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Comparison of Occurrence of Upper Urinary Tract Carcinomas in the Region with Endemic Villages and Non-Endemic Nephropathy Region in Croatia

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A B S T R A C T

Balkan endemic nephropathy (BEN) is a chronic tubulointerstitial renal disease of a still unknown etiology, associated with an increased frequency of urothelial carcinoma, particularly of the upper urinary tract (UUT). The aim of the study was to compare the occurrence of UUT carcinomas between Brodsko-Posavska Region (BPR) which is the region with endemic villages and the non-endemic region of Zagreb (ZG) in two six-year periods with a 20 year period separating the two, pointing out a possible difference in occurrence regarding war in Croatia (1991–1995). Comparing BPR and ZG regions we found a more then 5 times higher frequency of UUT carcinomas in BPR in the first period and more than 4.5 times higher frequency in the second period. Women in BPR were more frequently affected with UUT carcinomas then men.

Key words: *Balkan endemic nephropathy, urothelial carcinoma of renal pelvis and ureter, renal cell carcinoma*

Introduction

Balkan endemic nephropathy (BEN) is a chronic, non-inflammatory, bilateral, tubulointerstitial renal disease of still unknown etiology that slowly leads to renal failure. Histopathologically, fibrosis and atrophy of kidney cortex, with tubular degeneration are the most consistent findings[1]. It occurs more commonly in certain endemic regions in Croatia and neighboring countries[2]. In Croatia BEN is restricted to the fourteen villages in the region of Brodska Posavina (geographically compact area borded by the river Sava in the south and in the west from Slavonski Brod), where the prevalence of BEN reached 4.4% of population[1,3]. Women are more frequently affected than men[2,3]. Some authors suggested that the incidence of BEN is declining[4]. BEN is also associated with increased frequency of urothelial carcinoma that appear in 32% to 40% of cases with Balkan endemic nephropathy[5–8], particularly in the upper urinary tract and with a much higher mortality rate in women than in men[4,9,10,11]. In Serbia, it was reported that the incidence of UUT tumors was 57.1 times higher in endemic than in nonendemic areas in the period from 1969–1988[12], however only a 11.2 – fold increase in incidence was found in the same region in the period from 1989–1998, suggesting decrease of BEN. Furthermore it is proven that BEN is also connected with higher frequency of urothelial carcinoma of urinary bladder[2,12,13].

Some of our authors have also reported that renal cell carcinoma (RCC) occurred with a significantly higher frequency in the affected population[14].

The aim of the study was to compare the occurrence of urinary tract carcinomas, primarily those of the upper urinary tract, between the Brodsko-Posavska Region (BPR) and the non-endemic region of Zagreb (ZG) in two six-year periods with a twenty-year period separating the two. Knowing the strong association between BEN and urothelial carcinoma of the upper urinary tract, occurrence of this tumor type could roughly and indirectly show whether the occurrence of BEN is decreasing in our country as well.

We also wanted to explore whether the war in Croatia (1991–1995) influenced the occurrence of urinary tract

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carcinomas in the BPR in the post-war period, taking into consideration that some alterations in the population occurred due to ethnic migration during the war.

Materials and Methods

Histopathological data for the two periods (the first period from 1980 to 1985 and the second period from 2000 to 2005) were obtained from the Department of Pathology, General Hospital »Dr. Josip Benčević«, Slavonski Brod and from »Ljudevit Jurak« University Department of Pathology, »Sestre Milosrdnice« University Hospital, Zagreb. Patients with diagnosed malignant tumors of the urinary tract were assessed according to sex, age and localization of tumor. Following the anatomical site of tumors, urologic cancers in male patients were divided into five groups: primary cancers of the kidney (subdivided into urothelial carcinoma of the renal pelvis and ureter, renal cell carcinoma and other kidney tumors), carcinomas of the urinary bladder, prostate cancer, testicular tumors and other malignant tumors of the urinary tract (tumors of the urethra, penis, retroperitoneal tumors etc). Cancers of the urinary system in female patients were divided into 3 groups: primary kidney cancers (subdivided into urothelial carcinoma of renal pelvis and ureter, renal cell carcinoma and other kidney tumors), carcinomas of the urinary bladder and other malignant tumors of the urinary tract. Only patients with primary tumors of the urinary tract were included in this study.

Data obtained from the Department of Pathology at the General Hospital »Dr. Josip Benčević« in Slavonski Brod included all patients operated in this hospital (not only from endemic villages).

χ^2 test was used for the statistical analysis of data regarding occurrence of UUT and urinary bladder carcinomas between the two observed regions. $P<0.05$ was considered statistically significant.

Results

In the first period (1980–1985), 122 urologic cancers were reported in the Department of Pathology in Slavonski Brod (BPR), and 1095 in the Department of Pathology in Zagreb (ZG), as opposed to the second period (2000–2005) during which there were 588 cancers in Slavonski Brod, and 3017 in Zagreb.

Of all the kidney tumors, urothelial carcinomas of the renal pelvis and ureter were more than 5 times more frequent in the BPR than in ZG (79.4% opposed to 14.8%) in the first (pre-war) period, and more than 4.5 times more common in the second (post-war) period (65.8% in BPR and 14.3% in ZG) (Table 1 and Table 2). Significant differences in occurrence of UUT carcinomas between the BPR and ZG region was found in both analyzed periods ($p<0.05$). Analyzing the data from BPR, we found an almost equal number of urothelial carcinoma of the renal pelvis and ureter in both sexes (M 13, F 14) in the first period, but in the second period female patients were almost two times more frequently affected (M 37, F 65, Table 3). In ZG, urothelial carcinoma of the renal pelvis and ureter was diagnosed in 12 men and 4 women in the first period, but in the second period the number of cases was somewhat higher in women than in men (M 41, F 34). Data showed that the incidence of RCC was equal in both sexes, with a slightly lower occurrence in females in the BPR during both periods (M 3, F 3 in first period and M 27, F 21 in the second period), while the number of cases in Zagreb were two or more times higher in men (M 59, F 26 in the first period and M 291, F 156 in the second period).

Of all urologic cancers in the first period, 49.2% in the BPR and 61.5% in ZG were carcinomas of the urinary bladder, during the second period this percentage decreased to 44.2% in the BPR, and 37.1% in ZG. We found significant difference in the occurrence of urinary bladder carcinoma in the second period between ZG and BPR ($p< 0.05$), but no significant difference was found between the two regions during the first period. There were

TABLE 1
TOTAL NUMBERS AND FREQUENCIES OF URINARY TRACT AND MALE GENITAL TRACT CARCINOMAS IN ENDEMIC BRODSKO-POSAVSKA REGION DURING THE TWO OBSERVED PERIODS

	BRODSKO – POSAVSKA REGION 1980–1985		BRODSKO – POSAVSKA REGION 2000–2005	
	TOTAL	(%)	TOTAL	(%)
Renal pelvis and ureter	27 (79.4%*)	27.9%	102 (65.8%*)	26.4%
Renal cell carcinoma	6 (17.6%*)		48 (31.0%*)	
Other kidney tumors	1 (3.0%*)		5 (3.2%*)	
Urinary bladder	60	49.2%	260	44.2%
Prostate	18	14.8%	155	26.4%
Testis	2	1.6%	16	2.7%
Other localizations	8	6.6%	2	0.3%
Total	122	100.0%	588	100.0%

* Frequencies of different kidney tumor types within the group of all kidney tumors

TABLE 2
TOTAL NUMBERS AND FREQUENCIES OF URINARY TRACT AND MALE GENITAL TRACT CARCINOMAS IN NON-ENDEMIC REGION OF ZAGREB DURING THE TWO OBSERVED PERIODS

	ZAGREB 1980–1985		ZAGREB 2000–2005	
	TOTAL	(%)	TOTAL	(%)
Renal pelvis and ureter	16 (14.8%*)		75 (14.3%*)	
Renal cell carcinoma	85 (78.7%*)	9.9%	447 (85.0%*)	17.4%
Other kidney tumors	7 (6.5%*)		4 (0.7%*)	
Urinary bladder	673	61.5%	1120	37.1%
Prostate	224	20.5%	1164	38.6%
Testis	37	3.4%	166	5.5%
Other localizations	53	4.8%	41	1.4%
Total	1095	100.0%	3017	100.0%

* Frequencies of different kidney tumor types within the group of all kidney tumors

TABLE 3
MALE TO FEMALE RATIO OF UROTHELIAL CARCINOMA OF RENAL PELVIS AND URETER, RENAL CELL CARCINOMA AND CARCINOMA OF URINARY BLADDER IN ENDEMIC AND NON-ENDEMIC REGION DURING THE TWO OBSERVED PERIODS

	Male:Female		
	Renal pelvis and ureter	RCC*	Urinary bladder
Brodsko-posavska region, 1980–1985	1:1.1	1:1	1:0.4
Brodsko-posavska region, 2000–2005	1:1.8	1:0.8	1:0.4
Zagreb, 1980–1985	1:0.3	1:0.4	1:0.2
Zagreb, 2000–2005	1:0.8	1:0.5	1:0.3

*RCC – renal cell carcinoma

18 cases of prostate cancer (14.8% of all urologic tumors) in the BPR and 224 (20.5% of all urologic tumors) in ZG during the first period, as opposed to this, during the second period there were 155 cases (26.4% of all urologic tumors) in the BPR, and 1164 (38.6% of all urologic cancers) in ZG. Testicular tumors were represented in 2 cases (1.6%) in the BPR and 37 cases (3.4%) in ZG in the first period, whereas there were 16 cases (2.7%) in the BPR, and 166 cases (5.5%) in ZG during the second period.

The analyzed data concerning the ages of patients with diagnosed cancer, during the first period, in both observed regions, was insufficient as was data concerning patients with prostate cancer in the BPR during the second period.

In the second period urothelial carcinoma of renal pelvis and ureter was diagnosed at the average age of 67.2 years in males, and 75.3 years in females in the BPR, and 64.3 years in males, and 72.6 years in females in ZG. Ana-

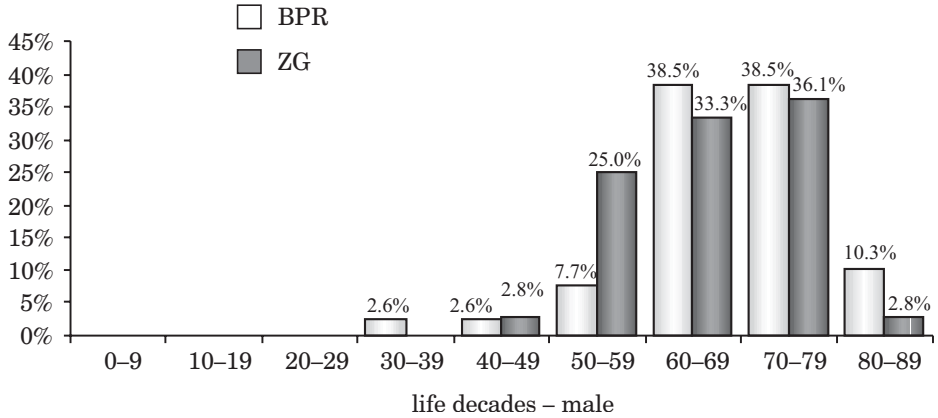

Fig. 1. Distribution of male cases of UUT carcinomas through life decades in Brodsko-Posavska Region (BPR) and Zagreb (ZG), in the second period (2000–2005).

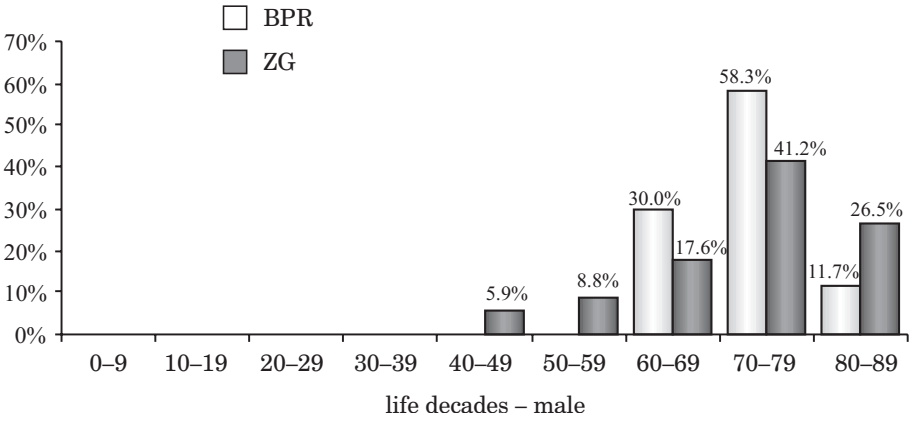

Fig. 2. Distribution of female cases of UUT carcinomas through life decades in Brodsko-Posavska Region (BPR) and Zagreb (ZG), in the second period (2000–2005).

lyzed data concerning the age of patients suffering from UUT carcinomas in the second period showed the following distribution during the decades of life: UUT carcinomas in males were most frequent in the 7th and 8th decade of life, in both regions, with the one difference being a higher percentage of cases during the 6th decade in ZG as opposed to the BPR (Figure 1). Females in ZG were most frequently affected in 8th and 9th decade whereas in the BPR they were more frequently affected in the 7th and 8th decade (Figure 2). RCC was diagnosed in the BPR at the average age of 64.0 years and in ZG at the average age of 60.0 years, in both sexes. Carcinoma of the urinary bladder was diagnosed at the average age of 67.5 years in males, and 69.8 years in females in the BPR, and 68.8 years in males and 70.6 years in females in ZG. The average age of patients with testicular tumors was 33.0 years in the BPR and 32.9 years in ZG.

Discussion and Conclusion

The frequency of urothelial carcinomas of the renal pelvis and ureter is significantly higher in the Brodsko-Posavska Region in both analyzed periods. Comparing the BPR (region with endemic villages) and ZG (non-endemic region) we found a more then 5 times higher percentages of urothelial carcinoma of the renal pelvis and ureter in the BPR in the first period (79.4% in the BPR comparing to 14.8% in ZG) and a more than 4.5 times higher frequency in the second period (65.8% in the BPR comparing to 14.3% in ZG). This is in concordance with literature[2, 6–11,15]. Our data also showed that women in the BPR were more frequently affected with urothelial carcinoma of the renal pelvis and ureter then men, especially during the second period (M:F=1:1.8). In the non-endemic region male patients were 3 times more frequently affected than female patients, during the first period, while during the second period the male to female ratio changed to 1:0.8.

Analyzing the age of male and female patients with urothelial carcinoma of the renal pelvis and ureter there was no significant difference between ZG and the BPR. As was shown in our study as well as in previous studies[1,9], women were more frequently affected, and they had a higher average age of onset than men.

Of all urologic cancers in the first period, carcinomas of the urinary bladder were represented in 49.2% in the BPR and 61.5% in ZG, as opposed to 44.2% in the BPR and 37.1% in ZG during the second period, but these differences may be the result of the progressive development of diagnostic procedures in urology more then true changes in the occurrence of tumors. Comparing occurrence of urinary bladder carcinoma in the BPR and ZG, male predominance was observed in both regions for both periods, with females only slightly more frequently affected in the BPR then in ZG during the both periods.

Unlike in ZG, where RCC was 2 times more common in male patients, in the BPR we observed both sexes to be equally affected during the first period, and an only slightly higher occurrence in males during the second period (M:F=1:0.8).

Although some authors reported that RCC also occurs with a significantly higher frequency in the affected endemic population[14], most of the previous studies showed that RCC was not connected with BEN. In our study we found that RCC appeared more often in the female population in the BPR then in ZG but the association between RCC and BEN should be further analyzed.

The frequencies of urothelial carcinoma of the upper urinary system and renal cell carcinoma in the non-endemic region were similar in both analyzed time periods. Observing the ratio between urothelial carcinoma of UUT and renal cell carcinoma in the BPR, we found a relative decrease of urothelial carcinoma in the second period (from 79.4% to 65.8%) and a relative increase of renal cell carcinoma (from 17.6% to 31.0%). This finding could be the result of the immigration of Bosnian refugees into the endemic region during the war in Croatia (1991–1995). For more precise conclusions and connections of ratio changes between urothelial carcinoma of UUT and RCC and the influence of ethnic migration of the population a longer post war time period is still needed before a study can be done.

Patients representing the BPR region (operated in General Hospital »Dr. Josip Benčević« in Slavonski Brod) included residents from endemic villages as well as residents from non-endemic parts of this region, suggesting that the frequency of UUT carcinomas would be even higher if only patients from endemic villages were analyzed. Considering the high number of patients suffering from urothelial carcinoma of the renal pelvis and ureter in the BPR, we can conclude that BEN is still present and persists in endemic areas. Therefore screening methods for early detection of urothelial carcinoma as well as further studies that will reveal etiology of BEN are more than justified.

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USPOREDBA POJAVNOSTI KARCINOMA GORNJEG MOKRAĆNOG SUSTAVA IZMEĐU REGIJE S ENDEMSKIM NASELJIMA I NEENDEMSKE REGIJE U HRVATSKOJ

SAŽETAK

Balkanska endemska nefropatija je kronična tubulointersticijska bolest bubrega nepoznate etiologije koja je povezana s povećanom učestalosti urotelnog karcinoma, osobito urotelnog karcinoma gornjeg mokraćnog sustava. Cilj ovog istraživanja je usporedba pojavnosti karcinoma gornjeg mokraćnog sustava u bolesnika iz Brodsko-Posavske regije (BPR) u kojoj se nalaze endemska naselja i bolesnika iz Zagreba koji je neenedemska regija (ZG), i to u dva šestogodišnja razdoblja razmaknuta dvadeset godina, naglašavajući i moguće razlike u pojavnosti obzirom na rat u Hrvatskoj (1991–1995). Uspoređujući regije BPR i ZG nađena je više od pet puta veća učestalost karcinoma gornjeg mokraćnog sustava u BPR u prvom razdoblju i više od četiri i pol puta veća učestalost karcinoma gornjeg mokraćnog sustava u BPR u drugom razdoblju. Žene u BPR češće obolijevaju od karcinoma gornjeg mokraćnog sustava nego muškarci.