

ЈАВНО ЗДРАВЈЕ

## ИНЦИДЕНЦИЈА И ПРЕВАЛЕНЦИЈА НА ТИРОИДЕН КАРЦИНОМ ВО РЕПУБЛИКА МАКЕДОНИЈА (1999-2010)

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### Извадок

**Цитирање:** Маказлиева Т, Васкова О, Трипуноски Т, Мајсторов В. Инциденција и преваленција на тироиден карцином во Република Македонија (1999-2010). *Арх Ј Здравје* 2017; 9 (1): 66-73.

**Клучни зборови:** тироиден карцином, епидемиологија, инциденција, преваленција, морталитет.

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**Примено:** 5-апр-2017; **Ревидирано:** 30-апр-2017; **Прифатено:** 15-мај-2017; **Објавено:** 30-јуни-2017

**Печатарски права:** © 2017 Тања Маказлиева. Оваа статија е со отворен пристап дистрибуирана под условите на Нелокализирана лиценца, која овозможува неограничена употреба, дистрибуција и репродукција на било кој медиум, доколку се цитираат оригинално(ите) автор(и) и изворот.

**Конкурентски интереси:** Авторот изјавува дека нема конкурентски интереси

Тироидните карциноми (ТК) се најчестите ендокринолошки тумори со околу 1% учество во сите малигноми, според епидемиолошките податоци. Поради недостаток на публикации кои се однесуваат на епидемиолошките трендови за ТК во последните декади во нашата земја, особено по воведување на корекцијата во јодната профилакса со повисока доза на јодна суплементација од 1999, се јави потреба од публикување на реален научен увид во епидемиолошката ситуација. Цел на студијата е да се презентираат епидемиолошки податоци за инциденција и преваленција на ТК во Р. Македонија за периодот од 1999 до 2010 година. Материјали и методи: Спроведовме ретроспективна анализа на медицинските податоци од сите дијагностицирани и лекувани пациенти со ТК на Институтот за патофизиологија и нуклеарна медицина (ИПНМ). Поради фактот што во соодветниот период ИПНМ беше единствен центар за радиојодна терапија на ТК, сметаме дека регистрираните епидемиолошки податоци се репрезентативни за состојбата на целата земја. Податоците од Државниот завод за статистика за пописот од 1994 и 2002 година ги употребивме за пресметка на годишната инциденција и преваленција, како и за анализа на географската и етничката дистрибуција на ТК. Резултати: Со анализа на 12 годишниот период вкупно беа детектирани 204 случаи на ТК, односно преваленција од 10,15/105. Највисока годишна инциденција е во 2000 година (1,18/105), а најниска во 2003 (0,49/105), континуиран пораст на инциденцијата се детектира во периодот 2006 - 2010 со просечна инциденција од 0,98/105. Резултатите укажуваат на слична дистрибуција меѓу етничките групи, а регионалната дистрибуција укажа на највисока преваленца во Скопски, Источен и Североисточен регион, а најниска во Полошки, Југоисточен и Пелагониски регион. Заклучок: Според анализираниите податоци за периодот 1999-2010, детектиран е пораст во инциденцијата и преваленцијата во нашата земја, но сепак пониски споредено со податоците од литературата. Не е утврдена значајна разлика во морбидитетот во однос на етничката дистрибуција, додека во однос на географската дистрибуција на ТК во осумте региони, констатирана е највисока преваленција во северни и источни региони, а пониска во западните региони. Потребни се понатамошни анализи за споредба со претходните епидемиолошки податоци во земјата, како и анализа за можни влијанија на фактори на околината во ниската инциденција, споредено со податоците од литературата.

PUBLIC HEALTH

## INCIDENCE AND PREVALENCE OF THYROID CARCINOMA IN REPUBLIC OF MACEDONIA (1999-2010)

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### Abstract

**Citation:** Makazlieva T, Vaskova O, Tripunoski T, Majstorov V. Incidence and prevalence of thyroid carcinoma in Republic of Macedonia (1999-2010). *Arch Pub Health* 2017; 9(1): 66-73. [English]

**Key words:** thyroid carcinoma, epidemiology, incidence rate, prevalence rate, mortality

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**Received:** 5-Apr-2017; **Revised:** 30-Apr-2017; **Accepted:** 15-May-2017; **Published:** 30-Jun-2017

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**Competing Interests:** The author have declared that no competing interests

Epidemiological data indicates that thyroid carcinoma (TC) is the most frequent endocrinological tumors, participating with around 1% from all malignomas. Because of lack of published papers related to the epidemiological data for TC in the last two decades in our country especially after the introduction of corrected Iodine prophylaxis program, with new higher Iodine supplementation in 1999, there is a need for publishing real scientific view of the epidemiological situations. The aim of the study was to present epidemiological data on incidence and prevalence rate of TC in R Macedonia for the period 1999-2010. Materials and methods: A retrospective analysis of medical data from all diagnosed and treated TC at the Institute of Pathophysiology and Nuclear Medicine during the period 1999-2010 was performed. The Institute is the only Center performing treatment of TC with I<sup>131</sup>, therefore the registered epidemiological data are representative for the country. Statistical State Office data from the census in 1994 and 2002 were used to calculate annual incidence and prevalence rate as well as geographical and ethnic country distribution of TC. Results: During 12-year period, a total of 204 TC cases were registered, with prevalence rate of 10.15/105. The highest incidence rate was detected in 2000 (1.18/105) followed by reduction in 2003 (0.49/105). Annual incidence rate showed continuously higher incidence rate in the period 2006-2010 with average incidence rate of 0.98/105. Results indicate quite similar incidence rate among the three ethnic groups while the regional distribution indicates the highest prevalence in Skopje region, East and Northeast region than Southwest region. The lowest prevalence rate was registered in Polog, Southeast and Pelagonia region. Conclusions: According to the analyzed data from the diagnosed patients with TC during the period 1999 - 2010, there is increase in the incidence and prevalence rate, but however compared with the literature is still very low. Major differences in morbidity rate concerning the ethnic distribution were not found. Related to the geographical distribution of TC in eight regions, the highest prevalence rate was found in northern and eastern parts, while the lowest in western territories. Further analyzes are needed to compare it with the previous epidemiological data in the country, as well as an analysis for possible environmental effects for the low incidence rate, compared to those from literature.

## INTRODUCTION

Thyroid carcinomas (TC) are predominant type of endocrine tumors, participating with around 1 % of all endocrine malignancies 1-5. According to data, published in Cancer Research (UK), American Cancer Society and numerous studies, continuous increase in incidence rate of TC is detected. Thyroid carcinomas (TC) are heterogeneous group of neoplasm. According to histopathological features TC are classified as differentiated thyroid carcinomas including Papillary thyroid carcinoma (PTC) and Follicular thyroid carcinoma (FTC) and poorly differentiated Anaplastic carcinoma (ATC), rarely but with unfavorable prognosis and average survival time of only 6 months. Separate type of TC is Medullary thyroid carcinoma (MTC) arising from calcitonin producing C - cells and very rare are intra-thyroid lymphomas originating from intra-thyroid lymph tissue and sarcomas arising from intra-thyroid connective tissue 6-8. Epidemiological studies have shown that almost all increases in incidence rate were due to increase of differentiated thyroid carcinomas, especially small PTC. Important observation from epidemiological data was that besides increase of the incidence rate, there was stable specific mortality rate of the disease. Scientific explanations for this global epidemiological trend are divided between possible over-diagnosis effect of thyroid micro-carcinomas, usually with indolent nature and possible increased exposition to some environmental factors promoting oncogenesis. Epidemiological studies conducted from different authors and from different countries in almost all continents suggest significant increase in incidence rate of differentiated thyroid carcinomas 9,10. Pelegriti et al., in their study concluded that increase incidence is almost entirely due to increase in incidence of papillary histotype, with no significant change for the follicular, medullary or anaplastic histotypes 11.

Because of lack of published papers related to the epidemiological data for TC in the last two decades in our country after introduction of corrected Iodine

prophylaxis program with new higher Iodine supplementation in 1999, we have set as objective of our study to analyze epidemiological trends for period after establishing new Iodine salt supplementation. The aim of our study is to present the incidence and the prevalence rate of TC in R Macedonia for the period 1999-2010, related to geographic and ethnic distribution.

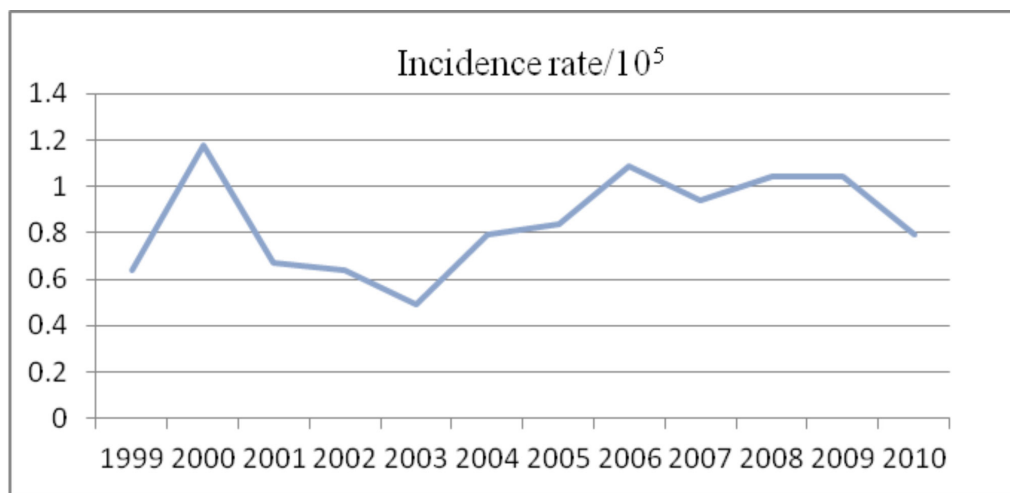
## MATERIALS AND METHODS

A retrospective analysis of medical data from medical histories of all diagnosed and treated thyroid carcinomas at Institute of Pathophysiology and Nuclear Medicine for period 1999 – 2010 was performed. For analyzed period our Institute was the only nuclear medicine center in the country performing treatment of TC with <sup>131</sup>I and registered data are representative for epidemiological analysis for the whole population. Total number of diagnosed patients with TC for above mentioned period were registered and evaluated for their demographic characteristics. Using data from Statistical State Office for census in 1994 and 2002 we have calculated yearly incidence rate per 100.000 citizens and prevalence rate for period 1999-2010. Regional distribution of thyroid carcinomas in Macedonia was also analyzed. Statistical analysis was performed on incidence and prevalence rate in eight geographical regions of the whole country using official data from the Republic State Statistical Office and according to the last evidence the territory of R Macedonia is divided into 8 regions (Vardar, East, Southwest, Southeast, Pelagonia, Polog, Northeast and Skopje). According to data from the State Statistical Office, from 2010 and from statistical population data from 1994 and 2002, the prevalence rate for eight geographical regions was calculated 12. Epidemiological trends among the ethnic groups living in our country were evaluated by quantification of the yearly incidence and prevalence rate for appropriate period among three major ethnic groups living in our country, Macedonians, Albanians and Others (including Serbs, Turks, Bosnian, Romani and etc.).

**Results**

During the period 1999 – 2010 204 patients with TC were registered of the total population of 2.022.547 at the territory of 25 713 km<sup>2</sup> and according to histopathology reports from all 204 TC only 9,8% were small tumors, less than 15 mm. The most frequently diagnosed tumors were 15–50 mm in diameter

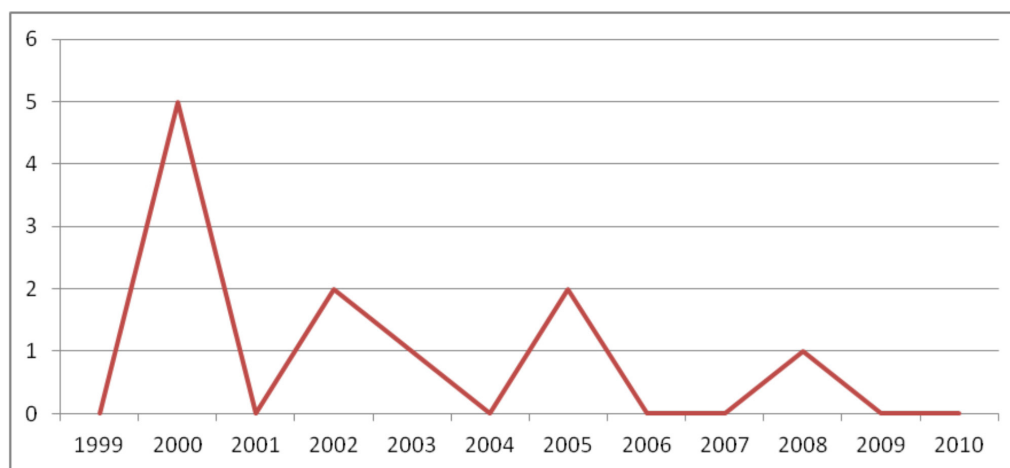
(42,65%). Annual incidence rate showed continuously higher incidence rate of TC in the period 2006-2010 with mean incidence rate of 0,98/105, comparing with lower incidence rate for previous period from 1999 till 2005 when average incidence was 0,75/105. The exceptions were noticed in 2000 with the highest (1.18/105) and 2003 with the lowest incidence rate (0,49/105) (Figure 1).



**Figure 1** Annual incidence rate per 100.000 (1999-2010)

The prevalence rate for the period 1999 – 2010 was 10,15/105 with 11 registered disease specific deaths from the total of

204 diagnosed TC – mean mortality rate was 0,044/105 (Figure 2).



**Figure 2** Annual number of deaths from TC (1999-2010)

Regional distribution of TC in R Macedonia was also analyzed. According to the analysis of eight regions: the highest prevalence of TC was registered in Skopje region (12,7/105) followed by the East region (11,6/105), Northeast re-

gion (11,5/105), and Southwest region (9,5/105). The lowest prevalence rate was registered in Polog (3,5/105), Southeast (4,1/105), Pelagonia region (5,1/105) and central Vardar region (7,2/105) (Figure 3)

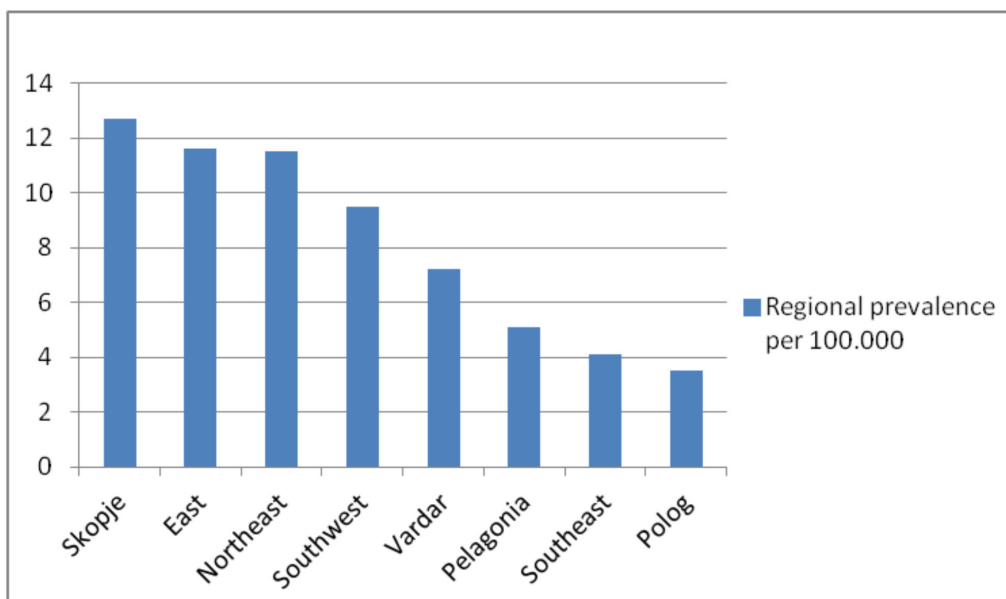


Figure 3 Regional prevalence rate of thyroid carcinoma

Results indicate quite similar incidence and prevalence rate among the three ethnic groups (Figure 4). Prevalence rate for Macedonians and Albanians for this

12-year period is the same and accounts 10,02/105 and slightly higher for other ethnic groups (0,67/105).

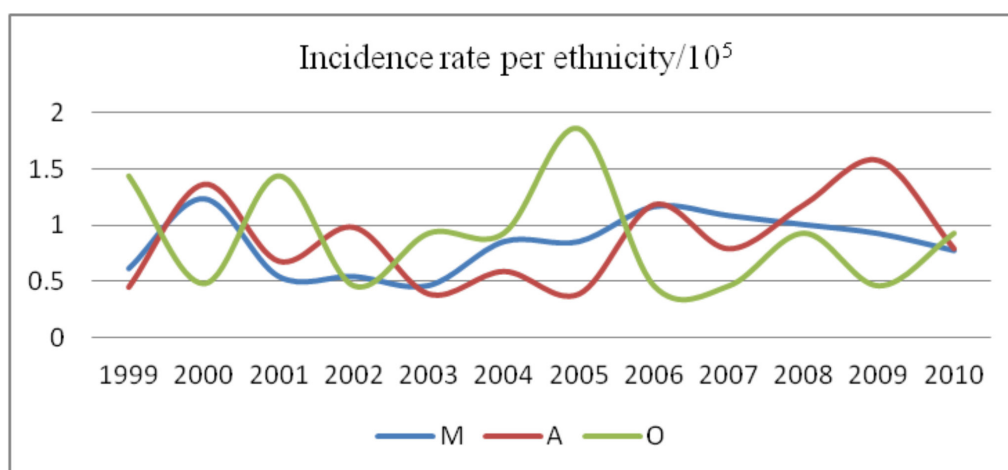


Figure 4 Incidence rate per 100,000 in different ethnic groups

## Discussion

Due to lack of published papers in the last 15 years about epidemiological trends in TC in Macedonia and the lack of cancer register, we decided to perform statistical analysis in order to analyze statistical trends in TC. Our study revealed total number of 204 TC and prevalence rate of 10.15/100.000 for the period 1999-2010. Statistical analysis detected increase in incidence rate from 0,49/100.000 in 2003 to 1,09 in 2006 and 0,79/100.000 in 2010, but

the highest number of diagnosed cases was in 2000 with 1,18/100.000.

United States National Cancer Institute's Surveillance Epidemiology and End Results (SEER) dataset, registered change in annual incidence rate from 5,9 up to 14,3 thyroid carcinomas per 100.000 citizens for period 2005 - 2009 13. One of the highest increase in incidence rate was found in South Korea from 2000, when ultra-sonographic (US) screening for thyroid nodules be-

came frequently preformed and significant increase in annual incidence rate was registered from 10 up to 70 cases per 100 000 individuals 14. Cancer Research (UK) published detailed statistical data about incidence rates and from 2.5/100.000 in 1999, registered continuous increase to 4,5/100.000 in 2010 15.

We have compared results with statistical data for our population from previous study for the period 1966 – 1980 (15 years) when total number of 107 thyroid carcinomas were diagnosed and prevalence rate of 6,5/105 16. Epidemiological data indicate increase of TC in our population when comparing the two decade period from 6.5/105 to 10.15/105 and one of the reasons for this increase is probably due to the improvement of diagnostic methodology and widespread introduction of US in routine clinical examination.

Great divergence exists in observations from different epidemiological studies and our analysis. According to our data Macedonia has still very low incidence and prevalence rate comparing with data from literature. This discrepancy may be result of low diagnostic accuracy in small lesions, less than 1 cm, probably due to the fact that fine needle biopsy was preformed only in palpable nodules, without US guidance. Pelegriti et al., C. La Vecchia et al. in their studies suggest that the increase in incidence rate of thyroid carcinomas is mostly in detection of small, less than 1 cm thyroid carcinomas 13,15,17. Many studies indicate that detection of non-palpable thyroid nodules has increased with wider application of US and other imaging modalities 18. Introduction of US FNAB lead to earlier detection of small micro-carcinomas. However, FNA cytology has limitation due to non-diagnostic results, which according some studies range from 6,4% to 33,6% 19.

Our study results indicate that, in our population, the incidence rate of smaller tumors (<15 mm) is only 9.8% of all diagnosed TC and is lower compared to data from other studies. Many reports suggested that spread of ultrasound guided fine needle aspiration biopsy (US-FNAB) facilitated the detection of

small TC 20. Regardless this diagnostic method, it has been suggested that constantly increasing incidence is present in general population 21.

Besides improved diagnostic sensitivity there may be some other reasons for differences in epidemiology, like genetic differences and environmental influences 13, 22, 23. Such distinctions may result from multiple environmental factors like differences in iodine intake, irradiation exposition, exposure to different chemical elements and compounds through soil, water and food intake. One well-known risk factor is neck irradiation exposition in childhood, unfortunately recognized after application of local irradiation treatment of the head and neck for infection, inflammation of tonsil and nasopharyngeal region and in therapy of acne and thymus in period 1940-1950, later confirmed after Hiroshima bombing and Chernobyl nuclear power plant accident. Increased incidence rate was detected even in the first 3-4 years after the accident, especially in the youngest population at the age group up to 4 years 24, 25. In our study this risk factor was very low because of well-known facts about the effect of radiation exposition in early childhood, only small possible effect may be from Chernobyl accident which happened in 1986, or 13 years before starting our analysis.

The second well-known fact is that low but also high intake of iodine may result in changes of TSH, which may be promoting factor in tumor-genesis. Experimental animal studies showed that both conditions could be stimulating cancerogenic factors. Territory of R Macedonia was iodine deficient region till 1956 when iodine prophylaxis program was started with introduction of salt iodination with 10mg KJ /1kg salt till 1999 when second program was initiated with 20 - 30 mg KJO3/1 kg salt. In 2003 the expert team by WHO, UNICEF, ICCID and National Committee conducted evaluation and concluded in their final report that iodine deficiency in R Macedonia was corrected 26.

Many studies indicate higher incidence rate in volcanic territories. Malandrino

et al., conducted analysis of regional incidence of thyroid carcinomas in territory of Sicily revealing significantly higher incidence rate in volcanic territories in the surrounding area of volcano Ethna. Authors evaluated possible etiopathogenetic association with many-fold increased presence of some compounds and elements in drinking water, soil and food, like for increased presence of microelement Vanadium in drinking water in surrounding regions near volcano Etna. Vanadium has potential effect on thyroid function and cell proliferation 27-29. Uthus and Nielsen (1990) conducted animal experimental studies on rats and detected that Vanadium has effect on iodine metabolism and thyroid function by reducing the activity of thyroid peroxidase and Zhang et al., (2001); Ingram et al. (2003) reported possible mitogenic effect through stimulating activity of unknown growth factor 28. High prevalence TC rate is detected in volcano islands, Hawaii, Island, Iceland, New Caledonia 14.

We analyzed differences in incidence rate in eight regions in R Macedonia and detected different incidence rate with the highest incidence rates in Skopje as north region, Northeast, East and Southwest regions, (12,7 ...11,5/105) and Polog, Pelagonia and Southeast region with the lowest number of diagnosed TC cases. Last recent geothermal activity on the Balkans was described in Duvalo, near the village of Kosel located in the Southwest region, recognized as active geothermal surface feature and releasing occasionally gaseous carbon dioxide and hydrogen sulfide. Our data didn't reveal extraordinary increase in incidence rate in Southwest region comparing to other regions in our country.

We have also evaluated the incidence rate among different ethnic groups in our country. Significant difference in incidence among distinct ethnicities was described in literature, like higher incidence rate in Caucasian population in comparison to Afro-American and Latin population in the USA. According to the global available data the highest incidence rate was detected in Korea and islands in the South Pacific, like volcano islands, Hawaii, Island, Iceland,

New Caledonia, Tahiti and the lowest incidence rate in Africa and Caribbean archipelago 13, 14, 28. Interesting fact was two-fold greater incidence in Japanese and Chinese population living in America than in native population from their original countries. Differences are probably due to the external influences, but genetic factors could not be excluded 13, 29. Statistical data in our analysis didn't reveal significant differences among the evaluated ethnic groups, which showed very similar prevalence rate for Macedonians and Albanians and for the third group consisting of other ethnicities living in R Macedonia.

## Conclusion

According to the analyzed data from patients with thyroid carcinomas for period 1999-2010, it can be concluded that there was increase in incidence and prevalence rate in comparison to the previously observed period. Evaluation of statistical parameters among different ethnicities in our country didn't reveal significant differences among evaluated groups. Analysis of distribution of thyroid carcinomas in eight regions showed the highest prevalence in northern and eastern regions of our country, while the lowest number of diagnosed patients was registered in western regions. The highest prevalence rates were registered in Skopje, East and Northeast region. Mostly diagnosed tumors were 15-50 mm in diameter. Our incidence rate is still very low in comparison to data from other European and American studies, probably due to the low detection rate of carcinomas less than 15mm in diameter. One possible explanation could be the fact that ultrasound guided biopsy was still not introduced in diagnostic algorithm for analyzed period and free hand biopsy was performed in lesions that were palpable. Further studies are needed to evaluate other potential factors for low number of diagnosed thyroid carcinomas, such as iodine intake and other environmental factors.

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