

Trends in thyroid cancer incidence and mortality in Central Serbia, 1999-2014

Miodrag Stojanović^{1,2}, Dijana Stojanović¹, Nataša Rančić^{1,2}, Aleksandra Ignjatović^{1,2}, Zorica Antić¹, Snezana Miljković³ and Tatjana Rajović⁴

¹Faculty of Medicine, University of Niš, Niš, Serbia

²Institute for Public Health, Niš, Serbia

³Clinical Center Nis, Niš, Serbia

⁴Specialised Hospital for Rehabilitation of Vrdnik, Vrdnik, Serbia

Abstract

Introduction. Thyroid cancer (TC) is the most common malignant disease of the endocrine system. The incidence of the TC has been increasing worldwide, especially in female population. However, mortality from TC is low in both males and females. The objective of the paper was to determine and to analyze incidence and mortality trends of TC in males and females in the central Serbia in the period 1999-2014.

Method. In this descriptive study data from the Serbian Cancer Registry were used. Crude and age-standardized rates (ASRs) of incidence and mortality were calculated. Trend and annual percentage change (APC) of the incidence and mortality rate with corresponding 95% confidence intervals (CI) were calculated by performing Joinpoint regression analyses.

Results. A total number of new cases of TC was 3113. TC was diagnosed in 2343 females and 770 males (female-to-male ratio, 3:1). A total number of fatal cases was 770 (while 504 female and 266 male died from TC, female-to-male ratio, 1.9:1). TC was not common before 30 years of age. The highest incidence was recorded both in males and females aged 50-59. Joinpoint regression analysis showed the statistically significant increase of ASRs of TC incidence in males in 1999-2014 period with APC 6.2% (95% CI: 4.2-8.3, $p < 0.001$) and there was also significant increase of ASRs of TC incidence in females in the same study period with a APC 6.1% (95% CI: 4.2-8.0, $p < 0.001$). Joinpoint regression analysis showed an insignificant increase of ASRs of TC mortality in males with APC 2.4% (95% CI: -0.5-5.5, $p = 0.1$). There was an insignificant decrease of ASRs of TC mortality in females with APC -1.3% (95% CI: -4.4-1.9, $p = 0.4$).

Conclusion. The increasing trend of age-standardized incidence rates of TC both in males and females and decreasing trend of age-standardized mortality rates during the observed period were registered. Females had higher age-standardized incidence and mortality rates than males. Female to male ratio of incidence was 3:1 and for mortality 1.9:1. Measures of primary and secondary prevention are needed.

Key words

- thyroid cancer
- trend
- incidence
- mortality

INTRODUCTION

Thyroid cancer (TC) is one of the most common malignant diseases of the endocrine system [1]. Worldwide, TC represents 3.8% of all the new cancer cases, approximately 5% of all cancers in females and 2% in males [2]. Over the last 10 years, incidence rates of new TC have been growing by a 5.5% annual average [3] whereas TC mortality rates have been increasing by a 0.8% annual average. Although TC has been considered an uncommon malignancy compared to other malig-

nant diseases, its incidence has been growing worldwide [3]. Its increase was registered in both genders, among many countries of the world such as the United States of America (USA), Canada, France, Great Britain, Italy, Israel, South Korea, and China [4-9]. The highest TC incidence rates in females (15 cases per 100 000 per year) were recorded in France, Italy, and Croatia – conversely, the lowest rates were found in Greece, in Netherlands, and Romania. Age-adjusted TC incidence rates in females were significantly higher compared to

the ones in males, and the differences between the genders were somewhat lower in Hungary, Germany, and Portugal. TC incidence, particularly in females, varied according to geographical region with one of the lowest incidence rates recorded in Ireland [10].

According to the USA Surveillance, Epidemiology and End Results (SEER) registry, TC incidence tripled from 1975 to 2011, in contrast, as seen in Europe, with steady mortality trends [11]. TC is the ninth most common cancer among women, worldwide [11]. In Europe, it represents the fifth most common cancer in females while in Italy it is the second most common cancer in women younger than 45 years of age [12]. According to a study from South Korea, TC ranks as the leading cancer in females, and the fifth most common cancer in males [13]. About 2% of TC cases occur in children and teenagers. Females are more often affected than males (3:1 ratio) and are usually diagnosed at a younger age [14]. Furthermore, TC incidence rates are higher among females than males and among Caucasians than other major racial groups [15].

Results from several studies have suggested that diagnostic improvements cannot wholly account for observed incidence trends, indicating a potential role of other factors, such as an increased environmental or hormonal exposure [16]. Known risk factors for TC are exposure to ionizing radiation (exposure through medical procedures, including x-rays, as well as radioactive fallout) especially in childhood, a history of goiter or thyroid nodules, family history of thyroid cancer, radioactive exposure, certain rare genetic syndromes, and female gender [17].

Our study aimed to verify and analyze TC incidence and mortality trends in females and males in central Serbia during the period 1999-2014.

METHODS

A descriptive study was conducted by analyzing data on all new TC cases and deaths for TC in the population of Central Serbia, excluding the territory of Autonomous Province Vojvodina and Autonomous Province of Kosovo and Metohija. The analysis was carried out based on the data extracted from publicly available Yearbooks of the Institute of Public Health of Serbia – Incidence and Mortality in Central Serbia, from 1999 to 2014. Cancer registry in Vojvodina is completely autonomous. Data about incidence and mortality for Kosovo and Metohija in the Cancer Register of the Republic Serbia has been missing since 1998. TC was coded according to the Tenth Revision of International Classification of Diseases-ICD-(codes C73) [18]. Age-standardized rates (ASRs) per 100000 persons during the period 1999-2014 were calculated using the direct method according to the World Health Organization (WHO) World Standard population. Data regarding population of Central Serbia were obtained from 1991, 2002, 2011 Censuses.

Trend and annual percentage change (APC) of the incidence and mortality rates with corresponding 95% confidence intervals (CI) were calculated by performing joinpoint regression analyses. The optimal number of Joinpoints was identified using the Monte Carlo

permutation method. For regression analyses, the Joinpoint Regression Program version 4.1.0 was used (available from: <http://surveillance.cancer.gov/joinpoint>). The trend was considered to be significant for an increase (positive change) or decrease (negative change) when the p-value was below 0.05 ($p < 0.05$).

RESULTS

From 1999 to 2014, the total number of new TC cases reached 3113. It was diagnosed in 2343 males and 770 males (female-to-male ratio, 3:1). The total number of fatal cases was 770 (504 females and 266 males died of thyroid cancer with a female to male ratio 1.9:1).

Table 1 shows the age-standardized incidence and mortality rates (per 100000 population) of TC in the male and female populations of Central Serbia for the period 1999-2014. In males, the number of new TC cases ranged from 27 (in 2000) to 80 (in 2012) and the average number of new cases was 48 and the ASRs of incidence in males ranged from 1.0 (in 2000) to 2.7 (in 2013 and 2014). In females the number of new TC cases ranged from 78 to 215 with an annual average number of 144 new cases. The ARSs in females ranged from 2.8 (in 1999) to 8.0 (in 2013). The annual ARS and annual-adjusted mortality rates of TC increased during the study period in both males and females. In the period 1999-2014, annual ASR of mortality ranged from 0.3 (in 2003) to 0.9 (in 2013 and 2014).

Table 2 reports the distribution of TC cases by gender and age, in central Serbia from 1999 to 2014. A total of 29.2% of new TC cases occurred in the 20-49-year age group. More than one quarter (27.4%) of new cases were recorded in the 50-59-year age group. Of all patients, 17.9% were aged over 70 years at the time of diagnosis. In the 40-49-year age group, new TC cases were significantly more frequent among females than among males (17.1% vs 11.8%, $p < 0.001$). Conversely, in the oldest group (over 70 years), new TC cases were significantly more frequent in males compared to females (22.7% vs 16.1%, $p < 0.001$).

Figure 1 shows the incidence trend, based on age-adjusted incidence rates in males and females, in the period 1999-2014, the Joinpoint analyses (world standard population) of TC in central Serbia, with annual percentage change (APC). Joinpoint regression analysis showed the statistically significant increase of ASR for TC incidence in males during the 1999-2014 period with APC of 6.2% (95% CI: 4.2-8.3, $p < 0.001$). Moreover, a significant increase of ASR was also present for TC incidence in females during the same study period, with APC of 6.1% (95% CI: 4.2-8.0, $p < 0.001$).

Figure 2 displays TC mortality in males and females in the period 1999-2014, Joinpoint analysis (world standard population) in central Serbia, with annual percentage change (APC). Joinpoint regression analysis showed an insignificant increase of TC mortality in males during 1999-2014 with APC of 1.52% (95% CI: 4.0-1.3, $p = 0.2$). In addition, a non-significant decrease of TC mortality was also present in females during the same study period with APC of -1.92% (95% CI: 0.4-1.8, $p = 0.10$).

Figure 3 shows TC mortality trend based on age-adjusted mortality rates in the period 1999-2014, in males and

Table 1

Age-adjusted* incidence and mortality rates (per 100 000 population) of thyroid cancer in male and female population of Central Serbia, 1999-2014

Year	Males				Females			
	No of cases	Incidence rate	No of deaths	Mortality rate	No of cases	Incidence rate	No of deaths	Mortality rate
1999	34	1.3	17	0.6	78	2.8	37	1.4
2000	27	1	17	0.6	87	3.1	40	1.4
2001	29	1.1	15	0.6	132	4.1	34	1.2
2002	33	1.2	17	0.6	104	3.7	25	0.9
2003	44	1.7	13	0.3	102	3.6	35	0.6
2004	41	1.5	15	0.6	133	4.8	35	1.3
2005	36	1.4	12	0.5	123	4.4	27	1
2006	45	1.7	19	0.7	153	5.5	35	1.3
2007	67	2.6	19	0.7	156	7.1	37	1.3
2008	38	1.5	16	0.6	193	7	35	0.9
2009	42	1.6	10	0.4	160	5.8	24	1
2010	58	2.2	16	0.6	161	5.9	27	1
2011	54	2.1	16	0.6	142	5.2	28	0.8
2012	80	2.6	19	0.7	181	6.8	24	0.5
2013	70	2.7	22	0.9	215	8	20	0.7
2014	69	2.7	23	0.9	183	6.8	41	1.5

*Standardization according to world population WHO.

Table 2

Distribution of thyroid cancer cases by gender and age, Central Serbia, 1999-2014

Age-group	Total N = 3113		Male N = 770		Female N = 2343		p-value ¹
0-19	109	3.5%	24	3.1%	85	3.6%	0.448
20-29	151	4.9%	43	5.8%	108	4.6%	0.274
30-39	293	9.5%	59	7.6%	234	9.9%	0.055
40-49	491	15.9%	91	11.8%	400	17.1%	< 0.001
50-59	849	27.4%	199	25.8%	650	27.7%	0.305
60-69	648	20.9%	179	23.2%	469	20.0%	0.055
≥ 70	553	17.9%	175	22.7%	378	16.1%	< 0.001

¹Chi squared test.

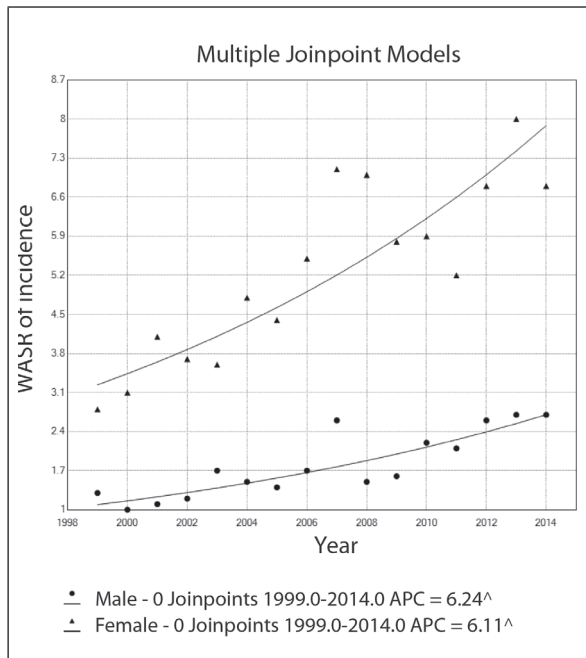
females, Joinpoint analyses (world standard population) in central Serbia, 1999-2014, with annual percentage change (APC). The Joinpoint regression analysis showed a non-significant ASR decrease of TC mortality in males during 1999-2014 with APC of 2.44% (95% CI: -0.5-5.5, p = 0.1). Also a non-significant ASR decrease of TC mortality was present in females during the same study period with APC of -1.31% (95% CI: -4.4-1.9, p = 0.4).

DISCUSSION

In our study results have shown an increasing trend of the age-adjusted TC incidence rate both in males and females, during the observed 1999-2014 period. A statistically non-significant increasing trend of age-adjusted TC mortality rate was found in males, and a non-significant decreasing trend of age-adjusted TC mortality rate was present in females. Indeed, females

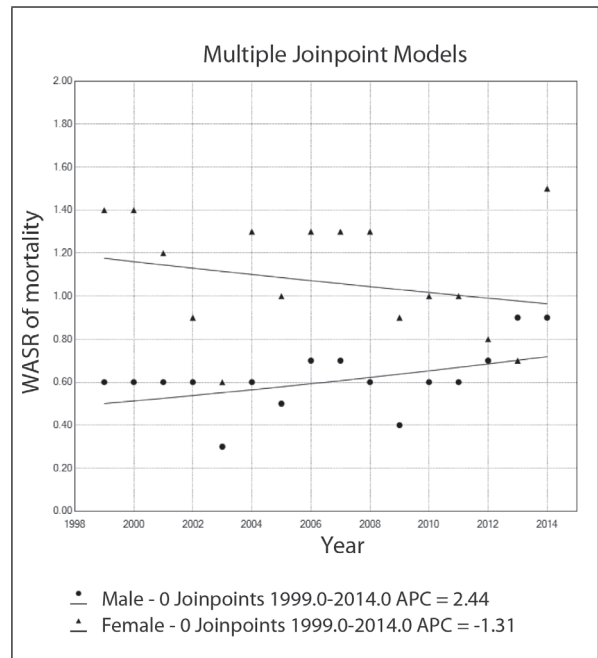
had higher annual age-adjusted incidence and mortality rates than males.

These results are in agreement with other studies, which have found a similar 3-to-1 ratio for females and males [5, 11, 12, 19, 20]. In agreement with findings from another study [8], which included 21 European countries, the average TC incidence rate ranged from 1.8 up to 5.0 for males and females respectively, for the 1995-2002 period. According to the average age-adjusted TC incidence rate in females (3.3 per 100 000 persons), Serbia ranks as a country with average TC incidence rates in females, and low incidence rates in males (1 per 100 000 persons). An increase in TC incidence in Serbia in both genders was found in the 1999-2008 period. The highest increase in TC incidence was found in females aged 20 to 29 years while the highest incidence was found in the 50-59-year age group [21].

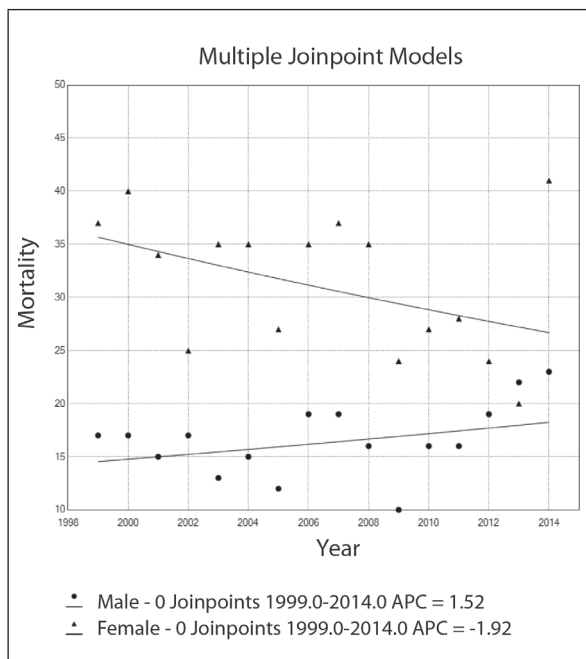
**Figure 1**

Incidence trend based on age-adjusted incidence rates in males and females in the period 1999-2014, Joinpoint analyses (world standard population) of thyroid cancer in central Serbia, with annual percentage change (APC).

WASR: World-Age-Adjusted Rate

**Figure 3**

Mortality trend of thyroid cancer based on age-adjusted mortality rates in the period 1999-2014, in males and females, Joinpoint analyses (world standard population) in central Serbia, 1999-2014, with annual percentage change (APC).

**Figure 2**

Mortality of thyroid cancer in males and females in the period 1999-2014, Jointpoint analysis (world standard population) in central Serbia, with annual percentage change (APC).

Between 1994 and 2007, TC incidence more than doubled in Vermont, USA [5]. The age-adjusted TC incidence in Vermont was 8.0 per 100 000 persons with a female-to-male ratio of 3.1:1, while mortality rate

was 0.5 per 100 000 persons. It was concluded that incidence among females peaked at 30-59 years of age, TC more than doubled in females aged between 30 and 59 years over the study period and the incidence even increased in males.

In our study, over the observed period, TC was registered in both genders. The steep increase of TC incidence after 30 years of age was observed in both females and males. The highest number of new TC cases was registered in the 50-69-year age group in both females (47%) and males (37%). These findings are consistent with similar published data, according to which, in Serbia in the 1999-2008 period, TC incidence increased substantially in both genders with the highest increase in 2007 for the 50-59-year age group. TC was three-fold higher in females (CR 4.7:1.5) than in males [21].

However, this increase of TC incidence has yet to be explained. Potentially, it could be due to enhanced diagnostic procedures. Indeed, the development and use of more sophisticated TC diagnostic technologies, which began in the late 1990s through the early 2000s, may have led to an over diagnosis of TC [16]. Conversely, TC mortality is stable and low [1, 14]. It is well-known that TC patients have a high survival rate [23]. Five-year relative survival for thyroid cancer ranged from 73% in Belgium to 96% in Iceland with a European average of 83% [8]. According to the GLOBOCAN 2012 database [22], TC mortality varied little, with slight differences between the sexes. In females, TC mortality rates were between 0.2 to 1.0 per 100 000 person-years, and in males, the range in TC mortality rates was from 0.1 to 0.7 per 100 000 person-years [22].

According to the findings reported by Olaleye *et al.* [23], the highest increase in TC was observed in the 50-59-year age group. The authors also found a significant increase in the 20-39-year age group, whereas we found the highest incidence increase between the 20-29-year and 30-39-year age groups, showing two-fold and four-fold increases in females and males, respectively. In Lithuania, a steep increase in incidence at the age of 30 years was observed in females [19]. The results from Croatia have shown that females had higher TC incidence than females in other European countries, including Serbia. Between of 1988-2010, TC was diagnosed in 5453 females and 1355 males (female-to-male ratio, 4:1), while 542 females and 282 males died from this malignant disease (female-to-male ratio, 2:1) [24-26]. The age-adjusted incidence rate among females in Finland was more than two-fold higher compared to that reported in Denmark in both time periods (1973-1977 and 1998-2002) [1].

It is also noteworthy that despite the wide inter-country variation in age-adjusted incidence rates, a consistent female-to-male ratio of three-to-one is observed within most of the countries included in the international comparison, in both the earlier (1973-1977) and later (1998-2002) periods [27, 28]. Possible explanations for the disparities between males and females with sporadic TC are biological sex differences, differential screening patterns, or gender-specific behavioral differences. One hypothesized mechanism is that increased levels of female hormones during reproductive years, due to pregnancy that increases thyroid stimulating hormone (TSH) levels, potentially lead to thyroid dysplasia and then to cancer [20, 28].

According to our results, discrepancies were observed between age-adjusted incidence rates in females and low rates in males. The TC is more common in females and the higher incidence might attribute to an increased detection of the disease in women than in men. Also a decline in mortality is due to the changes in diagnosis, treatment, and risk factors. These findings are in constancy with the literature [6, 18, 20, 23, 28].

Over the last three decades, TC incidence increased substantially also in the USA [5, 9, 11, 29]. Between 1998 and 2002, the highest age-adjusted rates were recorded in the USA and Israel in males (3.5 per 100 000 persons for both countries) and in females (10.0 per 100 000 persons and 12.1 per 100 000 persons, respectively), while the lowest rates were recorded in Uganda in males (0.5 per 100 000 persons) and in females (1.5 per 100 000 persons) [15, 16]. According to the National cancer registry of Ireland during the period 2006-2010, TC comprised just 0.9% of all invasive cancers registered (1.4% of all female cancers and 0.5% of male

cancers). Incidence rates increased significantly in both sexes, especially in females [10].

Trends in TC incidence and mortality vary widely by country, but for most areas of the world, the data indicate an upward trend in incidence and a downward trend in mortality. Those trends are supported by the present analysis of TC mortality and incidence, globally. The analyses were based on data maintained by the World Health Organization (1970-2012) and Cancer Incidence in Five Continents (1960-2007).

Limitations

Several limitations should be considered, such as lack of data regarding histological types of thyroid cancer, variations in tumor classifications related to analyses of registry data and possible incomplete data collection.

CONCLUSIONS

Our results highlighted a significantly increasing trend of age-adjusted TC incidence rates both in males and females, during the period 1999-2014. A statistically non-significant increasing trend of age-adjusted TC mortality rates in males and non-significant decreasing trend of age-adjusted mortality rates in females were observed during the observed period. Females had higher annual age-adjusted incidence and mortality rates compared to males with female-to-male ratios of 3:1 for incidence and 1.9:1 for mortality.

Authors' contribution statement

Conception and design of study: Stojanović Miodrag, Rančić Nataša, Zorica Antic, Miljkovic Snezana, Tatjana Rajovic.

Analysis and/or interpretation of data: Ignjatović Aleksandra, Stojanović Miodrag.

Drafting the manuscript: Stojanović Miodrag, Dijana Stojanović, Rančić Nataša.

Revising the manuscript critically for important intellectual content: Stojanović Miodrag, Dijana Stojanović, Rančić Nataša.

Approval of the version of the manuscript to be published: Stojanović Miodrag, Dijana Stojanović, Rančić Nataša, Ignjatović Aleksandra, Zorica Antic, Miljkovic Snezana, Tatjana Rajovic.

Conflict of interest statement

Authors of this original paper are not in conflict of interest. They did not receive any financial support.

All authors of the paper declare to be responsible for results, interpretation and conclusions in this paper.

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