Thyroid tumors: are we unveiling the puzzle?

Laura Sterian Ward

Laboratory of Cancer Molecular Genetics, Faculty of Medical Sciences, University of Campinas (Unicamp), 126, Tessalia Vieira de Camargo Street, Cidade Universitaria, Campinas, Sao Paulo 13083-887, Brazil

A steady and continuous upward trend in thyroid tumor diagnoses has been documented in most parts of the world, as population has been living longer and diagnostic technology becoming more sensitive and popular (Ward & Graf 2008, Kilfoy et al. 2009, Li et al. 2013). The annual percent change that was 2.4% from 1980 to 1997 in the USA increased to 6.6% from 1997 to 2009 according to Cancer of The Thyroid – SEER Stat Fact Sheets (Howlader et al. 2014). Although there are solid epidemiological evidences that this increase in incidence is related to the scrutiny, there are also several reasons to believe that other factors may be involved. In addition, recent evidences have demonstrated that most of these thyroid tumors do not represent a life threat, especially the small papillary thyroid tumors that may never evolve clinically and have been the tumors most frequently detected in the last few decades (Kilfoy et al. 2009, Li et al. 2013). However, because of the epidemic proportion of thyroid tumors that have been unraveled, mostly incidentally, physicians have been facing the challenge of diagnosis and management of this condition whose cause is still unsure and, although proved mostly indolent, still carries the burden of the term cancer and all its correlated threats.

In fact, most data indicate that we have largely been overtreating a large number of individuals with differentiated thyroid, whose quality of life is certainly affected by the treatment of tumors that would probably never evolve. On the contrary, side effects and morbidity due to this unnecessary treatment have been increasingly demonstrated.

Given the scenario above, clinicians and surgeons have been facing three major problems when dealing with patients with thyroid nodules: to determine which of these patients have malignant disease; once this is determined, to distinguish those with malignant tumors that will or will not evolve more aggressively; and, finally, how to explain and avoid the noticeable increase in thyroid tumors, saving not only the patient being submitted to aggressive treatments, but also public health money. This special issue of Endocrine-Related Cancer contains five reviews that aim to help readers better understand the fascinating issue of thyroid tumors.

In this special issue, Marcello et al. (2014a) present a new appraisal on the influence of the environment on the development of thyroid tumors. The authors review the influence of eating habits, iodine, xenobiotics, including the ones inhaled by smoking, and the risk of compounds that exist in certain areas and may explain the high incidence of thyroid tumors observed in the circle of fire of the volcanoes. A very interesting topic addresses the possible influence of viruses, in particular Herpes viruses. Finally, the authors analyze the influence of our inherited genetic profile of detoxification systems and the susceptibility to thyroid tumors, raising the exciting possibility that we may, in the future, recognize individuals at risk for certain exposures, hence proposing preventive measures according to this individual genetic profile of risk.

Obesity has reached epidemic proportions in the past few years. A second article from Marcello et al. (2014b) in this special issue addresses the role of thyroid hormones, insulin resistance, adipokines, inflammation, and sexual hormones in the pathophysiology of the connection between excessive weight and thyroid tumors, bringing new evidences that these factors might be related not only to the onset of thyroid tumors but also to their progression and aggressiveness.

Among sexual hormones, estrogen is certainly connected to thyroid tumor progression and perhaps with their development. In fact, in another review of this issue, Derwahl & Nicula (2014) explore the role of estrogen in thyroid tumors, demonstrating that, besides being a potent growth factor for both benign and malignant...
thyroid cells, estrogen exerts its growth-promoting effect via a membrane-bound link to the tyrosine kinase signaling pathways MAPK and PI3K. In addition, the fact that estrogen is involved in the regulation of angiogenesis and metastasis may explain the differences observed in the clinical evolution between genders (Jonklaas et al. 2012). It is important to notice that estrogen may also be an important stimulator of stem and progenitor cells (Derwahl & Nicula 2014). These cells may be responsible for a subset of thyroid tumors, which are resistant to chemo and radiation therapies. Lloyd et al. review the cancer stem cell model for thyroid cancers (Guo et al. 2014). This model suggests that a small number of cells within a cancer, known as cancer stem-like cells (CSCs), are responsible for tumor initiation, growth, resistance to chemotherapy, and radiation therapy, as well as for recurrent and metastatic disease. The processes of epithelial-to-mesenchymal transition (EMT), and mesenchymal-to-epithelial transition (MET) provide plasticity to CSC growth, leading to tumor progression. In addition, authors suggest that there is a role for microRNAs in CSC development and regulation. Several microRNAs regulate EMT and MET by targeting genes that control epithelial or mesenchymal characteristics. The miR200 family, for instance, regulates the EMT induced by EGF/EGFR or by targeting TGFβR1, some of the long-known proteins for their importance in thyroid cancers (Guo et al. 2014).

MicroRNAs are also considered as potential markers of diagnosis in the review by Hsiao & Nikiforov on the molecular approaches to thyroid tumor diagnosis. In addition, some of the molecular markers presented have been long studied, such as RAS, RET, PPARG/PAX8, PIK3CA, TP53, TSHR, PTEN, GNAS, CTNNB1, AKT1, whereas others have recently emerged as possible markers, such as genetic alterations in NTRK, TERT, and the fusion of the striatin (STRN) gene and anaplastic lymphoma kinase (ALK) gene. The authors point to a series of molecular markers that may define a molecular signature, not only helping clarify the diagnosis of malignancy, but also defining the potential of aggressiveness of each tumor (Hsiao & Nikiforov 2014).

Altogether, these five reviews bring important points to be considered in the understanding and managing of thyroid tumors and will, hopefully, stimulate our readers to persist in the quest of finding the still missing pieces in this puzzle called thyroid cancer.

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