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Thyroid Disruptors: How They Act and How We React

Natassia Elena Bufalo, Aline Carolina de Nadai da Silva,
Raquel Bueno Barbieri, Marjory Alana Marcello, Lucas Leite Cunha,
Elaine Cristina Morari and Laura Sterian Ward
*State University of Campinas – UNICAMP
Brazil*

1. Introduction

1.1 Actual thyroid disease demographics

Thyroid diseases increase in a ubiquitous global phenomenon suspected to further rise in the upcoming decades (Dua et al. 2008). Thyroid cancer is the most common endocrine malignancy, representing 2% of all malignancies. A rapid global rise in its incidence has been seen in recent decades, especially concerning the papillary type, which has been increasing in several countries (Liu et al. 2001; Reynolds et al. 2005; Davies and Welch 2006; Enewold et al. 2009; Kilfoy, Devesa et al. 2009; Kilfoy, Zheng et al. 2009). An estimated 44,670 new cases of thyroid cancer are expected to be diagnosed in the United States of America in 2010, with three out of four cases occurring in women. The incidence rate of thyroid cancer has been increasing sharply since the mid-1990s, and it is the fastest growing cancer in both men and women, as well as the ninth most common human malignancy in the USA (American Cancer Society: Cancer Facts and Figures 2010).

The reasons for the increase in occurrences of this type of cancer are still unclear and controversial. Earlier studies suspected that the upward trend was caused by the widespread use of radiation therapy for benign conditions of the head and neck among children and adolescents from the early 1920s to the late 1950s (Weiss 1979; Pottern et al. 1980). Other studies suggested that this trend could be associated with atmospheric nuclear fallouts (Catelinois et al. 2004; Gilbert et al. 1998; Kazakov, Demidchik, and Astakhova 1992; Kerber et al. 1993; Takahashi et al. 2003) or constant diagnostic X-ray exposures (Prokop 2001; Ron et al. 1995) suffered especially by children (Brenner et al. 2001; Golding and Shrimpton 2002; Maitino et al. 2003). More recent studies suggested that the prevalence of thyroid nodules depends on the screening method and population evaluated according to geographic regions and racial groups, indicating that the widespread use of ultrasonography and socioeconomic indicators of health care access could be the major players in this new demography of the thyroid cancer (Morris and Myssiorek 2010; Sprague, Warren Andersen, and Trentham-Dietz 2008).

The steep increase in thyroid cancer is certainly related to better cancer detection by ultrasonography and other imaging techniques in a population growing older, as well as a larger and easier access to health care and robust laboratory diagnostic tools such as TSH and thyroid antibody dosages (Davies and Welch 2006; Ward and Graf 2008). However,

there are strong indicators that other causes may be involved. Better techniques and larger access to health care cannot be held responsible for the increasing incidence rates of larger tumors, which have been similar to papillary microcarcinoma (Hughes et al. 2011).

In addition, an epidemiological study of thyroid cancer cases in a highly radiated territory in Poland - i.e. in the province of Opole after 1986 - indicate a significant increase in thyroid cancer incidence in males and females during the period 1995-2002, when comparing with the years 1987-1994. The data comprises all the thyroid cancer cases registered in Opole province in the years 1987-2002, originated from the Provincial Cancer Registry in Opole (Tukiendorf, Mischczyk, and McEwan 2010). Finally, the proportion of local staged thyroid cancer increased by 24% in the Black group, 14.4% in the Hispanic white group, 14.3% in the non-Hispanic white group, and only 4.0% in the Asian group between the periods 1992-1996 and 2000-2004. Five-year survival rates of patients with papillary tumor were approximately 95%; however, that of anaplastic tumor ranged from 5.6% to 11.4% among REGs (Race/Ethnicity Groups) (Yu et al. 2010).

Autoimmune thyroid disorders, comprising Graves' disease and Hashimoto's thyroiditis, are considered polygenic, multifactorial diseases characterized by an abnormal activation of the immune system as a result of interactions between genetic predisposition and environmental factors, the former accountant for approximately 70 - 80% of liability to develop autoimmune thyroid disorders (Wiersinga 1999). Accumulating data confirm that the burden of autoimmune diseases is rising as well, affecting 5 to 10% of the world population. They are a significant cause of morbidity and mortality accounting for soaring health care costs, comparable to those of cancer and heart disease (Cooper, Bynum, and Somers 2009; Eaton et al. 2007; Shoenfeld et al. 2008).

Hashimoto's disease and Graves' disease are the two most common forms of autoimmune thyroiditis, the archetypal organ-specific autoimmune disease in humans. Both are characterized by lymphocytic infiltrate and autoreactivity against thyroid autoantigens (Michels and Eisenbarth 2010; Rapoport and McLachlan 2001; Zenewicz et al. 2010). There are strong evidences for a major role of heredity in Graves' disease, as demonstrated with a population-based study of two Danish twin cohorts (Brix et al. 2001). This study indicated that 21% of the causes involved in Graves' disease development can be attributed to environmental factors (Brix et al. 2001; Prummel, Strieder, and Wiersinga 2004). However, recent analysis of thyroid disease demographics indicate that environmental factors probably have been playing an important role in the observed rise in thyroid disease incidence all over the world (Morris and Myssiorek 2010). Among these environmental causes, viral infections have been repeatedly demonstrated related to type 1 diabetes mellitus and multiple sclerosis (Cabrera-Rode et al. 2003; Dahlquist et al. 1995; Hiltunen et al. 1997; Hyoty and Taylor 2002; Lonnrot, Korpela et al. 2000; Lonnrot, Salminen et al. 2000). In addition, other factors including ionizing radiation, dietary iodine intake, reproductive factors like estrogens, and cigarette smoking might be considered as thyroid disruptors, working as triggers for thyroid disease.

2. Main disruptors

2.1 Ionizing radiation

Ionizing radiation has been being described as the known major risk factor for thyroid cancer, especially papillary carcinoma, the most common thyroid cancer type (Nikiforov 2010). Convincing evidence exists of an association between exposure to external radiation

and an increased risk of thyroid cancer (Mushkacheva et al. 2006; Pottern et al. 1990; Ron et al. 1995; Ron et al. 1989; Schneider et al. 1993; Shore et al. 1993; Shore et al. 2003; Yoshimoto et al. 1995); however, risks from internally deposited radioactive iodine were not well studied until recently (Zablotska et al. 2011; Kazakov, Demidchik, and Astakhova 1992; Shibata et al. 2001; Takahashi et al. 2003; Dobyns et al. 1974).

Well-documented examples include medical therapeutic external beam radiation and accidental exposure to c-radiation and radioiodine as a result of nuclear weapon explosions or nuclear reactor accidents (Ron et al. 1995).

Both radiations (Ostroumova et al. 2009) and thyroid benign nodules (Lyon et al. 2006; Brent 2010) are related to autoimmune processes.

2.2 Radiation and thyroid nodules

The growing incidence of thyroid cancer over the last decades is entirely due to papillary carcinomas, whereas the incidence of other thyroid cancer types, including the follicular type, remains unchanged or is decreasing (Nikiforov 2010). A better understanding of the biology and etiologic factors responsible for the development of papillary carcinomas is particularly important for unraveling the reasons behind the general increase in thyroid cancer incidence.

Mahoney et al (Mahoney et al. 2004) have described that marked increases in the incidence of thyroid cancer after the Chernobyl incident have occurred in all areas of the Republic of Belarus and among all age groups. However, the greatest increases have occurred in children, suggesting that a high prevalence of pre-existing iodine deficiency in combination with unique susceptibility among younger people might have contributed to potential carcinogenic exposures to the thyroid.

Ron et al. (Ron et al. 1995) presented a pooled analysis of five cohort and two case-control studies concerning external radiation and thyroid cancer. The study reported a statistically significant excess relative risk per Gy for individuals exposed before 15 years of age. There was no evidence of increased thyroid cancer risk for individuals exposed at older ages. More recent analyses of atomic bomb survivors confirmed a strong inverse association between ERR/Gy and age at exposure, but suggested that adult exposure is associated with a small increase in thyroid cancer risk (Preston et al. 2007). In 2011, Schonfeld et al. (Schonfeld, Lee, and Berrington de Gonzalez 2011) presented an overview of the use of radiation for medical purposes and its significance for thyroid cancer, especially among children, who seem to be more susceptible to the effects of ionizing radiation. In their study, Schonfeld et al analyzed data concerning x-ray use for dental purposes and did not find significant differences among patients that were more exposed to that type of radiation. In what concerns nuclear medicine, there are no data relating that segment to thyroid cancer, and the authors link that to the fact that kids are hardly ever exposed to those types of exams. To analyze data on diagnostic computed tomography, Schonfeld et al used Analytica software for the calculations to estimate means and 95% uncertainty limits. Using this methodology, they calculated that about 1000 future thyroid cancers could be related to computed tomography scans conducted in the United States of America during the year 2007.

There are also some reports on the effects of radiotherapy for cancers and development of thyroid cancer. Thyroid cancer is one of the most common second cancers after radiotherapy during childhood for Hodgkin lymphoma, and significant increased risks of thyroid cancer have been observed from 5 to more than 40 years after childhood radiotherapy (Ng et al. 2010). In addition to cancer treatment, radiotherapy for the treatment of benign conditions,

including (but not restricted to) *tinea capitis*, hemangioma, and enlarged thymus, has been clearly associated with increased thyroid cancer risk (Ron 2003).

Hayashi et al (Hayashi et al. 2010) found a statistically significant radiation dose-response for the prevalence of these tumors, with an excess odds ratio (OR) per gray of radiation (Gy) of 0.57. The excess risk was limited to women, and among them, the excess OR was 2.4 Gy. These data raise the possibility that the incidence of thyroid microcarcinomas may in fact be related to radiation exposure and point to another interesting issue on the fact that this effect is more important in females.

In fact, many studies have been associating thyroid cancer with exposure to ^{131}I , which can cause several molecular alterations in genes such as *RET*, *NTRK1*, *RAS*, and *BRAF* (Nikiforov et al. 1997). Remarkably, the mechanisms of activation of these genes are quite different in tumors associated with radiation exposure when compared with those from the general population. The dominant mutation mechanism in radiation-induced tumors consists of chromosomal rearrangements, such as those leading to the formation of oncogenic *RET/PTC*, *TRK*, and *BRAF/AKAP9* fusions. A very different mutation mechanism, i.e. a point mutation, is the most prevalent in sporadic tumors, which typically carry point mutations of *BRAF* and *RAS* genes (Nikiforov 2010). Correlation between radiation exposure and high frequency of *RET/PTC* in papillary carcinomas has been seen after accidental radiation exposure from Chernobyl, in patients treated by external beam radiation and, more recently, in atomic bomb survivors in Japan (Hamatani et al. 2008). In the study reported by Hamatani et al, the presence of *RET/PTC* rearrangement had direct correlation with increasing radiation dose, whereas *BRAF* point mutation had strong inverse correlation with the dose.

2.3 Radiation and thyroid autoimmune diseases

The most common thyroid manifestation of radiation is hypofunction, in addition to thyroid nodules and thyroid cancer. Autoimmune thyroid disease has been linked to therapeutic medical radiation, as well as environmental radiation exposure (Brent 2010; Sklar et al. 2000; Dunkelman et al. 2004; Simon et al. 2009). Both the atomic bomb detonations in Japan and nuclear contamination from the Chernobyl nuclear power plant accident were associated with an increased risk of autoimmune thyroid disease (Hamatani et al. 2008; Sklar et al. 2000; Brent 2010). This association, however, has not been a consistent finding, with several studies showing no effect (Imaizumi et al. 2006; Agate et al. 2008). Radiation effects are generally associated with greater radiation exposure and can be tracked with position of the exposed individual at time of the accident or, in the case of the Chernobyl exposure, the pattern of the wind currents dispersing radiation. The initial study of atomic bomb survivors in Japan showed an increase in the incidence of thyroid autoimmunity (Nagataki et al. 1994), but another study, with longer follow-up, did not confirm initial data (Sklar et al. 2000). The effect of radiation may, in fact, be related to the iodine intake by exposed individuals. The risk of both thyroid cancer and autoimmunity seems to be enhanced if diets deficient in stable iodine result in chronic thyroid stimulation. Exposure to ^{131}I alone appears to be associated with a lower risk when compared with acute exposures to the atomic bomb or medical radiotherapy, perhaps due to the associated low dose rate and nonuniform distribution of dose in the gland. A study of children exposed to radiation from Chernobyl showed an increase in thyroid size, higher serum TSH levels, and a greater incidence of thyroid autoantibody positivity in areas where the iodine intake was low (Vermiglio et al. 1999). A more recent study of those exposed to radiation from the Chernobyl accident showed an increase in thyroid autoantibodies, but

not in the incidence of hypothyroidism (Agate et al. 2008). These discrepant data may also be related to the study population. A study regarding exposures to radiation of Hiroshima and Chernobyl (Boice 2006) found disagreeing data on the effects of those exposures and their correlation with thyroid diseases and also suggested that the radiosensitivity of the young thyroid gland is high and most likely relates to subsequent proliferative activity of the gland during puberty and growth, but the reasons for the absence of risk following adult exposures are not entirely clear (Lyon et al. 2006).

A recent publication also confirmed antithyroid antibody production and autoimmune thyroid disease in patients submitted to external radiation for Hodgkin's disease (Brent 2010). In addition, patients receiving ^{131}I for toxic goiter, later develop Graves' disease and, in some cases, Graves' ophthalmopathy (Dunkelmann et al. 2004). In patients treated with radioiodine for thyroid autonomy, a sensitive TSH receptor antibody measurement showed that low level thyroid autoantibody positivity was associated with the development of Graves' disease after using radioiodine (Dunkelmann et al. 2004).

Although there are several studies reporting the relationship between radiation and thyroid disorders, the mechanisms and the pathways involved in that relationship remain not well understood and should be investigated (Ostroumova et al. 2009) The unfortunate recent events in Japan, i.e. the successive earthquake, tsunami, nuclear plants problems, as well as its weather conditions, led a large population to be exposed to radiation effects, demonstrating the urgent need to adopt international contingency measures related to radiation accidental exposure.

2.4 Iodide

The following text is a report of travelers who visited Brazil between the years 1873 and 1875 (Wells 1886). They traveled throughout different regions in the country and were able to report some interesting aspects of life of Brazilians in the Nineteenth century. Their observations demonstrate the ravaging effect of iodide deficiency, especially on certain segments of the population.

"Goiter is very prevalent amongst the very poor peasants, but is rarely seen in the more well-to-do farmers. The sex seems to make no difference, neither does the colour, for the lightcoloured, brown, and black appear to be equally disfigured. In some instances the excrescence attains an enormous size, like a huge feather pillow hung round the front of the neck and extending to the shoulders on each side, hanging over the chest and forcing the head backwards; they apply various herbs and burnt sponge, but admit that it is almost useless to treat it; a change of locality will often stop its continual development, and very rarely cause it to become reabsorbed. The presence of lime in the waters of the streams and a humid atmosphere are considered the primary causes of the evil; but a poor diet, indolent habits, and an absence of all hygiene and cleanliness, either in person or houses, are undoubtedly great promoting causes." In.: "Exploring and travelling three thousand miles through Brazil from Rio de Janeiro to Maranhão".

It was already clear in these early years that the mineral composition of water, diet profile, and habits were related to the presence of goiter. In addition, the travelers reported that these risk factors, but not gender and color, seemed to be associated with goiter. However, more than one 100 years after this publication, we still do not fully understand the mechanisms involved in goitrogenesis or thyroid disorders overall. Epidemiological evidences suggest that iodide play a key role not only as a major determinant of thyroid disorders but also influencing other factors affecting the thyroid, as previously explained concerning the effect of ionizing radiation.

2.5 Thyroid physiology is closely related to iodide homeostasis

Thyroid hormones are the only iodine-containing compounds with established physiologic significance in vertebrates. The thyroid gland produces two hormones, L-thyroxine (tetraiodothyronine, T4) and L-triiodothyronine (T3). Iodine is an indispensable component of these hormones. Ingested iodine is absorbed through the small intestine and transported in the plasma to the thyroid, where it is concentrated. Thyroid hormone synthesis requires the uptake of iodide by active transport, thyroglobulin (Tg) biosynthesis, oxidation and binding of iodide to thyroglobulin, and within this protein matrix, oxidative coupling of two iodotyrosines into iodothyronines. Initial Tg iodination produces monoiodotyrosine (MIT) and diiodotyrosine (DIT). Further iodination couples two DIT residues, both still in peptide linkage, to produce T4. When thyroid hormone is needed, Tg is internalized at the apical pole of thyrocytes, conveyed to endosomes and lysosomes and digested by proteases. After Tg digestion, T4 and T3 are released into the circulation. In addition, iodide is able to regulate thyroid activity by a mechanism called "autoregulation". Autoregulation in the thyroid refers to the regulation of iodine metabolism within the thyroid gland, independent of TSH. Wolff and Chaikoff reported that organic binding of iodide within the rat thyroid was blocked when the plasma iodide level achieved a critical threshold (Wolff and Chaikoff 1948). This inhibition defines the Wolff-Chaikoff effect. Afterwards, the researchers demonstrated that this inhibitory effect of excess iodide was transient, lasting from 26–50 hours, and that the thyroid escaped from or adapted to prolonged iodide excess, resuming near-normal hormone synthesis (Wolff, Chaikoff, and et al. 1949). The mechanism responsible for the acute Wolff-Chaikoff effect is not completely understood. Raben et al. demonstrated that the critical parameter of the Wolff-Chaikoff effect was the amount of intrathyroidal iodide but not plasma concentration (Raben 1949). In addition, Wolff-Chaikoff effect has been postulated to be caused by organic iodocompounds formed within the thyroid (Dugrillon 1996).

Studies on iodine metabolism were carried out in rats and demonstrated that adaptation to long-term iodide exposure was caused by a decrease in iodine transport, thereby reducing the intrathyroid iodine concentration below the critical inhibitory levels, therefore, allowing iodination to resume (Braverman and Ingbar 1963). Eng et al. suggested that iodide administration decreases both NIS mRNA and protein expression by a mechanism that is likely to be, at least in part, transcriptional. Their findings support the hypothesis that the escape from the acute Wolff-Chaikoff effect is caused by a decrease in NIS, with a resultant decreased iodide transport into the thyroid (Eng et al. 2001). Even though the control of NIS mRNA abundance by iodide excess is mainly associated with a transcriptional effect, there is evidence suggesting that it might occur at a posttranscriptional level. In fact, Serrano-Nascimento et al. showed for the first time that NIS mRNA abundance and poly(A) tail length were significantly reduced in all periods of iodide treatment, suggesting that iodide is able to regulate in a complex manner thyroid cell metabolism (Serrano-Nascimento, Calil-Silveira, and Nunes 2010).

2.6 Disturbs in iodine-intake are closely related to thyroid disorders

If the autoregulatory mechanism is not sufficient to keep thyroid hormone production normal, a further enhancement of thyroid activity will occur by an hypothalamic-pituitary feedback and other mechanisms that tend to stabilize the production of active thyroid hormone (Obregon, Escobar del Rey, and Morreale de Escobar 2005). These mechanisms are

able to guarantee that even small supplies of iodine will be sufficient to keep the thyroid function at a level 5.

Most recently, the situation has inverted: many patients are exposed to large quantities of iodide present in proprietary medications, food, and x-ray contrast media. Furthermore, there are data indicating an excess of iodine intake, probably related to salty snacks and industrialized food largely ingested in many occidental countries, especially by young people and children (Medeiros-Neto 2009).

Despite the widespread use of excess iodide in many places, a few apparently normal subjects with normal thyroid function prior to iodide exposure develop thyroid dysfunction, as previously reviewed (Markou et al. 2001). Many studies indicate that even a small change in the level of iodine intake by a population will lead to a reduced frequency of some thyroid disorders, including goiter, follicular cancer and thyroid nodules; however, other types of disease, such as autoimmune thyroiditis and papillary carcinomas, will become more common (Knobel and Medeiros-Neto 2007; Ward et al. 2007). Despite the evidence provided by previous studies, it is still controversial whether completely normal subjects may develop thyroid function disturbances when exposed to large doses of iodide, since there are some evidences that increased iodine intake is not associated with thyroid dysfunction (Markou et al. 2001; Nauman and Wolff 1993)

The only population in the world in which excessive intake of iodine had been described as a main cause of disease lived in some coastal areas of the Japanese island Hokkaido (Suzuki et al. 1965). The excessive iodine intake in this population was attributed to the daily use of iodine-rich seaweed for consumption. Iodide-induced goiter occurred in approximately 10% in the coastal regions of Hokkaido, a northern island of Japan (Higuchi 1964; Suzuki et al. 1965). Goiter has now disappeared after the restriction of intake of kelp products in the affected areas (Tajiri et al. 1986; Yoshinari et al. 1983). However, Kono et al. reported that the prevalence of nonautoimmune hypothyroidism was still 9.7% in coastal areas of the Hokkaido Islands, and it was proportional to iodide intake, whereas the incidence of nonautoimmune thyrotoxicosis was not related to iodide consumption (Konno et al. 1994). In addition, they also reported that when the iodine intake was restricted, the increased serum TSH concentrations were normalized in patients with negative antithyroid antibodies, but remained elevated in those with positive antibodies (Konno et al. 1993). This result suggests that both iodine intake and immunological features interact in the physiopathogeny of hypothyroidism.

In fact, histological examination of the thyroid of patients with iodine-induced hypothyroidism revealed extensive lymphocytic infiltration in half of the examined thyroids (Mizukami et al. 1993). Various findings were observed in other specimens, including hyperplasia in the follicles with papillary foldings, columnar or cuboidal changes in cells with clear and vesicular cytoplasm and markedly reduced colloid. Most of these findings may be reversed after iodine withdrawal (Mizukami et al. 1993). *In vivo* studies showed that while excess iodine is not necessary for the induction of thyroiditis, the ingestion of excess iodine works to exacerbate autoimmune thyroiditis in this genetically predisposed population (Burek and Talor 2009). Clearly, excess iodine intake has many roles in thyroid dysfunction, and one of these roles is to increase thyroglobulin immunogenicity (Papanastasiou et al. 2007), while another is to increase adhesion molecules on the thyrocyte itself (Sharma et al. 2005; Sharma et al. 2008).

Dietary iodine intake is among the possible environmental influences on the incidence and prevalence of thyroid disease in general and thyroid cancer in particular (Wartofsky

2010). Worldwide, incidence rates of thyroid cancer may vary widely, with the causes potentially related to inherent racial or ethnic, and geographical or environmental differences, including iodine excess or deficiency, and possible radiation exposure (Ain 1995). Increasing papillary thyroid cancer has also been related to increased dietary iodine intake (Dijkstra et al. 2007).

Cardis et al. indicated that iodine deficiency increases the risk of ^{131}I -related thyroid cancer (Cardis et al. 2005). In addition, they indicated that the use of a dietary iodine supplement containing potassium iodide can reduce the risk of ^{131}I -related thyroid cancer (Cardis et al. 2005). These authors reported that there would be two mechanisms by which dietary iodine supplementation could be related to the incidence of thyroid cancer after exposure to radioiodines. First, stable iodine given shortly before, during, or immediately after exposure reduces the radioactive iodine uptake by the thyroid and, therefore, reduces the radiation dose to the thyroid (Nauman and Wolff 1993; Zanzonico and Becker 2000). Second, long-term dietary iodine supplementation reduces the size of the thyroid in iodine-deficient areas, and a reduction in thyroid growth, particularly in children, would be expected to be associated with reduced incidence of cancer (Cardis et al. 2005).

In conclusion, iodine is very important for thyroid function and also plays a critical role on the pathogenesis of most thyroid disorders. Even though a body of evidence points iodide as one of the most important thyroid disruptors, it cannot explain, by itself, the increase in thyroid diseases that we have been experiencing in recent years. As stated long before on the above historic report of travellers in Brazil, multiple factors might be related to thyroid diseases, and we remain far from completely understanding how they work.

2.7 Reproductive factors – estrogen

In addition to their key role on the physiologic control of female development and reproduction, and the coordination of many other tissues and organ systems to support reproduction, estrogens are also associated with the development of cancers in estrogen-responsive tissues such as breast, uterus, and pituitary, and to thyroid diseases (Jeng and Watson 2011).

Thyroid diseases occur with a marked higher frequency in women than in men. Papillary thyroid carcinoma usually appears during the reproductive age (30-49 years old), in a ratio of three to five females to one male and has the highest incidence in premenopausal women (Ito and Miyauchi 2009; Pinchera 2007; Yeung and Serpell 2008). Thyroid autoimmune diseases are also five to 10 times more common in women than in men (Vanderpump et al. 1995).

Innumerable studies have demonstrated that the human thyroid gland expresses a low level of estrogen receptors (Ceresini et al. 2006; Kawabata et al. 2003; Money et al. 1989). Estrogen receptors expression seems to increase with proliferation of thyroid glandular tissue, both in cases of benign hyperplasia and, in certain instances, of thyroid malignancies as well (Ceresini et al. 2006; Kawabata et al. 2003; Money et al. 1989). Estrogen receptors are presented, in general, as two different isoforms: Estrogen receptors -alpha and Estrogen receptors -beta. It has been hypothesized that an imbalance in the expression of these two isoforms might play a role in the proliferation of thyroid lesions in the setting of estrogen exposure. This molecular interplay has been put forth as a key factor in the prevalence of thyroid carcinoma in young female patients (Ceresini et al. 2006; Zeng et al. 2007; Lee et al. 2005; Inoue et al. 1993).

Treatment with oral estrogen results in a marked increase in thyroxine-binding globulin (Tahboub and Arafah 2009), leading to an increase in the total serum capacity for thyroid

hormone. In normal subjects, this results in an increase in total T4 but only in a transient drop in free T4. However, in hypothyroid patients receiving thyroxine, a persistent elevation of TSH is observed and dose adjustments are necessary. This effect is not observed with transdermal estrogen therapy, as the absence of liver passage of the drug results in a much weaker effect on thyroxine binding globulin synthesis (Tahboub and Arafah 2009).

Soy protein and soybean isoflavones have been associated with reduced T4 absorption (important for hypothyroid infants on soy formula), interference with thyroid hormone action (Messina and Redmond 2006), and increased thyroid autoimmune disease. The usual intake of dietary soy in those with normal thyroid function has no consistent adverse effects (Doerge and Sheehan 2002). Doerge and Sheehan studied isoflavone interference with thyroid hormone action in vitro (Doerge and Sheehan 2002).

Chemicals with estrogen-mimicking activities were first documented as causing endocrine disruption in the 1950s. Starting the 1990s, additional mechanisms were demonstrated to be involved, encompassing androgen antagonism and disruption of thyroid hormone transport and action, as well as activities mediated by retinoid and peroxisome proliferator-activated receptors, steroidogenic enzymes and neurotransmitter receptors (Diamanti-Kandarakis et al. 2009). Environmental estrogens are manufactured products that contaminate food, water or air, which humans and animals are exposed to (Foster 2008; Sonnenschein and Soto 1998; Tapiero, Ba, and Tew 2002). Many environmental estrogens readily accumulate in the environment and in animal tissues and have been shown to affect both reproductive and nonreproductive organs/systems in animals and humans (Han et al. 2004; Hossaini et al. 2001; Moon et al. 2007; Tsai 2006). Although the genomic effects of these environmental estrogens have been studied extensively and found to be weak (causing government regulatory agencies to consider them "safe"), until recently little, it was known about their nongenomic effects of estrogens (Jeng and Watson 2011). A prominent characteristic that has greatly contributed to the confusion over their toxicity is the nonmonotonic concentration dependence of their nongenomic responses (Palanza, Parmigiani, and vom Saal 2001; Vandenberg et al. 2006; Watson, Jeng, and Kochukov 2010). Environmental estrogens are suspected of affecting a wide variety of functions by interfering with the actions of physiologic estrogens, but sufficiently sensitive techniques for quantitative documentation of these disruptions have generally been lacking (Jeng and Watson 2011).

In summary, estrogens are thought to be related to thyroid hormone deregulation, although the specific mechanisms involved in their action remain unclear.

2.8 Cigarette smoking

Tobacco consumption has multiple effects both on thyroid function and thyroid morphology. These include minor and probably physiologically unimportant alterations in thyroid hormones (Christensen et al. 1984; Hegedus et al. 1985; Karakaya et al. 1987; Lio et al. 1989; Petersen et al. 1991; Hegedus et al. 1992; Melander et al. 1981; Eden et al. 1984; Sepkovic, Haley, and Wynder 1984; Nystrom et al. 1993) and thyrotropin concentrations (Christensen et al. 1984; Hegedus et al. 1985; Karakaya et al. 1987; Lio et al. 1989; Petersen et al. 1991; Hegedus et al. 1992; Melander et al. 1981; Eden et al. 1984; Sepkovic, Haley, and Wynder 1984), central (thyroid) and peripheral antithyroid actions (Muller et al. 1995; Utiger 1995), thyroid gland stimulation or goitrogenic effects (Christensen et al. 1984; Hegedus et al. 1985; Lio et al. 1989; Ericsson and Lindgarde 1991), carcinogenic properties (McTiernan, Weiss, and Daling 1984; Ron et al. 1987; Kolonel et al. 1990; Preston-Martin et al. 1993; Shore et al. 1993; Hallquist et al. 1994; Galanti et al. 1996; Rossing et al. 2000; Hallquist et al. 1993;

Kreiger and Parkes 2000) and also an increase in the susceptibility to Graves' disease (Bartalena et al. 1995; Bufalo et al. 2008; Prummel and Wiersinga 1993) and, in particular, in the incidence and clinical severity of thyroid-associated ophthalmopathy (Bartalena, Pinchera, and Marcocci 2000).

2.9 Graves' disease and ophthalmopathy

There are innumerable environmental factors that can contribute to the development of Graves' disease (at least 20 - 30%), which certainly include smoking, probable stress, iodine and selenium intake, several drugs, irradiation, pollutants, viral and bacterial infections, allergy, pregnancy, and postpartum (Tanda et al. 2009). Cigarette smoking is one of the most studied environmental factor and has been demonstrated to increase the risk of Graves' disease (Bartalena et al. 1995; Bufalo et al. 2008; Prummel and Wiersinga 1993; Vestergaard et al. 2002) and decrease the chance of remission of hyperthyroidism, following antithyroid drug treatment (Glinioer, de Nayer, and Bex 2001; Kimball et al. 2002).

Graves' ophthalmopathy (Heufelder 1998; Krassas and Heufelder 2001) is more frequent and severe, and less responsive to medical treatment in smokers than in non-smokers (Prummel and Wiersinga 1993; Bartalena et al. 1989; Bartalena et al. 1998). The first possible connection between cigarette smoking and Graves' ophthalmopathy was made by Hagg and Asplund who showed that 10 out of 12 patients were current smokers, a figure much higher than that observed in Graves' patients without ophthalmopathy (46%) or in control subjects (31%). In addition, the prevalence of heavy smokers was higher in patients with more severe ophthalmopathy (Hagg and Asplund 1987). In a cross-sectional study reviewing the smoking habits of patients with different thyroid diseases, Bartalena et al (Bartalena et al. 1989) found a 64% prevalence of smokers among patients with Graves' ophthalmopathy, a percentage much higher than that of Graves' disease without eye involvement (48%), and 30% in patients with nontoxic goiter, toxic nodular goiter and Hashimoto's thyroiditis. Finally, Tellez et al showed that the prevalence of eye disease correlated not only with smoking but also with ethnicity. The percentage of smokers was higher in Caucasian than in Asian patients (42% and 7.7%, respectively). This suggests that the genetic background and/or geographic location may influence the prevalence of Graves' ophthalmopathy. Furthermore, this study demonstrated that the effect of smoking was dose-related with a higher proportion of patients developing eye involvement with increasing cigarette consumption (Tellez, Cooper, and Edmonds 1992).

Smoking probably affects cytokine production and effect on the orbit. In this regard, smoke extracts have been shown to synergistically interact with interleukin-1 to increase adipocyte differentiation of orbital preadipocytes in culture (Cawood et al. 2006) and to stimulate glycosaminoglycan production (Cawood et al. 2007). It is well accepted that cytokines play an important role in the pathogenesis of Graves' ophthalmopathy (Krassas and Heufelder 2001; Heufelder 1995; Krassas et al. 2001). Cigarette smoking may affect this process because smoking-induced hypoxia in the retrobulbar tissue has been shown to increase the release of cytokines from orbital fibroblasts and endothelial cells (Metcalf and Weetman 1994) and thereby may enhance the expression of adhesion molecules (Heufelder and Bahn 1992). Based on this evidence, refrain from smoking should be strongly recommended to patients with Graves' disease and Graves' ophthalmopathy (Bartalena et al. 2008). In an observational study, smoking cessation was associated with Graves' patients with a decreased risk to develop exophthalmos and diplopia (Pfeilschifter and Ziegler 1996). Smoking seems to influence not only the occurrence and the course of Graves'

ophthalmopathy, but also the response to various therapeutic interventions, such as orbital radiotherapy and glucocorticoid administration (Bartalena et al. 1998), reported that in patients submitted to orbital radiotherapy and high-dose systemic glucocorticoid treatment for severe Graves' ophthalmopathy; a favorable response to treatment was observed in 61 of 65 non-smokers (94%) but only in 58 of 85 smokers (68%).

2.10 Smoking and autoimmune thyroid diseases (AITD)

Hegedus et al (Hegedus et al. 1992) found no differences in thyroid-stimulating immunoglobulins (TSIS) among smoking and non-smoking healthy individuals.

Smoking is an independent risk factor for the development of both Graves' disease and Hashimoto's thyroiditis (Prummel and Wiersinga 1993; Vestergaard et al. 2002).

However, the effect of smoking on Hashimoto's disease seems to be the opposite of its effect on Graves' ophthalmopathy. A relationship between smoking and an increased risk of subsequent hypothyroidism has been demonstrated, possibly associated with an antithyroid effect of thiocyanate generated on tobacco smokers (Fukata, Kuma, and Sugawara 1996). Smoking also increased the risk of later development of hypothyroidism in a follow-up study of the general population (Nystrom et al. 1993). Furthermore, smoking seems to impair the effects of thyroid hormones, aggravating the effects of hypothyroidism in a dose-dependent manner (Muller et al. 1995). A study that evaluated the prevalence of eye signs in patients with Hashimoto's thyroiditis showed that there was no significant relationship between cigarette smoking and either eye abnormalities or calsequestrin or collagen XIII antibodies in these patients. The eye signs correlated only modestly with calsequestrin and collagen XIII antibodies. In contrast to patients with Graves' disease, where cigarette smoking is shown to be a major risk factor for ophthalmopathy (Bartalena and Tanda 2009; Lim et al. 2008; Nassar et al. 2009), there was no relationship between smoking status and eye abnormalities in patients with Hashimoto's thyroiditis (Tjiang et al. 2010).

Muller et al. found that among women with subclinical hypothyroidism, smokers had higher serum TSH levels, higher serum ratio of T3 to free T4, and also higher cholesterol and low-density lipoprotein cholesterol concentrations than non-smokers (Muller et al. 1995). In contrast, patients with overt hypothyroidism, either smokers or non-smokers, had similar serum TSH and thyroid hormone levels (Muller et al. 1995). These results do not indicate that smoking causes hypothyroidism, but that it may increase the severity of the effects of hypothyroidism (Utiger 1995).

Conversely, a decreased prevalence of TPO-Ab in smokers compared with non-smokers was reported among women of the Amsterdam autoimmune thyroid disorders cohort (Strieder, Prummel et al. 2003). The OR of current smoking for the presence of TPO-Ab was 0.69 (95% CI, 0.48–0.99). Data from the third National Health and Nutrition Examination Survey (NHANES III) (Belin et al. 2004) indicated that fewer smokers (11%; 95% CI, 10–13) had TPO-Ab and/or Tg-Ab compared with non-smokers (18%; 95% CI, 17–19). The relationship persisted when analyzing the presence of one antibody independently of the status of the other antibody. A Danish population study (Pedersen et al. 2008) found that smoking was negatively associated with the presence of thyroid antibodies, with the strongest association between smoking and Tg-Ab (OR, 0.5–0.6). More recently, Grigoris et al performed a prospective study that demonstrated that the discontinuation of smoking increased the risk of *de novo* occurrence of serum TPO-Ab and/or Tg-Ab in subjects susceptible for developing autoimmune thyroid disorders. The OR of smoking for developing TPO-Ab and/or Tg-Ab were 0.62 [95% confidence interval (CI), 0.37–1.04] one year before seroconversion, and 0.59

(95% CI, 0.35–0.99) at seroconversion. When only conversion to TPO-Ab is considered, the OR of smoking were 0.58 (95%CI, 0.31–1.09) one year before seroconversion and 0.54 (95%CI, 0.29–1.02) at the time of seroconversion (Effraimidis, Tijssen, and Wiersinga 2009). These studies showed good evidence that smoking decreases the prevalence (Strieder, Prummel et al. 2003; Belin et al. 2004; Pedersen et al. 2008) and incidence (Effraimidis, Tijssen, and Wiersinga 2009) of antibodies TPO and Tg, raising an important issue on the physiopathology of such opposite effects of smoking on autoimmunity.

2.11 Smoking and goiter

Differing results have been published concerning the association between tobacco smoking and goiter. Some authors found no association between smoking habits and goiter prevalence (Prummel and Wiersinga 1993; Bartalena et al. 1989; Petersen et al. 1991) or thyroid volume (Gomez et al. 2000; Olbricht and Hoff 1988; Berghout et al. 1987). Others have found a positive association between smoking habits and goiter prevalence (Hegedus et al. 1985; Ericsson and Lindgarde 1991; Christensen et al. 1984; Brix et al. 2000) or thyroid volume (Nygaard et al. 1993; Barrere et al. 2000; Hegedus et al. 1985; Georgiadis et al. 1997). It has been suggested that these discrepancies could be caused by differences in iodine status, as the association seems to be stronger in iodine-deficient areas (Bartalena et al. 1995; Bertelsen and Hegedus 1994). In addition, the association between smoking and thyroid volumes is stronger in areas with iodine deficiency. Serum thyroglobulin is also positively associated with smoking habits, and multiple nodules are found more often in smokers than in non-smokers (Knudsen et al. 2002). All these effects are most likely mediated by thiocyanate acting as a competitive inhibitor of iodine uptake and organification (Knudsen et al. 2002).

2.12 Thiocyanate

Thiocyanate, a perchlorate-like goitrogen, acts by preventing iodine trapping (Karakaya et al. 1987). It is generated from cigarette smoke as a detoxifying product of cyanide (Karakaya et al. 1987). The levels of the thiocyanate in the blood are related to the amount of cigarette smoke inhalation (Karakaya et al. 1987).

The competitive inhibition of iodide transport by thiocyanate may be important for understanding the action of thiocyanate *in vivo*. In fact, thiocyanate concentrations obtained by smoking competitively inhibit iodide transportation into the thyroid gland *in vitro* study on porcine thyroid follicles (Fukayama et al. 1992). Thiocyanate also acts independently of the TSH concentration, inhibiting iodide organification and increasing iodide efflux from the cells (Fukayama et al. 1992). Iodine deficiency may enhance the antithyroid action of thiocyanate and iodide excess may diminish this effect. Thereby, thiocyanate may be responsible for the goitrogenic effect of cigarette smoking seen at least in iodine deficient areas (Hegedus et al. 1985). This mechanism may, in part, explain the diverging results and the regional differences in the goitrogenic effect of cigarette smoking.

Although nicotine content in cigarette smoking does not influence iodide turnover (Fukayama et al. 1992), it might cause sympathetic activation, which could increase thyroid secretion (Melander et al. 1981; Bertelsen and Hegedus 1994). Alternatively, nicotine or other component(s) of tobacco smoking, such as benzopyrene, may have direct thyroid-stimulatory actions or stimulating effects on hepatic oxidative metabolism, which in turn may stimulate hepatic conversion of T4 to T3 (Jusko 1979).

It is well known that many factors are involved in the regulation of thyroid volume. TSH levels, iodine concentration, the presence of thyroid autoimmunity and several goitrogens

are generally accepted factors but others, such as sex, age, body weight or personal habits (e.g. cigarette smoking, alcohol abuse) are controversial in regard to their effect on thyroid volume (Pontikides and Krassas 2002).

2.13 Thyroid cancer

During the last two decades, several studies have reported a reduced risk of thyroid cancer, mainly in women, although not always statistically significant, in association with cigarette smoking (McTiernan, Weiss, and Daling 1984; Ron et al. 1987; Kolonel et al. 1990; Preston-Martin et al. 1993; Shore et al. 1993; Hallquist et al. 1994; Galanti et al. 1996; Rossing et al. 2000), in the two major histological groups (papillary and follicular cancers) from all geographic regions (Mack et al. 2003).

Kreiger and Parkers recently explored the association of cigarette smoking with thyroid cancer in both sexes in a case-control study (Kreiger and Parkes 2000). Reduced risk was observed for ever/never cigarette smokers of both sexes with an odds ratio of 0.71 for females (95% confidence interval (CI) = 0.60-0.83) and 0.77 (95% CI=0.58-1.02) for males.

Since thyroid cancer occurs more frequently in women than in men, hormonal factors may also be involved in its pathogenesis. The mechanism (s) by which cigarette smoking may be protective for thyroid cancer probably involves the lowering of endogenous levels of TSH [1, 8, 13, 42]. It has been suggested that increased levels of TSH or elevated levels of other thyroid stimulators, as occurs during pregnancy, are associated with an increased risk of thyroid cancer (Ron et al. 1987). Female preponderance of thyroid cancer has led to the hypothesis that estrogen metabolism may play a role in its pathogenesis. In fact, it has been suggested by some studies that smoking may have an anti-estrogen effect (Baron, La Vecchia, and Levi 1990). However, there is no evidence that smoking has similar effect(s) on androgen metabolism (Dai et al. 1988).

A highly significant correlation has been demonstrated between thiocyanate levels in the mother and cord blood, a finding indicating that thiocyanate freely crosses the placenta (Othman et al. 1990). An inverse correlation was found between thiocyanate levels in cord blood, birth weight, significantly decreased serum TSH levels and increased T4 levels in newborn babies of smoking mothers when compared with non-smoking ones (Othman et al. 1990). Thiocyanate has a biological half-life of 1-2 weeks (Gasparoni et al. 1998). Therefore, measurements in plasma may be used to detect the degree of exposure to smoking from days to weeks after the last consumption. Gasparoni et al (Gasparoni et al. 1998) found that infants whose mothers and fathers smoked had higher cord serum thyroglobulin and thiocyanate concentrations in comparison with infants whose parents did not smoke. However, the infants had no other evidence of thyroid abnormalities, such as increased T4, T3 or decreased TSH concentrations (Meberg and Marstein 1986).

Our group demonstrated an inverse association of germline cytochrome P4501A1 (CYP1A1) inheritance and smoking with the risk of thyroid nodules and papillary carcinomas, helping to explain the reduced risk of differentiated thyroid cancer in tobacco consumers observed in epidemiologic studies (Bufalo et al. 2006).

2.14 Infections

Infections have been implicated in the pathogenesis of several autoimmune, endocrine and nonendocrine diseases (Tomer and Davies 1993). Furthermore, they have long been invoked as an underlying etiology or trigger factor for the induction of autoimmune thyroid

diseases, such as subacute thyroiditis and autoimmune thyroiditis. They are also suspected to be involved in carcinogenesis and in the onset of thyroid lymphomas (Desailloud et al. 2009). Both viral and bacterial infections might represent a risk factor for autoimmune thyroiditis development in genetically predisposed individuals (Desailloud and Hober 2009; Lehmann et al. 2008; Thomas et al. 2008; Tozzoli et al. 2008; Tomer and Davies 1993).

It is possible that multiple exposures to infections are necessary to train our immune system to perform well, but some infections are able to break the tolerance of susceptible individuals and allow autoimmune diseases to develop (Davies 2008). Specific infections could be a triggering factor to disease initiation by liberating antigens (via cell destruction or apoptosis), by forming altered antigens or causing molecular mimicry, by cytokine and chemokine secretion, or by inducing aberrant human leukocyte antigen (HLA)-DR expression and toll-like receptor activation (Harii et al. 2005). Clearance of cell debris can lead to abnormal antigen presentation, especially that of previously sequestered antigens (Mackay, Leskovsek, and Rose 2008). Infection of a rat cell line with reovirus types 1 and 3 induces thyroid cell major histocompatibility complex class II, which may allow presentation of thyroid antigen to the immune system and participate in the initiation of autoimmune thyroid disease (Neufeld, Platzer, and Davies 1989).

Paradoxically, infections may both enhance autoimmune thyroiditis and also act as a protection against autoimmune thyroiditis. There is growing acceptance of a hygiene hypothesis which implies that the immune system is educated by multiple exposures to different infections, allowing better controlled autoimmune responses (Bach 2005; Bloomfield et al. 2006). Thus, improved living standards and decreased exposure to infections are associated with an increased risk of autoimmune disease and lower socioeconomic groups have a reduced prevalence of thyroid autoantibodies (Bach 2005; Kondrashova et al. 2008). A recent study carried out in two adjacent regions of Finland (good socioeconomic and hygiene conditions) and Russia (lower socioeconomic and hygiene conditions), with likely similar genetic background, showed that the presence of chronic autoimmune thyroiditis (and subclinical hypothyroidism) among schoolchildren was much higher in the Finnish population than in the Russian population (Kondrashova et al. 2008).

The best-studied infection in autoimmune thyroiditis is that with *Yersinia enterocolitica*. Humoral and cellular immunity against *Yersinia enterocolitica* in patients with autoimmune thyroid diseases has been demonstrated (Bech et al. 1974; Lidman et al. 1974), and Wenzel et al (Wenzel et al. 1988; Wenzel et al. 2003) have found antibodies against virulent plasmid-encoded proteins of *Yersinia enterocolitica* in a large proportion of patients with autoimmune diseases. A potential mechanism could be molecular mimicry (Albert and Inman 1999). In a recent Dutch study, an increased prevalence of antibodies to enteropathogenic *Yersinia enterocolitica* virulence proteins was found in relatives of autoimmune diseases patients, but this was unrelated to the higher prevalence of TPO antibodies in these subjects (Strieder, Wenzel et al. 2003). According to this hypothesis, the generated *Yersinia*-specific immune response cross-reacts with thyroid-specific components to cause tissue damage and disease (Albert and Inman 1999).

Epstein-Barr virus seems to play a role in the natural killer/T-cell lymphoma subtype of the orbit, as has long been described for Burkitt lymphoma. Bacteria seem to induce reactive lymphoid proliferation, while viruses directly infect the lymphoid cells, affecting the cell cycle and suppressing apoptosis, with subsequent malignant transformation. In general, proteins leading to cell cycle progression, like retinoblastoma protein, are elevated, and proteins inhibiting cell cycle progression, like p16 and p21, are absent or unable to function

normally. Inactivation of p53 by mutation of its DNA, which leads to elevation of defective p53 protein and inhibition of apoptosis, allows oncogenic by-chance mutations to become effective (Auw-Hadrich, Gobel, and Illerhaus 2010). Although apoptosis could help to control the reproduction of abnormal cells and, therefore, play a role in the protection of host cells against viral infection and antiviral immune response, there is also some evidence that it can also trigger autoimmunity. Virally induced apoptosis is considered to be at least partially responsible for the various associated pathologies (Young, Dawson, and Eliopoulos 1997). There is increasing evidence that apoptosis could play a role in the development of autoimmune thyroid diseases. Apoptosis induction may result in thyrocyte destruction and lymphocytic infiltration of the thyroid (Wang and Baker 2007)

Human herpesviruses are ubiquitous with widespread tissue tropism and have been found in the thyroid, which can be a reservoir of latent (Nahmias, Lee, and Beckman-Nahmias 1990; Staras et al. 2008). Herpesvirus infection might be involved in the pathophysiology of several chronic autoimmune inflammatory processes (Posnett 2008; Scotet et al. 1999). In fact, herpesviruses were demonstrated in thyroid tissues with both nodular and autoimmune diseases. Thomas et al isolated herpesviruses from 72.22% of thyroid tissue blocks of patients with Graves' disease and Hashimoto's thyroiditis (Thomas et al. 2008). Krueger et al showed that herpesviruses types 6 and 7 are highly prevalent in the healthy population with a cumulative probability for seropositivity of almost 100% in young age (Krueger et al. 1998). In addition, herpesviruses may use the thyroid gland and the gastrointestinal system as reservoirs (Kim et al. 2010). Like other infectious agents, herpes infection potentially increases the efficiency of T cell activation by enhanced expression of costimulatory molecules, upregulation of HLA expression on specialized antigen-presenting cells, and attraction of dendritic cells from peripheral to secondary lymphoid tissues (Leite et al. 2010). Herpesviruses human antiviral response includes two reciprocal cellular programs: cell survival with the production of protective cytokines and other cytokines that could lead to apoptosis for the elimination of infected cells; by that mechanism, virus would be involved in the initiation and progression of autoimmune thyroid disease. Continued activation of innate immunity against herpesviruses infection can also potentiate immune disorders. Using a subset of 280 Graves' disease patients carefully paired with a control group of 284 individuals, we demonstrated that patients with 72TP53 Pro/Pro variants (inherited diminished *TP53* apoptotic function) had five times more chance to develop Graves' disease and almost three times more chance to be infected by human herpesviruses type 7. This infection was associated with an increase of three times the susceptibility to Graves' disease (Leite et al. 2010). We suggested that human herpesviruses type 7 may take advantage of the poorer apoptotic ability of 72TP53 variants to trigger the autoimmune process that leads to Graves' disease. Thus, the inheritance of less efficient *TP53* genes would increase the risk of Graves' disease development and also favor human herpesviruses type 7 infection and perpetuation, which in turn may initiate and perpetuate the autoimmune process in Graves' disease (Leite et al. 2010).

Viruses are one of the high-risk factors closely related to human cancers. Many widespread chronic diseases, previously thought to be due to metabolic imbalances or genetic modifications, are increasingly linked to infectious events.

It is estimated that viruses are a contributory cause of 20% of all human cancers (Dimmock and Primrose 1994). Viruses, such as specific types of human papillomaviruses, Epstein-Barr virus, and human herpesviruses type 8, have been emerging as major causal factors of some human cancers (Tsai et al. 2005). Viral infection significantly affects the tumor

microenvironment, induces angiogenesis, and favors the development of metastases (Tsuji et al. 2008). There are several indicators of a possible role for viruses in thyroid cancer. Activation of virus-inducible signaling pathways, such as Toll-like receptor (TLR) signaling, has been shown in papillary thyroid carcinomas (McCall et al. 2007). Parvovirus B19 has been detected in thyroid cancer samples (Wang et al. 2008) and Epstein-Barr virus protein expression was demonstrated in poorly differentiated thyroid cancer (Shimakage et al. 2003). *In vitro* studies showed expression of herpesviruses entry mediator and nectin-1 in thyroid cancer cell lines (Huang et al. 2007).

Recent evidences also demonstrated that viruses could be directly involved in regulation of the epithelial-to-mesenchymal transition and contribute to the development of metastases. It has been shown that Epstein-Barr virus proteins can control the expression of Twist (Horikawa et al. 2007) and the development of metastases by regulating the metastasis suppressor *Nm23* (Kaul et al. 2009).

In humans, herpes simplex virus DNA was detected in thyroid samples from patients with autoimmune disorders (Thomas et al. 2008). Herpes simplex virus replication in epithelial cells is associated with activation of the RAS/MEK/MAPK pathway, which might be important to thyroid carcinogenesis (Smith et al. 2000), since these genes are commonly activated in thyroid cancer. Jensen et al showed that herpes simplex virus can be frequently detected in thyroid cancers, suggesting that during tumor progression, thyroid tumor cells acquire increased susceptibility to herpes simplex virus due to increased expression of nectin-1 and activation of mitogenic signaling (Jensen et al. 2010).

A viral disease is the result of an interaction between virus and host, in which the genetic background plays a role (Desailloud and Hober 2009). Further studies are needed to clarify the pathogenic mechanisms implicated in viruses-induced thyroid disease, aiming to propose new therapeutic strategies.

2.15 Thyroid disruptor action and human reaction

Endocrine disruptors act by physiological mechanisms replacing the hormones in our organism, blocking their natural action, or altering (increasing or decreasing) the original amount of hormones, thereby causing important endocrine function disturbances (Santamarta 2001). Most endocrine disruptor agents reduce circulating thyroid hormone levels or impair thyroid hormone action, and some may influence the pituitary and thyrotropin secretion, or even be partial thyroid hormone receptor agonists (Brent 2010). However, the thyroid is able to compensate their effect by increasing serum TSH and continue to produce a normal amount of thyroid hormone despite disruption (Brent, Braverman, and Zoeller 2007). Conversely, most carcinogens do not produce their biological effects per se, but require metabolic activation before they can interact with cellular macromolecules (Cascorbi 2006). Many compounds are converted to reactive electrophilic metabolites by oxidative (phase I) enzymes such as cytochrome P-450, which presumably most important effect is to activate the majority of carcinogens. Nevertheless, phase II enzymes usually act as inactivating enzymes catalyzing the conjugations of carcinogenic substance (Hein 2002). Phase II group of enzymes includes glutathione S-transferase, UDP-glucuronosyltransferase and N-acetyltransferase systems (Hein 2002).

We demonstrated that the inheritance of a series of these enzyme systems is involved in the risk for thyroid cancer development and in thyroid autoimmune disease susceptibility (Bufalo et al. 2006; Bufalo et al. 2008; Granja et al. 2005). Identifying a risk profile for thyroid diseases may help delineate polygenic models of susceptibility and prognosis. Such models

are particularly interesting, considering the elevated prevalence of thyroid diseases in the population, and may help select individuals for specific preventive interventions and determine which patients are most likely to benefit from specific measures.

3. References

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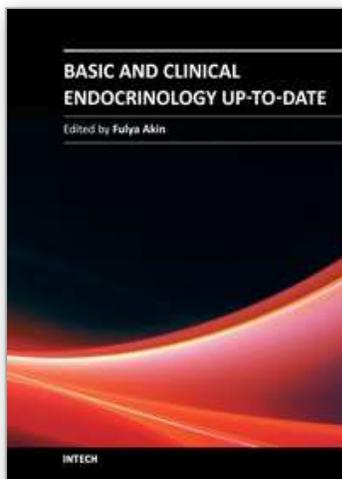
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Edited by Dr. Fulya Akin

ISBN 978-953-307-340-8

Hard cover, 350 pages

Publisher InTech

Published online 17, October, 2011

Published in print edition October, 2011

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How to reference

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Natassia Elena Bufalo, Aline Carolina de Nadai da Silva, Raquel Bueno Barbieri, Marjory Alana Marcello, Lucas Leite Cunha, Elaine Cristina Morari and Laura Sterian Ward (2011). Thyroid Disruptors: How They Act and How We React, Basic and Clinical Endocrinology Up-to-Date, Dr. Fulya Akin (Ed.), ISBN: 978-953-307-340-8, InTech, Available from: <http://www.intechopen.com/books/basic-and-clinical-endocrinology-up-to-date/thyroid-disruptors-how-they-act-and-how-we-react>

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Phone: +86-21-62489820
Fax: +86-21-62489821

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