IODINE INTAKE AND CANCER

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 in thyroid gland and the influence of thyroid hormone (T_3,T_4) and thyrotropin (TSH) secretion. Increase rates of the thyroid cancer are increasing after radiation exposure to ^{131}I in children or aldolescents.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.

Keywords: Iodine excess goiter; IIH and IIT; the pattern of papillary carcinoma(PTC); oncogenic thyroid hormone receptor mutants

Introduction

The main function of the thyroid gland is to make hormones(figure 1) [1] ,T_4 and T_3 are key regulation of metabolic effects such as the development of the brain in neonatals, the rapid development of frogs from thyrectomized tadpoles,the induction of growth hormone in the pituitary, and others lipogenesis, ketogenesis,and cellular proliferation and differentiation.

Iodine is a trace essential raw element where 65% of T_4 weight is iodine. According to WHO/ UNICEF/ICCIDD[2,3],daily iodine intake are 90ug for infants and young children (0-59 months), 120ug for children 6-12 years,150ug for adolescents and adults,and 250ug for pregnant and lactating women. 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 transportated 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 larger glycoprotein secreted into the lumen of follicles,whose tyrosyles 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 T_4 at residues 5 in the Tg polypeptide chain（figure 2). After Tg digestion,T_4 and T_3 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. In this paper,we are deliberating the topic entity of iodine excess induced thyroid diseases and papillary carcinoma（PTC）.

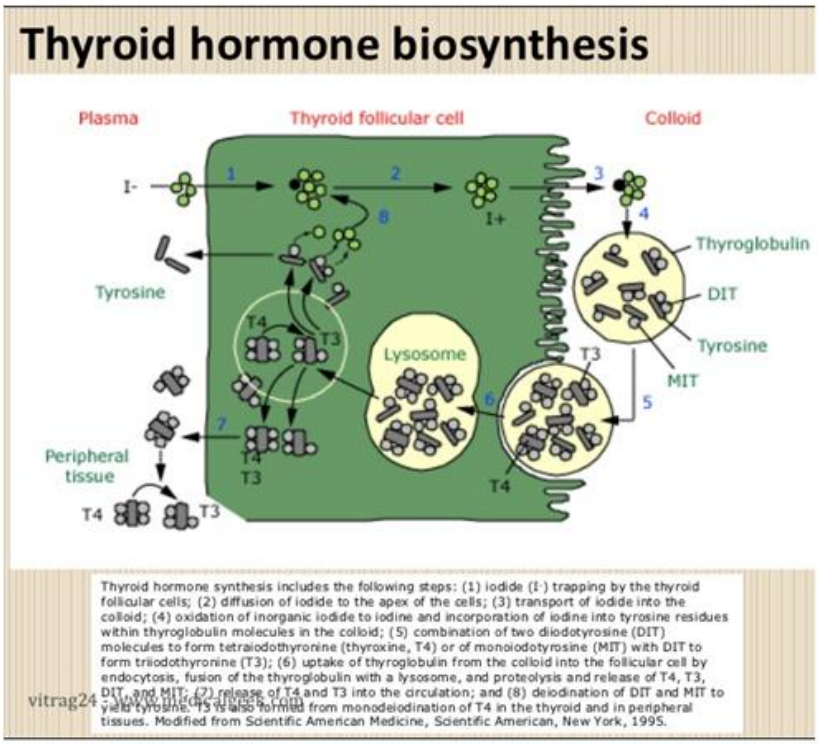

Fig.1.thyroid hormone biosynthesis and diagram steps of thyroid hormone synthesis(see above step contents).

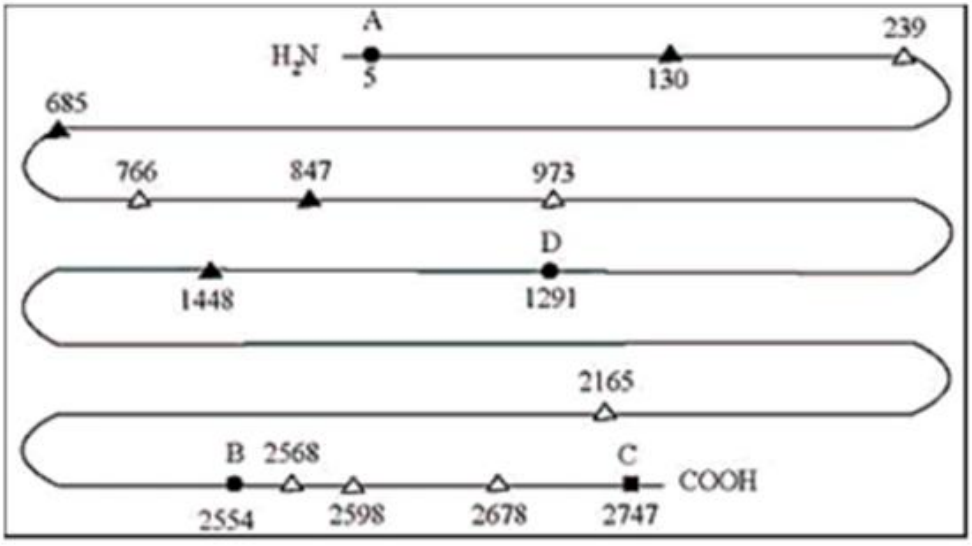

Fig. 2 : Diagram of the human Tg polypeptide chain; residue numbers refer to the human cDNA sequence; (a) sites forming T4 (sites A,B,D) (solid circles) and/or T3 (site C) (solid square); (b) early iodinated sites (solid triangles); (c) other iodinated sites (open triangles).

Fig. 2. Iodination of T_4 at residue 5,1291 and 2554 in the Tg chain. Diagram of the human Tg polypeptide chain; residue numbers refer to the human cDNA sequence; (a) sites forming T_4 (sites A,B,D) (solid circles) and/or T_3 (site C) (solid square); (b) early iodinated sites (solid triangles); (c) other iodinated sites (open triangles) (Data from Miot F and Rousset,etal,2015 [3]

Exposure to radioactive iodine in induction of thyroid neoplasm in rat

Since 1941,due to its lack of significant adverse effects and low cost, radioiodine-131(^{131}I) has been successfully administered therapy or diagnosis of patients with benign thyroid disease. Up to recent,there was the investigation of the relationship between cancer risk following the therapeutic use of ^{131}I in benign thyroid disease provide conflicting results regarding several long-term cohort studies in Sweden[4],England[5], Finland[6], Japan[7] and the US[8] . There was no increase in burden of cancer risk overall after ^{131}I administration. However,there was a tendency toward increase in thyroid cancer risk for women < 40 years old following diagnostic ^{131}I. Moreover, A significant risk of thyroid cancer has been observed after administration of therapeutic X- radiation with doses as high as 60 Gy in childhood[10].

In experimental animals,in rats development of thyroid neoplasm following radioactive iodine was well established in earlier 1950-1964 last century. Since 1950,an extensive study of benign and malignant thyroid tumors induced,in the rats and mice,with radioiodine[11,12]. Moreover,it has been found that animals on an iodine-restricted diet were more likely to develop cancer[13,14]. C3H/Hey strain-mice where placed in low-iodine diet can induce benign and malignant thyroid tumors[15]. Male Sprague-Dawley rats in chronic iodine-deficiency,long-term of approximately 10% of normal iodine dietary escalated to 60 times the normal concentration developed follicular hypertrophy and subsequent hyperplasia of follicular cells,and a massive increased proliferation rate[16]. This represent an in vivo model of low iodine dietary supply in tumorigenesis in the rats[13-18] (see table 1).

In rats with containing carcinogens N-nitrosobis（2-hydroxypropyl）amine（BHP）and an excessive iodine diet[19], the incidence of thyroid cancer was 29% in those fed the excessive iodine diet versus 33% in those fed the iodine sufficient diet. Kanno etal[20] examined the thyroid tumor-promoting effects of iodine deficiency and excess for 26 weeks in rats given saline or N-bis(2-hydroxypropyl)- nitrosamine (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 group. Boltze[16] fed rats over a peroid 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 carcinogenesis,but both promote thyroid carcinogenesis induced by radiation. Iodine excess may be a weak promoter of thyroid cancer.

The overall incidence of thyroid carcinoma is generally considered without influence from the iodine intake in a given population. Iodine deficiency caused a high incidence of follicular tumor,while iodine intake dietary supply shift the distribution towards papillary tumors[21-22]. In a Swedish study,papillary thyroid cancer was common in iodine-rich area. In a recent study on the effect of iodine intake on thyroid diseases in China,10 patients with thyroid cancer were identified in the area of excessive iodine intake. Moreover, another 13 new cases of thyroid cancer were diagnosed in this iodine excessive area[23]. A number of epidemiological studies have attempted to illustrate the association between excessive iodine intake and the risk of developing thyroid cancer,with the majority (80%) of papillary thyroid cancers(PTC) (Table 1). Chronically high iodine intake have been associated with the development of goiter (ie. hypertrophy and hyperplasia of the thyroid cells),and in turn,goiter linked to thyroid cancer risk,particuly in women.

Table 1 . Changing incidence of thyroid cancer in Tasmania during transition from iodine sufficiency to iodine deficiency : histologic types.

Years	mcg of iodine excreted/gram of creatinine* (median)	Papillary	Follicular	Ratio PTC/FTC
1978–1984	< 75	27	20	1.35
1985–1991	< 75	43	21	2.04
1992–1998	42	110	26	4.23

Optimal iodine intake: 120–200 µg of iodine/gram of creatinine. [adapted from ref. 78]

Table 1 showed the different histologic types of thyroid cancer in 1991-98 compared to 1978-84.Table also represented an in vivo changing of iodine deficiency in tumorigenesis(from Knobel & Neto M,2007[15]) .

Another recent examination was noted the association between breast cancer and hyperthyroidism, hypothyroidism, thyroxine replacement therapy and thyroiditis[24]. However,there is as yet no definitive conclusion. In Japanese women who had a diet containing iodine-rich seaweed,experimental findings has been shown a relative low rate of breast cancer. In my group[25], induction of thyroid tumor by *Sargassum* excessive iodine intake was uncovered in a patient with breast cancer during additional traditional medicine treatment. Otherwise,it has been found a high incidence of thyroid cancers in these children's neck solely by the ^{131}I irradiation[26]. Leukemia and thyroid cancer developed following radioiodine treatment of hyperthyroidism[27,28]. Available

evidence from animal experiments, epidemiological studies and iodine prophylax has demonstrated a shift toward an increase the risk of the more common papillary carcinoma.

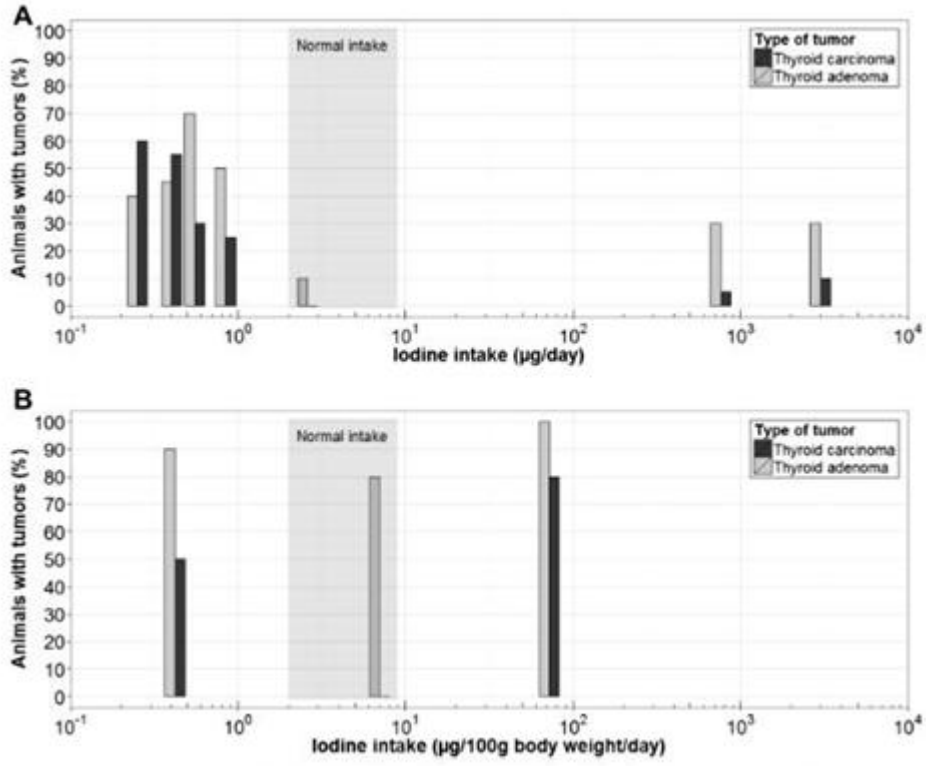

Fig.3. Incidence prevalence of tumors in animals versus iodine intake. a Prevalence of animals with thyroid adenoma and thyroid carcinoma at week 26 after a single 2.8 mg/kg DHPN dose at week 2 and under one of seven long-term deficient, sufficient or excessive iodine diets (deficient intake: 0.25, 0.4, 0.55, 0.84 µg/day; normal intake: 2.6 µg/day; excessive intake: 760, 3000 µg/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 µg/100 g body weight/day; normal intake: 7 µg/100 g body weight/day; excessive intake: 72 µg/100 g body weight/day). Shaded area: range of normal iodine intake. (Data from Zimmermann MB,etal,2015[29])

Epidemiology of thyroid cancer induced by Chernobyl ionizing radiation exposure and risk of thyroid cancer in man

An increased risk of thyroid cancer has been demonstrated in survivors of the atom bomb explosions in Japan in 1945 [30]. On 26 April 1986,the most serious environmental disaster at the Chernobyl nuclear power station in northern Ukraine led to a dramatic increase in the frequency of chilhood thyroid cancer in contaminated areas of

Belarus,Ukraine,and Western Russia[31-43]. The report of the United Scientific Committe on the Effects of Atomic Radiation (UNSCEAR)[31] provide estimate of the thyroid cancer risk in children from exposure to radioiodine. More than 10 million people were exposed to significant levels of radiation. The Chernobyl accident released huge amounts of radioactive materials into atmosphere,including 1.8x1018Bq of ^{131}I, 2.5x1018 of ^{133}I,and 1.1x1018 Bq of ^{132}Te,which decays to ^{132}I (UNSCEAR,2000)[31,32]. It has been estimated that more than 80% of thyroid dose came from internal exposure to ^{131}I,and the dose was 3-10 times higher in children than in adults. Beginning in 1990s,a dramatic increase in the incidence of pediatric thyroid cancer was noted in Belarus,and one or two years later in northern Ukraine and Western areas of Russia. In Belarus,children under the age of one year at the time of exposure had a relative risk of 237,whereas those aged 10 showed a relative risk of 6 [32,33]. Those radiation associated thyroid cancers showed a higher the excess relative risk(ERR) of thyroid cancer involving younger age at the time of exposure[32,34]. Moreover,there are also reports of a two- to fourfold increase in thyroid carcinoma in adults from exposed areas[32,33]. When comparision of typically 5-10 years prior to Chernobyl,in a series of 472 patients from Belarus[32,35],the average latency between exposure and cancer diagnosis was 6.9 years. The vast majority of post- Chernobyl pediatric thyroid cancers were papilliary carcinoma. Histopathological features appears as sheets of malignant epithelial cells surrounded by varying amounts of fibrotic stroma. Post- Chernobyl thyroid cancers were clinically high prevalence of solid growth pattern,and more aggressive at presentation. In molecular analysis(table 2),RET/PTC rearrangement has been found in 66-87% of all post-Chernobyl tumors. RET/PTC is formed by an intrachromosomal inversion of the long arm of chromosome 10 resulting in the fusion of RET with the H4/D10S170 gene,which implicate RET/PTC as a key first step in papillary thyroid cancer pathogenesis[36-38]. In post-Chernobyl children with PTC,RET/PTC3 rearrangement was strongly associated with solid variant PTC with a short latent period after exposure,while RET/PTC rearrangement was mainly linked to conventional PTC with a long latent period after exposure[39.40]. Another rearrangement was about 7% of radiation-induced papillary carcinomas involving the nerve growth factor gene NTRK1[41]. Recently,a new paracentric inversion of chromosome 7q leads to an in-frame fusion between exons 1-8 of the AKAP9 gene and exons 9-18 of BRAF. The fusion protein transforms NIH3T3 cells,confirming its oncogenic properties[42,43].

Radiation-associated PTC		Chromosomal rearrangements			Point mutations	
	A-bomb survivors (Our study)	RET/PTC	TRK &TRK-T1,2,3	AKAP9-BRAF	BRAFV600E	K, H, N-RAS
	Non-exposed	4%	0%	0%	70%	4%
	Exposed	18%	2%	0%	56%	0%
	Post-Chernobyl	34-87%	3%	11%	0-20%	0%
	Radiotherapy	51-84%	19%		4%	40-50%
Sporadic PTC	Adult-onset	3-61%	6-12%	1%	28-83%	0-58%
		Childhood	30-71%	0-11%	0-6%	0-7%

Table 2: Gene alterations in radiation-associated and sporadic PTC (*detected only in PTC developed 5-6 years after radiation exposure).

Table 2 presented a high prevalence of RET/PTC rearrangements in Ukrainian and Belarussian post-Chernobyl thyroid papillary carcinomas (from Hamatani K,etal,2015 [43]

Iodine induced goiter,hyperthyroidism（IIT）and thyrotoxicosis（IIT）

According to WHO in 1994[44] and the Korea Centers for disease control and prevention（KCDC）in 2012[45] food products such as processed, agricultural, meats,and marine products were monitored for measuring dietary iodine. The recommended iodine daily allowance of 70-150ug[46]. The median value of thyroid volume was 4.7ml（normal children 4.0-4.8ml) in the 7-9 year old. An excess of iodine through dietary intake,drugs or other iodine-containing compounds can lead to goiter[47], hyperthyroidism[48-51],hashimoto's thyroiditis[52] and thyrotoxicosis[53-56]through increasing thyroid hormone synthesis in the presence of underlying thyroid disease,particularly multinodular goiters containing previously existing area of autonomous function. Potassum iodide（KI）at 10-4 ~7 mol/L concentration stimulate the proliferation of thyroid cancer BPH 10-3 cells, increased levels of serum T_3 and T_4,increased cyclin D1 mRNA and protein（Nie,2005;Li,2013）.

In 1958, in French,introduction of potassium iodide（KI）in order to the prevention of goiter, many students developed iodine goiter with oral high dosage of 1% KI or 10mg KI daily. The earliest finding of close correlation between increased in 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%[57] Iodine-induced IIT was recognized as early as 1821 by Coindet[54], who reported that goitrous individuals treated with iodine developed hyperthyroidism. In the past

decades,there have been at least 46 reported cases of goiter in man that associated with iodine (K I,Na I,Lugol solution and antiarrhythmic agent amiodarone). In literature reports,there were at least 22 cases reports on IIH or IIT. The incidence of IIH in an endemic goiter has been up to 1.7% (Martin,1989). At the population of the metropolitan area of Greater Buenos Aires(11 million inhabitants) , an iodine sufficient area, Niepominszoze[58] examined the epidemiology of palpable goiter. In the Random Group,goiter prevalence was 8.7% while in the Induced Group,which concluded among relatives of patients with thyroid disorders and other complaints,it climed to 14.4%. Both group were mostly made up of women (87.2%) .The epidemic data presented the first arising from a screeing survey carried out in a large iodine-sufficient population of the Southernmost of the American Continent.

To further study the effect of excess iodine and excess tyrosine on goiter in mice[59],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 goitet was noted in only high tyrosine (AIHT) (figure 4) . The results implicate that both iodine and tyrosine played a key role in goiter, and iodine excess having a markedly stronger effect,and goiter was characterized by large follicles with flat epithelium and abundant colloid mixed 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[60]. The differential goiter rate of 10%,50% and 90% could be induced by drinking water at different iodine doses 250,1500 and 3000ug/L respectively. The dose of iodine 250ug/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 1570.0ug/l versus 6.4%, 32.4%,37.14% and 43.71% of goiter respectively [60].

From epidemiology,in China,there were 16% rate incidence of iodine goiter for tangle salt diet (iodine content 1089.2ug/kg) ; and 28.36% (total 4344 analyses) rate incidence of iodine goiter in higher iodine drinkers from deep well water (iodine content 661.2ug/L) compared to 8.37% (total 4158 analyses) of goiter in low iodine water drinker (iodine content 27.2ug/L)[61]. In china,children's goitet rate in excessive iodine regions with iodized salt was higher than that of without iodined salt (12.1% vs 8.6%)[62]. 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 327.0ug/l（range 35-2938.5ug/l）,and water iodine content from 376 samples of drinking water 112.1+/-91.3ug/l in mean,90.3ug/l（range 0.5-605.2ug/l in medium）[63]. Table 1 presented partly the occurrence rate of coast goiter as below.

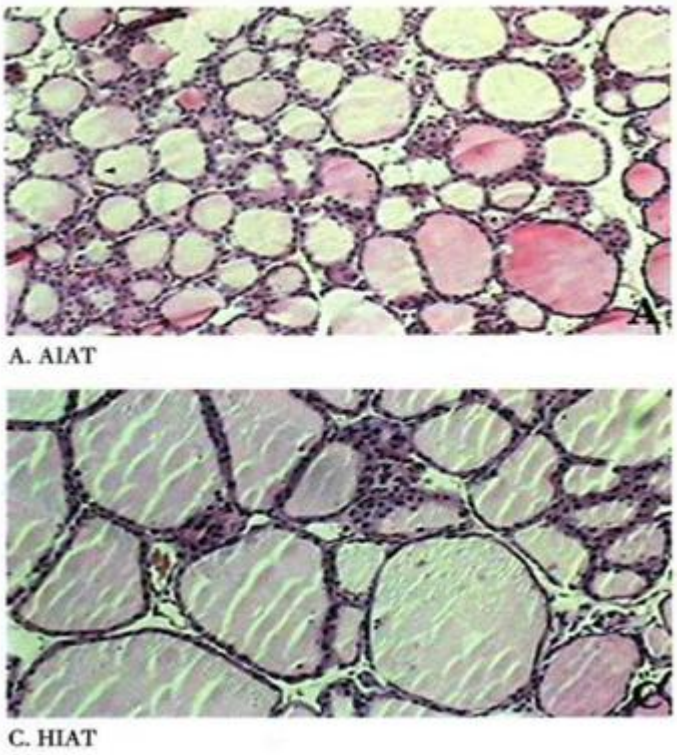

Fig.4. Hi iodine induced goiter in rat ghmodel(Data from Li N,2010[59])

Table 3. Iodine excess endemic goiter in coast,China(Data from Yu ZH,etal,2001[61])

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	Shiyouqi	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

Iodine-induced hyperthyroidism (IIH) has been frequently described when iodine is introduced into an iodine-deficient area[48],patients residing in iodine-sufficient areas[64] and iodinated preparation for water purification[65]. 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[67-69]. In a classical study,four euthyroid patients with a single autonomous nodule from the slightly iodine-deficient Brussels region received a supplement of 500ug iodine per day.This caused a slow but constant increase of thyroid hormone. After four weeks,the patients became hyperthyroid[70]. Therefore, IIH is frequently observed in patients affected by euthyroid iodine deficient goiter when suddenly exposed to excess iodine. The possibly the presence of autonomous thyroid function permits the synthesis and release of excess quantities of thyroid hormones. In rats serum thyroxine(TT_4,FT_4,rT_3) was higher in higher iodine than the result in lower iodine (Nie,2005). Individuals with multinodular goiters living in iodine-replete regions can also develop hyperthyroidism,confirming that nodular goiters are particularly prone to developing IIT[53]. In iodine-sufficient areas,IIH has been reported in euthyroid patients with previous diseases. For instance,euthyroid patients previously treated with antithyroid drugs for Grave's diseases are prone to develop IIH. In East-Jutland Denmark and Iceland,It has been found that in the elderly population high incidence of multinodular toxic goitre in a low iodine intake area whereas high incidence of Grave's disease in young in a high iodine intake area[71]. Other IIH has been occasionally observed in euthyroid patients with a previous episode of post- partum thyroiditis, type II thyrotoxicosis,and in people with iatrogenic episodes of thyroid dysfunction (eg. nonionic contrast radiography). 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[72]. In Vigo,Spain,dietary of 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 iodinized salt[73]. IIT has been reported after initiating iodine supplementation, also with use of iodinated drugs,radiographic contrast agents and food dietary iodine[64-73]. Table 4 represent iodine-containing compounds related to IIT[64].

TABLE 4. COMMONLY USED IODINE-CONTAINING DRUGS

Drugs	*Iodine content*
Oral or Local	
Amiodarone	75 mg tablet
Benziodarone[a]	49 mg/100-mg tablet
Calcium iodide (e.g., Calcidrine syrup)	26 mg/mL
Diiodohydroxyquin (e.g., Yodoxin)	134 mg/tablet
Echothiophate iodide ophthalmic solution (e.g., Phospholine)	5–41 μg/drop
Hydriodic acid syrup	13–15 mg/mL
Iodochlorhydroxyquin (e.g., Entero-Vioform)	104 mg/tablet
Iodine-containing vitamins	0.15 mg/tablet
Iodinated glycerol (e.g., Organidin,[b]	15 mg/tablet
Iophen)	25 mg/mL
Idoxuridine ophthalmic solution (e.g., Herplex)	18 μg/drop
Isopropamide iodide (e.g., Darbid.Combid)	1.8 mg/tablet
Kelp	0.15 mg/tablet
Potassium iodine (KI) (e.g., Quadrinal)	145 mg/tablet
	24 mg/mL
Lugol's solution	6.3 mg/drop
Niacinamide hydroiodide + KI (e.g., Iodo-Niacin)	115 mg/tablet
Ponaris nasal emollient	5 mg/0.8 mL
SSKI	38 mg/drop
Parenteral preparations	
Sodium iodide, 10% solution	85 mg/mL
Topical Antiseptics	
Diiodohydroxyquin cream (e.g., Vytone)	6 mg/g
Iodine tincture	40 mg/mL
Iodochlorhydroxyquin cream (e.g., Vioform)	12 mg/g
Iodoform gauze (e.g., NuGauze)	4.8 mg/100 mg gauze
Povidone iodine (e.g., Betadine)	10 mg/mL
Radiology contrast agents	
Diatrizoate meglumine sodium (e.g., Renografin-76)	370 mg/mL
Iodized oil	380 mg/mL
Iopanoic acid (e.g., Telepaque)	333 mg/tablet
Ipodate (e.g., Oragrafin)	308 mg/capsule
Iothalamate (e.g., Angio-Conray)	480 mg/mL
Metrizamide (e.g., Amipaque)	483 mg/mL before dilution

[a]Not FDA approved.
[b]Iodine was removed from Organidin and Tuss Organidin in 1995
(Adapted from Braverman LE 1986 Iodide-induced thyroid disease. In: Ingbar SH, Braverman LE (eds) Werner's The Thyroid, 5th ed. Philadelphia, JB Lippincott, p 734.)

Table 4 represent iodine-containing compounds and their iodine content (from Roti E,Uberti E,2001[64])

Two different types of Amiodarone-induced thyrotoxicosis（AIT）has been recognized and designated in type I and type II. Distinguishing between the two is often difficult. AIT is confirmed by suppressed serum TSH and elevated serum T_3 、T_4 and free T_3 concentration as well as by an increase in sex hormone- binding globulin. Type I, which typically develops in the background of pre-existing thyroid disease including nodular goiter or latent Grave's disease,is due to iodine-induced excess thyroid hormone synthesis（200mg of amiodarone containing 75mg of iodine). AIT type II is caused by cytotoxic effects of medication that results in the release of preformed thyroxine[74,75]. Type II is due to amiodarone-induced destructive thyroiditis. AIT occurs late after amiodarone withdrawal [76].

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[77]. The average iodine content of kelp of 1,500 to 2,000ug/g was measured[78,79]. Herbal medicine,including kelp and kelp-containing dietary supplements,are also used by an increasing numbers of patients[80]. Suzuki[81] 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 IIH or IIT after ingestion of kelp[77,82-87]. Another 12 thyrotoxicosis caused by weight-reducing herbal medicine[80]. In 2001,Zhu[25] 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[18,88]. More data,seaweed accounts for about 80% of Japanase people's iodine intake,seaweed consumption was clearly associated with an increased risk of papillary carcinoma (PTC) in postmenopausal women[89]. Table 5 showed those different seaweed types and their iodine contents in products[90].

Iodine intake and the prevalence of papillary carcinoma (PTC)

Dietary iodine intake act as a potential relavance risk factor of thyroid cancer[89,91-93]. Thyroid neoplasia can arise from many different causes. These include low iodine diets, radioactive iodine and natural goitrogens. Elevated incidence and mortality rate of thyroid cancer have been found in areas where iodione intake is high(Howaii,Iceland)[94,95]. In South India,among 300 patients with goiter and 100 euthyroid 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[96]. The prevance of PTC (80-90%) in thyroid carcinoma increased significant after USI. According to Zimmerann in recent review[29]and Williams the earlier review[100],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. 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[97]. Based on the data of pathological specimens of 1101 thyroid malignant tumors, constitional 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[98]. The same results was also reported based on 429 analyses[99]. 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 peroid from 1984 to 2001,the PTF:FTC increased from 2.3 to 11.5[101]. 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, together with other low level of radiation exposure and incidentally discovered thyroid nodules[102]. In China Shengyang, the ratio of PTC:FTC was from 2.3 to 21.9 before and after salt iodization. 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 114ug/l）and 2.7% in the iodine deficient area（mean UIC < 50ug/l)[103]. Japan had also its highest incidence rates for thyroid cancer, where iodine intake is high[100]. Occult thyroid cancer（OTC）was more common in glands with nodular goiter（range 15.7% ~ 28.4%）in areas of excessive iodine intake[104,105]. 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,Giusti, 2010 [106]). Compared with matched controls,urinary excretion of iodine excess was detected in 302 cases of thyroid benign tumors（519ug/L）and 240 thyroid cancers（524ug/L）（Liu,2008）. Higher urine iodine was associated with PTC（urine iodine:355.3+/-289.6ug/L in 53 PTC,Zhou,2014）

Table 5. Common and scientific names of seaweed types, their emergence, iodine content, and derived iodine content in products.

Common Name	Species	Fresh	Dried	*n* of Products Containing that Species		*n* of Products with Derivable Iodine Content
		Average iodine content (μg/g) *		*n*	% *	*n*
Fingered tangle	*Laminaria digitata*	700 [9]	6118	5	3	3
Kelp	Median value		1327	20	11	2
	Laminaria longicruris		1304			
Bull Kelp	*Nereocystis leutkaena*		407			
Split kelp	*Laminaria setchelli*		1070			
Sugar kelp	*Laminaria Saccharina*		238			
Winged kelp	*Alaria marginata*		151			
Giant kelp	*Macrocystis integrifolia*		240			
Kombu	Median value		2650	9	5	7
	Laminaria japonica		2380			
	Laminaria ochroleuca		6138			
Hijiki	*Hizikia fusiforme*		436	2	1	1
Wrack	Median value	182	725			
Egg wrack	*Ascophyllum nodosum*	182	725	62	32	0
Bladderwrack	*Fucus vesiculosus*		504	9	5	6
Wakame	Median value	39	172	21	12	11
	Undaria pinnatifida	39	189			
	Undaria pinnatifida		139			
	Alaria esculenta					
Sea spaghetti	*Himanthalia elongata*	107	117	3	2	1
Dulse	*Palmaria palmata*	102	75	14	8	7
Sea lettuce	Median value	16	90	11	6	2
	Ulva lactuca	16	114			
	Ulva rigida		66			
Nori	Median value		21	24	14	7
	Porphyra purpurea, *Porphyra tenera*, *Porphyra yezoensis*		11			
	Porphyra tenera		34			
Irish moss	*Chondrus crispus*	61	238	1	1	0
Chlorella	*Chlorella sp.*			4	2	0
Gracilaria	*Gracilaria verracosa*			3	2	0
Laver	Median value	15	117	5	3	0
	Ulva pertusa	16	163			
	Porphyra umbilicalis	13	80			
Pelvetia	*Pelvetia canaliculata*		243	5	3	2
Sea belt	*Laminaria saccharina*, *Saccharina latissima*			5	3	0
Other Shony Agar Sea fern Japanese moss Grapestone				14	6	1

Table 5 show the types of common seaweed and seaweed-containing foods in the UK,and iodine content, toxicity and nutrition (from Bouga M and Combet E,2015 [90])

In contrast, 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[107]. Increasing thyroid cancer rates were not been associated with national iodine intake according to UIC data from US population[107],Sweden[108] and Denmark[109]. The findings indicated the possible carcinogenesis of dietary iodine or/and radioactive iodine transformation on thyroid glands in the rats and man.

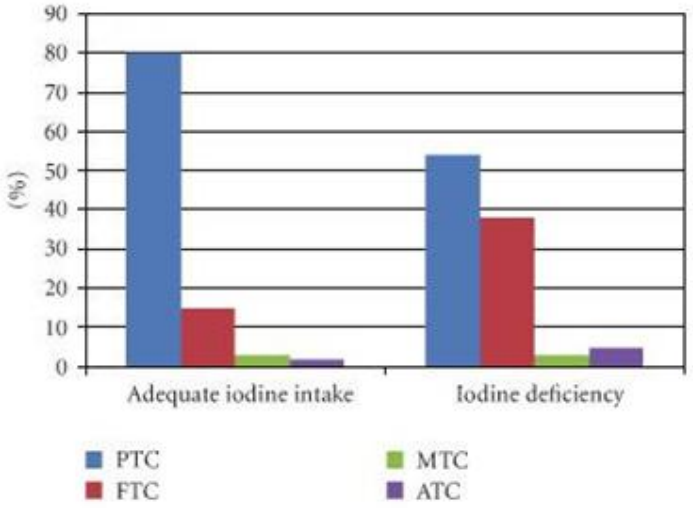

Fig.5. Contribution of iodine in the food to the thyroid tumorigenesis (Data from Giusti F,etal,2010 [106]

In case-control studies,more data,cruciferous plants were found to be the association with increased thyroid cancer risk. In epidemiology,a study from New Caledonia among Melanesion women who consume large qantities of cruciferous vegetables,and low iodine intake (< 96.0ug/day) showed a positive association[114]. In poland,frequent cruciferous vegetable consumption was associated with a 1.5-fold increase in the risk of thyroid carcinoma[113]. 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[112]. However, the study from Kuwait,high intake of cabbage showed an increased risk with only borderline significance[115]. Thus,in this area,more accumulated results are needed to be testable.

In summary,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[106,110,111] (Figure 5). Dietary iodine intake is another care of environmental relevance factor in thyroid diseases and papillary carcinoma.

Oncogenic thyroid hormone receptor mutants

It has been uncovered that thyroid status had a modulating effect on neoplasia. Ciosek[116] induced experimental model of rat hyperthyroidism using throxine. Administration of thyroid hormone to thyrectomized rodents is a prerequisite for the induction of hepatomas by chemicals,indicating a role of throxine in the initiating action of carcinogen[117]. This thyroid hormone(T3)signaling through thyroid hormone receptor(THRa1) regulates hepatoma cell growth[118]. In addition,the transformation of culture cells by radiation is in vitro faciliated by thyroxine[119]. 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[26,120-122]. The other 11 cases were further reported[79]. Among 10 hyperthyroidism,of whom 6 with Grave's disease complicated with thyroid cancer,2 hyperthyroidism with thyroiditis and thyroid cancer[121]. Another case of a 43-old-man with initial hyperthyroidism was also reported,and two years later, he developed transformation of thyroid adenoma complicated with hyperthyroidism (nodule:6x4x3cm). This case suggest an initiating role of thyroid hormone on neoplasm and a wide variety of metabolic effects,for instance, increased lipogenesis and hair growth[122].

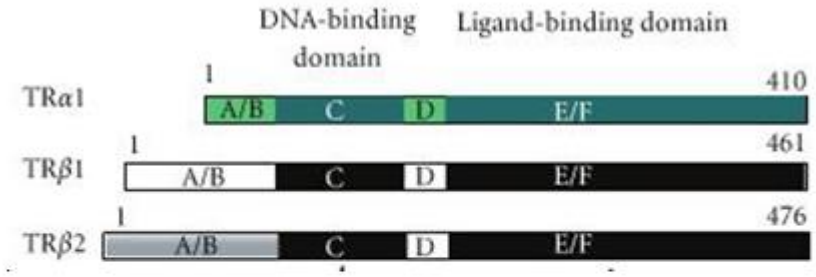

FIGURE 6: Domain comparison of different TR isoforms and schematic of DNA- and ligand-binding domain crystal structures. Each TR isoform is represented as a horizontal bar, from N to C termini. Total amino acid length is indicated at right [35, 36]. Within a given isoform, the location of each domain is lettered (A/B, C, D, and E/F). Identical domains of TRβ1 and TRβ2 are shown in matching colors. Note the unique A/B domain of TRβ2.

Fig.6. Structure of two thyroid hormone receptors(Data from Rosen M & Privalsky M,2011[123]

In vitro culture cells, the BFU-E,a derived pluripotent stem cell committed to the erythroid line and a high erythropoietin (EP) -responsive proliferative capacity,seems to be the precursor of the CFU-E,a cell of lower proliferative capacity. The thyroid hormone can enhance CFU-E-derived and BFU-E-derived colony formation. Addition of L-thyroxine (L-T4) at an optimal 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 (Dainiak,1978). Thyroid hormone can correct clinical thyroidal hypothyroidism with severe anemia(Hb < 30g/l → 90g/l [124]) via potentiation of human erythropoiesis and hemoglobin production in vitro by thyroxine (Dainiak,etal,1978) .

In vivo,mice harbouring activated THRalpha1 specifically in the intestinal epithelium increased cell proliferation and developed adenoma at low rate[125].This phenotype was due to cooperation between the activated THRa1 and WNT pathways[126]. In transgenic

mice mutation of thyroid hormone receptor-beta (THRbeta) developed mammary hyperplasia through aberrant activation of STAT5[127]. Moreover,THRbeta mutants also developed spontaneous follicular thyroid carcinoma (FTC) similar to human cancer in a knocking mouse model expressing a mutated THRbeta(Thrb,denoted PV)[128-130], and thyroid hormone play a critical role in promoting thyroid carcinogenesis of Thrb (PV/PV) mice via PI3K-AKT-beta-Catenin signaling pathway[130]. Otherwise, it has been detected a rearrangement of oncogenic THRA1/BTR fusion using southern blot analysis in the in mice breast cancer cell line[131,132]. This rearrangement represented a deletion of THRA1 allele that was coamplified with ERBB2 in breast cancer.

Moreover,in clinics,there were 63% of 16 papillary thyroid carcinoma (PTC) expressing mutations in THRa1,and a 94% in THRbeta1,in contrast to 22% and 11% of thyriod adenomas harboring mutations in these isoforms respectively,and no mutations were found in normal thyroid controls. The results indicated the differential effects of normal and oncogenic thyroid hormone receptor[133] signaling in PTC and normal controls. The findings suggest a possible oncogenic action of thyroid hormone receptor mutation in the tumorigenesis of human thyroid carcinoma[134]. Others, anaplastic thyroid cancers harbor novel oncogenic mutations of ALK gene[135]. Oncogenic receptor ALK belongs to an insulin receptor(IR) or oncogenic receptor IGF-1R family[136]. TLR4 stimulation with its ligand lipopolysaccharides promotes KSHV- induced cellular transformation and tumorigenesis via activating the STAT3 pathway[137] . 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[138]. More others,CLIC1 was identified as a novel dominant pro-oncogenic receptor from proteomic profiling of pleomorphic human sarcoma[139].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[140-142],is further perspective.

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