

Epidemiology of Thyroid Carcinomas in North Macedonia (1999-2015)

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Makazlieva Tanja¹ , Vaskova Olivija¹, Stojanoski Sinisha^{1,2},
Manevska Nevena¹, Miladinova Daniela¹, and Velikj Stefanovska Vesna¹

Abstract

Objective: We have set as objective to analyze epidemiological data of diagnosed thyroid carcinoma (TC) cases, incidence and prevalence rate by gender, age, histopathological type, and statistical regions in R. of N. Macedonia during the period 1999 to 2015. **Material and Methods:** Retrospective analysis of medical data collected from the 2 state thyroid departments. Inclusion criteria included newly diagnosed cases of TC in appropriate years for the period 1999 to 2015. We have evaluated: yearly incidence rate, incidence and prevalence by gender, age, the distribution in 8 statistical state regions and histopathological types and subtypes representation. **Results:** A total number of 422 TC patients were detected, average incidence rate of $1.22/10^5$, with most prevalent papillary TCs 79.5%, followed by follicular 10.9%, medullar 4.1%, anaplastic 3.1%, and other rare types with 2.3%. The highest incidence rate was detected in Skopje region, while the lowest in Southeast and the Polog region. The total prevalence rate for the female gender was $32.61/10^4$ and for male $9.27/10^4$ (f/m ratio = 3.52:1), with lowest female/male difference found in the elderly > 65 years (f/m = 2.21/1). **Conclusion:** Compared with regional epidemiological data we can conclude that Republic of N. Macedonia has very low incidence and prevalence rate, while female/male ratio was similar to that described in the literature. Our low incidence and prevalence rate may be due to 2 possible reasons, 1 would be insufficient diagnosis of only small portion of the real cases in the population, or the second reason may be a real low incidence resulting of specific etiopathogenetic circumstances.

Keywords

thyroid carcinomas, incidence rate, prevalence, epidemiology

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Introduction

Thyroid carcinomas (TC) are the most frequent endocrine neoplasms, accounting for 1% of all malignancies.¹⁻³ Epidemiological data from the US National Cancer Institute Surveillance, Epidemiology and End Results (SEER) program for the period of 1975 to 2012 detected 13.5/100 000 of newly diagnosed TC cases per year.⁴ According to data from 2015 of the American Thyroid Association (ATA), the yearly incidence rate for differentiated TC almost tripliated from 4.9/100 000 in 1975 to 14.3/100 000 in 2009. Most of these cases were due to increase in papillary thyroid carcinomas (PTC), while 39% of detected TCs from 2008/09 were <1 cm in size.⁵ La Vecchia et al published epidemiological study for incidence, prevalence and mortality rate of TC in European, North American, Central and South American and Asian countries, according to data

used from WHO. The main conclusions from this study showed a continuous trend of increase in incidence rate of TC in the last decades worldwide and 2 proposed reasons for globally detected increase were: improved diagnosis and detection of microcarcinomas defined as tumors smaller than 1cm in size; or real increase in incidence rate due to increased radiation exposure or exposition to other still unrecognized etiological factors that may induce genetical

¹University Ss Cyril and Methodius, Medical Faculty, Skopje, R. of N. Macedonia

²Lazarski University, Warsaw, Poland

Corresponding Author:

Makazlieva T, Institute of Pathophysiology and Nuclear Medicine, Medical Faculty, University Ss Cyril and Methodius, St. Mother Tereza, 17, Skopje 1000, R. of N. Macedonia.

Email: tmakazlieva@medf.ukim.edu.mk



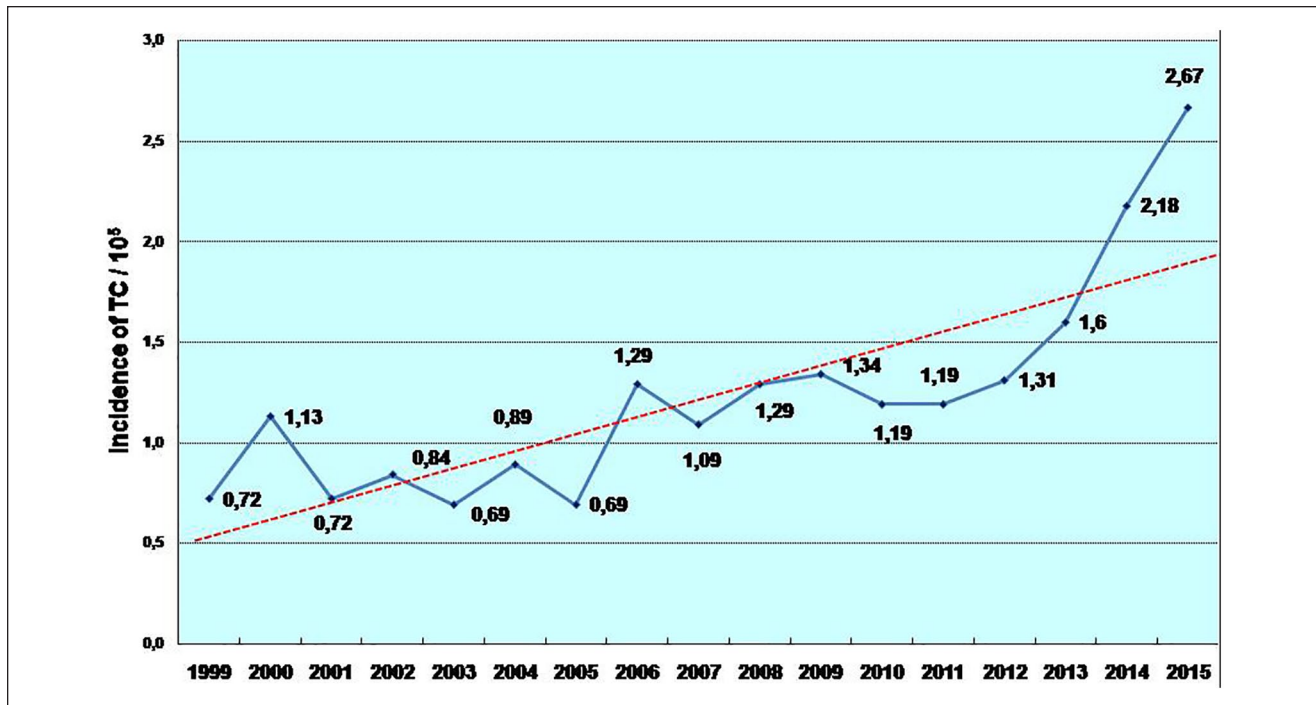


Figure 1. Incidence rate and trend of TC (1999-2015).
The graph shows the trend and the yearly incidence rate during the 17-year period.

changes and carcinogenesis.⁵⁻⁸ We have set as objective in our study to analyze epidemiological data of diagnosed TC cases, incidence and prevalence rate by gender, age, histopathological types and statistical regions in Republic of North Macedonia during the period 1999 to 2015.

Material and Methods

We performed a retrospective analysis of medical data for TC at national level, collected from the Institute of Pathophysiology and Nuclear Medicine, Clinical hospital center “Mother Teresa” in Skopje and Clinical hospital “Dr Trifun Panovski” in Bitola, as the main centers treating TCs in the country. The study elaborated newly diagnosed cases of TC in the period 1999 to 2015. Data from previous study done at the Institute of Pathophysiology for the time period of 1966 to 1988, were compared with the data from our study.

Protocol of data registration consisted of: patients’ age; gender; geographical distribution by state regions; and histopathological types.

Using data from the Republic State Statistical Office from 2009, we did yearly incidence rate as well as the crude and specific by gender and age prevalence rate of TC in 8 statistical regions (Vardar, East, Southeast, Southwest, Pelagonia, Polog, Northeast, and Skopje). We used medical records from routine outpatient examinations from the above mentioned hospitals. Frequency of distinct histopathological types of TC was evaluated, from

postoperative histopathology reports. The incidence rate for period 1999 to 2001 was calculated according to demographic data of the Republic State Statistical Office from 1994 (total population 1.945932); for the period 2002 to 2011 according to estimations from 2002 (total population 2.020157) and for the period 2012 to 2015, according to estimations from 2012 (with total population 2.061.044). Prevalence was calculated according to demographic data from the last census in 2002 (2.020157).⁹

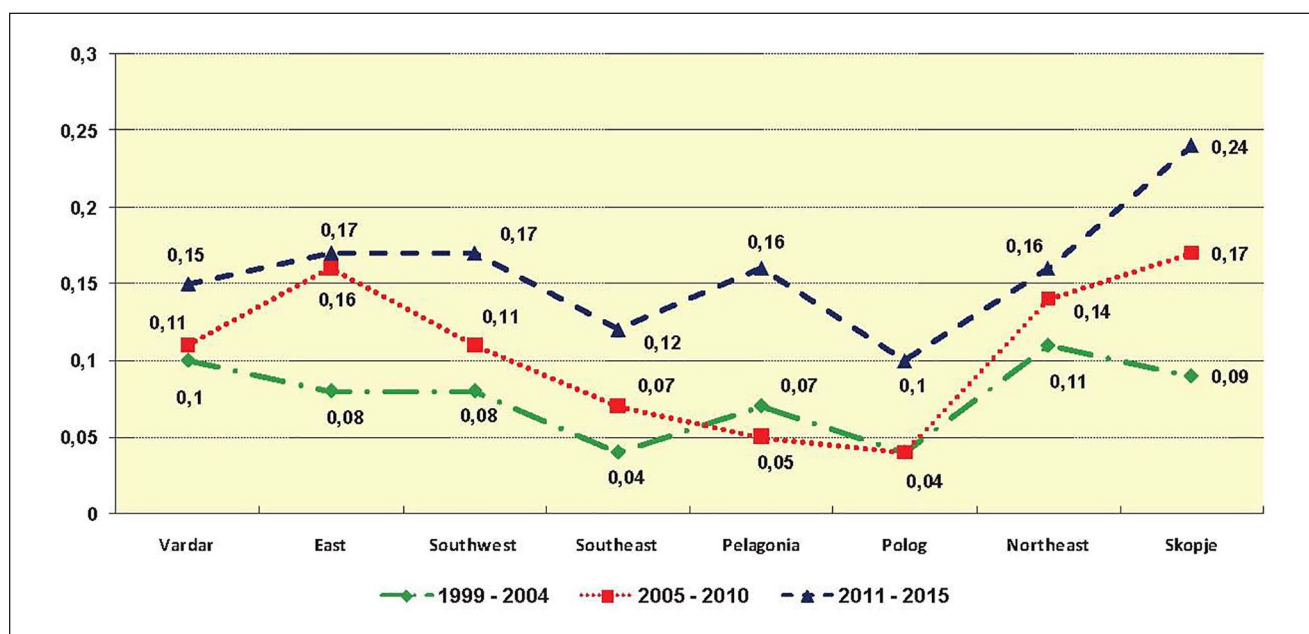
Results

A total number of 422 TC cases were detected for the period of 17 years (1999-2015), with 328 females (77.7%), and 93 males (22.3%), age 7 to 80 years (mean age 45.8 ± 15.5). The trend showed continuous increase in the number of diagnosed cases with average incidence of 1.22/100 000. The lowest yearly incidence of 0.69/100 000 was detected in 2003 and 2005 while the highest in 2015 with 2.67/100 000 cases (Figure 1).

From the total of 422 patients, histopathological reports were available for 386 cases and according to this data, the most frequent type was papillary thyroid carcinoma (PTC—including following subtypes: PTC typical variant, PTC—follicular variant, PTC with giant osteoclasts like cells, PTC fasciitis nodosa, PTC in cysta colli mediana and PTC—Warthin like subtype)—307 (79.5%), followed by follicular thyroid carcinoma (FTC) and including Hurthle

Table 1. Distribution of Histopathological Subtypes of TC.

Histopathological subtypes	Time periods (years)			Total (%)
	1999-2004 (%)	2005-2010 (%)	2011-2015 (%)	
ATC	4 (4.94)	1 (0.81)	7 (3.87)	12 (3.11)
FTC	6 (7.41)	12 (9.68)	14 (7.73)	32 (8.29)
PTC	52 (64.20)	71 (57.26)	115 (63.54)	238 (61.66)
MTC	7 (8.64)	4 (3.23)	5 (2.76)	16 (4.15)
Hurthle cell carcinoma	1 (1.23)	4 (3.23)	5 (2.76)	10 (2.59)
Metastatic deposits in thyroid gland	0 (0)	3 (2.42)	2 (1.10)	5 (1.30)
Lymphoma	2 (2.47)	0 (0)	1 (0.55)	3 (0.78)
Sarcoma	0 (0)	1 (0.81)	0 (0)	1 (0.26)
Insular carcinoma	0 (0)	0 (0)	1 (0.55)	1 (0.26)
PTC (cystic)	0 (0)	0 (0)	1 (0.55)	1 (0.26)
PTC in cysta colli mediana/ducti thyreoglossy	0 (0)	0 (0)	2 (1.10)	2 (0.52)
PTC—follicular variant	9 (11.11)	23 (18.55)	26 (14.36)	58 (15.03)
PTC—with giant osteoclast like cells	0 (0)	4 (3.23)	0 (0)	4 (1.04)
PTC—fasciitis nodosa	0 (0)	1 (0.81)	1 (0.55)	2 (0.52)
PTC—Warthin like	0 (0)	0 (0)	1 (0.55)	1 (0.26)
Total	81 (20.98)	124 (32.12)	181 (46.89)	386 (100)

**Figure 2.** Average incidence rate of TC for 3 time periods per 10000 population, per statistical regions. The graph shows the incidence rate for 3 time periods in 8 state statistical regions.

cell carcinoma in this group as well—42 (10.9%), medullary thyroid carcinoma (MTC) in 16 (4.1%) anaplastic (ATC) 12 (3.1%), and other rare types (ORT) 9 (2.3%). Further sub-classification revealed 15 different histopathological subtypes of TC. During the entire period PTC typicum variant was significantly the most frequent type found in 238 cases (61.7%), followed with PTC—follicular variant with 58 cases (15%) (Difference test: 23.34% [(16.23-29.98) 95%

CI]; Chi-square=41.93 df=1 $P < .0001$). Detailed presentation of the different TC variants is presented in Table 1.

From the total of 422 patients, in 13 (3.1% of cases) data for the geographical region of origin were missing. In the 17-year period the highest incidence was registered in Skopje with 0.44/10000 (2015). An average incidence rate was analyzed for 3-time periods 1999 to 2004, 2005 to 2010, and 2011 to 2015 (Figure 2).

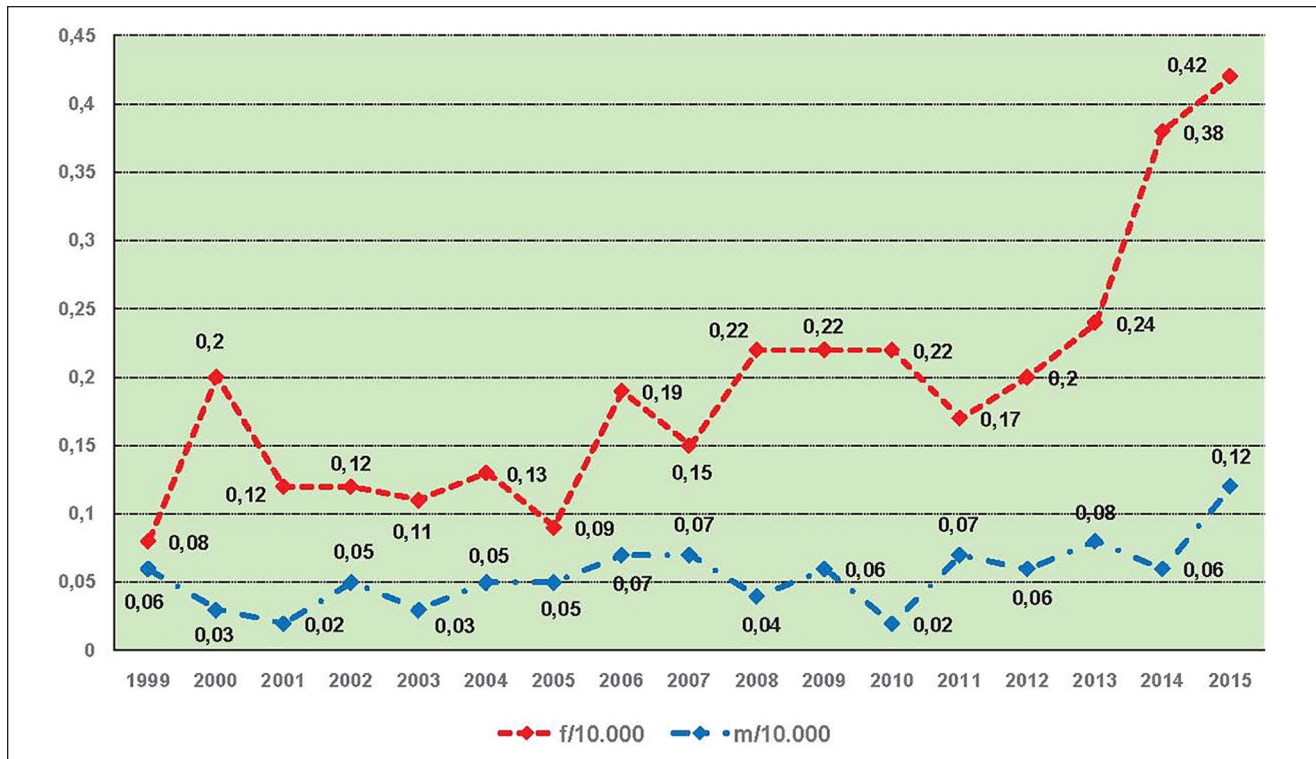


Figure 3. Yearly incidence rate per gender (1999-2015)/10 000 female/male.

Continuous trend of increase was detected in all, except for the Pelagonia region where lowering of the average incidence rate was registered for the period 2005 to 2010 compared to 1999 to 2004, or 0.05/10 000 versus 0.07/10 000 (reducing of incidence for 28.6%).

The highest increase in average incidence rate was found in Skopje from 0.09/10 000 in the period 1999 to 2004 to 0.24/10 000 for 2011 to 2015, with an increase of 62.5% (Figure 2).

Annual incidence rate by gender was calculated per 10 000.⁹ Average incidence rate in females was 0.19/10 000 and 0.05/10 000 in males (Figure 3).

We compared incidence rate by gender in 3 time periods. In the time period 2005 to 2010 compared with 1999 to 2004 the average increase in incidence rate in females was 27.8%, while in 2011 to 2015 compared to 2005 to 2010 the increase was 35.7%. Similarly, in males, the average incidence increased for 20% in 2005 to 2010 compared to 1999 to 2004 and for 37.5% in 2011 to 2015 compared to 2005 to 2010.

The prevalence rate for the period 1999 to 2015 amounts 20.89/100 000. The total prevalence rate for female was 32.61/10 000 and for male 9.27/10 000 (female/male ratio=3.52:1) (Figure 4).

For the period 1999 to 2015 we found the highest prevalence rate in age group 45 to 64 years (3.96/10 000)

(Figure 5). Highest difference in prevalence rate between genders was detected in the age groups 0 to 19 years (f/m=5.5/1) and 20 to 44 years (f/m=4.88/1). Lowest difference was found in the elderly >65 years with f/m=2.21/1.

Discussion

Thyroid carcinomas are detected in 5% to 10% of diagnosed thyroid nodules, according to literature.^{5,10,11} We diagnosed a total of 422 TC patients, age 7 to 80 years (mean age 45.8 ± 15.5), with 328 females (77.7%), and 93 males (22.3%). Comparison of our data with previously published from our Institute for the period 1966 to 1988^{12,13} and statistical estimation for the missing period 1989 to 1998 was performed, revealing a continuous trend of increase in TC cases, corresponding with the global increasing trend.^{5,10,11} Epidemiological parameters from literature showed significant differences between countries in incidence rates, probably due to discrepancies in diagnosis, availability of health care services, but also due to exposition of different environmental etiological factors, such as iodine intake, exposition to radiation, mutagenic chemical factors etc.^{5,10,11} Our results showed average incidence rate of 1.22/100 000, with continuous trend of increase and f/m ratio 3.9/1, with similar increase in incidence rate in both genders.

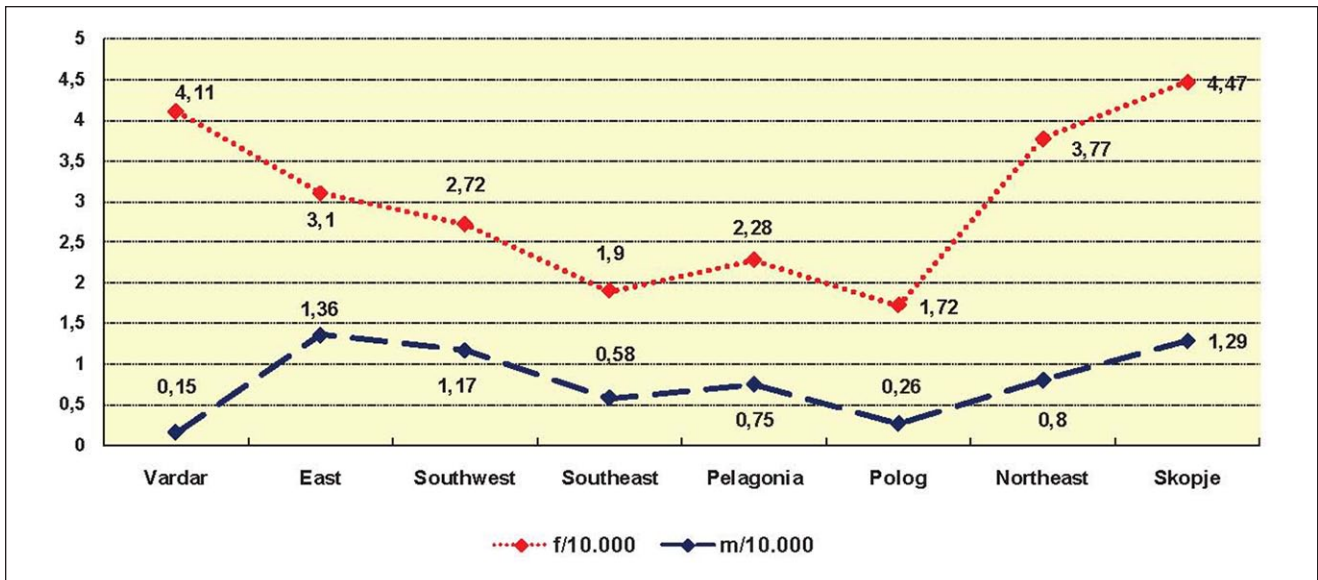


Figure 4. Prevalence rate by gender and statistical regions (1999-2015) per 10000.

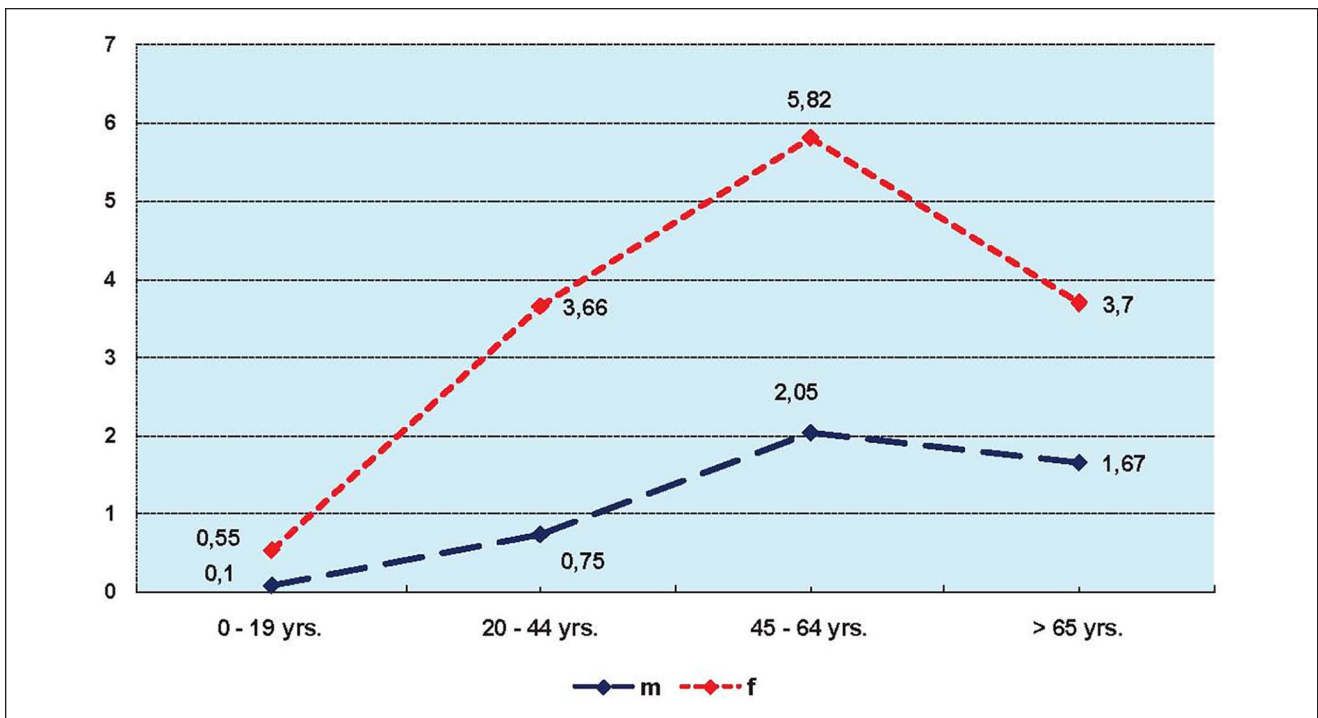


Figure 5. Prevalence rate of TC by age and gender (1999-2015).

Using data from WHO and Globocan for North Macedonia population, TC ranks as the twentieth malignoma, according to annual incidence, or according to 2014 WHO statistics the most frequent was breast cancer in females, with 1152 cases, while thyroid cancer was diagnosed in 39 females, and in males the most frequent was lung cancer with 1044 cases, but only 6 thyroid carcinoma cases.^{14,15}

Data from the Institute of Public Health of the Republic of North Macedonia for the analyzed period 2010 to 2019 showed that TC was ranked as the fifteenth tumor by primary site of malignoma frequency in female gender.¹⁶

According to state regions distribution, we found the highest incidence rate in Skopje region. This finding can be explained as expected because this region includes the

capital city where the largest number of health care institutions are available including the University clinical hospital, with the most advanced diagnostic technology and the most experienced personal. In 2012 at the Institute of Pathophysiology and Nuclear Medicine ultrasound-guided fine needle aspiration biopsy was introduced and that may be one of the main reasons of improved diagnosis of TC. The constant increase in number of US units and the quality of their functioning has improved detection of thyroid nodules. Besides availability of health care services, a possible explanation for the highest incidence rate in Skopje may be the migration process from peripheral regions into the capital. We found some differences in distribution of distinct histopathological types in various state regions that may be due to different environmental influences, like iodine intake, leading to differences in FTC, ATC, and PTC distribution. Population study for MTC with genotype-phenotype correlations in Macedonian patients was performed by Jovanovic et al showing low representation of familiar MTC and MEN2 syndrome in our population, leading to conclusion that those findings may be as a result of absence of appropriate molecular screening and diagnostic algorithm.¹⁷⁻²⁰

A population study from *RARECARE* project, based on the European cancer registries evaluated the frequency of all endocrine malignancies, including from Southeast Europe only Poland and Slovenia. According to this analysis, TCs were represented with 88% of all endocrine malignancies, but this percent was probably higher, since in this project MTC and mixed medullary-papillary and medullary-follicular carcinomas were not included in TC group, and reported average yearly incidence rate of TC was 4/100 000 with significant differences in gender distribution 2.8/1 f/m ratio.²¹

From countries in the Balkan region we found appropriate data for comparison from similar time periods from Serbia and Croatia. Slijepcevic et al evaluated epidemiological trends for the period 1999 to 2008 in Serbia and detected increase in incidence in both genders, most evident in the female age group 20 to 29 years, with the highest incidence rate in the female age group 50 to 59 years. Slijepcevic et al found that average incidence rate in Serbia in females for evaluated period was 3.3/100 000, which is 3 time lower than the incidence rate in Europe and 1.7 times higher than North Macedonia's average yearly incidence rate. For male gender in the same study the average incidence rate of 1/100 000 is found, which is twice lower as compared to the average incidence rate in the European study and twice higher than the average incidence rate for males in our country.^{22,23}

In a study of Croatian authors for the period 1988 to 2010, the average incidence rate of TC was 11.4/100 000. According to this epidemiological data, Croatia is ranked as

forth of all European countries, right after Lithuania with 15.5/100 000, Italy with 13.5/100 000, and Austria with 12.4/100 000.^{24,25} According to a report from the United Nations Scientific Committee, in relation to the effects from the Chernobyl nuclear disaster, Croatia was pointed among the territories as most exposed to high contamination. However, a previous study that analyzed the period 1989 to 1990 and 1998 to 1999 and compared it with 1980 to 1981, did not reveal significant difference in average age of the patients diagnosed with TC, before and after the Chernobyl disaster, differing from other studies where an increase in TC was found, especially among children only 3 to 4 years after the exposition.²⁶

In comparison with the regional data, North Macedonia has a very low incidence rate, with f/m ratio similar to that found in the literature.¹³⁻²⁷ Our low incidence and prevalence rates may be due to 2 possible reasons, 1: insufficient diagnostics, probably due to low aggressiveness, and indolent course of the disease, thus the cases remain unrecognized and second: the possibility of a low real incidence due to specific etiopathogenetic influences.

Gabriella Pellegrini et al found increase in the incidence rate of TC in USA of 2.4% for the period 1980 to 1997 to 6.6% for 1997 to 2009, equally in both genders.¹⁰ Compared with our data we can conclude that we have high yearly percent change, but low average incidence rate for the entire evaluated period.²⁸ Significant difference between f/m incidence rate in TC is a known fact, but the reason for such a high gender difference is not as yet elucidated. One assumption is that sex hormones may contribute to this predisposition, especially since estrogen receptors were detected in cell lines of differentiated TC.^{29,30} Kumar et al³¹ explore the role of hormone estradiol, estrogen receptor expression and effects of selective estrogen receptor modulators at NPA87 and KAT5 papillary and WRO follicular TC cell lines. Research data showed direct effect of estrogen on thyroid cell lines of normal thyroid tissue as well as cell lines of differentiated TC through estrogen receptors, activating effects of cell proliferation, modulation in NIS expression, increasing Tg gene expression and increase in production of matrix metalloproteinase 9.^{31,32}

Evaluation of the distribution of histopathological types of TCs showed highest frequency of PTC, followed by FTC and MTC. Compared with previously published data for our population, significant reduction was observed especially in frequency of ATC 17.9% and FTC 17.5% cases in 1966 to 1988^{12,13} to only 3.11% ATC and 10.88% FTC in 1999 to 2015. This effect of shift in histopathological types of TCs, with reduction of ATC and FTC cases and increase of PTC is recognized in other population studies as well and it is explained as a result in change of iodine intake through introduction of new law regulation regarding iodination of the salt in 1999.^{15,16,33}

Conclusion

Our results showed an average incidence rate of 1.22/100 000, with f/m ratio 3.9/1 and a continuous trend of increase. In comparison with the regional epidemiological data we can conclude that North Macedonia has a very low incidence rate, with f/m ratio similar to that in the literature. Our low incidence and prevalence rate may be due to 2 possible reasons: 1—insufficient diagnosis of only a small part of the real cases in the population, probably due to low aggressiveness and indolent course of the disease, or second— influence of specific etiopathogenetic circumstances.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ORCID iD

Makazlieva T  <https://orcid.org/0000-0003-0460-2116>

Statement of Ethics

The study was approved by the Ethics Committee of the Medical Faculty of Ss Cyril and Methodius University, in Skopje, Republic N Macedonia.

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