

## Etiology of thyroid cancer (C73) in Central and South America

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Although the etiology of thyroid cancer remains unknown and the reasons for the worldwide increase in its incidence are not well understood, exposure to ionizing radiation in childhood [1] and a medical history of goitre or thyroid nodules have been consistently associated with an increased risk. The most common explanation for the marked increase in incidence over time has been the growing use of better diagnostic tools (i.e., ultrasonography, fine-needle aspiration biopsy, computed tomography, and magnetic resonance imaging) [2–4]. A striking increase in the incidence of thyroid cancer has been reported in the USA (particularly among women) since the 1970s due to the improved detection of small papillary cancers, although mortality from this malignancy has remained stable over the past 40 years [5, 6] and reports have shown that small papillary thyroid carcinomas may never progress to cause symptoms or death [2, 5]. Thus, the discrepancy between the increased incidence of and stable mortality from thyroid cancer could be explained by the identification of subclinical diseases (over-diagnosis) which in consequence would lead to an excellent prognosis [2, 7]. However, a rise simply caused by over-detection would not easily account for the increases observed in the developing world, where imaging techniques are less affordable. Thus, changes in risk factors may also be related in part to these higher rates. A brief review the potential risk factors associated with this malignancy is presented below.

### **Ionizing radiation**

Exposure to ionizing radiation during infancy or early childhood has been consistently associated with the risk of thyroid cancer. Young children are more susceptible to such exposures because of the accelerated growth of the thyroid at this age and its tendency to concentrate iodine [8]. In a pooled analysis of seven epidemiological studies (5 cohort and 2 case–control), Ron et al. [9] reported that children irradiated before the age of 15 years (atomic bomb survivors, and those treated for tinea capitis, skin haemangiomas, enlarged tonsils, or an enlarged thymus gland) had a pooled excess relative risk per Gy of 7.7 (95% confidence interval [CI], 2.1–28.7) and an excess absolute risk (per 100 000) of 4.4 (95% CI, 1.9–10.1); however, the risk of thyroid cancer did not increase with increased age at exposure. In more recent studies, the incidence of thyroid cancer among children (aged 0–14 years) increased remarkably after the Chernobyl disaster in 1986 in the Ukraine and Belarus [10, 11]. Unlike childhood exposure, the evidence linking exposure to ionizing radiation in adult life and thyroid cancer is conflicting [9–11].

Areas that have not been affected by the nuclear fallout such as French Polynesia, Hawaii, Iceland, New Caledonia, and the Philippines have the highest rates of thyroid cancer in the world. These regions are characterized by the presence of numerous volcanos [12, 13] and conjectures have been made that some factors in these volcanic areas may act as endocrine disruptors and carcinogens. However, how the volcanic environment may affect the carcinogenesis process in the thyroid is unknown [13].

Although exposure to radiation (i.e., a possible 'Chernobyl effect') is unlikely to account for the increase in the incidence of thyroid cancer observed in the Central and South American region, this cannot be completely disregarded. Populations are increasingly being exposed to diverse sources of radiation from medical diagnostics or treatment for benign or malignant conditions, and the responses of radiosensitive organs such as the thyroid may differ, particularly when the exposures occur at different ages (childhood vs adulthood) [14]. Furthermore, the potential for work-related exposure to radiation is real in Argentina, Brazil, and Mexico where nuclear power plant programmes have been in existence since the 1990s [15]; monitoring the thyroid cancer trends in the regions where the nuclear plants are located could provide interesting results.

## Iodine intake

Iodine intake is essential for the function of the thyroid and iodine deficiencies or excesses have been related to thyroid cancer, although not consistently [16]. Positive correlations between endemic areas for goitre, an abnormal enlargement of the thyroid gland caused by iodine deficiency, and thyroid cancer have been reported in England, Sweden, and Wales but no such association was found in the USA [17]. In contrast, regions where the intake of iodine is high, such as Hawaii and Iceland, have a high incidence of thyroid cancer, although exposure to volcanic activity could also explain the observed rates [17].

Iodine intake may influence the distribution of thyroid cancer by histological subtypes [18]; follicular carcinoma is found more frequently in iodine-deficient areas whereas papillary carcinoma is more common in areas receiving iodine prophylaxis [8, 17–20]. Woodruff et al. [21] reported a modest increase in the frequency of papillary carcinomas in Nigeria when comparing the prevalence in 1980–89 (27.3%) with that in 1990–2004 (35.7%) and speculated that such an increase was related to the introduction of an iodization programme in 1993. In Denmark, Blomberg et al. [19] found that the incidence rates of thyroid cancer among women before iodine supplementation increased by 0.6% per year in 1943–60 and by 2.8% per year in 1981–2000; after iodine supplementation (2001–08), the rates rose by 4.0% per year ( $P < 0.001$ ). The same patterns were also observed among men. The striking increase in incidence was primarily due to a rise in papillary carcinoma, while the incidence of follicular and medullary carcinomas remained relatively stable and the rate of anaplastic carcinoma decreased. Worthy of note, the sharp increase in papillary carcinoma was observed before the initiation of iodine supplementation, suggesting that it cannot completely explain the increase in thyroid carcinoma in Denmark.

In Central and South America, iodine deficiency has been considered to be a public health problem since the early 1900s. Goitre was endemic in the region with a prevalence of 50% or higher, particularly in Bolivia, Brazil, Ecuador, Guatemala, Mexico, Paraguay, and Peru. Although most countries in the region implemented iodized salt programmes between the 1940s and 1960s, the prevalence of goitre in several countries remained high and almost unchanged (1980–90). Thus, despite all countries in the region reinforcing legislation to fulfil this universal goal, it remained a problem up until the last WHO report in 1999 [22].

Harach et al. [23] conducted a study in the province of Salta, Argentina, that has a population with iodine deficiency to investigate the relationship between changing concentrations of potassium iodide during two separate periods of iodine prophylaxis (with 40 mg/kg potassium iodide in 1962–63 and 33.3 mg/kg potassium iodide in 1970) and the incidence of anaplastic (undifferentiated) thyroid carcinoma. The incidence rates (per 100 000 person–years) of anaplastic carcinoma steadily decreased during this period; the incidence was 0.14 in 1960 (before prophylaxis) and 0.01 in 2010 (after prophylaxis) ( $P < 0.06$ ). The authors suggested that the decreased rate of anaplastic thyroid carcinoma could be explained by the establishment of primary health care centres in the area and the use of fine needle-aspiration cytology, which could have led to the early detection of papillary or follicular thyroid carcinoma. Therefore, iodine prophylaxis may not be the only reason for the observed decrease in the incidence of anaplastic disease.

## Hormones

The thyroid gland is composed mainly of follicular cells that contain thyroglobulin, a receptor protein for iodine, and the synthesis of thyroid hormones depends on the availability of iodine and thyroglobulin [24]. Thyroid-stimulating hormone (TSH) is the major growth factor for thyroid cells and is involved in the regulation of thyroid hormones (thyroxine and triiodothyronine), the maintenance of thyroid-specific gene expression, and glandular growth [8, 25]. TSH levels are particularly high during puberty and pregnancy [8, 18, 26] and iodine deficiency can also increase the levels of TSH [18].

Some evidence has suggested that patients with nodular thyroid disease have a high concentration of TSH and therefore might have an increased risk of thyroid carcinoma, although the results are contradictory [1, 27]. Fiore and Vitti [28] conducted a systematic literature review of 22 cross-sectional studies and found that the risk of thyroid cancer increased with increased serum TSH in patients with nodular thyroid disease and that higher TSH levels were related to a higher frequency and more advanced stage of thyroid cancer. The controls used for the comparisons were patients with thyroid nodular disease or patients undergoing surgical treatment for suspected thyroid cancer. The interpretation of the results from this meta-analysis is problematic because of the cross-sectional nature of the studies included which creates ambiguity in the temporal order of TSH levels and thyroid cancer. Furthermore, some thyroid nodules can produce high levels of thyroid hormone and consequently induce low levels of TSH. In contrast, in a nested case–control study, Rinaldi et al. [24] found that patients with high pre-

diagnostic blood TSH levels had a lower risk of thyroid cancer than those with low pre-diagnostic blood TSH levels (odds ratio [OR], 0.55; 95% CI, 0.37–0.80).

Patients with differentiated thyroid carcinoma may produce or release excessive amounts thyroglobulin into the blood stream [29], while patients with anaplastic thyroid cancers lack thyroglobulin expression [1]. Rinaldi et al. [24] found that patients with high pre-diagnostic blood levels of thyroglobulin had almost 9 times the risk of thyroid cancer than those with low pre-diagnostic blood levels (OR, 8.79; 95% CI, 5.04–15.30). They also reported a positive association between high thyroglobulin levels and the risk of papillary and follicular thyroid carcinomas (OR, 2.1; 95% CI, 1.74–2.54 high vs low for papillary; OR, 4.45; 95% CI, 2.31–8.56 high vs low for follicular).

Sex hormones have been suggested to be responsible for the worldwide increase in the incidence of thyroid cancer among women, particularly during the reproductive years [30, 31]. However, the relationship between sex hormones and thyroid cancer remains unclear. Polymorphisms in estrogen receptors, which mediate the effects of estrogen, have been postulated to be associated with an increased risk of thyroid cancer [31]. However, the results from a pooled analysis of 14 case–control studies revealed weak to null associations between female thyroid cancer and age at menarche, age at menopause, the number of births (compared to nulliparous), the number of miscarriages, or a history of infertility [26]. In a recent case–control study, Schonfeld et al. [30] failed to show an association between 1151 tag single nucleotide polymorphisms involved in sex hormone synthesis and metabolism, gonadotropins, and prolactin (58 genes) and the risk of developing papillary thyroid cancer.

## Other factors

### *Familial predisposition*

Most papillary and follicular thyroid carcinomas are sporadic, although familial tumours may account for 5% of all thyroid tumours [1, 32, 33]. Approximately 25% of all medullary thyroid carcinomas have a familial component and may occur in isolation or as a part of multiple endocrine neoplasia type II syndromes [1, 33]. Autosomal dominant genes involved in Gardner's syndrome, Cowen disease, and Carney complex, and autosomal recessive genes involved in Werner syndrome have been associated with non-medullary thyroid carcinoma [1, 34]. The risk of developing familial non-medullary thyroid carcinoma among first-degree relatives is 5–10 times higher than that of the general population [34]; for instance, in Gardner's syndrome (familial adenomatous polyposis), papillary thyroid carcinoma appears 10 times more frequently than sporadic papillary thyroid carcinoma [33]. Papillary and follicular thyroid carcinomas may also occur in Carney complex [33]. Point mutations of the RET proto-oncogene have been associated with multiple endocrine neoplasia syndromes (types IIA and IIB) and familial medullary thyroid carcinoma [1, 8, 32, 35, 36]. Among adults, approximately 2.6–34% of papillary thyroid carcinoma (PTC) cases have RET rearrangements (mainly RET/PTC1, RET/PTC2, and RET/PTC3), while about 80% of the paediatric cancer cases have these rearrangements (specifically RET/PTC1 and RET/PTC3) [36]. Although some

evidence suggests a familial predisposition for papillary and follicular thyroid carcinomas, this possibility should be given careful consideration because familial associations do not necessarily differentiate between inherited susceptibility caused by a single gene and the concurrence of multiple weak susceptibility genes [33].

### *Excess body mass index*

Increased body mass index (BMI) has been associated with several malignancies, including thyroid cancer, and such relationships may differ by sex and between populations [37–41]. Several mechanisms have been suggested to explain this association, such as increased hormone levels (steroid hormones, adipokines, estrogens, insulin, and insulin-like growth factor-1), oxidative stress, the nuclear factor  $\kappa$ B system, and an increased number of thyroid cells among those with a high BMI [42].

Maso et al. [39] conducted a pooled analysis of 12 case–control studies from China, Greece, Italy, Japan, Norway, Switzerland, Sweden, and the USA and found that women with a high BMI at the time of cancer diagnosis had a 20% higher risk of thyroid cancer than women with a low BMI (OR, 1.2; 95% CI, 1.0–1.4 for highest vs lowest tertile). Consistent findings were reported by Kitahara et al. [37] and by Renehan et al. [41]; for every 5-kg/m<sup>2</sup> increase in BMI, the risk of thyroid carcinoma among women increased by 14–16% (hazard ratio, 1.14; 95% CI, 1.06–1.23 [37]; hazard ratio, 1.16; 95% CI, 1.08–1.24 [41]).

In a meta-analysis of seven cohort studies from Austria, the Republic of Korea, Norway, Sweden, and the USA, Zhao et al. [42] reported that the risk of thyroid cancer was higher among people who were overweight and obese at baseline compared with those with a normal weight (pooled rate ratio [RR], 1.13; 95% CI, 1.04–1.22 for overweight; pooled RR, 1.29; 95% CI, 1.18–1.41 for obesity). They also found that the risk of thyroid cancer was 18% higher among those with excess weight (combining overweight and obese) compared with a normal weight (overall RR, 1.18; 95% CI, 1.11–1.25). Similar increases were also observed by sex (RR, 1.27; 95% CI, 1.14–1.41 for men; RR, 1.14; 95% CI, 1.06–1.23 for women) and by ethnic group (RR, 1.30; 95% CI, 1.13–1.49 for Asians; RR, 1.15; 95% CI, 1.08–1.24 for non-Asians).

In Latin America (including the Caribbean), 22% and 11% of the thyroid cancer cases estimated to occur in men and women, respectively, in 2012 were attributed to a high BMI (> 25 kg/m<sup>2</sup>) [43]. This is particularly important in the developing world where the prevalence of overweight and obesity has steadily increased since 1980, particularly among women [44]. Data from the early 1990s revealed that the prevalence of overweight/obesity in Central and South America ranged between 9.9% and 35.7%, with the highest prevalence reported among women and people living in urban areas [45]. In 2013, the prevalence of overweight/obesity in Central and South America ranged from 20% to 40% among women (aged  $\geq$  20 years) and from 5% to 30% among men (aged  $\geq$  20 years), with the highest estimates observed in adults in Chile, Mexico, Nicaragua, and Paraguay [44].

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