Available online on 15.07.2021 at <http://ujpr.org>
Universal Journal of Pharmaceutical Research
 An International Peer Reviewed Journal

Open access to Pharmaceutical research
 This is an open access article distributed under the terms of the Creative Commons Attribution-Non
 Commercial Share Alike 4.0 License which permits unrestricted non commercial use,
 provided the original work is properly cited

Volume 6, Issue 3, 2021

Open Access

REVIEW ARTICLE

IODINE INTAKE AND CANCER

George Zhu^{1*} , Hernando Vargas-Uricoechea²

¹University Hospital Leiden, The Netherlands

²Universidad del Cauca, Colombia.

ABSTRACT

Objectives: 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 (T₃, T₄) and thyrotropin (TSH) secretion. Increase rates of the thyroid cancer are increasing after radiation exposure to ¹³¹I in children or adolescents.

Methodology: In respective published reports in literature and in combination of our previous study, 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 systematically reviewed. Relative factors that should be considered when studying the effect of dietary iodine in the development of thyroid cancer include screening programs, pathological criteria, diagnostic techniques, radioactive iodine, and standard of medical care in the studied population.

Results and conclusion: In current surveys, papillary thyroid carcinoma forms the largest group of thyroid malignancies, after iodine intake excess or iodine prophylaxis where an increase in the papillary: follicular carcinoma ratio was uncovered. Also, there is clear temporal relationship in many countries between introduction of iodine intake excess especially as to radioactive iodine and an increase in incidence of PTC. Iodine goiter, IIH and IIT were also noted. Autoimmune hashimoto's thyroiditis are linked to dietary iodine. Dietary iodine intake is another care of environmental relevance factor in thyroid diseases and papillary carcinoma. 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; oncogenic thyroid hormone receptor mutants; the pattern of papillary carcinoma (PTC).

Article Info: Received 26 April 2021; Revised 23 May; Accepted 30 June, Available online 15 July 2021

Cite this article-

Zhu G, Vargas-Uricoechea H. Iodine intake and cancer. Universal Journal of Pharmaceutical Research 2021; 6(3):68-76.

DOI: <https://doi.org/10.22270/ujpr.v6i3.610>

Address for Correspondence:

Dr. George Zhu, University Hospital Leiden, The Netherlands; E-mail: zhu13574916119@163.com

INTRODUCTION

The main function of the thyroid gland is to make hormones¹. T₄ and T₃ are key regulation of metabolic effects such as the development of the brain in neonates, 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 T₄ weight is iodine. We have previously illustrated the biochemical synthesis of thyroxine². Iodine supply, either too much or too little, impairs adequate synthesis of thyroid hormone. 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^{3,4}. In this paper, we are in further deliberating the topic entity of iodine excess induced thyroid diseases and papillary carcinoma (PTC).

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 (¹³¹I) 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 ¹³¹I in benign thyroid disease provide conflicting results regarding several long-term cohort studies in Sweden⁵, England⁶, Finland⁷, Japan⁸ and the US⁹. There was no increase in burden of cancer risk overall after ¹³¹I

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 childhood⁹.

In animal models, it has been found that animals on an iodine-restricted diet were more likely to develop cancer^{10,11}. C3H/Hey strain-mice were placed in low-iodine diet can induce benign and malignant thyroid tumors¹⁰. 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 rate¹¹. This represents an *in vivo* model of low iodine dietary supply in tumorigenesis in the rats¹²⁻¹⁸. Moreover, in rats with containing carcinogens N-nitrosobis (2-hydroxypropyl) amine (BHP) and an excessive iodine diet^{15, 16}, the incidence of thyroid cancer was 29% in those fed the excessive iodine diet versus 33% in those fed the iodine sufficient diet. 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. The incidence of rats with benign nodules was 100% in both group. Boltze¹⁷ 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. These findings suggest that both long- term iodine deficiency and excess may be a weak promoter of thyroid cancer albeit its insufficient to stimulate thyroid carcinogenesis.

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 shifts the distribution towards papillary tumors¹⁸. 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 area¹⁹. Chronically high iodine intake have been associated with the development of goiter (i.e. hypertrophy and hyperplasia of the thyroid cells), and in turn, goiter linked to thyroid cancer risk, particularly in women. 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).

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 1945²⁰. 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 childhood thyroid cancer in contaminated areas of Belarus, Ukraine, and Western Russia²¹⁻²⁸. The report of the United Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)²¹ 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 $1.8 \times 10^{18} \text{ Bq}$ of ^{131}I , 2.5×10^{18} of ^{133}I , and $1.1 \times 10^{18} \text{ Bq}$ of ^{132}Te , which decays to ^{132}I (UNSCEAR, 2000)^{21,22}. 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^{22,23}. Those radiation associated thyroid cancers showed a higher the excess relative risk (ERR) of thyroid cancer involving younger age at the time of exposure^{22,24}. Moreover, there are also reports of a two- to fourfold increase in thyroid carcinoma in adults from exposed areas^{22,23}. When comparison of typically 5-10 years prior to Chernobyl, in a series of 472 patients from Belarus^{22,25}, the average latency between exposure and cancer diagnosis was 6.9 years.

Table 1: A high prevalence of RET/PTC rearrangements in Ukrainian and Belarussian post-Chernobyl thyroid papillary carcinomas (from Hamatani K, et al, 2015³³).

Radiation-associated PTC	Chromosomal rearrangements						Point mutations	
	A-bomb survivors (our study)	RET/PTC	TRK and TRK-T1, 2, 3	AKAPg-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%		

The vast majority of post- Chernobyl pediatric thyroid cancers were papillary 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 1), 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 pathogenesis²⁶⁻²⁸. 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^{29,30}. Another rearrangement was about 7% of radiation-induced papillary carcinomas involving the nerve growth factor gene NTRK1³¹. 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^{32,33}.

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

According to WHO in 1994³⁴ and the Korea Centers for disease control and prevention (KCDC) in 2012³⁵ food products such as processed, agricultural, meats, and marine products were monitored for measuring dietary iodine. The recommended iodine daily allowance of 70-150µg³⁶. 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 goiter³⁷, hyperthyroidism³⁸⁻⁴¹, hashimoto's thyroiditis⁴² and thyrotoxicosis⁴³⁻⁴⁶ through increasing thyroid hormone synthesis in the presence of underlying thyroid disease, particularly multinodular goiters containing previously existing area of autonomous function. Potassium iodide (KI) at 10⁻⁴ ~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 (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%⁴⁷. Iodine-induced IIT was recognized as early as 1821 by Coindet⁴⁴, 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 IIT or

IIT. The incidence of IIT 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, Niepominszoze⁴⁸ 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 climbed 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 further study the effect of excess iodine and excess tyrosine on goiter in mice⁴⁹, 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). 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 doses⁵⁰. The differential goiter rate of 10%, 50% and 90% could be induced by drinking water at different iodine doses 250, 1500 and 3000µg/L respectively. The dose of iodine 250µg/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 1570.0µg/l versus 6.4%, 32.4%, 37.14% and 43.71% of goiter respectively⁵⁰. From epidemiology, in China, there were 16% rate incidence of iodine goiter for tangle salt diet (iodine content 1089.2µg/kg; and 28.36% (total 4344 analyses) rate incidence of iodine goiter in higher iodine drinkers from deep well water (iodine content 661.2µg/L) compared to 8.37% (total 4158 analyses) of goiter in low iodine water drinker (iodine content 27.2µg/L)⁵¹. In China, children's goiter rate in excessive iodine regions with iodized salt was higher than that of without iodine salt (12.1% vs 8.6%)⁵². 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 327.0µg/l (range 35-2938.5µg/l), and water iodine content from 376 samples of drinking water 112.1+/-91.3µg/l in mean, 90.3µg/l (range 0.5-605.2µg/l in medium)⁵³. Iodine-induced hyperthyroidism (IIH) has been frequently described when iodine is introduced into an iodine-deficient area, patients residing in iodine-sufficient areas⁵⁴ and iodinated preparation for water purification⁵⁵ or a long-term topical iodine application or by intravenous administration of iodine-containing substances⁵⁶⁻⁵⁸. 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 hyperthyroid⁵⁹. 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 (TT₄, FT₄, rT₃) was higher in higher iodine than the result in lower iodine. Individuals with multinodular goiters living in iodine-replete regions can also develop hyperthyroidism, confirming that nodular goiters are particularly prone to developing IIT⁴³. 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 area⁶⁰. 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 (e.g. 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 milk⁶¹. 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 iodinated salt⁶². IIT has been reported after initiating iodine supplementation, also with use of iodinated drugs, radiographic contrast agents and food dietary iodine^{54,62}. Table 2 represent iodine-containing compounds related to IIH and IIT⁵⁴.

Table 2: Iodine-containing compounds and their iodine content (from Roti E, Uberti E, 2001⁵⁴).

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

Kelp belongs to the large brown algae and classified in the order Laminariales⁶³. The average iodine content of kelp of 1,500 to 2,000µg/g was measured^{64,65}. Herbal medicine, including kelp and kelp-containing dietary supplements, are now used by an increasing numbers of patients⁶⁶. Suzuki⁶⁷ 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^{63,68-73}. Another 12

thyrotoxicosis were caused by weight-reducing herbal medicine⁶⁶. In 2001, Zhu⁷⁴ reported a case of thyroid neoplasm following marine algae in a post-operative breast cancer. More data, seaweed accounts for about 80% of Japanese people's iodine intake, seaweed consumption was clearly linked to an increased risk of papillary carcinoma in postmenopausal women⁷⁵. From epidemiologic studies in Korean population, high intake

of iodine from marine products may increase thyroid cancer risk, particularly in women⁷⁶.

Iodine intake and the prevalence of papillary carcinoma (PTC)

Dietary iodine intake act as a potential relevance risk factor of thyroid cancer⁷⁷⁻⁷⁸. 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 iodine intake is high (Hawaii, Iceland)^{79,80}. 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 iodine⁸¹. The prevalence of PTC (80-90%) in thyroid carcinoma increased significantly after USI. According to Zimmermann in recent review¹² and Williams the earlier review⁸², 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' iodine intake (Argentina, Colombia, 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 USI⁸³. Based on the data of pathological specimens of 1101 thyroid malignant tumors, 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 USI⁸⁴. The same results were also reported based on 429 analyses⁸⁵. 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 11.5⁸⁶. 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 nodules⁸⁷. 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 114µg/l) and 2.7% in the iodine deficient area (mean UIC<50µg/l)⁸⁸. Japan had also its highest incidence rates for thyroid cancer, where iodine intake is high⁸². Occult thyroid cancer (OTC) was more

common in glands with nodular goiter (range 15.7%~28.4%) in areas of excessive iodine intake⁸⁹. 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 FTC⁹⁰. Compared with matched controls, urinary excretion of iodine excess was detected in 302 cases of thyroid benign tumors (519µg/L) and 240 thyroid cancers (524µg/L) (Liu, 2008). Higher urine iodine was associated with PTC (urine iodine:355.3±289.6µg/L in 53 PTC, Zhou, 2014). These findings indicated, 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 PTC⁹⁰⁻⁹³. 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. Ciosek⁹⁵ 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 carcinogen⁹⁶. This thyroid hormone (T₃) signaling through thyroid hormone receptor (THRa1) regulates hepatoma cell growth⁹⁷. In addition, the transformation of culture cells by radiation is *in vitro* facilitated by thyroxine⁹⁸. 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 goiters⁹⁹⁻¹⁰¹. Among 10 hyperthyroidism, of whom 6 with Grave's disease complicated with thyroid cancer, 2 hyperthyroidism with thyroiditis and thyroid cancer¹⁰⁰. 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 growth¹⁰¹.

In vivo, mice harbouring activated THRa1 specifically in the intestinal epithelium increased cell proliferation and developed adenoma at low rate¹⁰². This phenotype was due to cooperation between the activated THRa1 and WNT pathways¹⁰³. In transgenic mice mutation of thyroid hormone receptor-beta (THRbeta) developed mammary hyperplasia through aberrant activation of STAT5¹⁰⁴. Moreover, THRbeta mutants also developed spontaneous follicular thyroid carcinoma (FTC) similar to human cancer in a knocking mouse model expressing a mutated THR beta (Thrb, denoted PV)¹⁰⁵⁻¹⁰⁷, and thyroid hormone play a critical role in promoting thyroid carcinogenesis of Thrb (PV/PV) mice via PI3K-AKT-beta-Catenin signaling pathway¹⁰⁷. Otherwise, it has been detected a rearrangement of oncogenic THRA1/BTR fusion using southern blot analysis in the in mice breast cancer cell line¹⁰⁸⁻¹¹⁰. This rearrangement represented a deletion of

THRA1 allele that was co-amplified with ERBB2 in breast cancer.

CONCLUSION

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 thyroid 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 receptor¹¹¹ signaling in PTC and normal controls. The findings suggest a possible oncogenic action of thyroid hormone receptor mutation in the tumorigenesis of human thyroid carcinoma¹¹⁰. Others, anaplastic thyroid cancers harbor novel oncogenic mutations of ALK gene¹¹². Oncogenic receptor ALK belongs to an insulin receptor (IR) or oncogenic receptor IGF-1R family¹¹³. TLR4 stimulation with its ligand lipopolysaccharides promotes KSHV- induced cellular transformation and tumorigenesis via activating the STAT3 pathway¹¹⁴. TLR4 mediated tumorigenesis while TLR4 antagonist CL1095 inhibit it. Toll-like receptor (TLR4) induced pro-oncogenic or also protumoral function in head and neck carcinoma¹¹⁵. More others, CLIC1 was identified as a novel dominant pro-oncogenic receptor from proteomic profiling of pleomorphic human sarcoma¹¹⁶. 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 therapy¹¹⁷⁻¹¹⁹, is further perspective.

AUTHOR'S CONTRIBUTION

All authors have worked equally in this work.

ACKNOWLEDGEMENTS

Authors like to express their thanks to Prof. Herando Vargas-Uricoechea that this paper has been its chapter translation of spanish in iodine's book in Colombia. They are also thankful for those enthusiastic readers' demands to its in part previous publication of this paper in other journals.

CONFLICT OF INTEREST

There is no conflict of interest with this research.

REFERENCES

- Kendall EC. Isolation of the iodine compound which occurs in the thyroid: first paper. *J Biol Chem* 1919;39:125-147.
<https://doi.org/10.1515/bchm2.1919.108.1-2.50>
- Zhu G. Iodine intake, thyroid diseases and the prevalence of papillary carcinoma (PTC). *Hematol Med Oncol* 2018;3(1):1-9. <https://doi.org/10.15761/HMO.1000150>
- Goldberg RC & Chaikoff IL. Development of thyroid neoplasm in rats following single injection of radioactive iodine. *Proc Soc Exper Biol Med* 1951;76:563-566.
<https://doi.org/10.3181/00379727-76-18558>
- Goldberg RC, Chaikoff IL. Induction of thyroid cancer in the rats by radioactive iodine. *Arch Pathol* 1952; 53:22-28.
<https://doi.org/10.1002/path.1700650235>
- Franklyn JA, Maisonneuve P, Sheppard M, et al. Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. *Lancet* 1999; 353:2111-15.
[https://doi.org/10.1016/S0140-6736\(98\)12295](https://doi.org/10.1016/S0140-6736(98)12295)
- Metso S, Auvinen A, Huhtala H, et al. Increased cancer incidence after radioiodine treatment for hyperthyroidism *Cancer* 2007;109:1972-7.
<https://doi.org/10.1002/cncr.23124>
- Ozaki O, Ito K, Mimura T, et al. Thyroid carcinoma after radioactive iodine therapy for Graves' disease. *World Journal of Surgery* 1994; 18:518-21.
<https://doi.org/10.1007/BF00353753>
- Hoffman DA, McConahey WM, Fraumeni JF Jr, et al. Cancer incidence following treatment of hyperthyroidism. *International Journal of Epidemiology* 1982; 11:218-224.
<https://doi.org/10.1093/ije/11.3.218>
- Hieu TT, Russell AW, Cuneo R, et al. Cancer risk after medical exposure to radioactive iodine in benign thyroid diseases: a meta-analysis. *Endocrine-Related Cancer* 2012; 19:645-655.
<https://doi.org/10.1530/ERC-12-0176>
- Schaller RT, Stevenson JK. Development of carcinoma of the thyroid in iodine- deficient mice. *Cancer* 1966; 19:1063-80.
[https://doi.org/10.1002/1097-0142\(196608\)19:83.0.CO;2-A](https://doi.org/10.1002/1097-0142(196608)19:83.0.CO;2-A)
- Fortner JG, George PA, Sternberg SS. Induced and spontaneous thyroid cancer in the Syrian (golden) hamster. *Endocrinology* 1960; 66:364-76.
<https://doi.org/10.1210/endo-66-3-364>
- Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. *Thyroid Research* 2015; 8(1):8.
<https://doi.org/10.1186/s13044-015-0020-8>
- Axelrad AA, Leblond CP. Induction of thyroid tumor in rats by a low iodine diet. *Cancer* 1955; 8:339-367.
- Choi WJ, Kim J. Dietary factors and the risk of thyroid cancer: A review. *Clin Nutr Res* 2014; 3:75-88.
<https://doi.org/10.7762/cnr.2014.3.2.75>
- Yamashita H, Noguchi S, Murakami N, Kato R, Adachi M, et al. Effects of dietary iodine on chemical induction of thyroid-carcinoma. *Acta Pathol Japan* 1990; 40:705-12.
<https://doi.org/10.1111/j.1440-1827.1990.tb01534.x>
- Kanno J, Onodera H, Furuta K, Maekawa A, Kasuga T, et al. Tumor-promoting effects of both iodine deficiency and iodine excess in the rat-thyroid. *Toxicol Pathol* 1992; 20:226-35.
<https://doi.org/10.1177/019262339202000209>
- Boltze C, Brabant G, Dralle H, et al. Radiation-induced thyroid carcinogenesis as a function of time and dietary iodine supply: an *in vivo* model of tumorigenesis in the rat. *Endocrinol* 2002; 143(7):2584-92.
<https://doi.org/10.1210/en.143.7.2584>
- Segovia GI, Gallowitsch HJ, Kresnik E, et al. Descriptive epidemiology of thyroid carcinoma in Carinthia, Austria: 1984-2001. Histopathologic features and tumor classification of 734 cases under elevated general iodination of table salt since 1990: population based age-stratified analysis on thyroid carcinoma incidence. *Thyroid* 2004; 14:277-86.
<https://doi.org/10.1089/105072504323030933>
- Teng CJ, Hu YW, Chen SC, et al. Use of radioactive iodine for thyroid cancer and risk for second primary malignancy: A nationwide population-based study. *J Natl Cancer Inst* 2016; 108(2): 1-8.
<https://doi.org/10.1093/jnci/djv314>
- Nagataki S, Shibata Y, Inoue S, et al. Thyroid diseases among atomic bomb survivors in Nagasaki. *JAMA* 1994; 272:364-370.
<https://doi.org/10.1001/jama.1994.03520050044028>
- UNSCEAR, 2000 report, vol 2, Annex J, New York and Geneva: United Nations, 2000. PMID: 10949259

22. Fagin JA, Nikiforov. Radiation-induced thyroid cancer: Lessons from chernobyl. Practical Management of Thyroid Cancer 2012; 321-326.
https://doi.org/10.1007/1-84628-013-3_24
23. Williams D. Radiation carcinogenesis: lessons from Chernobyl. *Oncogene* 2009; 27:S9–S18.
<https://doi.org/10.1038/onc.2009.349>
24. Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res* 1995; 141:259-277.
<https://doi.org/10.2307/3579003>
25. Pacini F, Vorontsova T, Demidehik WF, et al. Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and France. *J Clin Endocrinol Metab* 1997; 82:3563-3569.
<https://doi.org/10.1210/jc.82.11.3563>
26. Sugg SL, Ezzat S, Rosen IB, et al. Distinct multiple RET/PTC gene rearrangements in multifocal papillary thyroid neoplasia. *J Clin Endocrinol Metab* 1998; 83:4116-22.
<https://doi.org/10.1210/jcem.83.11.5271>
27. Nikiforov YE, Koshoffer A, Nikiforov M, et al. Chromosomal breakpoint positions suggest a direct role for radiation in inducing illegitimate recombination between the ELE1 and RET genes in radiation-induced thyroid carcinomas. *Oncogene* 1999; 18:6330-34.
<https://doi.org/10.1038/sj.onc.1203019>
28. Corvi R, Martinez-Alfaro M, Harach HR, et al. Frequent RET rearrangements in thyroid papillary microcarcinoma detected by interphase fluorescence in situ hybridization. *Lab Invest* 2001;81: 1639-45.
<https://doi.org/10.1038/labinvest.3780377>
29. Thomas GA, Bunnell H, Cook HA. High prevalence of RET/PTC rearrangements in Ukrainian and Belarussian post-Chernobyl thyroid papillary carcinomas: A strong correlation between RET/PTC3 and the solid-follicular variant. *J Clin Endocrinol Metab* 1999; 84:4232-38.
<https://doi.org/10.1210/jc.84.11.4232>
30. Smida J, Salassidis K, Hieber I, et al. Distinct frequency of ret rearrangements in papillary thyroid carcinomas of children and adults from Belarus. *Int J Cancer* 1999; 80: 32-38.
[https://doi.org/10.1002/\(SICI\)1097-0215\(19990105\)80:1<32::AID-IJC7>3.0.CO;2-2](https://doi.org/10.1002/(SICI)1097-0215(19990105)80:1<32::AID-IJC7>3.0.CO;2-2)
31. Beimfohr C, Klugbauer S, Demidchik EP, et al. NTRK1 re-arrangement in papillary thyroid carcinoma of children after the Chernobyl reactor accident. *Int J Cancer* 1990; 80:842-47.
[https://doi.org/10.1002/\(SICI\)1097-0215\(19990315\)80:63.3.CO;2-Q](https://doi.org/10.1002/(SICI)1097-0215(19990315)80:63.3.CO;2-Q)
32. Ciampi R, Knauf JA, Kerler R, et al. Oncogenic AKAP9-BRAF fusion is a novel mechanism of MAP kinase pathway activation in radiation-induced and sporadic thyroid cancer. *J Clin Invest* 2005; 115(1):94-101.
<https://doi.org/10.1172/JCI200523237>
33. Hamatani K, Takashi K, Taga M. Thyroid cancer: Molecular characteristics of radiation-associated papillary thyroid cancer with a special reference to atomic radiation exposure. *Thyroid Disorders Ther* 2015;4(2):1000183.
<https://doi.org/10.4172/2167-7948.1000183>
34. Indicators for assessing iodine deficiency disorders and their control through salt iodization. Geneva,WHO,1994
<http://library.wur.nl/webquery/clc/920961>
35. Kang TS, Lee JH, Leem D, Seo IW, Lee YJ, et al. Monitoring of iodine in foods for estimation of dietary intake. Cheongwon:National Institute of Food and Drug Safety Evaluation 2012.
36. Dahl L, Johansson L, Julshamn K, Meltzer HM. The iodine content of Norwegian foods and diets. *Public Health Nutri* 2004; 7:569-576.
<https://doi.org/10.1079/PHN2003554>
37. Oppenheimer JH. The syndrome of iodide-induced goiter and myxedema. *Am J Med* 1961; 30:231.
[https://doi.org/10.1016/0002-9343\(61\)90099-7](https://doi.org/10.1016/0002-9343(61)90099-7)
38. Rajatanavin R, Safran M, Stoller WA. Five patients with iodine-induced by hyperthyroidism. *Am J Med* 1984; 17:378-384.
[https://doi.org/10.1016/0002-9343\(84\)90726-5](https://doi.org/10.1016/0002-9343(84)90726-5)
39. Martin FIR, Tress BW, Colman PG and Deam DR. Iodine-induced hyperthyroidism due to nonionic contrast radiography in elderly. *Am J Med* 1993; 95:78-82.
[https://doi.org/10.1016/0002-9343\(93\)90235-H](https://doi.org/10.1016/0002-9343(93)90235-H)
40. Laurberg P. Increase in incidence of hyperthyroidism predominantly occurs in young people after iodine fortification of salt in Demark. *J Clin Endocrinol Metab* 2006; 91:3830-34.
<https://doi.org/10.1210/jc.2006-0652>
41. Brotfain E, Koyfman L, Frenkel A, Smolikov A, Zlotnik A. Iodine-induced hyperthyroidism - An old clinical entity that is still relevance to daily ICU practice: A case report. *Case reports in endocrinology* 2013.
<https://doi.org/10.1155/2013/792745>
42. Okamura K, Inoue K, Omac T. A case of Hashimoto's thyroiditis with thyroid immunological abnormality manifested after habitual ingestion of seaweed. *Acta Endocrinol (Copenh)* 1978; 88:703-12.
<https://doi.org/10.1530/acta.0.0880703>
43. Kopp P. Thyrotoxicosis of other etiologies. In: Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–2010 Dec 1. PMID: 25905417
44. Coindet J. Nouvelles recherches sur les effets de l'iode,et sur les cautions survere dansle traitement du goiter par ce nouveau remide. *Ann Chimie Phys* 1821; 16:252-266.
45. Vagenakis AG, Wang CA, Burger F, Maloof F, Braverman LE. Iodine-induced thyrotoxicosis in Boston. *N Engl J Med* 1972; 287:523-27.
<https://doi.org/10.1056/NEJM197209142871101>
46. Shetty KR, Duthie JrEH. Thyrotoxicosis induced by topical iodine application. *Arch Intern Med* 1990; 150:2400-2401.
<https://doi.org/10.1001/archinte.1990.00390220132028>
47. Suzuki H, Higuchi T, Hashimoto H, Otaki S. A case of endemic goiter along the seashores of Hidaka District, Hokkaido. *Jpn J Med Sci Biol* 1962; 51:781-86. PMID: 13979457
48. Niepomniszoze H, Sala M, Danilowicz K, Bruno O. Epidemiology of palpable goiter in Greater Buenos Aires,an iodine-sufficient area. *Medicina (Buenos Aires)* 2004; 64:7-12.
<https://doi.org/10.1159/000080479>
49. Li N, Wen HY, Wang YJ, Wang ZP. Study on the effects of excess iodine and excess tyrosine on goiter in mice. *Inner Mongolia Med J (chinese)* 2010;42:10:1163.
50. Gao QJ, Zhang SY, Xu CL, Liu Y. The dose-reaction relationship study between the goiter rate and different iodine doses in mice. *Chinese Journal of Endemiology (chinese)* 2002; 21(3): 179-81.
51. Yu ZH, Ma T. Iodine-excess endemic goiter. *Nat Med J China (chinese)* 1980; 60:475
52. LV SM, Xu D, Chong ZS, et al. Research on factors affecting children's iodine nutrition and thyroid goiter in iodine excessive region. *Chinese Journal of control of endemic disease (chinese)* 2007
53. Zhai LP, Liu CJ, Huang FM. Regional distribution of iodine excess in drinking water and its epidemiology in Jinan. *Chinese J Pub Heal (chinese)* 2007;23:106-107
54. Roti E, Uberti E. Iodine excess and hyperthyroidism. *Thyroid* 2001; 11:493-500.
<https://doi.org/10.1089/105072501300176453>
55. Liel Y, Alkan M. Travelers' thyrotoxicosis, Transitory thyrotoxicosis induced by iodinated preparations for water purification. *Arch Intern Med* 1996; 156:807-810.
<https://doi.org/10.1001/archinte.156.7.807>
56. Martin FIR, Tress BW, Colman PG, Deam DR. Iodine-induced hyperthyroidism due to nonionic contrast radiography in elderly. *Am J Med* 1993; 95:78-82.
[https://doi.org/10.1016/0002-9343\(93\)90235-H](https://doi.org/10.1016/0002-9343(93)90235-H)
57. Stanbury JB, Ermans AE, Bourdoux P, Todd C, Oken E, Tonglet R. Iodine-induced hyperthyroidism: occurrence and epidemiology. *Thyroid* 1998; 8:83-100.
<https://doi.org/10.1089/thy.1998.8.83>
58. Higgs M, Hull E, Lujan E. A case report of post-operative Jod-Basedow phenomennon following oral and IV iodine

- contrast administration Case reports in endocrinology 2014. <https://doi.org/10.1155/2014/980283>
59. Ermans AM, Camus M. Modifications of thyroid function induced by chronic administration of iodide in the presence of "autonomous" thyroid tissue. *Acta Endocrinol (Copenh)* 1972; 70: 463-475. <https://doi.org/10.1530/acta.0.0700463>
 60. Laurberg P, Persen KM, Vestergaard H, Sigurdsson G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs high incidence of Grave's disease in the young in a high iodine intake area: comparative survey of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. *J Intern Med* 1991; 229:415-420. <https://doi.org/10.1111/j.1365-2796.1991.tb00368.x>
 61. Stewart JC, Vidor GI. Thyrotoxicosis induced by iodine contamination of food- a common unrecognized condition? *Br Med J* 1976;1:372. <https://doi.org/10.1136/bmj.1.6006.372>
 62. Galofre JC, Fernandez-Calvet L, Rios M, Garcia-Mayor RVG. Increased incidence of thyrotoxicosis after iodine supplementation in an iodine sufficient area. *Journal of Endocrinological Investigation* 1994; 17:23-27. <https://doi.org/10.1007/BF03344958>
 63. Mussig K, Thamer C, Bares R, Lipp HP, Haring HU, et al. Iodine-induced thyrotoxicosis after ingestion of kelp-containing tea. *J Gen Intern Med* 2006; 21:C11-C14. <https://doi.org/10.1111/j.1525-1497.2006.00416.x>
 64. Lee SM, Lewis J, Buis DH, Holcombe GD, Lawrance PR. Iodine in British foods and diets. *Br J Nutr* 1994; 72(03):435-446. <https://doi.org/10.1079/bjn19940045>
 65. Tears J, Pino S, Critcheley A, Braverman LE.. Variability of iodine content in common commercially available edible seaweeds. *Thyroid* 2004; 14:836-41. <https://doi.org/10.1089/thy.2004.14.836>
 66. Ohye H, Fukata S, Kanoh M, et al. Thyrotoxicosis caused by weight-reducing herbal medicines. *Arch Intern Med* 2005; 165:831-4. <https://doi.org/10.1001/archinte.165.8.831>
 67. Liu XH, Chen GG, Vlantis AC, et al. Iodine mediated mechanisms and thyroid carcinoma. *Crit Rev Clin Lab Sci* 2009; 46:302-318. <https://doi.org/10.3109/10408360903306384>
 68. Shilo S, Hirsch HI. Iodine-induced hyperthyroidism in a patient with a normal thyroid gland. *Postgrad Med J* 1986;62:661. <https://doi.org/10.1136/pgmj.62.729.661>
 69. de Smet PA, Stricker BH, Wilderik F, Wiersinga WM. Hyperthyroidism during treatment with kelp tablets. *Ned Tijdschr Geneesk* 1990; 134:1058-9. PMID: 2366899
 70. Sales Coronas J, Cruz Caparros G, Laynez Bretones F, Diez Garcia F. Hyperthyroidism secondary to kelp tablets ingestias. *Med Clin (Barc)* 2002; 118: 797-8. [https://doi.org/10.1016/s0025-7753\(02\)72534-7](https://doi.org/10.1016/s0025-7753(02)72534-7)
 71. Picco G, Dios-Romero A, Albanell N, Badia J. Regular intake of seaweed and hyperthyroidism. *Med Clin (Barc)* 2006; 127:199. <https://doi.org/10.1157/13090717>
 72. Eliason BC. Transient hyperthyroidism in a patient taking dietary supplements containing kelp. *J Am Board Fam Pract* 1998; 11:478-480. <https://doi.org/10.3122/jabfm.11.6.478>
 73. Ishizuki Y, Yamauchi K, Miura Y. Transient thyrotoxicosis induced by Japanese kombu. *Nippon Naibunpi Gakkai Zasshi* 1989; 65:91-8. https://doi.org/10.1507/endocrine.1927.65.2_91
 74. Zhu G, Musumeci F, Byrne P. Induction of thyroid neoplasm following plant medicine marine algae (*sargassum*): A rare case and review of the literature. *Curr Pharm Biotechnol* 2013; 14:859-863. <https://doi.org/10.2174/1389201015666140113100946>
 75. Michikawa T, Inoue M, Shimazu T, Sawada N, Iwasaki M, et al. Seaweed consumption and the risk of the thyroid cancer in women: the Japan Public Health Center-based prospective study. *Eur J Cancer Pre* 2012; 21:254-260. <https://doi.org/10.1097/CEJ.0b013e32834a8042>
 76. Schneider DF, Chen H. New developments in the diagnosis and treatment of thyroid cancer. *CA Cancer J Clin* 2013; 63:374-394. <https://doi.org/10.3322/caac.21195>
 77. Feldt-Rasmussen U. Iodine and cancer. *Thyroid* 2001; 11:483-86. <https://doi.org/10.1089/105072501300176435>
 78. Horn-Ross PL, Morris JS, Lee M, et al. Iodine and cancer risk among women in a multiethnic population: the Bay Area Thyroid Cancer Study. *Cancer Epidemiol Biomarkers Prev* 2001; 10(9):979-85. PMID: 11535551
 79. Kononel LN, Hankin JH, Wilkens LR, Fukunaga FH, Hinds MW. An epidemiologic study of thyroid cancer in Hawaii. *Cancer Causes Control* 1990;1(3):223-34. <https://doi.org/10.1007/BF00117474>
 80. Niedziela M, Korman E. Risk of neoplasm in autoimmune thyroid disease in children- transition from iodine deficiency to iodine sufficiency. 42nd Annual Meeting ESPE: Miniposters, 15(MP2-5/P1-380) Ljubljana (Slovenia), 18-21 September 2003
 81. Chandrasekaran M, Ramadevi K. Thyromegaly and iodine nutritional status in a tertiary care hospital in South India. *Indian J Endocrinol Metab* 2013;17:260-4. <https://doi.org/10.4103/2230-8210.109701>
 82. Williams ED. Dietary iodine and thyroid cancer. Hall R, Kobberling J, editors. *Thyroid disorders associated with iodine deficiency and excess*. New York: Raven
 83. Gu WL, Wu HS, Liang LS, et al. A retrospective survey of 8004 thyroid following post- operative evaluation. *Guangdong Medical Journal (chinese)* 2010;31: 1990-92
 84. Cui JS, Ni JS, Kong QY, Wang J. Analysis of detection rate of thyroid malignant tumor before and after universal salt iodization and histological types. *J Gilin Univ (medicine edition) (chinese)* 2008.
 85. Guan HX, Shan ZY, Mi XY, Wang EH, Teng WP. Incidence of thyroid carcinoma before and after universal salt iodization in 11-year retrospective analysis of pathological reports. *J Chin Med Univ (chinese)* 2006; 35:284-285.
 86. Rego-Iraeta A, Perez-Mendez LF, Mantinan B, Garcia-Mayor RV. The trends for thyroid cancer in northwestern Spain: true rise in the incidence of micro and larger forms of papillary thyroid carcinoma. *Thyroid* 2009; 19:333-40. <https://doi.org/10.1089/thy.2008.0210>
 87. Netea-Maier RT, Aben KKH, Caspaie MK, den Heijer M, Grefle JMM, et al. Trends in incidence and mortality of thyroid carcinoma in The Netherlands between 1989 and 2003: correlation with thyroid fine-needle aspiration cytology and thyroid surgery. *Int J Cancer* 2008; 123:1681-4. <https://doi.org/10.1002/ijc.23678>
 88. Belfiore A, La Rosa GL, La Porta GA, Giuffrida D, Milazzo G, et al. Cancer risk in patients with cold thyroid nodules: relevance of iodine intake, sex, age, and multinodularity. *Am J Med* 1992; 93:363-9. [https://doi.org/10.1016/0002-9343\(92\)90164-7](https://doi.org/10.1016/0002-9343(92)90164-7)
 89. Yamamoto Y, Maeda T, Izumi K, Otsuka H. Occult papillary carcinoma of the thyroid - a study of 408 autopsy cases. *Cancer* 1990; 65:1173-9. [https://doi.org/10.1002/1097-0142\(19900301\)65:5<1173::AID-CNCR2820650524>3.0.CO;2-2](https://doi.org/10.1002/1097-0142(19900301)65:5<1173::AID-CNCR2820650524>3.0.CO;2-2)
 90. Giusti F, et al. Thyroid cancer: current molecular perspective. *J Oncol Volume* 2010:351679. <https://doi.org/10.1155/2010/351679>
 91. Rasmussen LB, Jorgensen T, Perrild H, Knudsen N, Krejbjerg A, et al. Mandatory iodine fortification of bread and salt increases iodine excretion in adults in Denmark- a 11-year follow-up study. *Clin Nutr* 2014; 33:1033-40. <https://doi.org/10.1016/j.clnu.2013.10.024>
 92. Teng WP, Shan ZY, Teng XC, Guan HX, Li YH, et al. Effects of iodine intake on thyroid diseases in China. *New Eng J Med* 2006; 354:2783-93. <https://doi.org/10.1056/NEJMoa054022>
 93. Harach HR, Ceballos GA. Thyroid cancer, thyroiditis and dietary iodine: a review based on the Salta, Argentina model. *Endocr Pathol* 2008; 19:209-20.

- <https://doi.org/10.1007/s12022-008-9038-y>
94. Galanti MR, Hamsson L, Bergstrom R, Wolk A, Hjartaker A. Diet and the risk of papillary and follicular thyroid carcinoma: a population-based case-control study in Sweden and Norway. *Cancer Causes Control* 1997; 8:205-214. <https://doi.org/10.1023/A:1018424430711>
 95. Ciosek J, Drobnik J. Vasopression and oxytocin release and the thyroid function. *J Physiol Pharmacol* 2004;55:423-41
 96. Borck C, Guernsey DL, Edelman IS. Critical role played by thyroid hormone in induction of neoplastic transformation by chemical carcinogen in tissue culture. *Proc Natl Acad Sci USA* 1983; 80:5749-52. <https://doi.org/10.1073/pnas.80.18.5749>
 97. Huang YH, Li YH, Chi HC, Liao CH, Liao CJ, et al. Thyroid hormone regulation of miR-21 enhances migration and invasion of hepatoma. *Cancer Res* 2013; 73(8):1. <https://doi.org/10.1158/0008-5472.CAN-12-2218>
 98. Guernsey DL, Ong A, Borck C. Thyroid hormone modulation of x ray-induced *in vitro* neoplastic transformation. *Nature* 1980; 288:891. <https://doi.org/10.1038/288591a0>
 99. Hancock BW. Thyroid carcinoma and concurrent hyperthyroidism. A study of ten patients. *Cancer* 1977; 39:298. [https://doi.org/10.1002/1097-0142\(197701\)39:1<298::AID-CNCR2820390146>3.0.CO;2-C](https://doi.org/10.1002/1097-0142(197701)39:1<298::AID-CNCR2820390146>3.0.CO;2-C)
 100. Lin LS, Chen TS, Chen MC, et al. Thyroid carcinoma and concurrent hyperthyroidism and/or Hashimoto's thyroiditis. *Chin J Intern Med (chinese)* 1984; 23(2):91-94.
 101. Zong GX, Tong ZK. Toxic nodular goiter complicate with alopecia: a case report. *Chin J Intern Med (chinese)* 1982; 21(9):526.
 102. Kress E, Skah S, Siratov M, Nadjar J, Gadot N, et al. Cooperation between the thyroid hormone receptor TRalpha1 and WNT pathway in the induction of intestinal tumorigenesis. *Gastroenterology* 2010; 138:1863-74. <https://doi.org/10.1053/j.gastro.2010.01.041>
 103. Guigon CJ. Mutation of thyroid hormone receptor-beta in mice predispose to the development of mammary tumors. *Oncogene* 2011; 30:3381-90. <https://doi.org/10.1002/iub.180>
 104. Suzuki H, Willingham MC, Cheng SY. Mice with a mutation in the thyroid hormone receptor beta gene spontaneously develop thyroid carcinoma: a mouse model of thyroid carcinogenesis. *Thyroid* 2002; 12(11):963-969. <https://doi.org/10.1089/105072502320908295>
 105. Suzuki H, Willingham MC, Cheng SY. Mice with a mutation in the thyroid hormone receptor beta gene spontaneously develop thyroid carcinoma: a mouse model of thyroid carcinogenesis. *Thyroid* 2002; 12(11):963-969. <https://doi.org/10.1089/105072502320908295>
 106. Lu C, Mischra A, Zhu YLJ, Meltzer P. Global expression profiling reveals gain-of-function oncogenic activity of a mutated thyroid hormone receptor in thyroid carcinogenesis. *Am J Cancer Res* 2011; 1:168-191. <https://doi.org/10.1016/B978-0-12-385524-4.00004>
 107. Lu C. Activation of tumor cell proliferation by thyroid hormone in a mouse model of follicular thyroid carcinoma. *Oncogene* 2012; 31:2007-16. <https://doi.org/10.1038/onc.2011.390>
 108. Futreal PA. Mutation analysis of the THRA1 gene in breast cancer: deletion/fusion of the gene to a novel sequence on 17q in the BT474 cell line. *Cancer Res* 1994; 54:1791-4. <https://doi.org/10.1270/jsbbs.57.153>
 109. Cheng SY. Thyroid hormone receptor mutations in cancer. *Molecular and Cellular Endocrinology* 2013; 23:30. <https://doi.org/10.1016/j.mce.2003.10.051>
 110. Judeson C, Privalsky ML. DNA recognition by normal and oncogenic thyroid hormone receptor, unexpected diversity in half-site specificity controlled by non-zinc-finger determinants. *J Bio Chem* 1996; 271(18):10800-10805. <https://doi.org/10.1074/jbc.271.18.10800>
 111. Puzianowska-Kuznicka M, Krystyniak A, Madej A, Cheng SY, Nauman J. Functionally impaired TR mutants are presented in thyroid papillary cancer. *J Clin Endocrinol Metab* 2002; 87:1120-28. <https://doi.org/10.1210/jcem.87.3.8296>
 112. Murugan AK, Xing M. Anaplastic thyroid cancers harbor novel oncogenic mutations of the ALK gene. *Cancer Res* 2011; 71:4403-11. <https://doi.org/10.1158/0008-5472.CAN-10-4041>
 113. Zong CS, Zeng L, Jiang Y, Sadowski HB, Wang LH: Stat3 plays an important role in oncogenic ROS and insulin like growth factor 1 receptor-induced anchorage- independent growth. *J Biol Chem* 1998; 273:28065-28072. <https://doi.org/10.1074/jbc.273.43.28065>
 114. Gruffaz M, Vasan K, Tan B, Ramos da Silva S, Gao SJ. TLR4-mediated inflammation promotes KSHV-induced cellular transformation and tumorigenesis by activating the STAT3 pathway. *Cancer Res* 2017; 77(24):7094-7108. <https://doi.org/10.1158/0008-5472.CAN-17-2321>
 115. Ren G, Hu JZ, Wang RX, Han W, Zhao M, et al. Rapamycin inhibits Toll-like receptor 4-induced pro-oncogenic function. *Oncol Rep* 2014; 31:2804-10. <https://doi.org/10.3892/or.2014.3134>
 116. Murray E, Hernychova L, Scigelova M, Ho J, Nekulova M, et al. Quantitative proteomic profiling of pleomorphic human sarcoma identifies CLIC1 as a dominant pro-oncogenic receptor expressed in diverse sarcoma types. *Journal of Proteome Research* 2014; 13:2543-59. <https://doi.org/10.1021/pr4010713>
 117. Zhu G, Saboor-Yaraghi AA, Yarden Y, Santos J, Neil JC. Downregulating oncogenic receptor: From bench to clinic. *Hematol Med Oncol*, 2016, 1:30-40. <https://doi.org/10.15761/HMO.1000106>
 118. Zhu G, Saboor-Yaraghi AA, Yarden Y. Targeting oncogenic receptor: from molecular physiology to currently the standard of target therapy. *Adv Pharm J* 2017, 2:10-28
 119. Zhu G, Musumeci F, Byrne P, Gupta D, Gupta E. Targeting oncogenic receptor, currently the standard of care. *Clin Trails Pathol Case Stud* 2017; 2(2); 75-90.