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Source / Izvornik: **Acta clinica Croatica, 2000, 39, 155 - 160**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:220:957314

Acta clin Croat 2000; 39:155-160 Professional Paper

POSSIBLE EFFECTS OF THE 1990-1995 WAR IN CROATIA ON THYROID CANCER EPIDEMIOLOGY

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SUMMARY – A Thyroid Cancer Registry containing data of patients treated at our department during a 20-year period (1980-1999) has been established. The aim of the study was to analyze the possible effects of the 1990-1995 war in Croatia on the prevalence, type, and age and sex distribution of thyroid carcinoma. Three different 2-year periods were analyzed: distant prewar (1980-1981), immediate prewar (1989-1990) and postwar (1998-1999) period. There was no statistically significant difference in age at diagnosis and sex ratio among the three study periods. The incidence of follicular cancer was at the upper limit for countries with normal iodine uptake when the 20-year period was analyzed, however, in the 1980-1981 period follicular cancer accounted for 34.9%, and in 1998-99 for only 2.8% of all cases. Papillary cancer was diagnosed in less advanced stages than others. Five-year survival for papillary, follicular and anaplastic cancer was 100%, 100% and 0%, respectively. Analysis of the 2-year periods for all cancer types except anaplastic cancer showed the mean age at onset to be on a decrease. In the 1998-1999 period, papillary cancer was diagnosed in a more advanced stage. The number of follicular cancer cases decreased from 22 in 1980-1981 to 3 in 1989-1990 and 2 in 1998-1999. Analysis of the epidemiology of thyroid cancer in the pre- and post-Chernobyl period did not reveal any increase in the number of papillary cancer in younger patients. It was concluded that in the postwar period, patients presented in more advanced stages of the disease. However, the effects of war on the epidemiology of thyroid carcinoma and other malignant tumors should be further investigated.

Key words: *Thyroid neoplasms, epidemiology; Croatia, epidemiology; War; Risk factors*

Introduction

Thyroid cancer is a rare disease with a specific biological behavior. Long term survival after diagnosis makes it suitable for follow up studies. Some environmental factors have been recognized to induce thyroid cancer such as iodine deficiency and radioactivity in childhood. In 1980's, there still were problems with the presence of endemic goiter in Croatia, since iodine uptake had not matched the European standard[1]. Based on a nation wide study, the issue of iodine deficiency problem was solved thereafter[2]. However, iodine deficiency had an effect on thyroid cancer epidemiology in Croatia[1,2]. Other environmental factors including Chernobyl accident in 1986 could have also added to the increasing prevalence of thyroid cancer in children and adults[3-5].

In our previous study[6], we analyzed the prevalence, and sex and age distribution of various types of thyroid cancer at our Hospital. Our Thyroid Cancer Registry contains data on all patients treated at the Hospital over a 20-year period (1980-1999), representing almost one-fifth of all thyroid cancer patients in Croatia. Furthermore, the pathologic (pTNM) stage was analyzed in all patients

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Received May 29, 2000, accepted July 5, 2000

with adequate data. To our knowledge, this is the first detailed study of thyroid cancer epidemiology in Croatia, combining data from various sources.

In the literature, there are few reports on the impact of war on the prevalence of different malignant tumors. The Republic of Croatia was the scene of the last war in this century. Therefore, the aim of the study was to analyze the prevalence of thyroid cancer in three different two-year periods: 1980-1981 as a distant prewar period, 1989-1990 as an immediate prewar period, and 1998-1999 as a postwar period. For this purpose, we connected our Thyroid Cancer Registry with the National Registry of Cancer, which contains data on all deceased cancer patients.

Patients and Methods

The computer-based Thyroid Cancer Registry established at our Department contains data on all patients with thyroid cancer who underwent surgery during a 20-year period, i.e. from January 1, 1980 till December 31, 1999. Data were obtained from different sources. The patients underwent total thyroidectomy followed by neck dissection if needed. The material was referred to pathology together with basic data on each patient (age, sex and presence of distant metastases). Data on the pathologic diagnosis, size of primary tumor and presence of lymph node metastases (if such material was present) were obtained from biopsy findings. Personal identification number, date of birth, date of death, and primary cancer diagnosis as a key to recognize deceased patients were obtained from the National Registry of Cancer for follow-up purposes. Some patients were lost from the follow-up due to political and geographical changes in the region, which could primarily be attributed to the effects of war. Furthermore, we had inadequate clinical data to separate medullary carcinoma within MEN and without MEN, therefore both types were included in survival. Unfortunately, because of some administrative reasons, the Na-

Table 1. Frequency and sex distribution of all thyroid cancers diagnosed during the 1980–1999 period

Type	Papillary			Follicular			Medullary			Anaplastic			Other			Total
Year	M	F	T	M	F	T	M	F	T	M	F	T	M	F	T	
1980	3	13	16	2	13	15	1	1	2	3	3	6	1	1	2	41
1981	2	4	6	5	2	7	1	0	1	2	1	3	3	1	4	21
1982	2	12	14	4	13	17	1	0	1	1	5	6	1	5	6	44
1983	4	7	11	3	4	7	2	2	4	1	4	5	0	3	3	30
1984	7	3	10	0	1	1	0	3	3	0	0	0	0	2	2	16
1985	0	9	9	0	3	3	1	0	1	0	0	0	2	1	3	16
1986	3	8	11	0	0	0	0	0	0	1	0	1	0	0	0	12
1987	6	11	17	0	0	0	1	0	1	0	0	0	0	1	1	19
1988	3	11	14	0	2	2	0	2	2	0	1	1	0	2	2	21
1989	4	11	15	2	0	2	0	1	1	0	1	1	0	0	0	19
1990	4	9	13	0	1	1	0	0	0	1	0	1	1	0	1	16
1991	1	11	12	0	1	1	1	2	3	0	1	1	1	1	2	19
1992	3	12	15	0	1	1	1	0	1	1	0	1	1	2	3	21
1993	4	10	14	3	0	3	1	1	2	0	0	0	0	2	2	21
1994	1	9	10	2	0	2	2	1	3	0	0	0	0	0	0	15
1995	3	14	17	0	1	1	2	3	5	0	0	0	0	0	0	23
1996	2	12	14	0	1	1	1	2	3	0	0	0	1	0	1	19
1997	1	12	13	1	2	3	0	1	1	0	0	0	0	2	2	19
1998	7	21	28	0	0	0	1	1	2	0	1	1	0	0	0	31
1999	7	23	30	0	2	2	0	1	1	1	2	3	0	2	2	38
Total	**67**	**222**	**289**	**22**	**47**	**69**	**16**	**21**	**37**	**11**	**19**	**30**	**11**	**25**	**36**	**461**

M = male, F = female, T = total number of cases

tional Registry of Cancer was updated with a three-year delay, so follow-up was performed till 1996.

For study purposes, the study population were divided into three 2-year periods: 1980-1981 as a distant prewar period, 1989-1990 as an immediate prewar period, and 1998-1999 as a postwar period.

Results

The Thyroid Cancer Registry contains data on a total of 461 thyroid cancer patients. Papillary cancer was diagnosed in 62.7%, follicular cancer in 14.9%, anaplastic cancer in 8%, and medullary cancer in 6.5% of patients. Other types of thyroid cancer (lymphoma, epithelial tumors, and those with unclear histology) were found in 7.8% of cases. The latter group were not submitted to further analysis. The prevalence and distribution of all thyroid cancers diagnosed during the 1980-1999 period are shown in Table 1. Mean age at diagnosis, sex distribution, and female to male ratio for the total of 461 cases are presented in Table 2. Comparison of age distribution according to 10-year age groups for papillary and follicular cancer during two 10-year periods is shown in Figures 1 and 2. Pathologic staging for all thyroid cancer types during the 20-year period, with the number of cases in each stage, is shown in Table 3. The most common stage of all cancers was T2NXMX, followed by T1NXMX.

The five-year survival rate for patients with papillary or follicular cancer was 100%, and for those with anaplastic cancer 0%. Survival rate for patients with medullary cancer was not calculated due to inadequate data available. All our patients with anaplastic cancer died within a year of diagnosis.

The percentage of each type of thyroid cancer and mean age at diagnosis in the three 2-year periods are

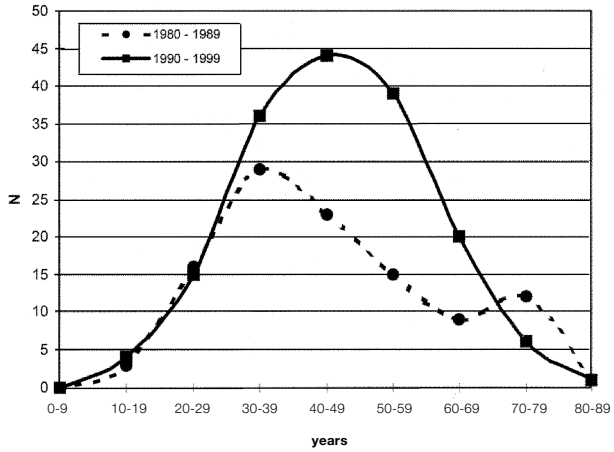

Fig. 1. Comparison of age distribution according to 10-year age groups for papillary cancer in two 10-year periods.

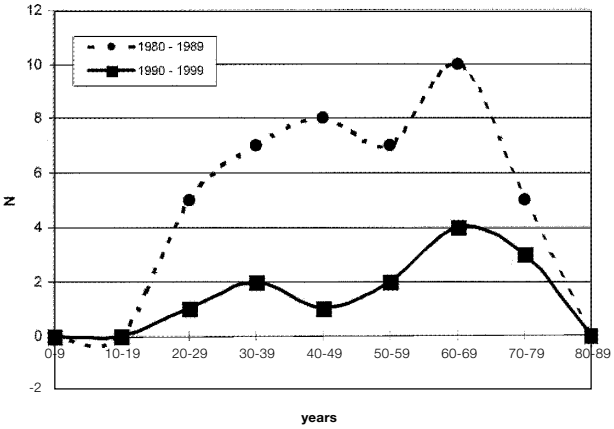

Fig. 2. Comparison of age distribution according to 10-year age groups for follicular cancer in two 10-year periods.

Table 2. Distribution of patients with thyroid cancer according to pathohistologic type, age and sex

Type	N	%	Age (yrs) mean ± SD	M	Age (yrs) mean ± SD	F	Age (yrs) mean ± SD	F/M
Papillary	289	62.7	45.7±14.9	67	49±15.3	222	44,7±14,7	3.3
Follicular	69	14.9	51.8±15.3	22	54.2±17.3	47	50.8±14.5	2.1
Medullary	37	6.5	50.3±13.8	16	51.9±10.2	21	48.9±16.4	1.3
Anaplastic	30	8	57.9±13.1	11	60.5±14.9	19	56.2±11.9	1.7
Other	36	7.8	56.3±16.2	11	51.1±13.8	25	58.4±16.9	2.3
Total	461	100	48.4±15.4	127	51.4±15	334	47.3±15.4	2.6

Table 3. Pathologic staging of all pathohistologic types of thyroid cancer during the 1980–1999 period

Period	1980 – 1999			
	Thyroid cancer type			
pTNM stage	Papillary	Follicular	Medullary	Anaplastic
TXN1MX	18	1	5	4
T1NXMX	67	8	2	2
T1N0MX	3	0	0	0
T1N1MX	19	3	1	0
T2NXMX	71	9	4	2
T2N0MX	1	0	0	0
T2N1MX	18	1	3	0
T3NXMX	11	8	1	3
T3N0MX	0	0	0	0
T3N1MX	6	0	1	1
T4NXMX	13	9	1	4
T4N0MX	0	0	0	0
T4N1MX	6	2	3	1

Table 4. Distribution and age range of patients with thyroid carcinoma during the three study periods

Period	1980-1981			1989-1990			1998-1999		
Type	n	%	Age (yrs) mean ± SD	n	%	Age (yrs) mean ± SD	n	%	Age (yrs) mean ± SD
Papillary	23	36.5	47.7±21.7	28	80	46±11.5	58	84.1	46.2±13.9
Follicular	22	34.9	51.4±14.6	3	8	63.5±0.7	2	2.8	40±11.3
Medullary	3	4.7	55.5±14.8	1	3	64	3	4.4	50.3±3.1
Anaplastic	9	14.4	51.4±12.4	2	6	65±12.7	4	5.8	68.2±3.8
Other	6	9.5	52.8±12.6	1	3	28	2	2.8	56±21.2
Total	63	100	50.5±16.4	35	100	48.2±13	69	100	47.8±14.3

shown in Table 4, showing that all types of cancer except anaplastic cancer were diagnosed in younger patients. In the 1980-1981 period, most of papillary cancers were in T1NXMX stage; in the 1989-1990 period, an identical number of cases were in T1NXMX and T2NXMX stage; and in the 1998-1999 period T2NXMX stage predominated, followed by T1NXMX stage. For other types of cancer, data needed for staging were inadequate or missing.

Discussion and Conclusions

The Thyroid Cancer Registry established at our Department contains data on 461 patients with a diagnosis of thyroid cancer, collected over the 20-year period. Sex distribution and female to male ratio showed a female predominance in all types of cancer, which is consistent with the state of the art on the biological behavior of thyroid cancer and with other literature reports[7-9].

Age at diagnosis showed the patients with papillary cancer to be youngest, and those with anaplastic cancer

oldest, as also reported in the literature, including other national cancer data base studies[7-9]. Women were younger at onset of thyroid cancer than men, and this held true for all cancer types[7-9]. Follicular cancer was on the upper limit (14.9%) of distribution for countries with normal iodine uptake (15%), but the number of follicular cancer decreased with years[10-12]. This could be explained by two possible reasons: the problem of low iodine uptake present in Croatia in 1980's was recognized and properly solved, so it could have been expected to record a lower number of follicular cancer cases[2]. In addition, the pathologic criteria for follicular cancer changed over years and some of these were now diagnosed as papillary cancer.

Papillary cancer was diagnosed in less advanced stages (T1NXMX and T2NXMX) than follicular (T2NXMX and T4NXMX), anaplastic (T4NXMX) or medullary cancer that was mostly diagnosed by local lymph node metastases (TXN1MX). These results are similar to literature data, since papillary cancer is less aggressive than other cancer types.

Five-year survival rates for papillary and follicular cancer were consistent with those reported by other authors, and failed to discriminate between these two types of thyroid cancer for the short period of observation[9]. Our results on medullary carcinoma could not be compared, since we were not able to separate the cases of MEN associated and non-MEN associated medullary cancer.

The number of follicular cancer cases decreased prospectively over the three 2-year pre- and postwar periods from 22 in 1980-1981 to 3 in 1989-1990 and 2 in 1998-1999. Also, the mean age at diagnosis of thyroid cancer in general and of each type of thyroid cancer was found to be on a decrease, except for anaplastic carcinoma which increased from 51.4 ± 12.4 years in 1980-1981 to 68.2 ± 3.8 years. In the same periods, papillary cancer was diagnosed in more advanced (T2NXMX vs T1NXMX) stages. These results are hard to explain, as the mean age at diagnosis decreased while the stage of carcinoma at diagnosis increased. It could possibly be attributed to better medical care and, paradoxically, the simultaneous lack of therapy for symptoms in our patients due to the war in Croatia.

Other environmental factors, especially Chernobyl accident, could have also influenced the prevalence of thyroid carcinoma in Croatia. It is well known that irradiation can cause mutations and chromosome abnormalities, cell death, alterations and transformations in cell growth, and malignant alterations[13,14]. According to the report of the United Nations Scientific Committee on the Effects of Atomic Radiation, Croatia was among the countries with the highest exposure to nuclear contamination from Chernobyl[15]. However, it seems that Chernobyl accident had a low or no effect on the prevalence of thyroid neoplasms in Croatia, since there was no increase in the number of younger patients in the post-Chernobyl period[4,6]. There was no difference in the mean age of thyroid cancer patients recorded before and after Chernobyl.

The available data from Ukraine and Belarus showed an increase in the incidence of thyroid cancer among children and adults only four years after Chernobyl accident[3,4]. Furthermore, a post-Chernobyl rise in the incidence of thyroid cancer was also observed in Connecticut, USA[5]. Similar data have been reported on the incidence of thyroid cancer in French Polynesia exposed to atmospheric nuclear bomb tests[16].

Finally, it is concluded that our study showed no significant increase in the incidence of thyroid cancer in the 1998-1999 and 1980-1981 periods. However, the number of thyroid cancer patients showed a decrease in the prewar period. It seems that the patients presented in a more advanced stage of the disease. This could be a coincidence, however, it could have been due to the effects of war and consequential poor socioeconomic conditions. The contribution of nuclear irradiation from Chernobyl could not be excluded either. Further epidemiologic studies are obviously needed.

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Sažetak

MOGUĆI UTJECAJI RATA U HRVATSKOJ (1990.-1995.) NA EPIDEMIOLOGIJU RAKA ŠTITNE ŽLIJEZDE

D. Šimunović, I. Cvjetko, V. Gladić, M. Elez, M. Glasnović, T. Leničeк, M. Vučić, M. Lechpammer, H. Čupić, M. Strnad, Z. Kusić, B. Krušlin i M. Belicza

Na našoj Klinici uspostavljeni Registar raka štitne žlijezde sadrži podatke o svim bolesnicima obrađenim u Klinici u 20-godišnjem razdoblju (1980.-1999.). Cilj ovoga istraživanja bio je utvrditi moguće učinke rata u Hrvatskoj na učestalost, histološki tip te spolnu i dobnu raspodjelu bolesnika sa zloćudnim tumorom štitne žlijezde. Analizom su obuhvaćena 3 dvogodišnja razdoblja uključujući vrijeme znatno prije rata (1980.-1981.), neposredno prije rata (1989.-1990.) i nakon rata (1998.-1999.). Nije utvrđena statistički značajna razlika u starosti i spolnoj raspodjeli tumora između tri navedena razdoblja. Učestalost folikularnog raka bila je na gornjoj granici učestalosti za zemlje bez gušavosti, s tim da je u razdoblju 1980.-1981. bilo ukupno 34,9%, a u razdoblju 1998.-1999. samo 2,8% folikularnog karcinoma. Petogodišnje preživljenje bilo je 100%, 100% odnosno 0% za papilarni, folikularni i anaplastični rak. U uspoređivanim razdobljima prosječna starost bolesnika se snižavala, ali se rak dijagnosticirao u sve uznapredovalijem stadiju. Analiza populacije prije i nakon Černobila nije pokazala povećan broj mladih bolesnika s papilarnim karcinomom. Na temelju rezultata ovoga istraživanja zaključeno je da nije bilo povećanja učestalosti karcinoma štitnjače u poratnom razdoblju, međutim, bolesnici su se javljali s uznapredovalijim stadijima tumora. Ovaj i moguće druge učinke rata na karcinom štitnjače, kao i na druge zloćudne tumore, valja dalje istraživati.

Ključne riječi: *karcinom, štitnjača, epidemiologija, rat, Hrvatska*