Thyroid Cancer: State of Art of in Morocco

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Thyroid Cancer: State of Art

Introduction

Thyroid cancer is the most frequent endocrine malignancy, and its worldwide increase incidence has been recently reported. However, both the cause of this alarming increase and its impact on the public health remain to be determined. In this review, we propose a brief update of thyroid cancer and its relevant risk factors in the light of new published data in the field. We also summarise data concerning the thyroid cancer in Morocco as well as its incidence. Finally, we propose some recommendations for a better management of thyroid cancer in Morocco.

Keywords: Thyroid cancer; Risk factors; Incidence in Morocco

Abstract

Thyroid cancer is the most frequent endocrine malignancy, and its worldwide increase incidence has been recently reported. However, both the cause of this alarming increase and its impact on the public health remain to be determined. In this review, we propose a brief update of thyroid cancer and its relevant risk factors in the light of new published data in the field. We also summarise data concerning the thyroid cancer in Morocco as well as its incidence. Finally, we propose some recommendations for a better management of thyroid cancer in Morocco.

Risk factors for Thyroid Cancer

Thyroid gland is sensitive to ionizing radiation (IR) and radiation exposure is the only well-established risk factor for this disease (for review see [4,8]). However, the molecular mechanisms of radio-carcinogenesis remain to be determined. It has been observed an increase in thyroid cancer incidence after Chernobyl accident and atomic bomb explosion due to radioactive reject of 131I and the capacity of human thyroid to concentrate this radionuclide depends on the expression of NIS in the thyrocytes. Histological, molecular and epidemiological studies reveals that PTC is predominantly the radio-induced type of thyroid cancer associated with higher occurrence of oncogenic chromosomal rearrangements RET/PTC, RET/PTC results from the fusion of a portion of ret proto-oncogene to an active promoter of another gene that drives expression of chimeric protein, a constitutive activation of the MAPK signalling pathway and thyroid tumorigenesis [4,8]. Medical radiation exposure is also a risk factor for thyroid cancer [8,9]. Indeed, 50% of cancer patients undergo radiation therapy and 5-10% of them develop several years later a secondary cancer including thyroid cancer [9]. Thyroid cancer incidence is higher when radiation exposure occurs at young age [4,8,9], highlighting the role of both cellular proliferation and DNA replication in the accumulation of genetic instability, and in thyrocytes transformation.

Recently, growing data support the role of both replication and oxidative stress in thyroid carcinogenesis [3,10-13], but the origin of these two potent mitogenic/mutagenic factors and the nature of activated downstream pathways remain to be determined. In thyroid gland, oxidative stress can be produced either by infiltrating immune cells or by thyrocyte sources of reactive oxygen species (ROS); and chronic inflammation might be a precancerous condition to favour...
thyroid transformation [14-16]. A high prevalence of thyroid nodules and thyroid cancers has been reported in Grave's disease patients, and a thyroid nodule diagnosed in Graves' patients is at higher risk for malignancy, as compared to euthyroid patients [17]. Interestingly, detection of oncogenic chromosomal rearrangement RET/PTC is reported in Hashimoto’s thyroiditis [16]. Finally, exposure of human thyrocyte to non toxic dose of extracellular H2O2 can mimic the effect of radiation exposure, induces DNA damage, and generates oncogenic chromosomal rearrangement RET/PTC [10,11]. Ret and CCDC6 involved in the formation of the most frequent form of RET/PTC are localized to the unstable genomic regions that break under replication stress (chromosomal fragile sites). In fact, treatment of human thyrocytes with agents able to compromise DNA replication dynamic can induce RET rearrangement through the expression of specific fragile sites [13]. All these data suggest that inflammatory context, as well as oxidative stress and replication stress, can explain the occurrence of some genomic instability detected in sporadic thyroid tumors without radiation exposure history.

Environmental conditions (e.g. iodide and selenium deficiency) can cause thyroid disorders; and the iodide contribution will be discussed in the next chapter.

Thyroid Cancer: State of Art in Morocco

Data collected from regional cancer registries in Morocco indicates that thyroid cancer is more frequent in women [18,19]. This finding is consistent with the fact that worldwide thyroid cancer is 2 to 3 times more common in women than in men according to the international epidemiological studies [20]. Understanding the predominant susceptibility of women to develop thyroid disease remains an enigma, even if sexual hormones appear to favor thyroid disorders with mechanisms not fully understood [21-24]. According to the Casablanca registry (2005-2007) and Rabat Cancer Registry (2006-2008), thyroid malignancies are classified respectively in the third (6.7 per 100 000 persons) and in the fifth range (3.9 per 100 000 persons) [18,19]. This result suggests that thyroid cancer is one of the most frequent female cancers in these two regions of Morocco. Thyroid cancer incidence is increasing worldwide at an alarming rate [20]; and by 2019, papillary thyroid cancer will double in incidence and become the third most common cancer in women in the United States of America [25]. Thereby, thyroid cancer is increasingly a major public health issue, particularly for women.

Iodide deficiency is a major public health problem in Morocco especially in the area of endemic goiter (Mountainous regions). Brain damage and irreversible mental retardation are the most Iodide Deficiency Disorders (IDD) in children [26]. Salt iodization is the proven effective strategy to mitigate iodide deficiency in the endemic area, and since a decree published in 1995, iodination of the salt intended for human consumption has become obligatory in Morocco [27]. Interestingly, introduction of iodized salt at recommended levels normalized iodide status and improved thyroid function in severely iodide-deficient children without provoking thyroid disorder [28]. Any correlating data between iodide deficiency and thyroid cancer incidence has been done in Morocco, and this point is under investigation in our group.

Iodide, the limiting substrate for thyroid hormone synthesis [1], could be a risk factor for thyroid pathogenesis including thyroid carcinogenesis [3,29]. The uptake and oxidation/organification of iodide are tightly regulated to avoid deleterious effect of iodide in the thyroid. When iodide exceeds the physiological level, thyrocytes may have recourse to both negative feedback and Wolff-Chaikoff mechanisms to avoid its toxicity [1]. However, in a prolonged iodide deficiency context, deficient-iodide cells may become more responsive to stimulatory effects of TSH and growth factors [30]. In iodide deficient areas, chronic stimulation by TSH causes multinodular autonomous growth, and the increased cellular proliferation might favor thyrocytes transformation. In fact, decreased intake of iodide is associated with higher frequency of follicular and anaplastic thyroid cancers [29,31]. Also, low concentration of iodide stimulates a basal H2O2 generation; and additional oxidative stress caused by iodide deficiency is suspected to be at the origin of the high rate of mutations detected in thyroid gland [3].

Medullary thyroid cancer (MTC), which originates from parafollicular or C cells is rare and represents about 3 to 5% of all thyroid cancers [4]. RET proto-onogene is frequently mutated in MTC [4], and screening of RET germline mutations in Moroccan MTC patients, reveals the presence of mutations in exon 11 (codon 634) previously reported in other countries [32,33].

Conclusions

Despite the large number of studies in thyroid cancer, the molecular mechanisms that promote both thyroid tumorigenesis and thyroid cancer resistance remain not fully understood in the world. In Morocco, establishment of detailed national cancer registry will allow a better understanding of the global incidence of thyroid cancer in this country, and will highlight which type of thyroid cancer is frequent and/or is increased. A retrospective studies, in Moroccan endemic regions, of thyroid cancer incidence and especially follicular thyroid cancer might be a relevant parameter for evaluation of a long time efficiency of iodide supplementation.

Finally, BRAFV600E hot spot mutation is often associated with high aggressiveness and dedifferentiation of thyroid tumors; and conventional metabolic radiotherapy is largely ineffective in Radioactive Iodine Refractory (RAI) patients whose tumors carried BRAF oncogene. Introduction of BRAF mutation as diagnostic and prognostic marker, will improve the management of patients with thyroid cancer in Morocco; and we are examining this possibility.

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