**REVIEW ARTICLE**

# IODINE INTAKE AND CANCER

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

**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）.

## INTRODUCTION

The main function of the thyroid gland is to make hormones[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. We have previously illustrated the biochemical synthesis of throxine[2]. 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 (^{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[5], England[6], Finland[7], Japan[8] and the US[9] . 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[9].

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 tumors[10]. 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[11]. This represents an *in vivo* model of low iodine dietary supply in tumorigenesis in the rats[12-18]. 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. Boltze[17] 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 tumors[18]. 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[19]. 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 1945[20]. 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 Russia[21-28]. 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 $1.8 \times 10^{18}$ Bq of ^{131}I, $2.5 \times 10^{18}$ of [133]I, and $1.1 \times 10^{18}$ 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*, 2015[33].**

| 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-Chemobyl | 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 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 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 pathogenesis[26-28]. 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 NTRK1[31]. 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 1994[34] and the Korea Centers for disease control and prevention (KCDC) in 2012[35] food products such as processed, agricultural, meats, and marine products were monitored for measuring dietary iodine. The recommended iodine daily allowance of 70-150µg[36]. 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[37], hyperthyroidism[38-41], hashimoto's thyroiditis[42] and thyrotoxicosis[43-46] 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%[47] .Iodine-induced IIT was recognized as early as 1821 by Coindet[44,] 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[48] 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 mice[49], 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). 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 doses[50]. 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 respectively[50]. 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 goitet 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 areas[54] and iodinated preparation for water purification[55] or a long-term topical iodine application or by intravenous administration of iodine-containing substances[56-58]. 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 hyperthyroid[59]. 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. Individuals with multinodular goiters living in iodine-replete regions can also develop hyperthyroidism, confirming that nodular goiters are particularly prone to developing IIT[43]. 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[60]. 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 milk[61]. 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[62]. 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 IIT[54].

**Table 2: Iodine-containing compounds and their iodine content (from Roti E, Uberti E, 2001[54]).**

| 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 |
| Echothiphate iodide ophthalmic solution (e.g., Phospholine) | 5-41µg/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 |
| Idoxuridine ophthalmic solution (e.g., Herplex) | 18µg/drop |
| Isopropamide iodide (e.g., Darbid, Combid) | 1.8mg/tablet |
| Kelp | 0.15mg/tablet |
| Potassium iodine (e.g., Quadrinal) | 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 |
| Iopdate (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 Laminariales[63]. 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 patients[66]. Suzuki[67] 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 medicine[66]. In 2001, Zhu[74] reported a case of thyroid neoplasm following marine algae in a post-operative breast cancer. More data, seaweed accounts for about 80% of Japanase people's iodine intake, seaweed consumption was clearly linked to an increased risk of papillary carcinoma in postmenopausal women[75]. From epidemiologic studies in Korean population, high intake

of iodine from marine products may increase thyroid cancer risk, particularly in women[76].

## Iodine intake and the prevalence of papillary carcinoma (PTC)

Dietary iodine intake act as a potential relavance risk factor of thyroid cancer[77-78]. 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 (Howaii, 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 iodine[81]. The prevance of PTC（80-90%）in thyroid carcinoma increased significant after USI. According to Zimmerann in recent review[12] and Williams the earlier review[82], 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, 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 USI[83]. 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[84]. The same results were also reported based on 429 analyses[85]. In northwestern Spain, iodized salt was introduced in 1985, the thyroid cancer incidence increased in females from 1.56/100,000 during 1978-1985 to 8.23/100,000 in period from 1984 to 2001, the PTF: FTC increased from 2.3 to 11.5[86]. 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[87]. 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 high[82]. Occult thyroid cancer (OTC) was more common in glands with nodular goiter (range 15.7%~28.4%) in areas of excessive iodine intake[89]. 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[90]. 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 PTC[90-93]. 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. Ciosek[95] 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[96]. This thyroid hormone ($T_3$) signaling through thyroid hormone receptor (THRa1) regulates hepatoma cell growth[97]. In addition, the transformation of culture cells by radiation is *in vitro* facilited by thyroxine[98]. 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[99-101]. Among 10 hyperthyroidism, of whom 6 with Grave's disease complicated with thyroid cancer, 2 hyperthyroidism with thyroiditis and thyroid cancer[100]. 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[101].

*In vivo*, mice harbouring activated THRalpha1 specifically in the intestinal epithelium increased cell proliferation and developed adenoma at low rate[102]. This phenotype was due to cooperation between the activated THRa1 and WNT pathways[103]. In transgenic mice mutation of thyroid hormone receptor-beta (THRbeta) developed mammary hyperplasia through aberrant activation of STAT5[104]. 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 pathway[107]. Otherwise, it has been detected a rearrangement of oncogenic THRA1/BTR fusion using southern blot analysis in the in mice breast cancer cell line[108-110]. This rearrangement represented a deletion of

THRA1 allele that was co-amplified 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[111] 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[110]. Others, anaplastic thyroid cancers harbor novel oncogenic mutations of ALK gene[112]. Oncogenic receptor ALK belongs to an insulin receptor (IR) or oncogenic receptor IGF-1R family[113]. TLR4 stimulation with its ligand lipopolysaccharides promotes KSHV- induced cellular transformation and tumorigenesis via activating the STAT3 pathway[114]. TLR4 mediated tumorigenesis while TLR4 antagonist CL1095 inhibit it. Toll-like receptor (TLR4) induced pro-oncogenic or also protumoral function in head and neck carcinoma[115]. More others, CLIC1 was identified as a novel dominant pro-oncogenic receptor from proteomic profiling of pleomorphic human sarcoma[116]. 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[117-119], is further perspective.

## AUTHOR'S CONTRIBUTION

All authors have worked equally in this work.

## ACKNOWLEDGEMENTS

## CONFLICT OF INTEREST

There is no conflict of interest with this research.

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