DOI: 10.15386/cjmed-518

INVESTIGATION OF THYROID NODULES IN THE FEMALE POPULATION IN CYPRUS AND IN ROMANIA

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Abstract

Background and aims. *The most common thyroid disorders, with an increasing detection worldwide, are the thyroid nodules and thyroiditis, which leads to an increase of thyroid cancer incidence . In two different countries with a different exposure to risk factors for thyroid cancer, such as Cyprus and Romania, the rank of thyroid cancer among other neoplasms is very different: the 3rd most prevalent cancer among females in Cyprus and the 12th in Romania, respectively. Environmental chemicals, such as bisphenol A have a proven effect on the thyroid function. However, the relation between the exposure to the endocrine disruptor and the development of thyroid nodules, with a potential of malignant transformation has not been previously studied. The aim of the study was to investigate the potential factors that lead to the difference of thyroid nodules incidence in the mentioned countries.*

Methods. *A pilot case-control study has been conducted in 2014-2015 in the "Prof. Dr. Ion Chiricuță" Institute of Oncology, Cluj-Napoca, Romania and the Endocrinology Department of Archbishop Makarios III Hospital, Nicosia, Cyprus. Females older than 20 years with no medical history were recruited. Cases were women with ultrasound-confirmed thyroid nodules of size >3mm. Controls were women without thyroid nodules after ultrasound confirmation. All participants provided blood samples for measurements of the thyroid stimulating hormone (TSH), free thyroxin (FT4), anti- thyroglobulin (ATg) and anti-thyroid peroxidase (ATPO); urine samples. Demographics, anthropometrics and other relevant information were provided through the administration of a questionnaire.*

Results. *In Romania we selected 51 patients with thyroid nodules (case group) and 41 without thyroid nodules (control group) and in Cyprus 57 cases, respectively 65 controls. After the statistical analysis of the data collected we observed statistically*

significant differences between the populations of the two countries regarding BMI and the value of the thyroid hormones and antibodies.

Conclusions. *Using the data observed in this study, differences were found between Cyprus and Romania among females with thyroid nodules the BMI, and the level of thyroid hormones had statistically significant differences. This study reports preliminary data, further analysis of environmental exposures to chemical factors that might have a certain influence over the thyroid in the two countries will follow.*

Keywords: thyroid nodules, thyroiditis, thyroid cancer, Bisphenol A, environmental exposure

Background and aims

Thyroid disorders such as thyroid nodules and thyroiditis have registered an increasing incidence since the Chernobyl nuclear fallout in 1986, mainly in the Central, Northern and Eastern Europe. Both pathologies are susceptible of causing thyroid cancer [1–6]. Between 1970 and 2014 in the "Prof. Dr. Ion Chiricuță" Institute of Oncology, Cluj-Napoca (IOCN) the incidence of thyroid cancer increased constantly, 5-10 times in the last decade, 657 new cases being registered in 2014 [2]. According to the International Agency for Research on Cancer (IARC), in 2012 thyroid cancer was a very frequent malignant pathology in Cyprus, being the 3rd most frequent cancer in the female population, whereas in Romania, despite the dramatic increase of the number of new cases per year, it was only on the 12th position [7]. The important increase of the incidence of thyroid cancer both in Romania and Cyprus justifies the numerous epidemiological studies on this pathology [8–10].

The thyroid nodules are frequently identified in the general population, the majority of them being asymptomatic; they occur in more than 50% of the adult females in menopause [11]. Fortunately, most of the thyroid nodules identified by ultrasound are benign at the fine needle examination (FNA) and only very few represent a thyroid carcinoma. Thus, thyroid cancer is a rare cancer with an incidence of less than 6 cases for 100,000 inhabitants [12], but still considered the most frequent endocrine tumor. Thyroid cancer can be classified, regarding the histology in: differentiated thyroid carcinoma (DTC), medullary thyroid carcinoma and anaplastic thyroid carcinoma. The most frequent type of thyroid cancer, representing more than 85% is the DTC, are also divided into two major forms: papillary and follicular thyroid cancers [13,14].

Among the causes of appearance of the thyroid nodules and their transformation in thyroid cancer one can include the ionizing radiations, which are the most important factors that determine the metaplasia of the thyroid tissue [15]. Another cause is represented by the environmental factors, such as the iodine deficiency in food and water, or the radiation in the soil, leading to the appearance of the endemic goiter, determining a thyroid stimulating hormone (TSH) excessive stimulation of the thyroid growth [16]. Also, regarding the immunological factors, a relation between the development of thyroiditis, such as the Hashimoto disease and the thyroid nodules or even thyroid cancer is being cited [17–19]. Last but not least, the genetic mutations, such as the BRAF [20,21], RAS [21,22] genes or RET/PTC proto-oncogene [23] are susceptible of determining different forms of thyroid cancer.

For the diagnosis of the thyroid nodules the clinical examination, represented by the palpation of the cervical region and the thyroid ultrasound performed in the Doppler mode are the first intention procedures and they are sufficient for a positive and quantitative diagnosis [11,24] (Figure 1). For a further diagnosis of the nature and histology of the nodule a fine needle aspiration (FNA), as well as the determination of the thyroid hormones, TSH and FT4 are needed [11,25].

The difference observed between Cyprus and Romania regarding the incidence of the thyroid cancer led to a bilateral research cooperation between the two countries that would explain the convergent numbers in the two population and could prevent its appearance and help implement a screening, an early stage detection and treatment.

Methods

A case-control study was conducted between July 2014 and May 2015 in the IOCN, Romania and the Endocrinology Department of Archbishop Makarios III Hospital in Nicosia, Cyprus. For this current study both centers in which the patients were recruited obtained an approval from medical ethical commission, of the IOCN and of the Cyprus Bioethics Committee respectively. Thus,

Manuscript received: 29.07.2015
Accepted: 14.08.2015
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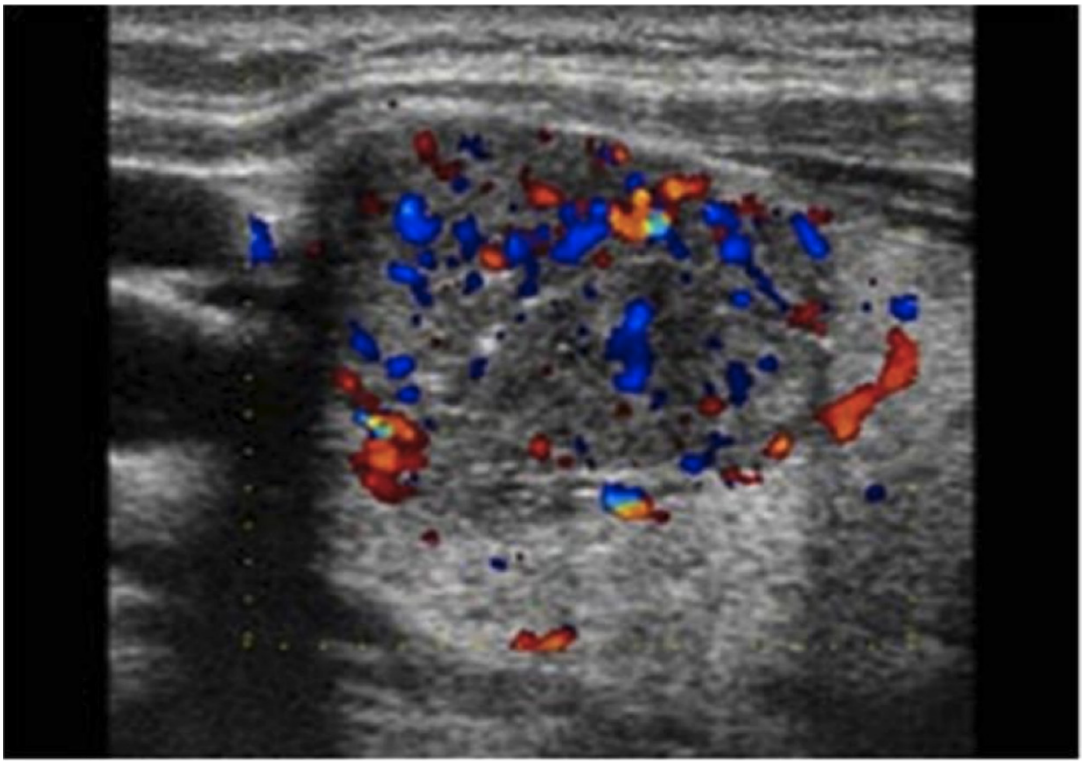

Figure 1. Ultrasound image of a malignant thyroid nodule, showing a hyper-vascularized thyroid nodule, with intranodular vascularization.

this study included only females older than 20 years with no other known medical history. The females that have been recruited to the study were divided into two groups according to the existence or not of the thyroid nodules detected by ultrasound. Therefore, from both sides of the study included females with thyroid nodules >3mm identified while performing the ultrasound (case group) and controls, females with no thyroid nodules determined (control group).

After signing the informed consent of participating in the study, for all the females accepted in the study, in both centers, the investigators performed clinical, biological and imaging investigations. For all the females in the study, the following were recorded: age, weight, height, body mass index (BMI), expressed in kg/m^2, geographic location, education and profession.

Regarding the serological determinations we collected blood samples of the TSH (N.V.-0.27-4.20 mIU/L), of FT4 (N.V.- 10.6-22.7 pmol/L) of the ATg (N.V<115 UI/mL) and ATPO (N.V<34 IU/mL). All analyses were performed in the same accredited (ISO 15189) laboratory, using electrochemiluminescence detection method (ECLIA) and Cobas instruments (Roche Diagnostics, Basel, Switzerland). In Cyprus the analysis of the hormone levels and antibodies took place routinely at the laboratories of the Nicosia General Hospital.

A thyroid ultrasound was performed for all the patients investigated. The existence of the thyroid nodules was noted, the number of the nodules identified, if any, their minimum and the maximum size, expressed in millimeters (mm), the lateralization in the thyroid lobes. The thyroid ultrasounds in Romania were done on Siemens Acuson X300 system.

Additionally, all the participants were asked to collect urine samples, which were deposited in Deltalab bisphenol A (BPA) free 10ml vials at -80 degrees Celsius in the refrigerator in order to be able to determine the amount of toxic exposure to BPA, in the next step of our study.

Apart the data collected from the patients, the females included in the study were asked to fill in a standardized questionnaire for both countries regarding the exposure to toxic, such as smoking status, drinking habits, exposure to cosmetics, canned food, detergents and mostly the water sources used, especially those of polycarbonate, with a high amount of BPA.

For the collection of the data, the EpiData program was used in order to introduce the information from the blood and urine samples, the thyroid ultrasound and the questionnaires applied. For the statistical results, MediCalc was used.

Results

At the end of the period of investigation the Romanian team managed to provide 51 cases and 41 controls, while the Cypriot research team collected 57 cases and 65 controls. After digitization of the data collected from all the females included from both the Romanian and Cypriot cases and controls, the database of the study was

created and analyzed.

The mean age±SD of the Romanian cases was 49.74±12.08 and of 53±12 for the Cypriot cases. The mean ±SD BMI between the two population's cases was determined with a difference of statistical significance of p=0.0126 being 28.8±6.9 for the Romanian cases and of 25.9±4.9 for the Cypriot cases. A predominance of non-smokers was observed in all populations, with a percentage of more than 50% of the cases investigated, 68% (35/51) in Romania, respectively 75.4% (43/57) in Cyprus.

Regarding the parameters investigated, the antibodies were positive in the Romanian cases in 23.4% (11/47) of the situations and in Cypriot cases in 7.4% (2/27). In the Romanian population investigated there was a statistically significant difference of the mean+/-SD value of the TSH between the cases and the controls recruited, 1.75±1.57 and 2.58±1.72 respectively, with a p=0.0019 (Figure 2). Meanwhile, the mean±SD value of the FT4 was statistically different with a p=0.0001 between the Romanian cases (14.5±2.36) and the Cypriot cases (12.69±2.22). In our study we observed a correlation between the higher level of FT4 and the higher probability to discovered by ultrasound one or multiple thyroid nodules (Figure 3).

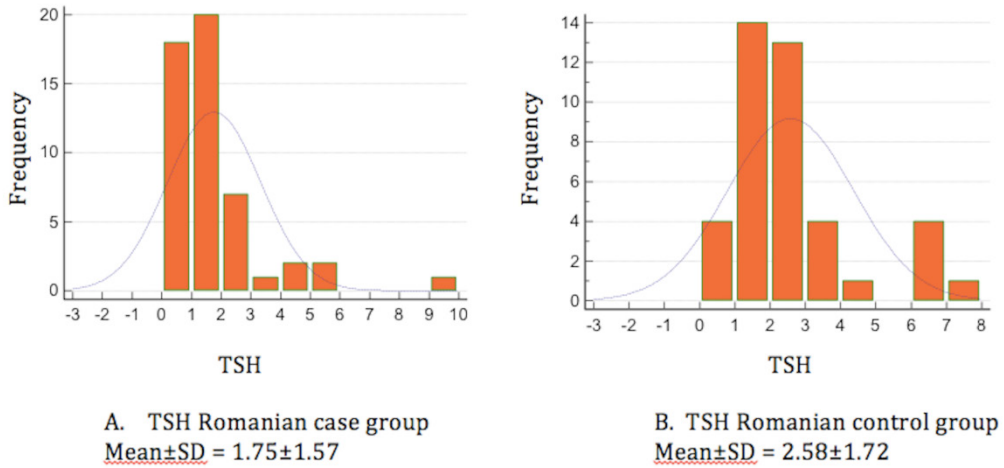

Figure 2. Difference between the mean+/-SD value of the TSH in the Romanian case group, A (1.75±1.57) and the mean+/- SD value of the TSH in Romanian control group, B (2.58±1.72), p=0.0019.

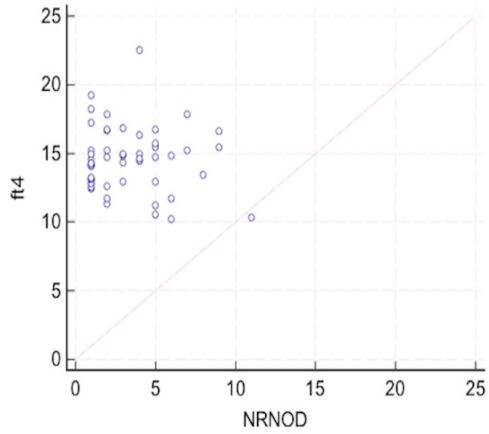

Figure 3. Correlation between the value of the FT4 level and the probability of causing thyroid nodules.

In both case populations, most of the thyroids showed multiple nodules that were localized in both lobes of the gland, in 64.7% (33/51) in Romania and 80% (20/25) in Cyprus. Data on the size and number of thyroid nodules were available for all the Romanian cases but only for approximately 50% of the Cypriot cases. The mean±SD minimum size of the nodule was higher in the Romanian cases compared to the Cypriot cases, 9.46±5.68 versus 4±4.53, with a p=0.0002. The results observed after investigating the thyroid nodules in the cases from Romania and Cyprus determined a difference with a statistical significance (p=0.021) between the mean+/-SD size of the nodules identified in the two populations, 3.37±2.53 respectively, 2.3±2.22. Meanwhile, regarding the maximum mean+/-SD size of the nodules determined, it was higher in the Cypriot cases compared to the Romanian cases, with a p<0.0001, 27±4.2 versus 17.29±6.75.

Discussion

The difference of thyroid cancer incidence between the female population in Cyprus and in Romania reported by IARC in 2012 represents the main justification for the studies performed on the thyroid cancer and any other thyroid pathologies, such as thyroiditis or thyroid nodules [7].

It is known that thyroid cancer is caused by environmental, immunological and genetic factors [15-23], valid for both populations. This fact led the researchers to the idea that some of the three determinants may vary in the two sites, and most plausible was the supposition that some environmental factors or some habits could be different in Romania and in Cyprus and could influence more or less the appearance of the disease.

It is known that the exposure to ionizing radiation is one of the determinants of thyroid disease, mainly thyroid cancer, and the most important accidental event was the nuclear fallout in Chernobyl in 1986. The data regarding the distribution of the radioactive clouds is available and provided by the International Atomic Energy Agency (IAEA). Thus, it is known that Romania was touched by the atomic clouds in the north-western part and in the south-eastern part, but Cyprus has no data regarding any relation to the atomic event [26]. In the light of these data, we expect to have a higher incidence of thyroid nodules and thyroid cancers in Romania, not in Cyprus.

Low iodine in the food and water are considered causes of the thyroid disease [16], mainly in correlation with the chronic TSH stimulation in case of iodine deficiency. Romania is subject of a legislation of compulsory commercialization of only iodinated salt since 2002, whereas Cyprus has no such law, to our knowledge. Thus, the iodine deficiency might have a major impact on the higher incidence of thyroid cancer in Cyprus; unfortunately there are no national available data on the general population iodine levels, so a direct causality is difficult to establish. Furthermore, Cyprus is an island in the Mediterranean sea, with a specific diet rich in fish; in this conditions, the probability of iodine deficiency is almost excluded.

This study presents some initial results of the ongoing project and therefore the presented information cannot be generalized. Facing such differences in thyroid disease incidence in the two countries, the study remains open to further research and correlations between the existence of any other environmental factors, such as the endocrine disruptors, among which BPA and the appearance of the thyroid nodules and the thyroid cancer.

Conclusions

Relying on the observations made on the results of the study, as conclusion we can state that the Romanian female population suffering from nodular thyroid disease has a higher mean body mass index compared to the Cypriot female correspondents. The thyroid function investigated by the levels of thyroid hormones was lower in the Cypriot females with thyroid nodules compared to the thyroid function of the Romanian females with thyroid nodules. It was observed that in more than 50% of the cases investigates, both in Cyprus and in Romania, the patients presented more than one thyroid nodule and they were located in both lobes, a fact that bears a very important correlation with the incidence of the multifocal thyroid cancer.

Acknowledgements

The current study was conducted as a bilateral cooperation research grant between Romania and Cyprus, THYROCHEM, PN-II-CT-RO-CY-2013-1 through the contract number: 761/05.03.2014 and Cyprus Research Promotion Foundation BilateralCY-RO 0713/18.

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