Distribution of histopathological types of thyroid tumors in 1999-2015 compared to 1966-1988 year period

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SUMMARY

Background: *The most common thyroid tumors originate from the epithelial follicular cells. Etiology involved in the development of thyroid carcinoma is multifactorial, including external influences and genetic predisposition.* **Aim:** *The objective of our study was to analyze the distribution of the histopathological types of thyroid carcinoma during 1999-2015 year period, to evaluate papillary and follicular thyroid carcinoma ratio and to compare thyroid carcinoma types with the data from prior epidemiological study referring to the period from 1966 -1988.* **Methods:** *A retrospective analysis was performed. The trend for thyroid carcinoma cases was evaluated in the time period of 50 years. Percentages of different histopathological types of thyroid carcinoma were presented and papillary and follicular thyroid carcinoma ratio was calculated for the two evaluated periods.* **Results:** *A total number of 422 thyroid carcinoma patients were diagnosed in the 1999-2015 year period vs. 323 patients in the period from 1966-1988. Analysis revealed no statistically significant difference in histopathological types of thyroid carcinoma during 1999-2015 year period, but statistically significant difference was detected between the two analyzed periods with a significant increase of papillary and follicular thyroid carcinoma ratio (from 3.1 to 7.3), and a significant reduction of anaplastic thyroid carcinomas cases in the more recent evaluated period (1999-2015).* **Conclusion:** *The analysis of the fifty-year-period in population of North Macedonia showed an increase in number of thyroid carcinoma cases, especially papillary and reduction of follicular thyroid carcinoma and anaplastic thyroid carcinomas cases. Further, genetic profiling studies could be useful in evaluating possible mechanisms behind this shift in histopathology of the thyroid carcinomas.*

Keywords: *Thyroid carcinomas, Histopathological change, PTC/FTC ratio, Periodicity*

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INTRODUCTION

The thyroid tumors are a heterogeneous group of neoplasms including two basic variants: tumors of epithelial and tumors of non-epithelial origin (1). The most common are tumors from the epithelial follicular cells consisting of well-differentiated (DTC), poorly differentiated (PDTC) and undifferentiated or anaplastic thyroid carcinomas (ATC). The most frequent DTCs are papillary thyroid carcinomas (PTC) accounting for around 80% of all thyroid carcinomas (TCs) (2-8), followed by the follicular thyroid carcinomas (FTC), representing approximately 10% of the total number of TCs (9-11); PDTC class was included in the classification of thyroid tumors in 2004 (12). The ATC is a rare form of TC, characterized by aggressive biology and represents only 1-2% of all TC cases (13). Non-epithelial thyroid tumors and secondary metastatic deposits in the thyroid gland are a rare occurrence of thyroidal malignancy (10, 14). Epidemiological studies worldwide have shown increase in incidence rate of TC, mostly due to increase of PTC cases, but also observed a change in the ratio between FTC and PTC cases that was related to modifications in iodine intake (16-18). Iodine deficiency was present on the territory of the Republic of North Macedonia until the year 1956 (15). The first iodine supplementation for human nutrition program was introduced in year 1956 with 10 mg KI per 1 kg of NaCl and corrected later in 1999 to 20-30 mg KIO_3 per 1 kg of NaCl (15).

We have set as an objective to analyze distribution of histopathological types of TC during a period of 17 years (1999-2015), to compare TC types and PTC/FTC ratios with the data from prior epidemiological study (for the 1966-1988 year period) and to gain insight in the fifty-year trend of TCs occurrence in our country. Since these two time periods correspond well with time before and after the implementation of new regulations regarding iodine supplementation for human consumption in our country our aim was also to determine the possible differences in distribution of histopathological types of TCs in relation to changes in iodine intake.

MATERIALS AND METHODS

A retrospective analysis was performed using medical data from TC patients diagnosed during 1999-2015 period. Since medical data were obtained from two main state centres treating thyroid disorders (University of Saints Cyril and Methodius, Faculty of Medicine, Institute of Pathophysiology and Nuclear Medicine "Akademik Isak S. Tadzer" Skopje and Nuclear Medicine Department of the "Dr. Trifun Panovski" hospital Bitola), they were representative for whole country. We also evaluated epidemiological data of the TCs previously reported for the period from 1966-1988 (19, 20). Due to missing evaluation data for TC cases in 1989-1998, statistical estimation was performed for that period. Histopathological types of TCs were registered from postoperative histopathological findings. Thyroid carcinomas were divided into five groups: papillary thyroid carcinoma (PTC), follicular (FTC) including Hurthle cell carcinoma in this group, medullary thyroid carcinoma (MTC), anaplastic (ATC) and other rare types of thyroid tumors (ORT), including non-epithelial tumors and secondary intra-thyroid deposits. We have selected two periods for comparison and analysis of distribution of the histopathological types of TCs: 1966-1988, during which iodine supplementation with 10 mg KI per 1 kg NaCl was applied and 1999-2015, when 20-30 mg KIO_3 per 1 kg NaCl was implemented (15).

Statistical analysis

The statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, IBM) Version 21.0 for Windows. The trend of

TC cases was evaluated for 50 years, with the statistical estimation of missing data for the period from 1989-1998, according to figures from previous and latest analyzed period. Data were expressed as number of patients per year, percentage and ratio. Different histopathological types of TCs were presented as percentage and PTC/FTC ratios were calculated for the periods from 1966-1988 and from 1999-2015.

RESULTS

A total number of 422 patients were diagnosed with TCs during 1999-2015, while only 323 patients were diagnosed in the period from 1966-1988 (19, 20). The number of diagnosed TC cases showed a continuous tendency of increase during 1966–2015 period (Figure 1).

Evaluation of distribution of histopathological types of TC at three time points during the period from 1999-2015 (Figure 2) revealed no statistically significant differences; Pearson's Chi-square (χ^2) test: 10.257, df=8, p=0.2475 (significant at $p<0.05$).

Distribution of histopathological types of TCs and PTC/FTC ratios were correlated for different periods i.e. 1966-1988 (19, 20) and 1999-2015. Results revealed a significant change in PTC/FTC ratio. Most evident result was the reduction in ATC cases, from 17.9% (the second most common variant in period from 1966-1988) to only 3.11% in 1999-2015 (the fourth most common variant according to frequency in detection) (Table 1 and Figure 3).

The prevalence of ATC, FTC and ORT were significantly higher in the 1966-1988 period, compared to 1999-2015 period. For the two analyzed periods PTC/FTC ratio was 3.1 *vs* 7.3 (Figure 3).

Gender analysis for 1999-2015 time period revealed increased female/male ratio of 3.5:1 (77.8% female and 22.2% male TC patients) compared to previous report from year 1982 by Karanfilski *et al.* (19) (2:1 or 66% female and 33% male TC patients).

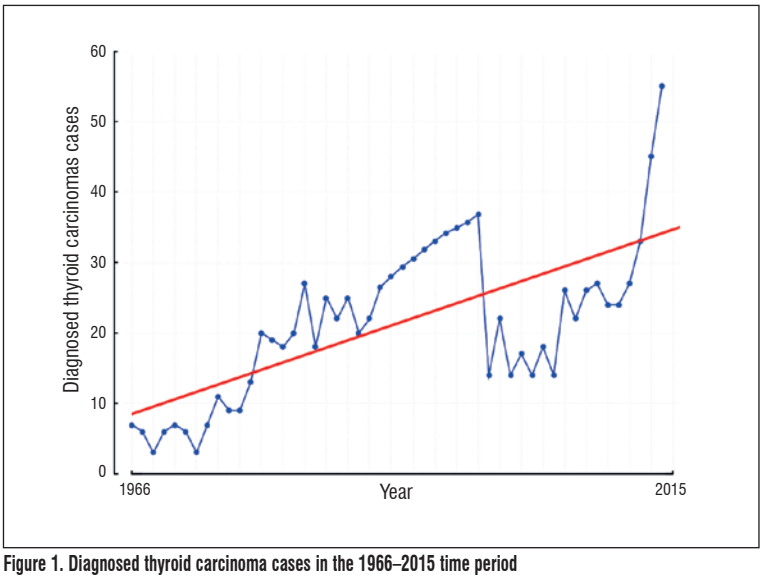

Figure 1. Diagnosed thyroid carcinoma cases in the 1966–2015 time period

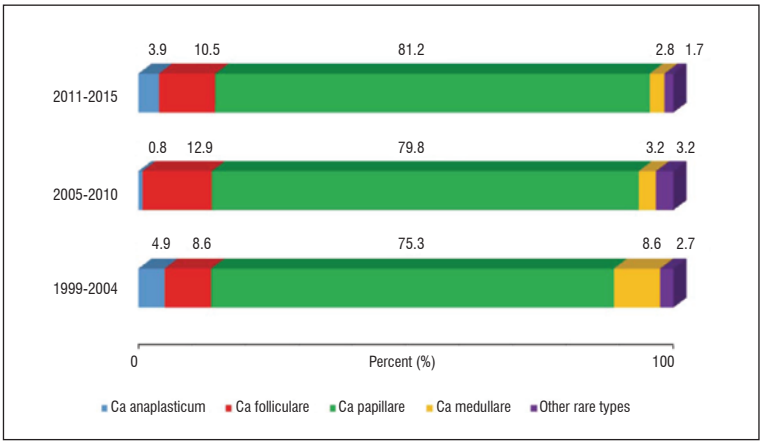

Figure 2. Histopathological types of thyroid carcinomas at three-time points during 1999-2015 time period

DISCUSSION

A total number of 422 patients were diagnosed in the period from 1999-2015 compared to 323 patients in the period from 1966-1988. A trend of continuous increase in diagnosed TC cases was confirmed during the analyzed period of fifty years in population of North Macedonia. Our observations of more frequent detection of TCs correspond with the results of number of studies done worldwide reporting on increase in incidence rate of these malignancies. Comparison of epidemiological data from different countries reveals significant, even ten fold diferences. (16-18). This can be the consequence of various factors such as differences in diagnostic practices, accessability of health care or the different etiopathogenetic factors such as level of iodine supplementation, and exposure to radiation or different mutagenic factors (21-26).

Etiology involved in the development of TC is multifactorial and includes external influences, as well as genetic predispositions (6, 14). When it comes to external influences apart from irradiation (the most common cause among children) (21-24) another external factor that is linked to the development of these malignancies is the inappropriate iodine intake (25, 26). Both excess and lack of iodine can result in changes in the TSH and can promote carcinogenesis (27, 28). Study on animals with prolonged io dine deficiency and exposure to chemical mutagens revealed a significantly higher number of developed TC cases in the exposed groups, suggesting that iodine deficiency has a role of a promoter rather than of a direct carcinogenic factor (28). The presumed mechanism involved TSH increase that stimulate epidermal growth factor (EGF) but decrease levels of transforming growth factor β1(TGFβ1), which acts like a negative factor for the thyroid cell proliferation, increases the angiogenesis and promote tumor growth (28).

When compared with previous study for the 1966-1988 period (19, 20), it was evident that there has been a change in the frequency of different histopathological types of TCs in population of North Macedonia. The data from 1966–1988 had shown that the most common were PTC cases (55.1%), the second most frequent were ATC cases (17.9%), the third FTC (17.5) and MTC with only 2.2% (19, 20). In the more recent period (from 1999-2015) PTC was the most frequently diagnosed type (79.53%), followed by FTC (10.88%), MTC (4.15%), and ATC (3.11%). Lowest percentage was noted for the ORT (intra-thyroidal lymphoma, sarcoma, metastatic tumors and the poorly differentiated insular type of carcinoma) covering only 2.33% of all TC cases.

We have detected a significant change in the percentage of the histopathological types, with significantly lower number of cases of aggressive ATC and FTC variants. However, increase of PTC and MTC cases was detected. Change of the ratio of different histopathological types has

been described in other regions previously known as iodine deficient and it was stipulated that this was due to implementations of iodine supplementation projects (26, 27). Zimmermann and Galetti (27) performed a detailed analysis regarding the possible influence of iodine sufficiency and deficiency as possible etiopathogenetic factors of the TC incidence (27). It was initially expected that iodine deficiency, through the adaptive mechanism of the TSH, would promote a proliferative effect thus influencing the appearance of TC. However, the data from the population studies revealed the opposite – the average TSH values in populations from iodine deficient regions were lower compared to iodine sufficient regions. But, this can also be due to the fact that iodine deficient regions are often characterized by the common occurrence of toxic adenomas (27). Several studies indicated a higher rate of FTC and ATC in populations from iodine deficit regions (16, 27, 28). Also, higher mortality rate was found in iodine deficient territories, due to more frequent development of aggressive types of TC, such as ATC and FTC (27). Studies on animals revealed that both iodine sufficiency and deficiency on their own does not act as a direct cause or carcinogenic activity. They can only act as an additional factor regarding tumorigenesis and this was especially evident in cases of iodine deficiency (27, 28). The study conducted in Switzerland, for the 1925-1941 and 1962-1973 periods, showed a significant change in the histopathological TC types with even above 40% incidence rate of FTC, 38% of ATC and only 8% of PTC during the initial period, which then turned into 33% incidence rate of PTC, 30% of FTC and 24% of ATC in the more recent period (29). Another interesting fact that was observed in this study concerned increase in female/male ratio i.e. it was 1.4 to 1.6 in regions without iodine prophlaxis, while in the regions with iodine prophylaxis, the ratio was 2.1 to 3 (29). In our study, data for female/male ratio correlate well with data obtained from regions with iodine prophylaxis showing an increase in female/male ratio from 2 to 3.5 for 1999-2015 year period. The data from the Switzerland study from 1994-2007 period when a stable intake of iodine by the population was achieved, still revealed an increase in the TC incidence rate, mainly due to the increase of PTC variety (29). On the other hand, the data gathered from iodine sufficient regions such as Island also showed increase in the incidence of TC and especially PTC type. When compared to other regions with adequate intake of iodine such as North Scotland, it was observed that PTC/FTC ratio was significantly higher in Island i.e. 6.5 compared to 3.6 in North Scotland population. High incidence of TC in Island was connected with iodine sufficiency. However, another argument which pointed that volcanic activity of the Island and naturally higher levels of radiation in the volcanic regions can surely render it as a risk factor (30). This study detected a significant difference in PTC/FTC ratio, from 3.4 to 6.5 in regions with high iodine intake in comparison with 1.6 to 3.7 PTC/FTC ratios in regions with adequate intake and from 0.19 to 1.7 in the iodine deficient regions (27). A high PTC/FTC ratio of 7.3 obtained for the more recent evaluated period (1999-2015) in our study, indicate that in this period intake of iodine in North Macedonia can be regarded as high.

In order to clarify link between evident changes in the distribution of histopathological types of TC after the implementation of iodine supplementation, several genetic research studies were conducted (31, 32). But, results from those studies are inconclusive and contradictory. In a study by Guan H et al. (33) on the territory of China in five different regions with different levels of iodine intake (three regions with normal levels of iodine intake and two with sufficiency in the drinking water) the aim was to analyze the possible connection of the iodine intake and the appearance of the BRAFV1799A mutation, in connection with PTC. The researchers concluded that the BRAFV1799A mutation was much more present in patients with PTC from iodine sufficient regions in comparison with regions that had normal intake (33).

Other experimental studies focused on the effect of iodine sufficiency on the PTC3–5 cells, which are rat normal thyroid cells harboring a doxycycline (DOX)-inducible RET/PTC3 oncogene (34). In this study authors concluded that treatment with high iodine concentrations can delay oncogenic activation effects, reduce cell growth, and rescue thyroid-specific gene and protein expression. Excess iodine can act as a protective agent in thyroid follicular cells during RET/PTC3 activation, thereby attenuating the oncogenic process in the thyroid, but it must be noted that the levels of iodine were significantly higher than the physiological concentration of iodine in human thyrocytes (34).

The data from the Manuel Sobrinho-Simões et al. study pointed towards a decrease in the incidence rate of FTC and the reasons for this finding were not quite clear (11). The results of our study are in agreement with the literature since the increase of the incidence rate of TC during more recent evaluated period can be attributed to increase of diagnosed cases of PTC,

Histopathological types of TCs	1966-1988 N (%)	1999-2015 N (%)	Comparison of proportions
ATC[1]	58 (17.9%)	12 (3.1%)	Difference 14.79% [(10.38-19.53) CI 95%]; Chi-square=43.266; df=1 p=0.0001*
FTC[2]	57 (17.5%)	42 (10.9%)	Difference 6.62% [(1.49-11.89) CI 95%]; Chi-square=6.432; df=1 p=0,011*
PTC[3]	178 (55.1%)	307 (79.5%)	Difference 24.43% [(17.57-31.03) CI 95%]; Chi-square=48.488; df=1 p=0,0001*
MTC[4]	7 (2.3%)	16 (4.2%)	Difference 1.85% [(-0.92-4.59) CI 95%]; Chi-square=1.879; df=1 p=0,171
ORT[5]	23 (7.2%)	9 (2.3%)	Difference 4.9% [(1.79-8.42) CI 95%];
Total	323 (100%)	386 (100%)	Chi-square=9.744; df=1 p=0,002*

*significant for p<0.05

[1] ATC – anaplastic thyroid carcinoma; [2] FTC – follicular thyroid carcinoma; [3] PTC – papillary thyroid carcinoma; [4] MTC-medullary thyroid carcinoma; [5] ORT – other rare types

Table 1. Comparison of histopathological types of thyroid carcinoma in two evaluated time periods

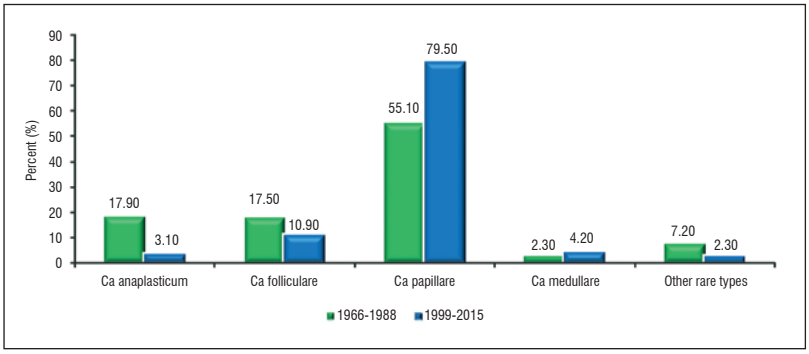

Figure 3. Distribution of histopathological types of thyroid carcinomas

whereas there was a significant reduction of ATC cases–from 17.9% to only 3.11% in the total number of TC. Regarding the total mortality rate of TC, ATC holds the greatest contribution. In light of that fact, we can state that the change in the distribution of the histopathological variants may be due to iodine prophylaxis, which was first introduced in 1956, and corrected later with change of the iodine formulation and dosage (from 10 mg KI per1 kg NaCl to 20-30 mg KIO_3 per1 kg NaCl) in 1999 (15). In 2003 expert team from WHO, UNICEF, ICCID and the National Committee for iodine deficiency evaluated implemented iodination scheme and in their final report they stated that number of patients with iodine deficiency in the Republic of North Macedonia was lowered (35). The alteration in the iodine intake during analysed period was the possible cause for decrease of aggressive TC forms incidence rate, thus moving it towards more indolent TC forms.

CONCLUSION

The analysis of the fifty-year period showed a continuous increase in TC cases in population of North Macedonia. The most commonly diagnosed histopathological type of TC was PTC, followed by FTC and MTC. When compared with data from the period prior to the implementation of the latest regulative for iodization of the salt in 1999, a significant change in the PTC/FTC ratio in favor of PTC can be noticed. Furthermore, there was a decrease in the presence of ATC in the total number of cases of TC from 17.5% to only 3.11% in the more recent period (from 1999 – 2015). The PTC/FTC ratio in our country, according to literature, corresponds to the values typical for regions with iodine sufficiency. It is very possible that the decrease of the incidence rate of the more aggressive forms of TC occurred due to the alterations regarding the iodine intake, since these changes took place during the period of analysis. Further studies with included genetic profiling between the analyzed periods could be useful in evaluating the possible mechanism of histopathological change in TCs.

Declaration of Interests

Authors declare no conflicts of interest.

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