

Dietary iodine intake, thyroid diseases and the prevalence of papillary carcinoma (PTC)

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Abstract

Iodine is a trace element that is essential for the synthesis of thyroid hormone. Both chronic iodine deficiency or iodine excess have been associated with hypertrophy and hyperplasia of follicular cells and the influence of thyroid hormone (T₃,T₄) and thyrotropin (TSH) secretion. Increase rates of the thyroid cancer are increasing after radiation exposure to ¹³¹I in children or adolescents. In respectively, dietary iodine excess goiter, iodine induced hyperthyroidism (IIH) and IIT, Iodine intake and the prevalence of papillary carcinoma (PTC), as well as the case-control and cohort studies of thyroid cancer and intake of seafood and milk products, were reviewed. Moreover, available evidence of oncogenic thyroid hormone receptor mutants from animal experiments and clinical investigation have been a shift toward the oncogenic function of human thyroid carcinoma, and also its target therapy.

Introduction

The main function of the thyroid gland is to make hormones (Figure 1) [1]. T₄ and T₃, which are essential for the regulation of metabolic effects for instance increased lipogenesis, ketogenesis, and cellular proliferation and differentiation such as the rapid development of frogs from thyrectomized tadpoles, the induction of growth hormone in the pituitary and the development of the brain in neonates by promoting dendrite formation and myelination.

Iodine is a trace essential raw element where 65% of T₄ weight is iodine [2]. Ingested iodine is absorbed and carried in the circulation as iodide. Intracellular iodide across the plasma membrane of thyrocytes by the sodium/iodide symporter is transported in the lumen of thyroid follicles. Meanwhile, the thyrocyte endoplasmic reticulum synthesizes two key proteins, TPO (thyroperoxidase) and Tg (thyroglobulin). Tg is a 660 KDa glycoprotein secreted into the lumen of follicles, whose tyrosyls serve as substrate for iodination and hormone formation. TPO sites at the apical plasma membrane, where it reduces H₂O₂, elevating the oxidation state of iodide to an iodinating species, and attaches the iodine to tyrosyls in Tg. H₂O₂ is generated at apex of the thyrocyte by Duox, a NADPH oxydase. Initial iodination of Tg products MIT and DIT. Further iodination couples two residues of DIT produce T₄ at residues 5 in the Tg polypeptide chain (Figure 2). After Tg digestion, T₄ and T₃ are released into circulation. Nonhormonal iodine is retrieved intrathyroidally by DEHAL1, an iodotyrosine deiodinase and made available for recycling within the gland. Iodine supply, either too much or too little, impairs adequate synthesis of thyroid hormone. According to WHO/UNICEF/ICCIDD [3], daily iodine intake are 90 µg for infants and young children (0-59 months), 120 µg for children 6-12 years, 150 µg for adolescents and adults, and 250 µg for pregnant and lactating women. In this paper, considering that iodine-deficiency endemic goiter and deficiency of thyroid hormone synthesis and secretion (Cretinism) and defective thyroid hormone receptor alpha are well clinically established and readily understandable, we are deliberating the topic entity of iodine excess induced thyroid diseases and papillary carcinoma (PTC).

Induction of thyroid neoplasm in rat

In rats development of thyroid neoplasm following radioactive iodine was well established in earlier comparative experiments in 1950-1964 last century [5-8]. Recent, thyroid tumor-promoting effects of iodine deficiency and excess have also been investigated in two-stage models in rats given carcinogens, such as N-bis (2-hydroxypropyl)-nitrosamine (BHPN) or N-nitrosomethylurea (NMU). In rats exposure to N-nitrosobis (2-hydroxypropyl)amine (BHP) and an excessive iodine diet [9], the incidence of thyroid cancer was 29% in those fed the excessive iodine diet versus 33% in those fed the iodine sufficient diet. Kanno, *et al.* [10] examined the potential thyroid tumor-promoting effects of iodine deficiency and excess for 26 weeks in rats given saline or BHPN. In saline-treated rats, iodine deficiency or excess alone was not carcinogenic, but in BHPN-treated rats, both iodine deficiency and excess increased thyroid follicular tumors, with iodine deficiency having a markedly stronger effect (Figure 3a). The incidence of rats with benign nodules was 100% in both groups. Boltze [11] fed rats over a period of 110 weeks high (~10 fold of normal), normal, and low (~0.1 fold of normal) daily iodine intake and subjected them to single external radiation of 4 gray (Gy) or sham radiation. Alone, both iodine deficiency and excess increased the thyrocyte proliferation rate and induced thyroid adenomas, but induced no thyroid carcinomas. Combined with radiation, both iodine deficiency and iodine excess induced thyroid carcinomas (PTC and follicular thyroid carcinomas, FTC) in 50-80% of animals, while iodine sufficient animals did not develop thyroid carcinomas (Figure 3b). These data suggest both long-term iodine deficiency and excess are insufficient to stimulate thyroid

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Thyroid hormone biosynthesis

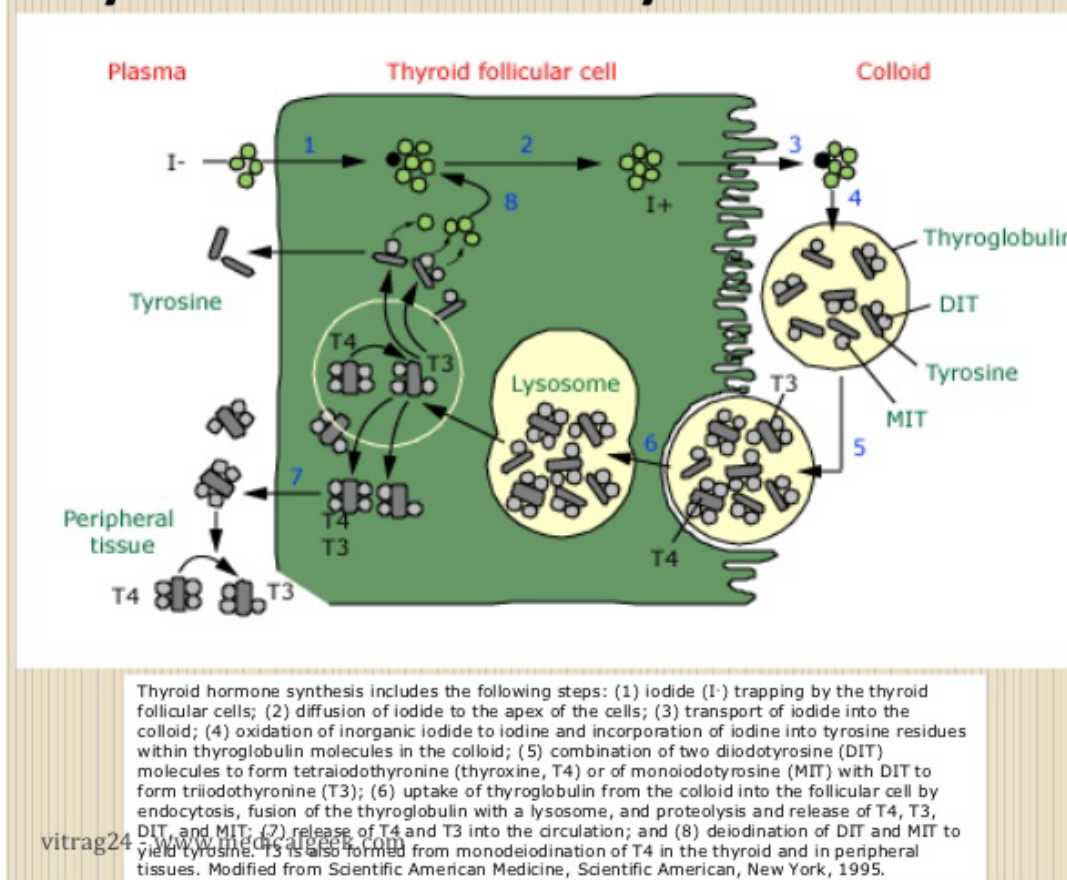


Figure 1. Thyroid hormone biosynthesis.

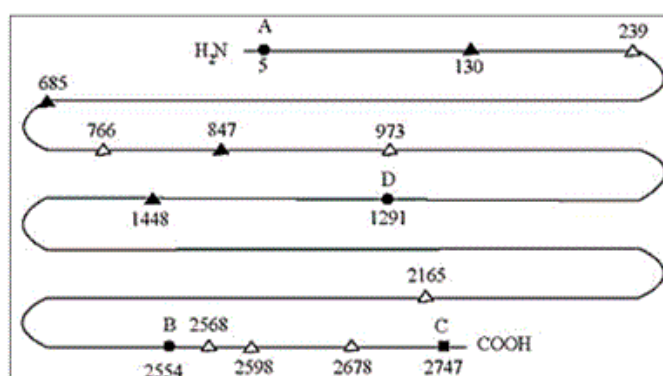


Figure 2. Iodination of T_4 at residue 5 in the Tg chain.

carcinogenesis, but both promote thyroid carcinogenesis induced by radiation. These less convincing evidence suggest that iodine excess may be a weak promoter of thyroid cancer.

Radiation exposure and risk of thyroid cancer in man

External radiation to the thyroid increases risk of thyroid cancer, particularly when the radiation occurs in children or adolescents [12-20]. The Chernobyl nuclear accident in 1986 exposed population of Belarus, Ukraine, and the Russian Federation to internal radiation from radioactive iodines deposited in the thyroid, resulting in sharp

increase in pediatric and adolescent thyroid cancer [18]. About 60% of the Belarusian thyroid cancer and 30% of the Ukrainian cases, mainly PTC, were identified about 20 years after the accident [21]. Historically, the areas exposed to Chernobyl fallout were affected by varying degrees of past iodine deficiency [22]. Chronic iodine deficiency increases thyroidal clearance of plasma iodine, increases thyroid blood flow and thyrocyte proliferation, and increases thyroid size, all of which may increase thyroid uptake of ingested radioiodines, also thereby increasing vulnerability of thyroid to the accumulated radioiodines [15,23]. A history of goiter was associated with the risk of thyroid

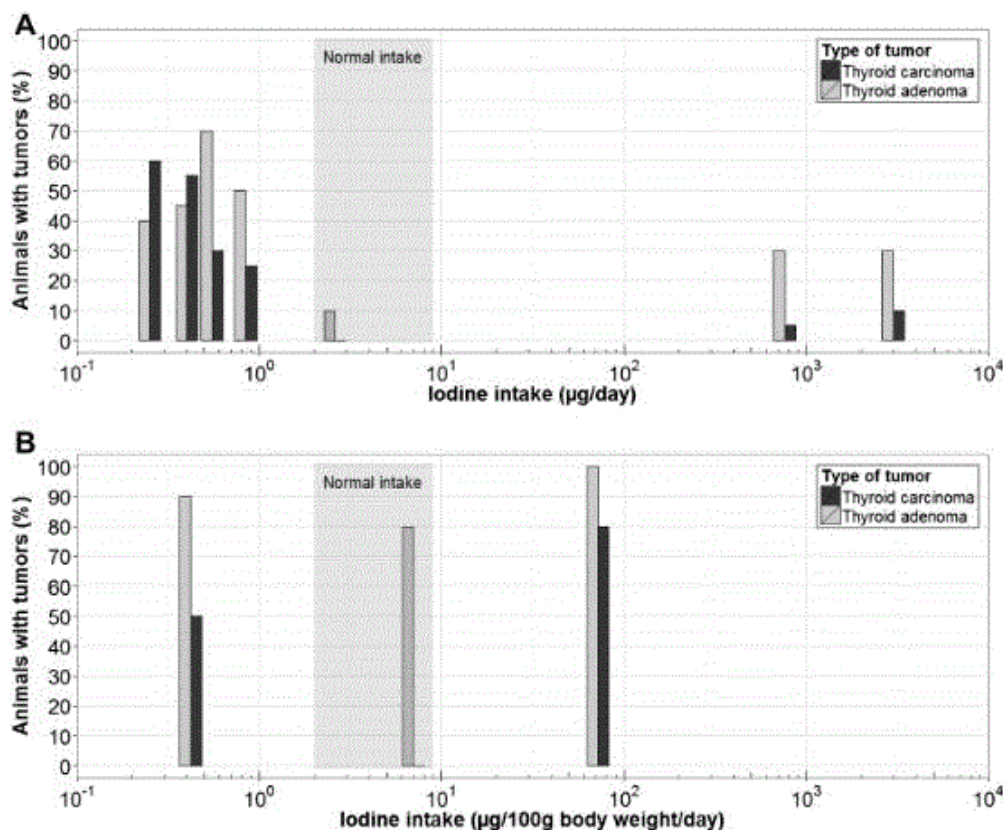


Figure 3. Prevalence of tumors in animals versus iodine intake. a Prevalence of animals with thyroid adenoma and thyroid carcinoma at week 26 after a single 2.8 mg/kg DHPN dose at week 2 and under one of seven long-term deficient, sufficient or excessive iodine diets (deficient intake: 0.25, 0.4, 0.55, 0.84 $\mu\text{g/day}$; normal intake: 2.6 $\mu\text{g/day}$; excessive intake: 760, 3000 $\mu\text{g/day}$). b Prevalence of animals with thyroid adenoma and thyroid carcinoma at week 110 after a single exposure to 4-Gy external radiation at week 6 and under one of three long-term deficient, sufficient or excessive iodine diets (deficient intake: 0.42 $\mu\text{g/100 g body weight/day}$; normal intake: 7 $\mu\text{g/100 g body weight/day}$; excessive intake: 72 $\mu\text{g/100 g body weight/day}$). Shaded area: range of normal iodine intake.

cancer (OR 2.19), but the study was limited due to a small number of cancer cases ($n=45$) [17,20].

Iodine excess goiter - A diverse etiological subtype of goiter

In the 7-9 year old, the median value of thyroid volume was 4.7ml (normal children 4.0-4.8ml) [24]. The main finding of close correlation between increased thyroid volume and high iodine intake in children is based mainly on data from coast Hokkaido in 1962-69. The incidence of endemic coast goiter among students had 6.8% to 8.9%, but never been documented to be $> 25\%$ [25,26]. Niepominszoz [27] examined the epidemiology of palpable goiter at the population of the metropolitan area of Greater Buenos Aires (11 million inhabitants), an iodine sufficient area. In the Random Group, goiter prevalence of 8.7% while in the Induced Group, which conclude among relatives of patients with thyroid disorders and other complaints, it claimed to 14.4%. Both groups were mostly made up of women (87.2%). The epidemic data presented the first arising from a screening survey carried out in a large iodine-sufficient population of the Southernmost of the American Continent.

To study the effect of excess iodine and excess tyrosine on goiter in mice [28], high iodine feed (high iodine and adequate tyrosine, HIAT) could result in the typical colloid goiter in mice and the goiter rate was 89.5% whereas 35% of goiter was observed in both iodine and tyrosine excess (HIHT), and no goiter was noted in only high tyrosine (AIHT) (Figure 4), which implicates that both iodine and tyrosine

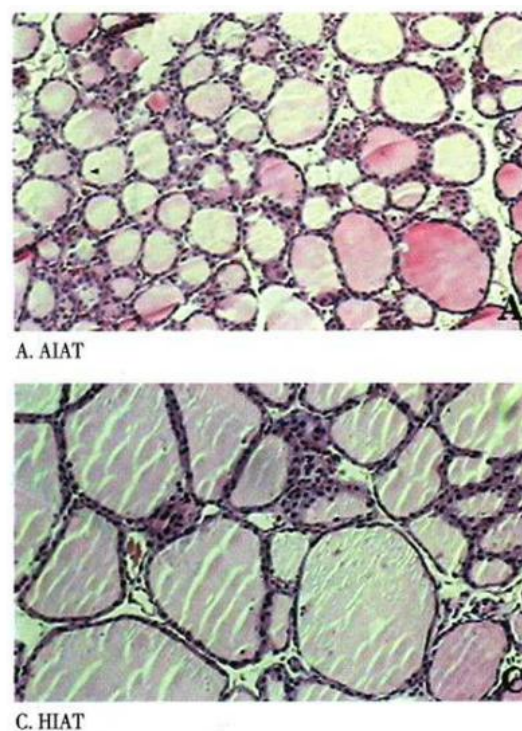


Figure 4. High iodine induced goiter in rat model.

played important role in goiter, with iodine excess having a markedly stronger effect, and which characterized by large follicles with flat epithelium and abundant colloid admixed with normal or larger-sized follicles lined by epithelium of increased thyroid weight. Moreover, there existed positive association between goiter rate of mice and iodine (KI) doses [29]. The differential goiter rate of 10%, 50% and 90% could be induced by drinking water containing different iodine doses accordingly 250, 1500 and 3000 µg/L respectively. The dose of iodine 250 µg/l was able to induce colloid goiter in mice. The findings were compatible with the epidemiologic results by authors in man. Iodine content in drinking water was 244.63, 533.83, 963.75 and 1570.0 µg/l versus 6.4%, 32.4%, 37.14% and 43.71% of goiter respectively [29].

Accumulated data, in the past decades, there have been at least 46 reported cases of goiter in man associated with iodine (KI, Na I, Lu gol solution and antiarrhythmic agent amiodarone). From epidemiology, in China, there were 16% rate incidence of iodine goiter for tangle salt diet (iodine content 1089.2 µg/kg); and 28.36% (total 4344 analyses) rate incidence of iodine goiter in higher iodine drinkers from deep well water (iodine content 661.2 µg/L) compared to 8.37% (4158) of goiter in low iodine water drinker (iodine content 27.2 µg/L) [30]. In China, children's goiter rate in excessive iodine regions with iodized salt was higher than that of without iodized salt 12.1% vs 8.6% [31]. In Jinan, among 725 inhabitants investigation, thyroid goiter rate was 4.8% (35/725). The UIC (urinary iodine concentration) in 725 subjects from 29 rural areas were 327.0 µg/l (range 35-2938.5 µg/l), and water iodine content from 376 samples of drinking water 112.1 ± 91.3 µg/l in mean, 90.3 µg/l (range 0.5-605.2 µg/l in medium) [32]. Table 1 presented partly the occurrence rate of coast goiter as below.

Iodine induced hyperthyroidism (IIT) and thyrotoxicosis (IIT)

According to WHO above in 1994 [33] and the Korea Centers for disease control and prevention (KCDC) in 2012 [34], food products such as processed, agricultural, meats, and marine products were monitored for measuring dietary iodine. The recommended iodine daily allowance of 70-150 µg [35]. An excess of iodine through dietary intake, drugs or other iodine-containing compounds can lead to goiter [36-37], hyperthyroidism [38-45], Hashimoto's thyroiditis [46] and thyrotoxicosis [47-54] through increasing thyroid hormone synthesis in the presence of underlying thyroid disease, particularly multinodular goiters containing previously existing area of autonomous function. In 1958, introduction of potassium iodide (KI) in order to the prevention of goiter in French, many students developed iodine goiter with oral high dosage of 1% KI or 10 mg KI daily. Uptil now, in literature, there were at least 22 cases reports on ITH or IIT. Potassium iodide (KI) at 10⁻⁴-10⁻⁷ mol/L concentration stimulate the proliferation of thyroid cancer BPH 10-3 cells, increased levels of serum T3 and T4, increased cyclin D1 mRNA and protein. In rats serum thyroxine (TT4, FT4, rT3) was higher in higher iodine than the result in lower iodine [55-57].

Iodine-induced hyperthyroidism (IIT) has been frequently described when iodine is introduced into an iodine-deficient area [38], patients residing in iodine-sufficient areas [43] and iodinated preparation for water purification [40]. Excessive iodine intake might also be due to a long-term topical exposure (iodine solution dressing or topical iodine application) or by intravenous administration of iodine-containing substances [39, 41, 45, 58]. In a classical study, four euthyroid patients with a single autonomous nodule from the slightly iodine-deficient Brussels region received a supplement of 500 µg iodine per day. This caused a slow but constant increase of thyroid hormone.

After four weeks, the patients became hyperthyroid [47]. Therefore, individuals with multinodular goiters living in iodine-replete regions can also develop hyperthyroidism, confirming that nodular goiters are particularly prone to developing IIT [48]. Iodine-induced IIT was recognized as early as 1821 by Coindet [40], who reported that goitrous individuals treated with iodine developed hyperthyroidism. Comparative survey of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. It occurs that high incidence of multinodular toxic goitre in the elderly population in a low iodine intake area whereas high incidence of Grave's disease in young in a high iodine intake area [56]. In northern Tasmania in UK, in 1964 and in 1971 respectively, the incidence of thyrotoxicosis rose substantially because of the addition of iodate to bread to prevent goitre or iodine residues in milk [51]. In Vigo, Spain, dietary iodine supplementation in iodine sufficient areas may induce the increase of thyrotoxicosis (TT) (7.68/100,000), as opposed to 3.1/100,000 in area without iodinated salt [57]. IIT has been reported after initiating iodine supplementation, also with use of iodinated drugs, radiographic contrast agents and food dietary iodine [48-58] (Table I). Table I presents iodine-containing compounds related to IIT.

Table I. Iodine-containing compounds potentially associated with IIT

Radiological contrast agents: Diatrizoate, Ipanoic acid, Iodate, Iothalamate, Metrizamide, Iopromide, Iopamidol, Iotrolan.

Topical iodine preparation: Iodine tincture, povidone iodine (Betadine), Iodoform gauze.

Solution: saturated potassium iodide, Lugol solution, iodinated glycerol (organidin), echthiophate iodide, hydriodic acid syrup.

Drugs: Amiodarone, vitamins containing iodine, potassium iodide, Isopropamide iodide.

Food components: kelp, kombu and other marine algae, iodine compounds in bread, Hamburger thyroiditis.

Amiodarone is the most common source of iodine in the United States. Amiodarone-induced thyrotoxicosis (AIT) type I results from iodine increase in thyroxine synthesis (200 mg of amiodarone containing 75 mg of iodine). Patients developing AIT type I usually have a preexisting nodular goiter. AIT type II is caused by cytotoxic effects of medication that results in the release of preformed thyroxine [48]. AIT occurs late after amiodarone withdrawal [59].

Kelp are large seaweeds, belonging to the brown algae and classified in the order Laminariales, and are an important food source in many Asian cultures [60]. The average iodine content of kelp of 1,500 to 2,000 µg/g was measured [61-62]. Herbal medicine, including kelp and kelp-containing dietary supplements, are also used by an increasing numbers of patients [63]. Suzuki [23] was the first to report a case of endemic seashore goiter following marine algae. At present there have been reported at least 8 patients with ITH or IIT after ingestion of kelp [60, 64-69]. Another 12 thyrotoxicosis caused by weight-reducing herbal medicine [63]. In 2001, Zhu [70] reported a case of thyroid neoplasm following marine algae in a breast cancer. From epidemiologic studies in Korean population, high intake of iodine from marine products may increase thyroid cancer risk, particularly in women [71, 72]. Accumulated data, seaweed accounts for about 80% of Japanese people's iodine intake, seaweed consumption was clearly associated with an increased risk of papillary carcinoma (PTC) in postmenopausal women [73].

Table 1. Iodine excess endemic goiter in coast, china (Data from Yu ZH,etal,2001[30]).

Year	Province	Rural areas	Water iodine(ug/l)	Urine iodine(ug/l)	Goiter crude incidence (%)
1978	Hebei	Bohai Bay	661.2		28.36(total 4344 analyses)
			27.2		8.37(total 4158)
1983	Shandong	Bohai Bay	1272-1920		50-70
		Rizhao	1089.2		16.0
1983	Xinjiang	Kuitunwusu	66-2375		8.0
1986	Shanxi	Xiaoyi	533.8	2428.5	32.54
1987	Fukien	Tongan	290.0-584.0	849	32.84
1993	Henan	Guiqian	1059.8	924.9	22.4
1994	Inner Mongolia	Shiyuqi	380-1757	1151.7	10.84
1997	Jiangsu	Huashan	520-1875	931.5	23.9
		Zhangjiazhuang	397-6403.3		11.5
1999	Beijing	Daxing	337.1-698.6	586.7	11.9

Dietary iodine intake and the prevalence of papillary carcinoma (PTC)

Thyroid neoplasia can result from many different causes. These include low iodine diets, radioactive iodine and natural goitrogens. Dietary iodine intake act as a potential relavance risk factor of thyroid cancer [21,71-76].Elevated incidence and mortality rate of thyroid cancer have been found in areas where iodine intake is high(Hawaii, Iceland)[76-78].In South India, among 300 patients with goiter and 100 euthyroid health non-goitrous volunteers, iodine-induced hyperthyroidism or IIT (34%)and thyroid cancer (15%)have been observed after continued supplement of edible salt fortified with excess iodine[79]. In China, using comparative analysis of 4679 post-operative patients with universal salt iodization (USI)during 1994-2008 and 3325 post-operative patients without USI during 1979-1993,the incidence ratio of thyroid carcinoma after USI was 5.6% (308/4679)compared to 2.9% (95/3325) in patients without USI,32.7% (1530)of thyroid adenoma after USI compared to 20% (665)before USI, and 4.5% (212) of toxic goiter after USI compared to 2.7% (95) before USI [80].According to 1101 thyroid malignant tumors confirmed by pathological specimens, constitutional ratio of PTC (70.17%)increased obviously after USI compared with the results (55.84%)before USI whereas the proportion of FTC (11.05%)decreased accordingly after USI compared with the results (24.58%) before USI [81]. The same results was also reported based on 429 analyses [82]. The prevalence of PTC (80-90%) in thyroid carcinoma increased significant after USI. In Shengyang, china, the ratio of PTC:FTC was from 2.3 to 21.9 before and after salt iodization. Therefore, in the presence of sufficient iodine intake, more than 80% of thyroid cancer consisted of papillary carcinoma (PTC),whereas in area with iodine-deficiency, in contrast, have a higher incidence of FTC (Figure 1) [83].Compared with matched controls, urinary excretion of iodine excess was detected in 302 cases of thyroid benign tumors (519 µg/L)and 240 thyroid cancers (524 µg/L). Higher urine iodine was associated with PTC (urine iodine:355.3 ± 289.6ug/L in 53.

And more, According to Zimmermann in recent review[11]and Williams the earlier review [22],there were reports that in countries with 'high' iodine intake (US, Iceland) the ratio of PTC:FTC ranged from 3.4 to 6.5,while in countries with 'moderate' iodine intake (the UK and northern Germany)the ratio was from 1.6 to 3.7,and in countries with 'low' iodide intake (Argentina, Columbia, Finland, Southern Germany, Austria and Switzerland) the ratio was from 0.19 to 1.7.The incidence of PTC in the Netherlands has increased by 2.1% per year between 1989 and 2003,which was partly explained by the stable and sufficient iodine intake of the Dutch population during the last 4 decades, together with other low level of radiation exposure and incidentally discovered thyroid nodules[84]. In northwestern Spain, iodized salt was

introduced in 1985,the thyroid cancer incidence increased in females from 1.56/100,000 during 1978-1985 to 8.23/100,000 in period from 1984 to 2001,the PTF:FTC increased from 2.3 to 11.5 [85].Italy had one of the highest incidence rates for thyroid cancer,nearly 20/100,000 women in 2007,the frequency of thyroid cancer in females with cold nodules was 5.3% in the iodine sufficient area (mean UIC 114 µg/l) and 2.7% in the iodine deficient area (mean UIC < 50 µg/l) [86].The highest incidence rates for thyroid cancer are Japan, where iodine intake is high [22]. Occult thyroid cancer (OTC)was more common in glands with nodular goiter (range 15.7% ~ 28.4%)in areas of excessive iodine intake [87-90]. A case-control study in Hawaiian adults reported the association between dietary iodine intake and thyroid cancer in 191 cases (85% PTC) and 442 controls [91]. But increasing thyroid cancer rates were not been associated with national iodine intake according to UIC data from US population [92,93], Sweden [94] and Denmark [95,96]. Overall, in the past 2 to 3 decades, there is clear temporal relationship in many countries between introduction of iodized salt and an increase in incidence of PTC [83,97-100] (Figure 5).

In case-control studies, cruciferous plants were found an association with increased thyroid cancer risk. In epidemiology, in sweden, the risk of thyroid cancer associated with a high cruciferous vegetable intake was higher among female who had ever lived in an endemic goiter area [101]. In poland, frequent cruciferous vegetable consumption was associated with a 1.5-fold increase in the risk of thyroid carcinoma [102]. However, A study from New Caledonia among Melanesian women who consume large quantities of cruciferous vegetables, and low iodine intake (< 96.0 µg/day) showed a positive association [103]. The study from Kuwait, high intake of cabbage showed an increased risk with a borderline significance [104]. Thus, in this area ,more accumulated results are needed to be testable.

Overall, the findings indicated clearly carcinogenesis of I131 or/ and radiogenic transformation on thyroid glands in the rats and man. Dietary iodine intake is another care of environmental relevance factor in thyroid diseases and papillary carcinoma.

Oncogenic thyroid hormone receptor mutants

It has been demonstrated that thyroid status had a modulating effect on neoplasia. Like iodine- induced hyperthyroidism and IIT, using thyroxine L-T4 which 65% of T4 weight is iodine, Ciosek [105] induced experimental model of rat hyperthyroidism. Administration of thyroid hormone to thyrectomized rodents is a prerequisite for the induction of hepatomas by chemicals, indicating a role in the initiating action of carcinogen [106]. This thyroid hormone (T3)signaling through thyroid hormone receptor (THRa1)regulates hepatoma cell growth [107]. In literature, there have been more 10 cases of earlier reports

on the thyroid carcinomas and concurrent hyperthyroidism (Grave's disease), and also concurrent toxic nodular goiters [108-110]. The other 11 cases were further reported [111,112]. Among 10 hyperthyroidism, of whom 6 with Grave's disease complicated with thyroid cancer, 2 hyperthyroidism with thyroiditis and thyroid cancer [111]. Another case was reported in a 43-old-man with initial hyperthyroidism, and two years later transformation of thyroid adenoma complicated with hyperthyroidism (nodule: 6x4x3cm), suggesting an initiating role of thyroxine on neoplasm and a wide variety of metabolic effects, for instance, increased lipogenesis and hair growth [112]. In addition, the transformation of culture cells by radiation is in vitro facilitated by thyroid hormone [113] (Figure 6).

In vitro, the BFU-E, a cell which arise from the pluripotent stem cell committed to the erythroid line and which has a high erythropoietin (EP)-responsive proliferative capacity, seems to be the precursor of the CFU-E, a cell of lower proliferative capacity. Both CFU-E-derived and BFU-E-derived colony formation were enhanced by the hormone. Addition of L-thyroxine (L-T4) at an optimal final concentration of 10-8M and L-triiodothyronine (L-T3) at 10-9M to culture containing EP resulted in doubling and tripling in erythroid colony formation of normal human bone marrow. Clinical thyroxine can correct thyroidal hypothyroidism with severe anemia (Hb < 30g/l - 90g/l, [114,115]) via potentiation of human erythropoiesis (erythroid proliferation) and hemoglobin (hemin) production in vitro by thyroid hormone.

In vivo, mice expressing THR α 1 specifically in the intestinal epithelium in wild-type THR α 1 presented mucosal architecture and increased cell proliferation and develops adenoma at low rate [116]. This phenotype is due to cooperation between the activated THR α 1 and WNT pathways [116]. Mutation of thyroid hormone receptor-beta (THR β) in mice promotes the development of mammary hyperplasia

via aberrant activation of STAT5 [117]. THR β mutants can also induce spontaneous development of follicular thyroid carcinoma (FTC) similar to human cancer in a knocking mouse model harbouring a mutated THR β (Thrb, denoted PV) [118-120], and thyroid hormone play a critical role in promoting thyroid carcinogenesis of Thrb (PV/PV) mice via PI3K-AKT-beta-Catenin signaling pathway [120,121]. Moreover, southern analysis revealed a rearrangement of oncogenic THRA1/BTR fusion in the BT474 breast cancer cell line [122]. This rearrangement represented a deletion of THRA1 allele that was coamplified with ERBB2 in breast cancer.

In clinics, almost 63% of 16 papillary thyroid carcinoma (PTC) were found to have mutations in THRA1, and a remarkable 94% in THR β 1, in contrast 22% and 11% of thyroid adenomas harboring mutations in these isoforms respectively, and no mutations were found in normal thyroid controls, which implicate the differential effects of normal and oncogenic thyroid hormone receptor [123] signaling in PTC and normal health controls [124]. The findings suggest a possible oncogenic action for thyroid hormone receptor mutation in the tumorigenesis of human thyroid carcinoma [125]. Others, anaplastic thyroid cancers harbor novel oncogenic mutations of ALK gene [126]. Oncogenic receptor ALK belongs to an insulin receptor (IR) or oncogenic receptor IGF-1R family [127]. TLR4 stimulation with its ligand lipopolysaccharides promotes KSHV-induced cellular transformation and tumorigenesis by activating the STAT3 pathway [128] TLR4 mediated tumorigenesis while TLR4 antagonist CL1095 inhibite it. Toll-like receptor (TLR4) induced pro-oncogenic or also protumoral function in head and neck carcinoma [129]. More others, CLIC1 was identified as a novel dominant pro-oncogenic receptor from proteomic profiling of pleomorphic human sarcoma [130]. Thus, an extensive study of thyroid hormone receptor (THR) mutations in oncogenic signaling, TSH/TSHR in thyroid disease and thyroid cancer, and also its target therapy [131-133], is further perspective.

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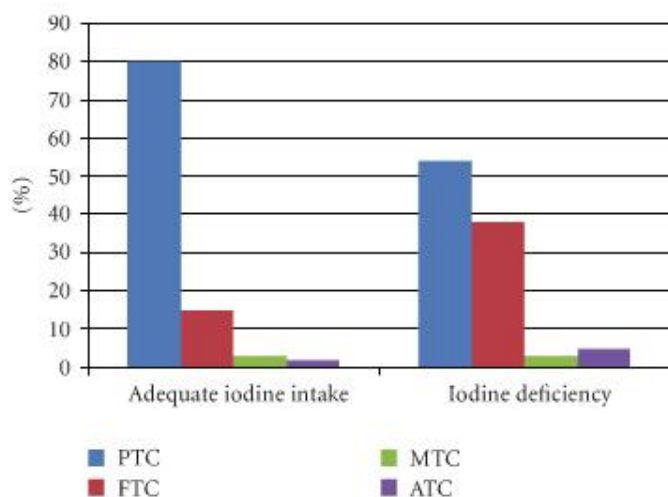


Figure 5. Contribution of iodine in the food to the thyroid tumorigenesis.

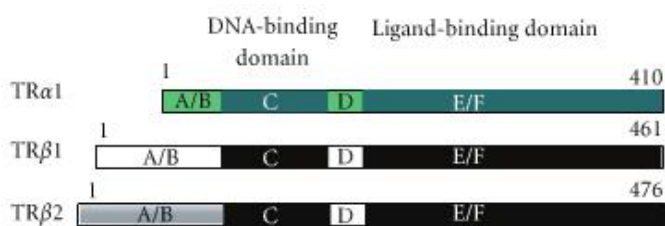


Figure 6. Structure of two thyroid hormone receptors.

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