottir EA, Hrolfsdottir L, et al. Insufficient iodine status in pregnant women as a consequence of dietary changes [J]. Food & Nutrition Research, 2020, 64(10): 29219-29219. DOI: 10.29219/fnr.v64.3653.

[18] Nystrm HF, Brantster AL, Erlund I, et al. Iodine status in the Nordic countries – past and present [J]. Food & Nutrition Research, 2016, 60(1): 31969-31969. DOI: 10.3402/fnr.v60.31969.

[19] Zhang YL, Li P, Liu Z Y, et al. Does relatively low iodine intake contribute to thyroid cancer? An ecological comparison of epidemiology [J]. Medicine, 2019, 98(41): 17539-17539. DOI: 10.1097/MD.0000000000017539.

[20] Bertinato J. Iodine nutrition: Disorders, monitoring and policies [J]. Adv Food Nutr Res, 2021, 96(2021): 365-415. DOI: 10.1016/bs.afnr.2021.01.004.

[21] Hou CC, Liu ZH, Li F, et al. An investigation of iodine intake and iodine nutrition status of pregnant women in different water iodine areas of Tianjin [J]. Chin J Endemiol, 2022, 41(5): 373-378. DOI: 10.3760/cma.j.cn231583-20210805-00252.

[22] Zhang XD, Jia QZ, Guo BS. An investigation of the source and the nutritional status of iodine after termination of iodized salt supply in high water iodine areas in Shanxi province [J]. Chin J Endemiol, 2013, 32(2): 196-200. DOI: 10.3760/cma.j.issn.2095-4255.2013.02.020.

[23] Hou D, Xu H, Li P, et al. Potential role of iodine excess in papillary thyroid cancer and benign thyroid tumor: A case-control study [J]. Asia Pac J Clin Nutr, 2020, 29(3): 603-608. DOI: 10.6133/apjcn.20200929(3).0020.

[24] Ma X, Zhang LI, Yang ww, et al. Corraltion of Serum Selenium and Urinary Iodine Levels with Thyroid Cancer [J]. Chinese General Practice, 2017, 20(34): 4270-4274. DOI: 10.3969/j.issn.1007-9572.2017.34.011.

[25] Yang T, Zhang JY, Huang YH, et al. Correlation between iodine nutrition and differentiated thyroid cance in the past 12 years [J]. Guangdong Medicl Journal, 2015, 36(20): 3208-3210. DOI: 10.13820/j.cnki.gdyx.20151104.013.

[26] Chen XI, Qian HB, Hong J, et al. Strong Correlation of Abnormal Serum and Urinary Iodine Levels with Papillary Thyroid Cancer: A Case-control Study [J]. Biomedical and Environmental Sciences, 2020, 33(1): 62-67. DOI: 10.3967/bes2020.009.

[27] Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: a com prehensive review of animal and human studies [J]. Thyroid Research, 2015, 8(1): 1-21. DOI: 10.1186/s13044-015-0020-8.

[28] Wang Y, Wang W. Increasing incidence of thyroid cancer in Shanghai, China 1983-2007 [J]. Asia Pac J Public Health, 2015, 27(2): 223-229. DOI: 10.1177/1010539512436874.

[29] Song J, Wang ZY, Zhu ZN, et al. Iodine Nutritional Status and Goiter Rates in Children Aged 8-10 Years Before and After Universal Salt Iodization in Shanghai [J]. Environmental & Occupational Medicine, 2016, 33(3): 256-258. DOI: 10.13213/j.cnki.jeom.2016.15181.

[30] Huang F, Cong W, Xiao J, et al. Association between excessive chronic iodine exposure and the occurrence of papillary thyroid carcinoma [J]. Oncology letters, 2020, 20(5): 189. DOI: 10.3892/ol.2020.12051.

[31] Yan AR, Zhang X, Shen H, et al. Urinary iodine is increased in papillary thyroid carcinoma but is not altered by regional population iodine intake status: a meta-analysis and implications [J]. Endocrine Journal, 2019, 66(6): 497-514. DOI: 10.1507/endocrj.EJ18-0532.

[32] Jasim S, Baranski TJ, Teefey SA, et al. Investigating the Effect of Thyroid Nodule Location on the Risk of Thyroid Cancer [J]. Thyroid, 2020, 30(3): 401-407. DOI: 10.1089/thy.2019.0478.

[33] Kornelius E, Lo SC, Huang CN, et al. The Risk of Thyroid Cancer in Patients with Thyroid Nodule 3 Cm Or Larger - ScienceDirect [J]. Endocrine Practice, 2020, 26(11): 1286-1290. DOI: 10.4158/EP-2020-0136.

[34] He NL, Li H, An W, et al. Study on constructing the U-shaped response relationship of urinary iodine level and thyroid nodule prevalence based on piecewise function quantile regression method [J]. Chinese Journal of Preventive Medicine, 2020, 54(11): 1268-1274. DOI: 10.3760/cma.j.cn112150-20200322-00403.

[35] Jia QZ, Guo JM, Wang QP, et al. The prevalence of thyroid nodule in adults in different water iodine areas of Shanxi Province [J]. Chin J Endemiol, 2020, 39(3): 187-190. DOI: 10.3760/cma.j.cma.j.cn231583-20190725-00205.

[36] Wang MH, Cai XY, Chen ZF, et al. Correlation between urinary iodine, salt iodine, and thyroid nodules in children aged 8-10 years and pregnant women in different regions of Fujian Province [J]. ChinJ Endemiol, 2022, 41(3): 209-215. DOI: 10.3760/cma.j.cn231583-20210415-00125.

[37] Gao M, Chen W, Sun H, et al. Excessive iodine intake is associated with formation of thyroid nodules in pregnant Chinese women [J]. Nutr Res, 2019, 66(5): 61-67. DOI: 10.1016/j.nutres.2019.02.009.

[38] Kim HJ, Kim NK, Park HK, et al. Strong association of relatively low and extremely excessive iodine intakes with thyroid cancer in an iodine-replete area [J]. European Journal of Nutrition, 2016, 6(3): 1-7. DOI: 10.1007/s00394-015-1144-2.

[39] Carvalho DP, Dupuy C. Thyroid hormone biosynthesis and release [J]. Mol Cell Endocrinol, 2017, 458(2017): 6-15. DOI: 10.1016/j.mce.2017.01.038.

[40] Schmutzler C, Köhrle J. Implications of the molecular characterization of the sodium-iodide symporter (NIS) [J]. Exp Clin Endocrinol Diabetes, 1998, 106(13): S1-S10. DOI: 10.1055/s-0029-1212036.

[41] Cazarin J, Dupuy C, Pires de Carvalho D. Redox Homeostasis in Thyroid Cancer: Implications in Na+/I- Symporter (NIS) Regulation [J]. Int J Mol Sci, 2022, 23(11): 1-15. DOI: 10.3390/ijms23116129.

[42] Morais RM, Sobrinho AB, Souza SCM, et al. The Role of the NIS (SLC5A5) Gene in Papillary Thyroid Cancer: A Systematic Review [J]. Int J Endocrinol, 2018, 2018(9): 1-11. DOI: 10.1155/2018/9128754.

[43] Ma Y, He J, Shen N, et al. Expression of NIS, VEGF-A and Thyroid Autoa ntibody in Papillary Thyroid Carcinoma with or without Hashimoto's Disease [J]. ORL, 2019, 81(5-6): 1-6. DOI: 10.1159/000501620.

[44] Ullmann TM, Liang H, Moore MD, et al. Dual inhibition of BRAF and MEK increases expression of sodium iodide symporter in patient-derived papillary thyroid cancer cells in vitror [J]. Surgery, 2020, 167(1): 56-63. DOI: 10.1016/j.surg.2019.04.076.

[45] Trovisco V, Soares P, Preto A, et al. Molecular genetics of papillary thyroid carcinoma: great expectations [J]. Arq Bras Endocrinol Metabol, 2007, 51(5): 643-653. DOI: 10.1590/s0004-27302007000500002.

[46] Prete A, Souza PBD, Censi S, et al. Update on Fundamental Mechanisms of Throid Cancer [J]. Frontiers in Endocrinology, 2020, 11(1): 102-102. DOI: 10.3389/fendo.2020.00102.

[47] Poller DN, Glaysher S. Molecular pathology and thyroid FNA [J]. Cytopathology, 2017, 28(6): 475-481. DOI: 10.1111/cyt.12492.

[48] Shimamura M, Kurashige T, Kuatov R, et al. Acceleration of BRAFV600E -induced thyroid carcinogenesis by TGFβsignal deficiency in mice [J]. 2020, 13(8): 571-577. DOI: 10.1007/s12020-020-02298-1.

[49] Kim M, Kim S J, Xu Z, et al. BRAFV600E Transduction of SV40-immortalized Normal Human Thyroid Cell Line Induces Dedifferentiated Thyroid Carcinogenesis in a Mouse Xenograft Model [J]. Thyroid, 2020, 30(4): 487-500. DOI: 10.1089/thy.2019.0301.

[50] Kim HJ, Park HK, Byun DW, et al. Iodine intake as a risk factor for BRAF mutations in papillary thyroid cancer patients from an iodine-replete area [J]. Eur J Nutr, 2018, 57(2): 809-815. DOI: 10.1007/s00394-016-1370-2.

[51] Özçelik S, Bircan R, Sarıkaya Ş, et al. BRAFV600E mutation in papillary thyroid cancer is correlated with adverse clinicopathological features but not with iodine exposure [J]. Endokrynol Pol, 2019, 70(5): 401-408. DOI: 10.5603/EP.a2019.0025.

[52] Vuong HG, Kondo T, Oishi N, et al. Genetic alterations of differentiated thyroid carcinoma in iodine-rich and iodine-deficient countries [J]. Cancer Medicine, 2016, 5(8): 1883-1889. DOI: 10.1002/cam4.781.

[53] Jing Z, Xiaochen Z, Yanan L, et al. Low dose of Bisphenol A enhance the susceptibility of thyroid carcinoma stimulated by DHPN and iodine excess in F344 rats [J]. Oncotarget, 2017, 8(41): 69874-69887. DOI: 10.18632/oncotarget.19434.

[54] Liu XH, Chen GG, Vlantis AC, et al. Iodine mediated mechanisms and thyroid carcinoma [J]. Crit Rev Clin Lab Sci, 2009, 46(5-6): 302-318. DOI: 10.3109/1040836 0903306384.

[55] Zhang D, Xu X, Li J, et al. High iodine effects on the proliferation, apoptosis, and migration of papillary thyroid carcinoma cells as a result of autophagy induced by BRAF kinase [J]. Biomed Pharmacother, 2019, 120(1): 109476-109476. DOI: 10.1016/j.biopha.2019.109476.

[56] Jeon MJ, Kim WG, Kwon H, et al. Excessive Iodine Intake and Thyrotropin Reference Interval: Data from the Korean National Health and Nutrition Examinat ion Survey [J]. Thyroid, 2017, 27(7): 967-972. DOI: 10.1089/thy.2017.0078.

[57] Sun Y, Du X, Shan Z, et al. Effects of iodine excess on serum thyrotropin-releasing hormone levels and type 2 deiodinase in the hypothalamus of Wistar rats [J]. Br J Nutr, 2021, 12(8): 1-30. DOI: 10.1017/S0007114521002592.

[58] Colbert L, Cristo AP, Faccin CS, et al. Serum TSH levels as a predictor of malignancy in thyroid nodules: A prospective study [J]. PLoS One, 2017, 12(11): 1-12. DOI: 10.1371/journal.pone.0188123.

[59] M AE. Preoperative thyroid-stimulating hormone associated risk of differentiated thyroid cancer in patients with thyroid nodules [J]. Cell Mol Biol, 2021, 67(3): 85-91. DOI: 10.14715/cmb/2021.67.3.11.

[60] Su A, Zhao W, Wu W, et al. The association of preoperative thyroid-stimulating hormone level and the risk of differentiated thyroid cancer in patients with thyroid nodules: A systematic review and meta-analysis [J]. Am J Surg, 2020, 220(3): 634-641. DOI: 10.1016/j.amjsurg.2020.01.009.

[61] Fernández-Trujillo C, Pérez-Zaballos J, Rodríguez-Pérez CA, et al. TSH Level and Risk of Malignancy in Patients with Bethesda Category IV Thyroid Nodules [J]. Horm Cancer, 2020, 11(3-4): 200-204. DOI: 10.1007/s12672-020-00384-4.

[62] Krashin E, Silverman B, Steinberg DM, et al. Opposing effects of thyroid hormones on cancer risk: a population-based study [J]. Eur J Endocrinol, 2021, 184(3): 477-486. DOI: 10.1530/EJE-20-1123.

[63] Wang G, Ren N, Wang S, et al. Serum TSH is not a risk factor for malignancy of pediatric thyroid nodules [J]. Endocrine-related cancer, 2021, 28(4): 247-255. DOI: 10.1530/ERC-20-0508.

[64] Franco AT, Malaguarnera R, Refetoff S, et al. Thyrotrophin receptor signaling dependence of Braf-induced thyroid tumor initiation in mice [J]. Proc Natl Acad Sci U S A, 2011, 108(4): 1615-1620. DOI: 10.1073/pnas.1015557108.

[65] Shimamura M, Shibusawa N, Kurashige T, et al. Mouse models of sporadic thyroid cancer derived from BRAFV600E alone or in combination with PTEN haploinsufficient under physiologic TSH levels [J]. PLoS ONE, 2018, 13(8): 1-19. DOI: 10.1371/journal.pone.0201365.

[66] Wu Z, Xi Z, Xiao Y, et al. TSH-TSHR axis promotes tumor immune evasion [J]. J Immunother Cancer, 2022, 10(1): 4049-4049. DOI: 10.1136/jitc-2021-004049.

[67] Qu M, Wan S, Ren B, et al. Association between TSHR gene methylation and papillary thyroid cancer: a meta-analysis [J]. Endocrine, 2020, 69(3): 508-515. DOI: 10.1007/s12020-020-02284-7.

[68] Mon SY, Riedlinger G, Abbott CE, et al. Cancer risk and clinicopathological characteristics of thyroid nodules harboring thyroid-stimulating hormone receptor gene mutations [J]. Diagn Cytopathol, 2018, 46(5): 369-377. DOI: 10.1002/dc.23915.

[69] Zhou C, Li J, Wang Y, et al. Association of BRAF gene and TSHR with cervical lymph node metastasis of papillary thyroid microcarcinoma [J]. Oncol Lett, 2019, 17(1): 183-194. DOI: 10.3892/ol.2018.9572.

[70] Chu YD, Yeh CT. The Molecular Function and Clinical Role of Thyroid Stimulating Hormone Receptor in Cancer Cells [J]. Cells, 2020, 9(7): 1730-1747. DOI: 10.3390/cells9071730.

[71] Li T, Qian M. Whether iodized salt consumption increases thyroid cancer incidence Asia Pac J Clin Nutr, 2021, 30(2): 311-315. DOI: 10.6133/apjcn.20210630(2).0017.