IODINE INTAKE AND EPIDEMIOLOGICAL CHARACTERISTICS OF THYROID CANCER: COMPARISON BETWEEN INLAND AND LITTORAL CROATIA

Nikola Kolja Poljak[1], Mirko Kontić[1], Zaviša Čolović[1], Iris Jerončić[2], Boris Lukšić[3] and Rosanda Mulić[2]

[1]University Department of ENT, Head and Neck Surgery, Split University Hospital Center; [2]Department of Public Health, School of Medicine, University of Split; [3]University Department of Infectious Diseases, Split University Hospital Center, Split, Croatia

SUMMARY – The aim of the study was to determine epidemiological characteristics of thyroid cancer in Dalmatia and Slavonia, to analyze regional differences in its incidence, and to determine whether iodine intake had an impact on the incidence. This epidemiological study was based on data published by the Croatian National Cancer Registry (CNCR) in the Croatian Health Service Yearbook and CNCR Bulletin. Data on 651 thyroid cancer patients operated on in Dalmatian hospitals between 1997 and 2006 were analyzed. Control group consisted of thyroid cancer patients operated on in Slavonia (N=498). Incidence rates recorded in Dalmatia were compared with those in Slavonia. Iodine intake was measured in elementary schoolchildren in the Split-Dalmatia and Osijek-Baranya Counties. Iodine excretion levels were measured in 131 children. In the 10-year period, the mean age-standardized incidence rate (ASR) of thyroid cancer was 9.32 *per* 100,000 inhabitants in Dalmatia and 6.02 in Slavonia. The difference was statistically significant ($P<0.001$). Incidence rates (World ASR, European ASR, crude incidence rate and research rates) showed an increase and were significantly higher in Dalmatia than in Slavonia. Patient sex structure showed the disease to be 4 times more common in women than in men. In Dalmatia sample, women accounted for 81.4% of all patients and papillary cancer accounted for 80.03% of all thyroid cancers. Median age of new patients was 50 in Dalmatia and 48 in Slavonia. Papillary cancer accounted for 63.7% of all patients in Slavonia. Follicular thyroid cancer accounted for 20.9% of patients in Slavonia and 12.4% in Dalmatia. Epidemiological characteristics of thyroid cancer in Dalmatia were found to be consistent with the characteristics of this cancer in iodine-sufficient areas: papillary carcinoma was the most common type and the papillary to follicular ratio was 6.4:1. Follicular cancer accounted for 12.4% of the total number of patients. In Slavonia, the papillary form predominated, the papillary to follicular ratio was 3:1, and follicular cancer accounted for 20.88% of all patients. Median urinary iodine excretion in elementary schoolchildren was 23.6 μg/dL in the Split-Dalmatia County and 28.1 μg/dL in the Osijek-Baranya County. The difference was not statistically significant ($P<0.050$). In conclusion, the average iodine intake levels in Dalmatia and Slavonia were not the cause of the high thyroid cancer incidence in the 1997-2006 period. Improved thyroid cancer diagnosis may be one of the causes of the increased thyroid cancer incidence in Dalmatia.

Key words: *Thyroid cancer – epidemiology; Croatia – epidemiology*

Correspondence to: *Prof. Rosanda Mulić, MD, PhD*, Department of Public Health, School of Medicine, Šoltanska 2, HR-21000 Split Croatia
E-mail: rosanda@pfst.hr

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Introduction

Thyroid cancer incidence rates worldwide vary between 2 and 14 cases *per* 100,000 inhabitants[1]. The highest incidence rates have been recorded in island countries like Hawaii, Japan, Iceland, the Philippines, and in some regions of Sicily and Cyprus. In women in the USA, thyroid cancer accounts for 3% of all cancers and is the eighth most common cancer[1-4]. Around 120 cases of thyroid cancer are recorded every year in Denmark, a country of some 5 million inhabitants[5]. In Croatia with a little fewer than 4.5 million, 394 new thyroid carcinoma cases were recorded in 2004 and 411 cases in 2009[6-8]. In the period between 1968 and 2004, the age-standardized rate (ASR) of thyroid cancer incidence (*per* 100,000 inhabitants) in Croatia increased 8.6-fold in women (1.1:9.4) and 3.6-fold in men (0.8:2.9)[9]. Since the year 2000, thyroid cancer has ranked among the ten most common cancers in women[8,10], ranking Croatia in the group of countries with a high incidence and low mortality of thyroid cancer, along with Italy, France, Finland, the USA and Australia[1,11]. Thyroid cancer incidence is constantly increasing, but death rates remain low and even show a slight decline. However, incidence rates differ significantly among parts of Croatia: Slavonia has 3 times lower thyroid cancer incidence rates than Dalmatia[12,13].

The fact is that Croatia has one of the highest incidence rates in Europe, that they vary among particular regions of the country, and that the highest rates seem to be recorded in Dalmatia. At the same time, the lowest prevalence of goiter among schoolchildren detected by palpation and/or ultrasound is also recorded in Dalmatia and is 8%[14].

Some authors claim that the use of iodized salt or higher iodine intake in previously iodine deficient areas was the likely cause of the increased incidence of papillary carcinoma[15,16]. Countries that have tackled endemic iodine deficiency report higher rates of differentiated (papillary and follicular) than undifferentiated thyroid cancers[15].

In addition to iodine intake, some research on the role of diet indicate that excessive consumption of dairy products, root vegetables and multivitamins can be a risk factor for differentiated thyroid carcinoma[16].

The present study starting point was the geographical position of Croatia consisting of the islands, the littoral (coastal) and the inland regions, i.e. to compare thyroid cancer incidence with iodine intake and to determine whether iodine intake influenced the higher incidence of this type of cancer.

The aim of the study was to determine epidemiological characteristics of thyroid cancer in Dalmatia, to compare them with epidemiological characteristics of thyroid cancer in Slavonia, to interpret the reasons for or the causes of the increasing incidence, to look into the possible incidence among younger age groups and to analyze regional variations in the incidence. The hypothesis was that papillary thyroid carcinoma had a higher incidence and was more common in Dalmatia than in Slavonia, as a consequence or result of the higher iodine intake.

Materials and Methods

Data of the Croatian National Cancer Registry (CNCR) published in the Croatian Health Service Yearbook and CNCR Bulletin[6-8,10] and data on 651 surgically treated patients operated on in Dalmatian hospitals between 1997 and 2006 were used in the study. The number of inhabitants was based on the 2001 census of the Croatian Bureau of Statistics.

The geographical and geopolitical term "Dalmatia" covers the area of four present-day counties: Zadar, Šibenik-Knin, Split-Dalmatia and Dubrovnik-Neretva counties (861,060 inhabitants, area of 11,960 km^2). Dalmatian coastline spans some 1200 km, which is almost 2/3 of the Croatian Adriatic coast.

Slavonia was taken as a control group (891,259 inhabitants, area of 12,466 km^2); it is a region in Croatia covering four counties: Virovitica-Podravina, Požega-Slavonia, Slavonski Brod-Posavina, Osijek-Baranya and Vukovar-Srijem counties.

Age- and sex-specific incidence rates were calculated using population estimates from the 2001 census[17], the European Standard Population (ESP) and the World Standard Population (WSP). In the first part of the study, crude and standardized incidence rates were calculated with 95% confidence interval (CI). Patient age and sex structure and the structure of histopathologic types in the available data on 651 surgically treated patients operated on in Dalmatian hospitals between 1997 and 2006 were also calculated. All persons included in the study permanently resided in Dalmatia and had the histopathologic diagnosis of thyroid cancer.

Data on histopathologic types of cancer in Slavonia were extracted from a study published by Mihaljević[11].

The second part of the study focused on the correlation between iodine intake and urinary excretion. This included respondents from Slavonia (Osijek-Baranya County) and Dalmatia (Split-Dalmatia County). Urine samples were collected in April 2009 from 131 children: 71 from the Osijek-Baranya County and 60 from the Split-Dalmatia County. The group consisted of 75 (57.3%) boys and 56 (42.7%) girls. Urine iodine content was measured at the Sestre milosrdnice University Hospital Center Laboratory in accordance with the International Council for the Control of Iodine Deficiency (ICCIDD) and the World Health Organization (WHO) recommendations. Concentration was determined using the modified colorimetric method according to Wawschinek *et al*., based on the Sandel-Katoff reaction[18].

In this study, threshold value for statistical significance was set at $P \leq 0.05$.

The incidence is presented as crude and world age standardized rates *per* 100,000 population, with trend analysis. Differences in the frequency of particular

Table 1. Standardized incidence rates (per 100,000 population) for thyroid cancer in Croatia in the 1997-2006 period

	Year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Crude incidence	Total rate	5.25	5.02	7.35	8.98	8.63	6.53	7.12	7.47	9.33	10.27
	M rates	1.91	1.44	4.31	1.67	2.87	2.39	2.15	3.35	4.07	4.79
	F rates	8.42	8.42	10.24	15.93	14.11	10.47	11.84	11.38	14.34	15.48
WSP	Total	4.54	4.16	6.39	7.26	7.36	5.6	5.65	5.83	7.66	8.16
	M	1.79	1.19	3.8	1.43	2.39	2.13	1.56	2.53	3.34	4.07
	F	7.27	7.01	8.91	12.85	12.18	9.18	9.67	9.03	11.77	11.93
ESP	Total	5.13	4.75	7.21	8.57	8.53	6.26	6.67	6.8	8.97	9.61
	M	1.87	1.35	4.07	1.53	2.57	2.41	2.02	3.16	3.83	4.77
	F	8.37	8	10.26	15.28	14.28	10.23	11.22	10.31	13.83	14.02
Crude incidence 0-64	Total 64	5.52	5.11	7.6	8.7	8.42	6.77	6.49	6.63	8.56	9.53
	M 0-64	1.92	1.65	4.12	1.65	2.2	2.2	1.37	3.02	3.3	5.22
	F 0-64	9.16	8.61	11.11	15.83	14.72	11.39	11.66	10.28	13.89	13.89
WSP 0-64	WSP 64 total	4.62	4.13	6.44	6.99	7.16	5.62	5.23	5.32	7.14	7.61
	WSP 64 M	1.77	1.3	3.66	1.41	2.02	1.86	1.11	2.28	2.87	4.18
	WSP 64 F	7.43	6.93	9.11	12.51	12.22	9.4	9.34	8.37	11.31	10.92
ESP 0-64	ESP 64 total	5.31	4.79	7.37	8.35	8.38	6.39	6.2	6.2	8.43	9.06
	ESP 64 M	1.85	1.51	3.91	1.51	2.06	2.15	1.44	2.86	3.23	5.16
	ESP 64 F	8.72	8.01	10.69	15.09	14.58	10.65	10.94	9.54	13.48	12.93
Crude incidence 0-74	Total 0-74	5.44	5.19	7.35	9.02	8.9	6.67	7.41	7.41	9.27	10.13
	M 0-4	1.74	1.49	4.31	1.74	2.98	1.99	2.24	3.23	3.98	4.97
	F 0-74	9.09	8.84	10.24	16.21	14.74	11.3	12.53	11.55	14.49	15.23
WSP 0-74	0-74 total	4.62	4.23	6.53	7.25	7.48	5.64	5.77	5.75	7.58	8.02
	0-74 M	1.67	1.23	3.75	1.48	2.47	1.76	1.61	2.43	3.27	4.2
	0- 74 F	7.5	7.14	9.19	12.9	12.38	9.47	9.88	9.04	11.75	11.71
EWP 0-74	0 - 74 total	5.27	4.87	7.43	8.61	8.72	6.35	6.87	6.76	8.94	9.51
	0-74 M	1.72	1.4	4	1.59	2.67	2	2.1	3.03	3.76	4.97
	0-74 F	8.72	8.21	10.69	15.43	14.63	10.65	11.56	10.38	13.92	13.86

F = female; M = male; WSP = World Standard Population; ESP = European Standard Population

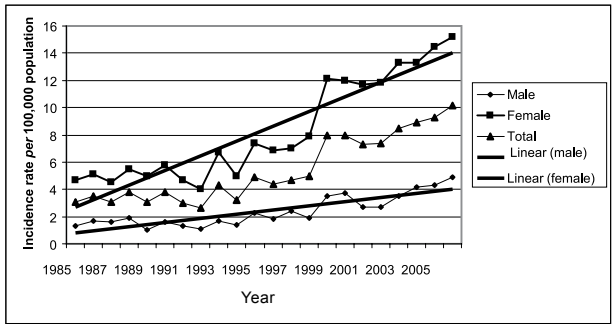

Fig. 1. Trends in thyroid cancer according to sex, Croatia, 1985-2007 (data obtained from the Croatian National Cancer Registry).

thyroid cancer types by sex are expressed as odds ratio (OR) with 95% confidence interval (CI) and *P* value. Statistical analyses were performed using the Statistical Package for Social Sciences, version 8.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Thyroid cancer incidence in Croatia

Thyroid cancer incidence in Croatia was observed during a period of ten years (1997-2006) and rates were standardized to the ESP and WSP (Table 1). In all study years, the rates were statistically significantly higher in women than in men ($P<0.001$) and all rates (crude, ESP and WSP) showed an increasing trend.

Trends in thyroid cancer incidence in Croatia

Analyzed data were taken from the CNCR, refer to the period between 1985 and 2007, and were expressed as morbidity rate *per* 100,000 inhabitants. There was an obviously rising trend in the incidence, more pronounced in women than in men (Fig. 1).

New cases – incidence in Dalmatia and Slavonia

According to the CNCR run by the Croatian National Institute of Public Health, county data have been collected since 1998; that is why new thyroid cancer cases (incidence) were observed for the 1998-2006 period. During that period, 723 new thyroid cancer patients were recorded in Dalmatia, yielding an incidence rate of 9.32 *per* 100,000 inhabitants. In the same period, 483 new cases with a mean incidence of 6.02 *per* 100,000 inhabitants were recorded in Slavonia.

Incidence rates were statistically significantly higher in Dalmatia ($\chi^2=56.24$; df 1; $P<0.001$). Comparison of the overall incidence rates for Croatia, Dalmatia and Slavonia revealed the rates in Slavonia to be lower

Table 2. Thyroid cancer incidence (per 100,000 inhabitants) in Dalmatia and Slavonia in the 1998-2006 period

Year	Dalmatia	Inhabitants	Incidence/ 100000	Slavonia	Inhabitants	Incidence/ 100000	χ^2	df	*P*
1997									
1998	44	861482	5.11	36	891259	4.04	1.1	1	0.295
1999	69	861482	8.01	39	891259	4.38	9.39	1	0.002
2000	87	861482	10.10	37	891259	4.15	21.9	1	<0.001
2001	75	861482	8.71	41	891259	4.60	11.16	1	<0.001
2002	72	861482	8.36	54	891259	6.06	3.22	1	0.072
2003	90	861482	10.45	67	891259	7.52	4.2	1	0.041
2004	72	861482	8.36	59	891259	6.62	1.77	1	0.183
2005	114	861482	13.23	77	891259	8.64	8.48	1	0.004
2006	100	861482	11.61	73	891259	8.19	5.18	1	0.023
Total	723	861482	83.93	483	891259	54.19	56.24	1	<0.001
Mean			9.32			6.02			

df = degree of freedom; data obtained from the Croatian National Cancer Registry

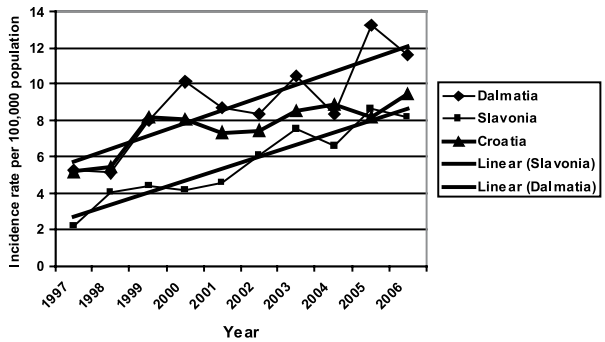

Fig. 2. Thyroid cancer trends in Croatia, Dalmatia, and Slavonia 1997-2006.

than the national ones, with all three rates showing rising trends in recent years. The most prominent rise was recorded in Dalmatia (Fig. 2).

Comparison of some clinical and epidemiological thyroid cancer indicators between Dalmatia and Slavonia is illustrated in Table 3. The two regions differed in the length of the period observed; median patient age (patients in Dalmatia were generally older); frequency of metastases, which were less common in Dalmatia (19.5% in Slavonia and 12.6% in Dalmatia); and structure or occurrence of tumor histologic types. Although papillary cancer was the most common type, followed by follicular cancer in both regions, there were some differences: papillary cancer accounted for 63.7% and 80% of all thyroid cancers in Slavonia and Dalmatia, respectively. Differences were also found in follicular types; they accounted for 20.9% of cases in Slavonia and 12.4% of cases in Dalmatia. The papillary to follicular thyroid carcinoma ratio was 6.4:1 in

Table 3. Comparison of some thyroid cancer indicators in Dalmatia and Slavonia

	Slavonia	Dalmatia
Inhabitants in 2001	891259	861482
Research period	1969-2005 (36 years)	1997-2006 (10 years)
Patients registered during the study period according to the Croatian National Cancer Registry	533	723
Respondents	498	651
Median patient age	48	50
Sex structure of patients: female to male ratio	4.9:1 (413/85)	4.4:1 (530/121)
Regional lymph node metastases	19.5%	12.6%
Remote lymph metastases	1.2 %	0.9%
Papillary ca. (M+F)	63.7%	80.0%
Follicular ca. (M+F)	20.9%	12.4%
Papillary to follicular cancer ratio in overall number of thyroid cancer patients	3:1	6.4:1
Medullary ca. (M+F)	9.03%	6.5%
Anaplastic ca. (M+F)	2.2%	1.1%
Papillary ca (M)	13.2%	17.5%
Papillary ca. (F)	86.8%	82.5%
Follicular ca. (M)	18.3%	21.0%
Follicular ca. (F)	81.7%	79.0%
Anaplastic ca. (M)	27.3%	28.6%
Anaplastic ca. (F)	72.7%	71.4%
Standardized incidence in the 1998-2006 period	6.02 *per* 100000 inhabitants	9.32 *per* 100000 inhabitants

Table 4. Age and sex structure of children with their iodine levels measured

Age group (yrs)	Split-Dalmatia		Osijek-Baranya		Total
	M	F	M	F	
5-9	11	10	19	12	52
10-14	18	21	25	15	79
Total	29	31	44	27	131

Dalmatia and 3:1 in Slavonia (Table 3).

Medullary thyroid cancer was slightly more common in Slavonia (9.03%) than in Dalmatia (6.5%). Anaplastic forms were rare but again more common in Slavonia (2.2%) than in Dalmatia (1.1%).

Urinary iodine excretion in schoolchildren

The study included 131 elementary schoolchildren from the Split-Dalmatia and Osijek-Baranya counties (Table 4).

Measurements of urinary iodine excretion (UIE) levels in children of elementary school age showed median UIE of 23.6 μg/dL in the Split-Dalmatia County and 28.1 μg/dL in the Osijek-Baranya County. The difference was not statistically significant (P<0.50).

Discussion

The role of iodine in the pathogenesis of thyroid cancer has not been clarified to a satisfying degree and has instigated many discussions and contrasting viewpoints. Numerous epidemiological studies compared the incidence and risk of developing thyroid cancer between regions with iodine deficiency and those with sufficient iodine intake[19-24]. Some studies compared thyroid carcinoma incidence before and after the introduction of iodine prophylaxis[25,26].

Inland Croatia used to be a region with a high goiter prevalence and socioeconomic consequences of insufficient iodine intake were inconceivable; that is why salt iodination was prescribed mandatory by law as early as 1953. The results were visible 10 years later, i.e. threefold reduction of goiter prevalence and eradication of cretinism. Salt iodination levels were corrected in 1996 following the modification of iodine deficiency levels from high to moderate[14,27].

During the past decades, thyroid cancer incidence has shown multiple increases all over the world, including Croatia. The higher rate of papillary carcinoma has been associated with higher iodine intake. This effect of increased iodine intake on the histopathologic characteristics of thyroid cancers is known as "papillarization"[12,14,25,26]. Moreover, for the past few years, thyroid cancer has been among the ten most common cancers in women in Croatia[6-8,10]. At the same time, mortality rates have remained low or have even shown a falling tendency both in Croatia and many countries worldwide[9,12].

The main cause of the increasing numbers of thyroid cancer worldwide is believed to lie in improved diagnosis and evolution of clinical practice, which is mostly due to the introduction of ultrasound and cytologic biopsy in the early 1980s[5].

Most authors believe that cancer incidence has increased because of improved diagnostic methods, higher healthcare availability and better detection[28-32]. Hall *et al*. compared the number of health checks made using the ultrasound, magnetic resonance imaging (MRI) and computerized tomography with the increasing incidence of thyroid cancers and found a clear link between the two and an explanation to the question why thyroid cancer is more frequently diagnosed in women. Their results show that until age 60 women have been exposed to such tests twice as often as men of the same age. The authors believe that the increase in the incidence is exclusively due to better detection[28]. Enewold *et al*. were more careful when interpreting the increased thyroid cancer incidence[31]. They looked into the reasons for the rising incidence in the USA in the 1980-2005 period and were unable to identify an exclusive cause. Moreover, in discussion on the reasons that might have led to the increase they state that the increased detectability should result in the increased incidence of all types of thyroid cancers, and not just of the papillary type.

Our study also suggested the rising incidence of thyroid cancer to be almost exclusively due to the increase in papillary cancer. Thyroid cancer incidence is higher in most island countries (Iceland, the Philip-

pines, Japan, Hawaii, some areas of Sicily) when compared to other countries[1]. On the Croatian side of the Adriatic Sea, there are 1245 islands, islets and reefs[33], making Croatia an island country as well. One of the reasons why island countries have higher thyroid cancer incidence rates could be volcanic lava radiation. Another reason lies in the diet, i.e. increased iodine intake through seafood, a common dietary element on the islands and along the coast. The highest iodine quantities are taken in with milk and fish[34,35]. It is worth noting here that on the Croatian side of the Adriatic Sea, there are only two islands of volcanic origin (Jabuka and Brusnik), both uninhabited. This fact eliminates the factor of lava radiation as a cause of thyroid carcinoma in the Croatian littoral.

Since the increased incidence coincides with higher iodine intake, many researchers today wonder if it is the increased iodine intake that causes higher thyroid cancer incidence.

Croatia is a country with two distinct regions: the inland area that used to have low iodine intake levels[27], and the islands and the littoral area that used to be a iodine-sufficient area due to higher iodine intake with food. This fact was used in the present study to determine whether iodine intake caused the higher thyroid cancer incidence in Dalmatia.

Epidemiological characteristics of thyroid cancer in Slavonia (inland region) and Dalmatia (islands and the littoral) were compared with the respective iodine intake. The Slavonian sample[12] included 498 respondents and the Dalmatian sample[36] 651 respondents.

Factors such as median patient age, occurrence of metastases, lymph node metastases and percentage of histologic types of thyroid cancer were compared overall and by sex. Iodine intake/excretion in schoolchildren was measured as one of the external (environmental) factors that could have an impact on thyroid cancer occurrence.

The main reason for the present study was the significant difference in the incidence between Slavonia and Dalmatia. Crude incidence rates were eliminated and standardized rates showed statistically significant differences. In the 1998-2006 period, the mean thyroid cancer incidence was 9.32 *per* 100,000 inhabitants in Dalmatia and 6.02 *per* 100,000 inhabitants in Slavonia. The difference is clearly statistically significant (χ^2=56.24, d.f.=1; P<0.001).

In addition to standardized incidence rates, regions differed in respondent age, i.e. they were 2 years older in Dalmatia than in Slavonia. However, since the observation period was longer in Slavonia (35 years) than in Dalmatia (10 years), definite conclusions on the mean patient age would not be advisable as the circumstances and factors that had an impact on the incidence could have been different. The authors of this study are of the opinion that over the past ten years both healthcare availability and the quality of diagnosis have improved.

Most studies have shown that papillary thyroid carcinoma is three to four times more common in women than in men. A study conducted in Dalmatia showed a ratio of 4.7:1 (430/91) and that conducted in inland Croatia a ratio of 4.5:1[23].

Well differentiated thyroid cancers (papillary and follicular) usually occur in younger people, with papillary type being more common than follicular type[37,38].

In the Dalmatian sample of patients (N=651), 430 of 521 (80.0%) persons suffering from papillary type were women. Thyroid cancer overall and papillary thyroid cancer were both more commonly found in women, who accounted for 81.1% of all patients (430 of 530 women suffering from all thyroid cancer types).

According to histologic type of cancer, there were no statistically significant sex differences (P=0.318), although papillary cancer was somewhat more common in women.

One of the observed indicators was the occurrence of regional lymph metastases (neck lymph nodes), which were identified in 19.5% and 12.6% of patients in Slavonia and Dalmatia, respectively. These data can only be compared with certain limitations because the observed period was longer in Slavonia and included a period when healthcare availability was not at the same level as between 1997 and 2006. The study conducted in Dalmatia confirmed the results of other authors: thyroid cancer was not as common in men as in women and when malignant change did occur, metastases were statistically significantly more common in men than in women (P<0.001).

UIE levels were measured as part of the study on thyroid cancer characteristics and the possible effect of iodine intake on papillary cancer occurrence. In accor-

dance with the International Committee for Control of Iodine Deficiency Disorders (ICCIDD) criteria, UIE of 10 μg/dL or higher indicates sufficient iodine intake. The aim of this study was to determine whether UIE levels differed between schoolchildren in the two regions with different thyroid cancer incidence: in 2005, crude incidence was 14.88 *per* 100,000 inhabitants in Dalmatia and 4.3 in Slavonia, while the national rate was 9.55 *per* 100,000 inhabitants. If iodine intake (and consequently iodine excretion) is higher in the region with the higher incidence, then a correlation clearly can be established between the increased iodine intake and increased thyroid cancer incidence.

Many authors state that the use of iodized salt, i.e. higher iodine intake in previously iodine deficient areas probably leads to increased papillary cancer incidence[15,16,28-30,39]. Although data on Slavonia and Dalmatia are not completely compatible for comparison due to the observed period in Dalmatia being 25 years shorter, this hypothesis could not be confirmed based on the structure of histopathologic types of thyroid cancer in both regions. According to the hypothesis that a higher iodine intake causes higher papillary thyroid cancer incidence, the occurrence of papillary thyroid cancer should be higher in Slavonia. However, it is not the case: papillary cancer accounted for 63.65% of all thyroid cancers in Slavonia and 80.0% in Dalmatia. The follicular type was more common in Slavonia (20.88% of all cancer patients) than in Dalmatia (12.4%), which is probably due to previous iodine deficiency in Slavonia. The papillary to follicular thyroid cancer ratio was 6.4:1 in Dalmatia and 3:1 in Slavonia. Studies have shown that the introduction of iodine prophylaxis has in many countries led to reduction in anaplastic and follicular thyroid cancers and an increase in papillary cancers, resulting in a higher papillary to follicular cancer ratio (coefficient)[1,11,26,36,40,41].

Follicular types are not as common, although according to literature data they account for 10% to 15% of thyroid cancers. In our sample, this type of cancer was found in 12.4% of patients. Other studies show that it is more common in women and tends to occur in the fifties. In our sample, this type was somewhat more common in men (14.0%; 17/121) than in women (12.1%; 64/530), but the difference was not statistically significant. The average patient age for this type of cancer is 51 and metastases to regional lymph nodes are rare[42]. In the Dalmatian sample of patients, the occurrence of metastases in papillary and follicular cancers together was 11.8% (71/602).

Medullary thyroid cancer is the third most common type and accounts for 10% of all thyroid cancers[1,12,36]. In the Dalmatian sample, medullary cancer accounted for 6.5% (42/645); the mean patient age was 55.6 and the youngest patient aged 20 was suffering from the MEN syndrome (family type). It was more common in men (9.1%; 11/121) than in women (5.8%; 31/530). In the Slavonia sample, it accounted for 9.03% of all thyroid cancer cases, while the mean patient age was 44.1, i.e. 10 years younger than in Dalmatia. The reasons for such age difference are difficult to pinpoint as, again, the study in Slavonia covered a 35-year period and in Dalmatia 10 years. In the Dalmatian sample, metastases in medullary cancer patients were more common (31%; 13/42) than in papillary and follicular cancers (11.8%).

Anaplastic cancer was found in 1.1% (7/651) of patients in Dalmatia, patient mean age 69.7.

The role of iodine in thyroid cancer pathogenesis is a complex issue, which is at the root of many conflicting opinions. Some studies suggest that the increase in thyroid cancer in areas with previous iodine deficiency is caused by the addition of iodine to food[15,16,28-30,39]. Studies have shown that goiter is an important factor in thyroid cancer development, particularly benign thyroid nodes (adenoma)[1,5,14]. Various epidemiological studies have compared the incidence and risk of thyroid cancer in iodine deficient and iodine sufficient areas. A study on Sicily compared two areas with different iodine intake and the result was statistically higher thyroid cancer frequency in areas with insufficient iodine intake than in the control area. The same authors showed the thyroid cancer frequency in patients with a dysfunctional node in areas with insufficient iodine intake to be twice as high as that in iodine sufficient areas[9,20].

There is a relatively clear correlation between iodine intake and the histopathologic type of thyroid cancer. Follicular and anaplastic types are more common in areas with iodine insufficiency, whilst papillary type is more common in iodine sufficient areas[1,11,20,21].

The ratio of papillary to follicular cancer was 3:1 in Slavonia and 6.4:1 in Dalmatia, which might seem illogical when compared with the findings of other au-

thors. This, however, can be explained: in our study, urinary iodine content in schoolchildren was higher in Slavonia and follicular cancer was more common in this region than in Dalmatia. This fact could be explained by lower iodine intake during the preceding period. In fact, epidemiological studies conducted in the early 1990s recorded a mild to moderate iodine deficiency in Croatia, with goiter frequency of 8% to 35% in schoolchildren. Results of a new epidemiological research conducted in 2002 have shown appropriate levels of iodine intake and eradication of goiter in schoolchildren in Croatia[14]. Having in mind that the median age of thyroid cancer patients is 50, these are mostly generations of people who were children at the time of insufficient iodine intake, which is the most likely reason why follicular thyroid cancer is more common in Slavonia than in Dalmatia.

Since there was no statistically significant difference in median urinary iodine content between children from the two counties, iodine intake was ruled out as the possible environmental factor influencing the higher thyroid cancer incidence in Dalmatia. In fact, the median iodine content was somewhat higher in Slavonia children (where thyroid cancer incidence was lower) than in Dalmatian children, but the difference was not statistically significant.

Somewhat higher median iodine content among children in the Osijek-Baranya County was probably due to different dietary habits (higher consumption of cured meat). However, it is just an assumption that is yet to be proven in a standardized survey on eating habits, which should include an appropriate number of respondents in both study counties.

Consistent with the results reported by Mihaljević[11], the present study clearly show that papillary cancer is less common in Slavonia than in Dalmatia. Overall thyroid cancer incidence rates were significantly lower in Slavonia than in Dalmatia (P<0.001). Measurements of UI levels in primary schoolchildren from Slavonia and Dalmatia indicated the UI content to be higher in Slavonia children (P<0.05), thus refuting the hypothesis that a higher iodine intake in previously iodine deficient areas leads to an increased incidence of papillary thyroid cancer.

Conclusions

The mean standardized thyroid cancer incidence rate *per* 100,000 inhabitants was 9.32 in Dalmatia and 6.02 in Slavonia. The incidence rates recorded in Dalmatia were statistically significantly higher (χ^2=56.24; df 1; P<0.001).

Epidemiological characteristics of thyroid cancer in Dalmatia comply with the described characteristics of this cancer in iodine-sufficient areas: papillary carcinoma was the most common type and the papillary to follicular ratio was 6.4:1. Follicular cancer accounted for 12.4% all study patients. Epidemiological characteristics in Slavonia were found to be typical of previously iodine-deficient areas: papillary type predominated, the papillary to follicular ratio was 3:1, and follicular cancer accounted for 20.88% of all patients.

In 2009, the median urinary iodine excretion among schoolchildren in the Osijek-Baranya County (Slavonia) and Split-Dalmatia County (Dalmatia) was 28.1 μg/dL and 23.6μg/dL, respectively. It is assumed that higher median UIE levels in Slavonia children were most likely due to different eating habits, i.e. higher intake of salted, dried and cured meat products.

Higher iodine intake cannot be said to be the cause of the high thyroid cancer incidence in Dalmatia. Improved diagnosis is one of the possible reasons for the increased thyroid cancer incidence.

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Sažetak

UNOS JODA I EPIDEMIOLOŠKE ZNAČAJKE KARCINOMA ŠTITNJAČE: USPOREDBA KONTINENTALNOG I PRIOBALNOG DIJELA HRVATSKE

N.K. Poljak, M. Kontić, Z. Čolović, I. Jerončić, B. Lukšić i *R. Mulić*

Cilj istraživanja je bio utvrditi epidemiološke osobitosti karcinoma štitnjače u Dalmaciji i Slavoniji, analizirati regionalne razlike u incidenciji te utvrditi ima li unos joda utjecaja na visinu incidencije. U ovoj retrospektivnoj epidemiološkoj studiji rabili su se podaci Hrvatskoga registra za rak objavljeni u Hrvatskom zdravstveno-statističkom ljetopisu i godišnjim Biltenima Hrvatskoga registra za rak. Analizirani su podaci o 651 bolesniku s rakom štitnjače operiranom u bolnicama Dalmacije u razdoblju od 1997. do 2006. godine. Kao kontrolna skupina uzeti su podaci o operiranima od karcinoma štitnjače u Slavoniji (N=498). Stope incidencije u Dalmaciji uspoređene su sa stopama u Slavoniji. Kao mogući okolišni čimbenik od utjecaja na karcinom štitnjače uzet je unos joda. Unos joda mjeren je kod djece osnovnoškolske dobi na području Splitsko-dalmatinske i Osječko-baranjske županije. Količina izlučenog joda izmjerena je kod 131 djeteta. Prosječna, dobno standardizirana stopa incidencije karcinoma štitnjače posljednjih deset godina u Dalmaciji bila je 9,32 na 100.000 stanovnika, a u Slavoniji 6,02 na 100.000 stanovnika. Razlika je statistički značajna (P<0,001). Sve promatrane stope incidencije (dobno standardizirana na europsko i svjetsko stanovništvo, gruba, na temelju istraživanja) pokazuju trend porasta i značajno su više na području Dalmacije u odnosu na Slavoniju. Spolna struktura oboljelih pokazuje da žene u odnosu na muškarce četiri puta češće obolijevaju. U Dalmaciji u ukupnom uzorku žene čine 81,4% oboljelih, a papilarni karcinom čini 80,03% oboljelih od karcinoma štitnjače. Medijan životne dobi novooboljelih na području Dalmacije je 50 godina, a na području Slavonije 48 godina. U Slavoniji papilarni karcinom čini 63,65% oboljelih. Folikularni tip karcinoma štitnjače u Slavoniji čini 20,88%, a u Dalmaciji 12,4% oboljelih. Epidemiološke značajke karcinoma štitnjače na području Dalmacije u skladu su s opisanim značajkama ovoga karcinoma područjima s dostatnim jodom: najzastupljeniji je papilarni karcinom, a omjer papilarnog i folikularnog karcinoma je 6,4:1. Folikularni karcinom je zastupljen u 12,4% ukupno oboljelih. Na području Slavonije epidemiološke značajke su tipične za područja koja su nekad bila obilježena nedostatnim unosom joda: iako prevladava papilarni karcinom, omjer papilarnog i folikularnog karcinoma je 3:1, a folikularni karcinom je zastupljen kod 20,88% oboljelih. Medijan joda izlučenog u mokraći bio je 23,6 μg/dL kod školske djece iz Splitsko-dalmatinske županije i 28,1 μg/dL kod djece iz Osječko-baranjske županije. Nije bilo statistički značajne razlike u količini izlučenog joda (P<0,050). U zaključku, prosječna unešena količina joda na području Dalmacije i Slavonije nije bila razlog za razliku u visini incidencije karcinoma štitnjače u razdoblju od 1997. do 2006. godine. Poboljšana dijagnostika karcinoma štitnjače jedan je od mogućih uzroka porasta incidencije karcinoma štitnjače u Dalmaciji.

Ključne riječi: *Štitnjača, tumori – epidemiologija; Hrvatska – epidemiologija*