

Environmental Risk Factors for Differentiated Thyroid Cancer (DTC)

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Abstract

In the last 20 years, we are seeing a dramatic increasing of incidence of thyroid cancer, especially papillary variant. It is controversial whether the real increase is due to the improvement of detection, screening and overdiagnosis or a real increase is possible, as recent observations suggest.

Several risk factors are suspects to be responsible of the etiology.

Some environmental risk factors are strongly correlated with thyroid cancer as radiation exposure and iodine status. Others as diabetes and obesity, estrogen and lifestyle factors have been suggested as possible element of risk.

This review is analysing the possible environmental risk correlate with the increasing thyroid cancer incidence.

Keywords: Differentiated Thyroid Cancers (DTC); Papillary Thyroid Cancer (PTC); SEER Data (Surveillance, Epidemiology and End Result); Risk Factors

Introduction

Differentiated thyroid cancers (DTC) comprise the vast majority (> 90%) of all thyroid cancers, include papillary and follicular histotypes, and have a favorable prognosis according to the American Thyroid Association [1].

In particular the differentiated thyroid cancer incidence has dramatically increased, (mainly papillary thyroid cancer PTC), in the paste decades [2]. However, there is still a debate if is due to the improve detection and screening and overdiagnosis or to a real increase.

A recent study using SEER data (Surveillance, Epidemiology and End Result), indicate that incidence base mortality is increased in USA in particular in patient with advanced stage of cancer, suggesting a true increase, possible related to environmental factors [3].

The environmental risk factor for thyroid cancer includes radiation exposure, iodine intake, obesity and diabetes, estrogen and reproductive factors, hashimoto thyroiditis, lifestyle factor.

Radiation exposure

The relationship between radiation exposure and thyroid cancer has been well documented and is the only established environmental risk factor for thyroid cancer [4]. The thyroid gland is highly sensitive to the carcinogenic effects of exposure to ionizing radiation during childhood and adolescence.

In 1950 for the first time was observed a relationship between radiation of the thymus at birth and increased incidence of thyroid cancer [5].

Thyroid carcinoma was the first solid malignant tumor found with an increased incidence among Japanese atomic bomb survivors [6]. Later, an increased risk of thyroid carcinoma was observed as a consequence of fallout from thermonuclear explosion in the Marshall Island and from the nuclear plant accident in Chernobyl and Fukushima.

Since 1950, the Radiation Effects Research Foundation has been investigating the late health effects of the radiation exposure in atomic bomb survivors. About 36% of the thyroid cancer cases among subjects exposed before age 20 were attributable to radiation exposure [7].

In a cohort of subject observed following the Bikini atoll nuclear test, it was found that the prevalence of hypothyroidism, thyroid nodules, and thyroid carcinoma in exposed subjects increased with the radiation dose to the thyroid gland. Females were at a higher risk (3.7 fold) of developing a thyroid nodule than males, and the risk decreased with increasing age at exposure. The risk of radiation-induced thyroid tumors decreased with longer follow-up [8].

Following the accident of the nuclear power plant at Chernobyl in Ukraine in 1986 it was recorded an increase in the incidence of childhood thyroid carcinoma. The quantity of radiation including radioactive iodine released was enormous. In particular region of the Belarus, Ukraine and south Russian the level of contamination was very high and thyroid uptake was elevated due to iodine deficit and lack of iodine prophylaxis. The radioactive cloud spread over a large area in northern and western Europe [9].

In 1995, the incidence rate of childhood thyroid carcinoma in Belarus reached 40 per million. It is estimated that 7,000 thyroid cancer cases occurred among the 2 million highly contaminated subjects who were younger than 18 years at the time of the accident. In children, a strong relationship was found between the dose of radiation delivered to the thyroid gland and the risk of developing a thyroid cancer [10]. Following the Fukushima nuclear plant accident in Japan, despite large amounts of radioactive isotopes, including 131I were released, the incidence of thyroid cancer in the exposed population was low because the authorities ordered shielding, evacuation from the most contaminated territories, and food restriction. Furthermore, the thyroid uptake of iodine was low in relation to the high iodine alimentary intake [11].

The main factor influencing the sensitivity to developing radiation related thyroid cancer are the dose of radiation delivered to the thyroid gland, the age of exposure to radiation and latency, iodine status and other conditions. As showed, children are highly susceptible to radiation risk of thyroid cancer and there is no limit below which the risk can be totally excluded, therefore is recommended to avoid irradiating procedures such a CT scan in young children. Studies done in patient exposed to external radiation before the age of 4 showed a fivefold increased risk of developed thyroid cancer compare to those of 10 - 14 year when exposed to the same dose of radiation [12].

Iodine deficit is associated with increase iodine uptake and proliferation rate of thyroid cells. The elevated radioiodine uptake in children of Belarus, Ukraine and Russia may have facilitate the elevated occurrence of thyroid cancer in this population [9].

Recent evidence also showed that chemotherapy during childhood increases the risk of subsequent thyroid carcinoma by 4 folds if given alone and the risk of chemotherapy is additive to the risk of radiation therapy when both are given [12].

A recent published compressive meta-analysis showed that multiple (or repeated) exposures to dental x- rays were significantly associated with an increased risk of thyroid cancer and meningioma [13].

Relevant Points

- The risk is significantly increased for elevated dose of exposure to radiation.
- The risk is maximal for radiation exposure during the first years of life and decreases with increasing age at exposure, and is low in exposed adults
- One third of thyroid tumors occurring after radiation exposure are malignant, and most radiation-induced thyroid cancers are papillary thyroid carcinoma (PTC)
- These cancers have a clinical behavior similar to that of PTC that occurs at the same age in non-irradiated individuals and that are usually not aggressive.

PTC is the most frequent form of thyroid carcinoma diagnosed after radiation exposure. Ionizing radiation causes DNA strand breaks and somatic mutations that are thought to be a risk factor for cancer in general [14]. This DNA damage includes single- or double-strand breaks that will result in deletions and chromosomal rearrangements. Normal thyrocytes multiply during body growth, especially before the age of 5 years, and this will favor the accumulation of genetic defects after radiation exposure. Mitotic rate decreases with age and becomes very low in adults. This may explain the high sensitivity of the thyroid gland to the carcinogenic effects of radiation at birth, which decreases with increasing age, becoming low or not significant after the age of 15 - 20 years. RET/PTC3 rearrangement was the most frequently observed rearrangement in aggressive PTC that occurred in young children soon after the Chernobyl accident, and RET/PTC1 rearrangement was more frequently observed in classical PTC that occurred later after the accident [15,16].

An international multidisciplinary Expert Group convened by the International Agency for Research on Cancer (IARC) evaluated scientific evidence to formulate recommendations about long-term strategies for thyroid health monitoring after a nuclear power plant accident. In view of the established association of thyroid cancer risk with radiation exposure, particularly during childhood and adolescence, appropriate preparedness and response regarding thyroid cancer-related issues are crucial. The Expert Group recommends against population thyroid screening after a nuclear accident, and it recommends that consideration be given to offering a long-term thyroid monitoring programme for higher-risk individuals after a nuclear accident [18].

Iodine status

Iodine is a critical element involved in thyroid gland function, thyroid hormone synthesis and secretion [18]. Low iodine intake has been associated to increased risk of thyroid cancer, favoring the development of more aggressive histotypes.

The introduction of iodine prophylaxis in a previously iodine-deficient population led to a reduction of follicular Thyroid (FTC) cancer but led to a predominant papillary histotype. This supports the hypothesis that iodine deficiency is associated with an increased risk of Follicular thyroid cancer, whereas chronically high iodine intake may increase the risk of Papillary thyroid cancer.

Iodine deficiency may lead to reduced thyroid hormone (T3 and T4) production and consequent hypersecretion of thyroid stimulating hormone (TSH). This induces hypertrophy and hyperplasia of thyroid follicular cells and promotes the onset of cancer.

Data between the association of iodine intake and BRAF mutation are contrasting. High iodine intake has been associated with presence of BRAF mutation.

A detailed molecular analysis of PTCs and FTCs from an iodine-rich country (Japan) and an iodine-deficient country (Vietnam) was recently conducted by Voung, *et al.* BRAF (V600E) mutation, RET rearrangements, and RAS mutations were analyzed, but the authors did not identify significant differences in genetic alterations in DTCs among the two examined regions, concluding that iodine intake did not influence the presence of mutations in patients with Thyroid cancer [19].

Fish is considered an important source for iodine and other micronutrients, but it can contain also several contaminants that may potentially affect the thyroid or influence TC risk. The large prospective study EPIC (European Prospective Investigation into Cancer and Nutrition) performed in Europe, where both iodine deficiency and excess are rare, demonstrated that the consumption of fish or shellfish is not associated with changes in DTC risk [21].

Diabetes and obesity

Diabetes mellitus (DM) is considered a major global public health concern, and likely to be among the 5-leading disease by 2030 [22]. Diabetes and obesity have been associated with risk of cancer. However, there are contrasting result regards the risk of thyroid cancer and diabetes. A recent meta-analysis explored the relationship between thyroid cancer and diabetes mellitus. The results suggested that DM patients had overall 20% increase in thyroid cancer incidence compared with those without DM. Furthermore, when pooling for men, no significant difference was detected, whereas in women DM had a harmful impact on the risk of thyroid cancer [23].

Previous meta-analyses of the association of DM with thyroid cancer risk have reported similar findings. Hemminki, *et al.* performed a large-scale cohort study covering approximately half of the Swedish diabetic patients and found elevated thyroid cancer risk after hospitalization, suggesting the profound metabolic disturbances of the underlying disease. Such increase might be due to DM patients having variable serum insulin levels, affecting the progression of thyroid cancer through enhanced cancer cell proliferation or reduced apoptosis, and indirectly through insulin-like growth factor-1, estrogen and thyroid stimulating hormones [24]. Lo, *et al.* found that the relationships between DM and thyroid cancer risk might differ by follow-up duration, likely because the mean age and duration of diabetes course play an important role in such association. In addition, diabetes treatment might affect the progression of thyroid cancer due to insulin resistance, which is associated with increased thyroid volumes and higher risk of thyroid nodule. However, the specific effects of hyperinsulinemia and insulin resistance on promoting thyroid cancer risk are not well understood [25,26]. However other studies did not support the association. A large U.S. cohort study, with a median follow-up of 15.9 years, found no significant associations between thyroid cancer risk and diabetes, diabetes treatment, or duration of diabetes, among postmenopausal women [27].

Given the possible association regular thyroid examination for type 2 DM patients may be worthwhile until these results can be further confirmed or clarified.

Both thyroid cancer incidence and obesity has increased rapidly over time. A link between the two appears plausible, but the relation of adiposity to thyroid cancer remains incompletely understood. A metanalysis of adiposity measures and thyroid cancer using studies, found a statistically significant 25% greater risk of thyroid cancer in overweight individuals and a 55% greater thyroid cancer risk in obese individuals as compared with their normal-weight peers. When evaluated by histologic type, obesity was significantly positively related to papillary, follicular and anaplastic thyroid cancers, whereas it revealed an inverse association with medullary thyroid cancer [28].

Several biologic mechanisms may explain the link between overweight, obesity and risk of cancer. Adiposity is associated with insulin resistance which poses a potential risk factor for thyroid cancer, although studies relating insulin resistance to thyroid cancer are sparse and findings remain controversial. Chronic inflammation induced by adipokine secretion from adipose tissue, oxidative stress and the nuclear factor κ B system are linked to cancer development and may also contribute to thyroid-specific carcinogenesis. Epidemiologic data show a positive association between obesity and thyroid-stimulating hormone (TSH) levels in euthyroid individuals. TSH is involved in mitogenic pathways of the thyroid gland, and increased TSH levels have been related to greater risk of thyroid cancer [28]. A recent metanalysis observed that Insulin Resistance is related to increased risk of thyroid cancer, especially in papillary thyroid and the components of the metabolic syndrome like dysglycemia, high BMI and hypertension significantly, are associated with thyroid cancer risk [29].

Estrogen and reproductive factors

The incidence of thyroid cancer is three times higher in women than men during the period between puberty and menopause. Such striking gender discrepancies strongly suggest that female sex hormones may be involved in thyroid carcinogenesis. Estrogen has been historically considered as a potential mechanism mediating the risk of breast, ovarian and endometrial cancer [30].

A comprehensive meta-analysis concluded that menopause was associated with an increased risk of papillary thyroid cancer but not significant association was demonstrated between papillary thyroid cancer risk and other hormone-related factors, including oral contraceptive, hormone replacement therapy, age at menarche, parity, age at first birth, menopausal status, and breast feeding. The meta-analysis firstly suggests that late age at menopause is a risk factor for papillary thyroid cancer [31].

Estrogens and estrogens receptors signals play critical roles in the growth of thyroid gland by enhancing the secretion of thyroid stimulating hormone. Many studies have implicated that estrogens can influence the proliferation and invasion of thyroid cancer cells by modulating molecular signaling pathways involved in thyroid growth and function. Taken all together, female sex hormones are highly associated with the risk of thyroid cancer. However, the underlying molecular mechanisms remain largely unknown [31,32].

A retrospective case-control study suggested that the overall risk of second primary thyroid cancer or breast cancer is significantly increased in patients who previously had a history of both thyroid or breast cancer [33]. The etiologies of thyroid and mammary gland cancers share common features, such as iodine intake and transport, the levels of thyroid function, Thyroid Hormones Receptors, obesity and sex hormones. Factors that contribute to the initiation of Thyroid cancer, such as low dietary iodine, hypothyroidism, and other thyroid disorders, may also contribute to the increased risk of Breast cancer [34].

Autoimmune disease and thyroid cancer

Autoimmune disease of the thyroid are a group of common disorders with different clinical presentations, associated with either hypothyroidism, Hashimoto thyroiditis (HT) or hyperthyroidism, Graves' disease (GD) due to an immune system deregulation that leads to a T-cell mediated damage against the thyroid gland.

The immune system contains the development of cancer through immune surveillance, but cancer cells can develop several strategies of escape. Cancer development is often concomitant with autoimmunity phenomena. A wide range of autoantibodies can be produced and detected in serum of different types of cancer patients. Since the past century, an increasing number of studies performed *in vitro* and *in vivo* have demonstrated the coexistence of thyroid autoimmunity and cancer, especially the papillary type [35].

A recent review explored the association of HT and thyroid cancer, concluding that the prevalence rate of papillary thyroid cancer in patients with HT was 1.2% in fine-needle aspiration specimens and 27.6% in thyroidectomy specimens.

Patients with PTC associated with HT tend to be young women, with less aggressive disease, less frequent nodal metastasis, are less likely to develop recurrence and have a higher survival rate. However, the data provided inconsistent evidence favoring a causal relationship between Hashimoto's thyroiditis and PTC [36].

One of the mechanisms considered promoting risk for PTC was the increased levels of TSH. Indeed, hypothyroidism represents the most common clinical presentation of autoimmune disease of the thyroid, and TSH is the major growth factor for thyrocytes. Several studies demonstrated the close relationship between TSH serum levels and the risk of TC [35].

The association between thyroid carcinoma and GD is controversial. In a series of patient with GD, 32% were found to have thyroid carcinoma, concluding that thyroid nodular lesions in patients with GD should raise a high suspicion of carcinoma and these lesions are frequently clinically significant tumors. Incidental thyroid carcinomas in patients with GD are not uncommon, but most of them are low-risk papillary thyroid microcarcinoma without lymph node metastasis [37].

Another retrospective study on 423 patients with GD undergoing to surgical treatment found out, the total incidence of thyroid carcinoma was 13.7% and the incidence of nodules in malignant GD even reached 47.9%. Compared to Graves' disease patients with diffuse goiter, those with thyroid nodules were at higher risk of developing thyroid cancer but most of them were micropapillary thyroid cancers. Age was one of the most important factors predictive of locally advanced cancers in Graves' patients, according to the potential metastatic characteristics of the nodules [38].

Lifestyle factor

Cigarette smoking is a well-known risk factor for many cancers. However, pooled analysis showed an inverse association of thyroid cancer occurrence with cigarette smoking. A recent meta-analysis found that cigarette smoking could be inversely associated with thyroid cancer risk. Several underlying mechanisms could be proposed to explain the role of smoking in thyroid carcinogenesis. First, smoking may affect thyroid function. Several studies suggest that TSH levels and thyroid autoantibodies, which were positively associated with thyroid cancer risk, are lower in smokers than nonsmokers. The smoking-related reduction in TSH occurs in both men and women. Second, cigarette smoking could also potentially influence thyroid cancer risk by altering sex steroid hormone levels. Estrogens are suggested to affect thyroid malignancy based on the higher incidence rates among women compared with men and its proliferative effect on thyroid cells [39].

Nitrate, with its increasing presence in our dietary composition, was postulated to be a risk factor for thyroid cancer. Dietary nitrate is found in cured meats, various types of vegetables, and as contaminant of drinking water, thereby potentially posing bigger public health risks. Nitrate is regarded as a plausible risk factor for thyroid cancer, as it competitively inhibits iodide uptake by the thyroid, potentially affecting thyroid functions. Some epidemiologic evidence is available to demonstrate elevated thyroid cancer risk linked to excess dietary nitrate intake [30].

Physical activity is commonly thought to play a role in mediating cancer risk. Moreover, many chronic conditions are believed to be attributable to an increasingly sedentary lifestyle. However, the findings from systematic review and meta-analysis do not support a protective role for physical activity in thyroid carcinogenesis [40].

<p>Relevant Points</p> <ul style="list-style-type: none">• Iodine status: Low iodine intake has been associated with increased follicular thyroid cancer, high iodine with papillary thyroid cancer.• Diabetes Mellitus and Obesity and thyroid cancer: possible increase risk of Thyroid Cancer• Estrogen and Reproductive Factors: possible increased risk• Autoimmune diseases: Controversial, possible associated• Lifestyle factor: smoking inverse association with thyroid cancer.• Dietary nitrate intake: possible association.
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Conclusion

Radiation exposure is well recognised as a risk factor for thyroid cancer. Several studies shown a high risk of thyroid cancer in population exposed to high dose and younger age. Although the mortality remain low is highly recommended the screening and long follow up of the population exposed to nuclear accident.

Although there is no strong evidence yet for the other environmental risk factors, we suggest to includes them, in the history of patients with thyroid cancer, to stratify the possible risk of malignancy.

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