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Thyroid Cancer in Tuzla region of Bosnia and Herzegovina: A 10-year study (1999–2008)

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A B S T R A C T

Bosnia and Herzegovina (B&H) is one of the Eastern European countries with lacking data on thyroid cancer (TC) epidemiology. We aimed to assess the incidence of TC in Tuzla Canton of B&H during a 10-year period (1999–2008). We retrospectively evaluated 65000 hospital records of both inpatients and outpatients with possible thyroid symptoms residing in Tuzla Canton of B&H (total of 496280 inhabitants) between 1999 and 2008. Patients with histological proof of TC were included in study. Incidence rates were calculated with age standardisation using European standard population. Trends in incidence were evaluated as moving three-year averages. During observed period 117 patients met the diagnostic criteria for TC with male to female ratio of 1:4.85. Median age of all cases was 51 years (interquartile range: 41 to 60) with men in average 9 years older than women at the time of diagnosis. The mean annual standardized incidence was found to be 2.30/10^5 (%95 CI=1.38–3.22) inhabitants ranging from 1.0 to 3.2 per 10^5. The average crude incidence in men was 0.82/10^5 and 3.83/10^5 in women. The prevalence of TC, at the end of the observed period was found to be 23.58/10^5 (%95 CI=19.3–27.58). There is a slight decline of incidence in our region during the observed period, but with the increase in the latest years of the study. This increase is probably the result of combination of various factors, mainly the better detection of new cases due to wider availability of diagnostics. Based on depicted trends, we believe that in the future years, TC incidence in our region will continue to rise.

Key words: *thyroid cancer, epidemiology, incidence, prevalence*

Introduction

It is estimated that thyroid cancer (TC) accounts for around 0.5 to 1 percent of all malignancies in human pathology[1]. Thyroid cancer is therefore, not as frequent when compared to more common benign thyroid diseases. Still, more than 1200 people die every year in USA as a consequence of this disease.

Although epidemiology of TC throughout the World and Western Europe is well described[1–9], data on epidemiology of TC in the region of southeast Europe is sparse and almost non-existent. There are several incomplete reports from Croatia and Serbia[10,11], while Bosnia and Herzegovina remains a region without reported data on epidemiology of TC. The only data available is the GLOBOCAN 2002 estimate – calculated by using the average rates in neighbouring countries[12].

Therefore, we aimed through 10-year retrospective review of our hospital records to assess epidemiological data on TC in a geographically well-defined region of Tuzla in northeast of Bosnia and Herzegovina.

Subjects and Methods

Settings

Bosnia and Herzegovina (B&H), since the end of Bosnian War (1992–1995) has two entities – Federation of Bosnia and Herzegovina and Republic of Srpska. Federation of Bosnia and Herzegovina further consists of 10 cantons, among which is the Tuzla Canton – well defined region in northeast of Bosnia and Herzegovina (Figure

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1). Estimated population in the region on December 31st, 2006 is 496280 (Federal Office of Statistics, Federation of Bosnia and Herzegovina, Sarajevo). Population in the region have been relatively stable since the war, yet the latest national census has not been performed since 1991, so most of the population data is based on estimates.

Fig. 1. Map of Bosnia and Herzegovina, showing the Tuzla Canton (solid black area).

University Clinical Centre Tuzla is a regional hospital centre and serves as a secondary and tertiary referral centre for the region. All patients with TC, residing in the region are therefore, mostly diagnosed in our centre. Medications used for treating TC are on Tuzla Canton Formulary List and are either free of charge or at a reduced price rate. But they can be prescribed only after written recommendation given by physicians in our hospital. Hence, one can assume that, in order for a patient with TC to receive medications, he has to be evaluated by a specialist in our hospital, which allows us to register and follow up most (if not all) of the patients residing in our region.

Patients and Methods

We retrospectively analyzed 65000 hospital records of both inpatients and outpatients with possible thyroid disease residing in Tuzla Canton of B&H between 1.1. 1999 and 31.12.2008. We excluded all patients that did not reside in Tuzla Canton. After that, we selected all patients with histological confirmation of thyroid cancer. We also recorded age, gender, date of initial diagnosis, size of primary tumour (cm), presence of extra thyroid invasion, presence of metastases, pTNM stage and clinical stage. Our records did not always contain sufficient clinical data to separate medullary carcinoma within multiple endocrine neoplasia (MEN) and without MEN, therefore both types were included in survival.

We classified tumours into 4 main histological types (papillary, follicular, medullar and anaplastic) according to WHO classification and using methodology previously described[7]. Patients with other types of tumours of thyroid gland such as other types of carcinomas, lymphomas, mesenchimal tumours and metastatic tumours were excluded from further analysis, mainly due to a very small (or non-existent) number of cases.

Statistical analysis

Statistical analysis was performed using SPSS 15.0 (SPSS, Chicago, IL, USA). Descriptive statistics has been used for determination of baseline characteristics. The year of diagnosis was used to date incidence. Calculations of TC incidence have been performed based on the latest (December 31st, 2008) population estimates in our region obtained from the Federal Office of Statistics, Federation of Bosnia and Herzegovina, Sarajevo. Ninety five per cent confidence intervals (95% CI) of incidence rates were estimated assuming a Poisson distribution of cases. Crude annual incidence rates were calculated based on the number of patients diagnosed and the number of inhabitants for both sexes while average incidence rate during observed period was calculated based on number of study years. Age standardized incidence rates were calculated using European standard population weights (22, 14, 14, 14, 14, 11, 7, 4) for each of our age group[13]. Trends in incidence from 1995–2006 were evaluated as moving three-year averages with %95 CI. Trends in incidence were also evaluated using linear regression model where applicable. Prevalence estimate during observed period was estimated based on the total number of cases detected and the number of inhabitants according to latest population estimates. Statistical level of 95% ($p< 0.05$) was considered as significant for all performed tests.

Results

During the 10-year period we registered 117 cases of TC with 97/117 (82.9%) of female and 20/117 (17.1%) of male patients – male to female ratio 1 to 4.85.

The median age in all patients with TC was 51 year (interquartile range 41 to 60 years) with a range spanning from 11 to 77 years. Female patients (48.7±13.3 years) were in average 9 years (%95 CI=2.4–15.5; $p= 0.008$) younger than male patients (57.7±14.3 years).

The largest proportion of patients in our sample (77/117; 66%) had papillary type of carcinoma, 33 patients (28%) had follicular type, 5 patients (4%) had medullar type while remaining 2 (2%) had anaplastic type of thyroid carcinoma.

The TNM stage of patients at the time of diagnosis is presented at the table 1. Most of the patients (46/117; 39%) were at the clinical stage III, followed by 39 (33%) patients at stage I, 17 (15%) at stage IV and 15 (13%) at stage I.

The average annual crude incidence of thyroid cancer during the observed period was $2.36/10^5$ population (%95 CI=1.93–2.78). The average crude incidence in men was $0.82/10^5$ and $3.83/10^5$ in women.

After we performed standardization according to standard European population, the average annual standardized incidence during the time period 1999–2008 was $2.30/10^5$ (%95 CI=1.38–3.22).

TABLE 1
PROPORTION OF STAGES OF THYROID CANCER ACCORDING TO PTNM CLASSIFICATION

pTNM classification			T				N		M	
			1	2	3	4	0	1	0	1
Age	≤45 years	N	13	7	16	7	31	12	40	3
		%	43.3%	35.0%	37.2%	29.2%	36.9%	36.4%	37.4%	30.0%
	>45 years	N	17	13	27	17	53	21	67	7
		%	56.7%	65.0%	62.8%	70.8%	63.1%	63.6%	62.6%	70.0%
Total			30	20	43	24	84	33	107	10

The sum prevalence during the study period calculated for population numbers on 31.12.2008, was 23.58/10^5 population (%95CI=19.30–27.85). Prevalence among men was 8.24/10^5 (%95 CI=4.63–11.85) and 38.27/10^5 (%95 CI=30.66–45.89) among women.

The annual incidence for men and women and complete sample is depicted in Figure 2. As demonstrated incidence rates for the complete sample spanned between 1/10^5 and 3.2/10^5. The largest incidence recorded was among women in year 2000 (5.92/10^5).

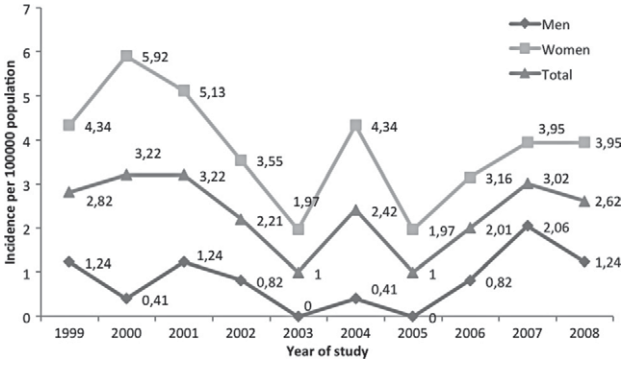

Fig. 2. Annual incidence of thyroid cancer in Tuzla region of Bosnia and Herzegovina during the period 1999–2008 in both gender and complete sample.

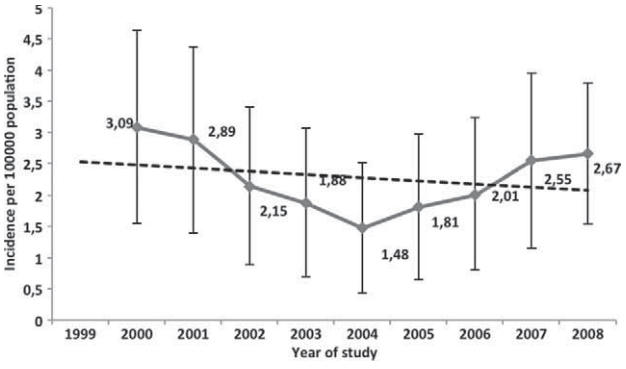

Fig. 3. Trend of annual incidence of thyroid cancer in Tuzla region of Bosnia and Herzegovina during the period 1999–2008. Dotted line represents the linear regression trendline; vertical lines represent confidence intervals.

A trend in incidence during the observed period is depicted in figure 3 as moving three-year average with 95% confidence intervals. The slight decline in incidence during the observed period is indeed noticeable which was confirmed with linear regression line which is also presented in the same figure.

The graphic display of incidence according to gender and age is presented in figure 4. The largest incidence was found in women age 55–64, while peak incidence in men was in older age group of 65–74.

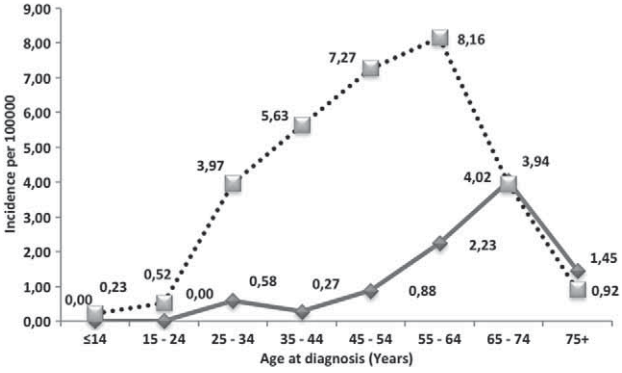

Fig. 4. Incidence of thyroid cancer according to age at the time of diagnosis and gender of the patient.

Out of 117 cases of TC we recorded total of 5 patients with lethal outcome (4,3%). Anaplastic TC was cause of death in 2/5 (40%) of patients, while follicular cancer was cause of death in the remaining 3 (60%) patients. The mean time to death was 28 months (%95CI=6–50 months), with significant difference (X^2=4,26; df=1; p=0,04) between anaplastic cancer (mean time to death 2 months; %95 CI=0–4 months) and folicular cancer (mean time to death 45 months; %95 CI=33–57 months).

Discussion

As already stated, the only data on epidemiology of TC in the Bosnia and Herzegovina is available through GLOBOCAN 2002 project that is based on the estimate – the crude average of the numbers in the neighbouring countries. According to GLOBOCAN it was estimated

that the average crude incidence of TC among men equals to $1.8/10^5$ and $5.2/10^5$ among women.[12] Our results indicate that numbers regarding the incidence in the Tuzla region of B&H may be a little smaller with $0.82/10^5$ among men and $3.83/10^5$ among women.

Compared to published data on incidence in the neighbouring countries it appears that Croatia has significantly higher incidence (8.8 and 2.5 per 10^5 for women and men, respectively) again, according to GLOBOCAN report. At the other end of the spectre is another neighbouring country – Serbia and Montenegro (numbers reported before those two countries separated) with incidence rates of $2.1/10^5$ among women and $0.9/10^5$ among men. Apparently our figures reside in the middle. However it is important to discuss the reasons for such differences in a relatively small region.

The most probable explanation for lower incidence is that is the result of a poor ascertainment and lack of reliable diagnostics. It is not a secret that B&H is a developing country struggling to cope with the consequences of the terrible war. The availability of both the equipment and trained physicians may be an important contributing factor to false reduction of incidence rates. This is reason why we encounter more patients with advanced TC at diagnosis (Table 1); they are probably detected later during the natural course of their disease.

Another possible explanation may be the Chernobyl accident; according to United Nations Scientific Committee on the Effects of Atomic Radiation, Croatia was one of the countries with the highest exposition to nuclear contamination after the accident[14]. It has been widely speculated that beside improved diagnostics, Chernobyl incident may be another contributing factor in the rise of incidence of thyroid cancer witnessed throughout the Europe in the last 20 years[3–5,9,10]. Tuzla region lies behind the rather high mountainous region in the north, which might have provided some protection against wind carried radioactive clouds during the incident.

Of course there is an issue of high variability of TC incidence in different countries that also needs to be mentioned. Recently published study analyzed trends in incidence of TC in various countries on several continents[3]. With exception of Sweden, all of the analyzed countries reported rise in incidence rates. However, there were significant variations in incidence rates among countries belonging to the same continents, with the exception of Africa with a very low incidence reported in all of countries.

Incidence of TC is on the continuing rise in the last 10–20 years; several studies from various regions of the World irrefutably confirm this fact[4,6,9,15–19]. Although this trend in rise of the incidence is a consequence of the exposure to various risk factors such as radiation, iodine supplementation etc, an important additional factor that at least partially results in the rise of incidence is increase in the number of diagnostic procedures, availability of sophisticated diagnostic methods and change in histological criteria[20].

There is also an interesting phenomenon observed during the study period. During the 3-year time period of 2003–2005 there is apparent nadir of incidence with a subsequent rise in the later study years. The corresponding line consequently has the shape of the wide letter V (Figure 3). This also does not correspond with the real decline in incidence but rather with the lower availability of diagnostic procedures in our hospital in that particular time period. This is purely a result of frequent equipment malfunctions, lack of educated physicians that we encountered. Rise of incidence in the following years, once we successfully remedied all of the listed problems is another indirect proof of our claim.

The higher ratio of female patients with TC (4.85 to 1) in our study is not surprising. Domination of female patients is a well established fact reported in numerous studies[3–8,20,21]. Also, according to our results men were in average 9 years older at the moment of the diagnosis. This was also recognized in several previously published studies[2,4,6]. This is why female gender is a firmly established risk factor for all types of thyroid cancer[22].

There are several limitations of this study that need to be mentioned. This is a hospital-based series and there is a possible limitation of referral bias. Survey is retrospective, but given the challenging conditions we were in, it was the only possible way of collecting data. Also, it is based on patient records from a single hospital. Yet, our hospital is the only centre in our region with the full diagnostic capability for diagnosing TC, and it is explained that due to our peculiar conditions every TC patient eventually ends up in our centre. Nevertheless, we allow for possibility that small number of patients remains undetected.

Another important fact we have to mention is lack of completely reliable data on general population in our region. Due to known reasons (war, political situation) national census has not been conducted since 1991. War casualties and extensive population migration, together with change of administrative borders make estimation of population numbers a very difficult task. Estimate figures we used in our paper are the best that could be obtained at the moment and are based on the official estimate by our Federal Office of Statistics. As a consequence this period is not optimal to conduct epidemiology studies even if done prospectively, but it was our intention to purposely study it, due to specific conditions. Figures from the last 5 years of study are however, more reliable.

Despite limitations, we believe that this study brings information of great local and regional importance. Given the fact that data on TC epidemiology from Bosnia and Herzegovina does not exist, providing as accurate estimate as possible in our setting is certainly better than having no data at all. Also, demonstration of a possible link between the availability of diagnostics and TC incidence, in our opinion, provides a good explanation why we are encountering increase in frequency of TC in Eastern Europe including Bosnia.

In conclusion we demonstrated the slight decline of incidence in our region during the observed period, but with the increase in the latest years of the study. This increase is probably the result of combination of various

factors, mainly the better detection of new cases due to wider availability of diagnostics. Based on depicted trends, we believe that in the future years, TC incidence in our region will continue to rise and it is up to prospective surveys in the years to follow to confirm our projections.

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KARCINOM ŠTITINJAČE NA PODRUČJU TUZLANSKOG KANTONA BOSNE I HERCEGOVINE: 10 GODIŠNJA STUDIJA (1999–2008)

SAŽETAK

Bosna i Hercegovina (BiH) je jedna od država istočne Europe bez valjanih podataka o epidemiologiji karcinoma štitnjače. Ciljevi su istraživanja utvrditi incidenciju karcinoma štitnjače u Tuzlanskom kantonu BiH tijekom 10-godišnjeg razdoblja (1999–2008).Retrospektivno smo evaluirali 65.000 medicinskih kartona, kako bolničkih tako i ambulantnih bolesnika s mogućim simptomima bolesti štitne žlijezde, a koji su nastanjeni i Tuzlanskom kantonu (ukupno 496.280 stanovnika) u periodu između 1999 i 2008. Pacijenti s histološki dokazanim karcinomom štitinjače bili su uključeni u studiju. Stope incidencije izračunate su uz dobnu standardizaciju koristeći europsku standardnu populaciju. Trendovi u incidenciji su procijenjeni koristeći pokretni trogodišnji prosjek. Za vrijeme posmatranog perioda 117 pacijenata je zadovoljavalo dijagnostičke kriterije za karcinom štitnjače, uz omjer muškog i ženskog spola od 1:4.85. Medijan dobi za sve slučajeve bio je 51 godina (interkvartilni raspon: 41 – 60) sa muškarcima u prosjeku za devet godina starijim od žena u vrijeme uspostavljanja dijagnoze. Prosječna standardizirana godišnja incidencija je iznosila 2.30/105 (%95 CI = 1,38–3,22 95) stanovnika sa rasponom kretanja za vrijeme posmtranog perioda od 1,0–3,2/105 stanovnika. Prosječna godišnja incidencija u muškaraca je iznosila 0.82/105 dok je u žena ona iznosila 3.83/105. Prevalenca karcinoma štitinjače na kraju promatranog perioda je iznosila 23.58/105 (% CI = 95 19,3–27,58).Postoji blagi pad incidencije u našoj regiji u toku posmatranog perioda, ali s povećanjem u posljednjim godinama studije. Taj porast je vjerojatno rezultat kombinacije različitih čimbenika, uglavnom bolje detekcije novih slučajeva zbog šire dostupnosti dijagnostike. Na temelju opisanih trendova, vjerujemo da će u narednim godinama incidencija karcinoma štitinjače u našoj regiji i dalje rasti.