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Original Scientific Paper

KIDNEY CANCER IN CROATIA – TRENDS IN INCIDENCE AND MORTALITY IN THE 21ST CENTURY

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SUMMARY – Kidney cancer is estimated to be responsible for more than 400 000 new cancer cases and 180 000 cancer deaths a year. Its incidence is increasing in the majority of developed countries, due to an increased prevalence of recognized risk factors such as smoking, alcohol use and obesity, as well as incidental findings on unrelated diagnostic imaging procedures. Mortality is decreasing in the majority of European countries, due to improvements in treatment and stage at diagnosis shift with more tumors being diagnosed at an early stage. In this paper, we present kidney cancer incidence and mortality trends in Croatia using joinpoint regression analysis. The incidence was rising throughout the 2001-2019 period, with an annual percent change (APC) of 2.5%; more so in men (APC of 2.5%) than in women (APC of 2.2%). Mortality increased during the 2001-2014 period (APC of 2.4%), but started to decrease in recent years (APC -2.7%, 2014-2020). Unlike sex differences observed in other European countries, with more favorable mortality trends found in women, our study showed a constant increase in mortality in women (APC of 1.2%) and a recent decrease in mortality in men, starting in 2013 (APC of -2.8%), after a period of increase from 2001 (APC of 3.3%).

Key words: *Kidney cancer; Incidence; Mortality; Joinpoint regression; Croatia*

Introduction

Kidney cancer is a major public health issue and, according to the latest GLOBOCAN 2020 estimates, it ranks among 15 most common cancers both in the incidence (14th; over 430,000 new diagnosed cases) and mortality (15th; almost 180,000 deaths) in 2020. The cumulative risks are around twice higher in males, both for the incidence and mortality[1]. Over 90% of these cancers are renal cell carcinomas, with clear cell carcinoma and its subtypes accounting for around 75% of these entities[2].

The incidence of renal cell cancer has increased in many countries due to the greater use of abdominal imaging diagnostic methods, capable of detecting kidney cancer as incidentalomas. These countries often have higher survival rates both owing to their higher economic development and detection of neoplasms in the early stages[3].

According to the EUROCARE-5 study[4], the 5-year survival rate in the 2000-2007 period was 60%, with better prognosis in Southern and Central Europe. The same report has indicated that adult kidney cancer relative survival in Croatia was 60.7%[4], with the lowest survival rates recorded in Bulgaria (44%) and Den-

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mark (45%). The more recent worldwide cancer survival study, CONCORD-3[3], has not included kidney cancer among the fifteen cancer types it was evaluating.

Risk factors for kidney cancer such as tobacco smoking and obesity are still prevalent in our modern lifestyle[5]. Smoking increases the risk of kidney cancer by 50% in male and 20% in female smokers. An increase in body mass index (BMI) is considered responsible for 26% of the incidence, so 5 kg/m^2 increments in BMI increase the risk by 24% in men and 34% in women[5,6]. Independent risk factors include hypertension, maintenance dialysis, and occupational exposure to trichloroethylene[7]. Furthermore, it has been reported that alcohol consumption has a protective effect, which is probably attributed to the indirectly increased insulin sensitivity[6]. Regular physical activity can reduce the risk, as well as a diet with increased fruit and vegetable consumption[6,7].

Recent findings in the fields of pathology, epidemiology, and genetics led to revision of the 2004 World Health Organization (WHO) renal tumor classification, providing the new 2016 WHO classification. The updated version includes 48 entities, excluding miscellaneous and metastatic tumors[8]. Renal cell carcinoma is the most common type (90%), with two main histologic types, clear cell (70%) and papillary carcinoma (10%-15%)[7].

Croatia has one of the oldest population-based cancer registries in the World, with the first report published for the year 1968[9]. The most recent report (for the year 2019) has shown that the incidence proportion of kidney cancer (including other parts of the urinary tract) was 4.3% in men (newly detected n=581) and 2.8% in women (n=335)[10]. According to the latest estimates for Europe for 2020[11], Croatia ranks 13th with an age-standardized incidence rate (ASIR-W) of 10.5/100,000 (Lithuania, Czech Republic and Estonia having the highest ASIR-W) and ninth in age-standardized mortality rates (ASMR-W) of kidney cancer, with ASMR-W of 3.5/100,000 (with Slovakia, Czech Republic and Latvia having the highest ASMR-W).

Despite regular publishing of descriptive epidemiologic data in the yearly bulletins of the Croatian National Cancer Registry, an in-depth analysis of the long-term trends in the incidence and mortality of kidney cancer has not yet been reported. Therefore, the aim of this study was to provide an overview of the incidence trends for 2001-2019 and mortality trends for 2001-2020 of kidney cancer in Croatia.

Methods

The incidence data for the 2001-2019 period were obtained from the Croatian National Cancer Registry (CNCR) in March 2022 and mortality data for the 2001-2020 period were obtained from the official mortality data of the Croatian Bureau of Statistics and Croatian Institute of Public Health. The CNCR is a population-based cancer registry founded in 1959 that records all cancer cases in Croatia, compiling data received from primary and secondary health care institutions. This includes mandatory cancer notifications, pathology reports and patient discharge diagnosis, as well as death certificates from the Croatian Bureau of Statistics[9]. The registry data have been included in the Cancer Incidence in Five Continents publications, the latest being Volume XI[12].

Kidney cancer was defined according to the International Classification of Diseases, 10th Revision (ICD-10) code C64. We used the population mid-year estimates by age and sex for the 2001-2020 period from the Croatian Bureau of Statistics for the calculation of age-specific rates, while for calculating age-standardized rates (ASR) we used the age-structure of Croatian population from the 2011 Census as a standard population (an analysis using European Standard Population 2013 was also performed, with no major differences observed).

In order to analyze the incidence and mortality trends of kidney cancer, we used regression analysis using Joinpoint Regression Software, ver. 4.9.1.0, according to a previously described methodology[13].

Results

During the 2001-2019 period, the total number of new kidney cancer cases in Croatia was 13 290, with an average of 549 cases diagnosed annually in the first 5-year period, and 845 in the last five years observed (54% increase). The ASIR increased from 12.8/100 000 in 2001 to 20.7/100 000 in 2019. In women, the ASIR increased from 8.5/100 000 in 2001 to 13.6/100 000 in 2019, while in men the increase was from 18.3/100 000 to 29.5/100 000 (Tables 1 and 2).

In the 2001-2020 period, there were 6 614 deaths due to kidney cancer in Croatia. The average annual number of deaths was 257 in the first 5-year period, and 373 in the last five years observed, yielding a 45.1% increase.

Table 1. Male kidney cancer incidence and mortality data, Croatia 2001–2019 (2020): number of cases, crude rate per 100 000 (CR) and age-standardized rate (ASR) using 2011 Census Croatian Population per 100 000

	Incidence			Mortality		
Year	N	CR	ASR	N	CR	ASR
2001	326	15.8	18.3	169	8.2	10.6
2002	347	16.8	20.4	149	7.2	10.0
2003	349	16.9	20.8	163	7.9	10.5
2004	309	14.9	17.9	171	8.3	10.5
2005	384	18.5	21.0	183	8.8	11.0
2006	387	18.7	21.7	196	9.4	12.4
2007	400	19.3	22.3	212	10.2	12.9
2008	382	18.4	20.6	196	9.4	11.1
2009	476	22.9	26.2	227	10.9	13.4
2010	431	20.,8	23.2	228	11.0	13.5
2011	436	21.1	23.4	216	10.5	12.6
2012	498	24.2	26.4	252	12.2	14.3
2013	467	22.7	24.8	270	13.1	15.1
2014	532	26.0	27.6	272	13.3	15.2
2015	491	24.2	25.5	227	11.2	12.4
2016	498	24.7	25.8	275	13.6	15.1
2017	556	27.9	28.2	216	10.9	11.5
2018	594	30.1	30.2	236	11.9	12.4
2019	582	29.5	29.5	247	12.5	12.9
2020				232	11.8	12.1

Total ASMR increased from 6.5/100 000 in 2001 to 7.7/100 000 in 2020. ASMR in women increased from 3.7/100 000 to 4.4/100 000, and in men from 10.6/100 000 to 12.1/100 000.

Joinpoint analysis of the incidence trend showed a stable and significant rise in the incidence rate of kidney cancer, with annual percent change (APC) of 2.5% (95% confidence interval (CI), from 2.1 to 2.9) for the whole period observed (Fig. 1). The increase was more pronounced in men, with APC of 2.5% (95% CI, from 2.0 to 3.1), and somewhat slower in women, with APC of 2.2% (95% CI, from 1.6 to 2.8) (Fig. 2).

Table 2. Female kidney cancer incidence and mortality data, Croatia 2001-2019 (2020): number of cases, crude rate per 100 000 (CR) and age-standardized rate (ASR) using 2011 Census Croatian population) per 100 000

	Incidence			Mortality		
Year	N	CR	ASR	N	CR	ASR
2001	194	8.7	8.5	85	3.8	3.7
2002	217	9.7	9.3	87	3.9	3.7
2003	197	8.8	8.7	79	3.5	3.4
2004	212	9.5	9.2	105	4.7	4.5
2005	212	9.5	9.0	96	4.3	4.0
2006	228	10.2	9.7	92	4.1	3.7
2007	246	11.0	10.3	92	4.1	3.6
2008	239	10.7	9.9	128	5.7	5.1
2009	257	11.5	10.9	116	5.2	4.6
2010	234	10.5	9.7	117	5.3	4.6
2011	306	13.8	12.6	124	5.6	4.7
2012	258	11.7	10.5	123	5.6	4.6
2013	246	11.2	10.0	105	4.8	3.8
2014	294	13.4	11.7	142	6.5	5.2
2015	275	12.6	11.1	129	5.9	4.8
2016	309	14.3	12.4	134	6.2	4.8
2017	289	13.5	11.8	149	7.0	5.5
2018	298	14.1	12.3	115	5.4	3.9
2019	334	15.9	13.6	133	6.3	4.8
2020				126	6.1	4.4

N = number of cases; CR = crude rate *per* 100,000; ASR = age-standardized rate *per* 100,000

Joinpoint analysis of mortality rates showed a significant increase in the 2001-2014 period, with APC of 2.8% (95% CI, from 2.0 to 3.6) (Fig. 1). A change in trend is observed in 2014, when mortality from kidney cancer started decreasing with APC of -2.7% (95% CI, from -4.9 to -0.5) for the rest of the observed period.

This pattern was similar in men, with a significant increase of kidney cancer mortality in the 2001-2013 period (APC=3.3%; 95% CI, from 1.7 to 4.8), and a decrease from 2013 to 2020 (APC=-2.8%; 95% CI,

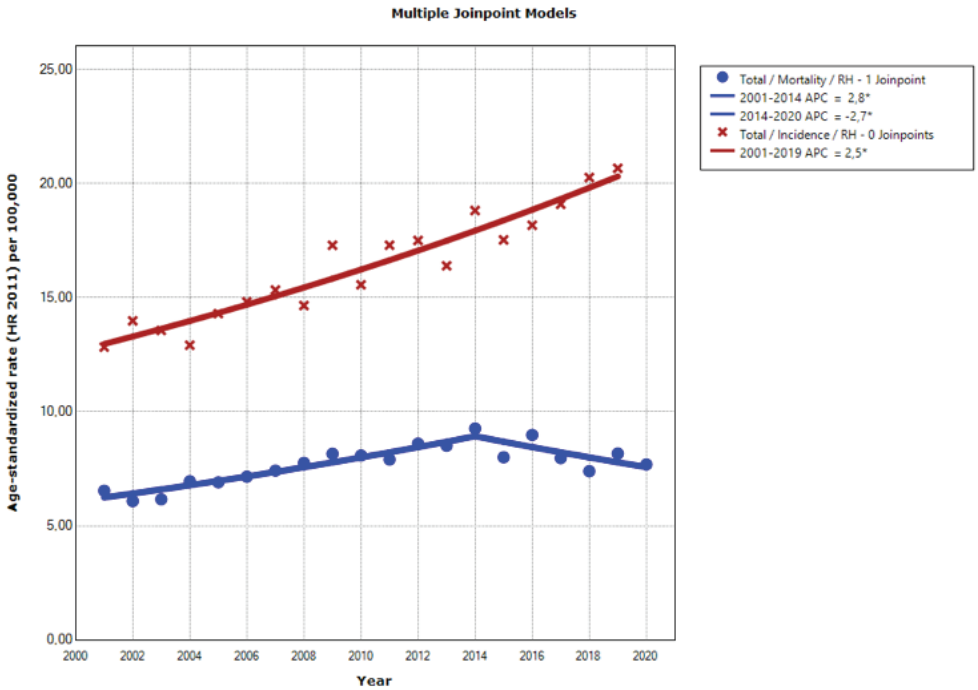

Fig. 1. Joinpoint analysis of kidney cancer incidence and mortality trends in Croatia, 2001–2020, both sexes combined.

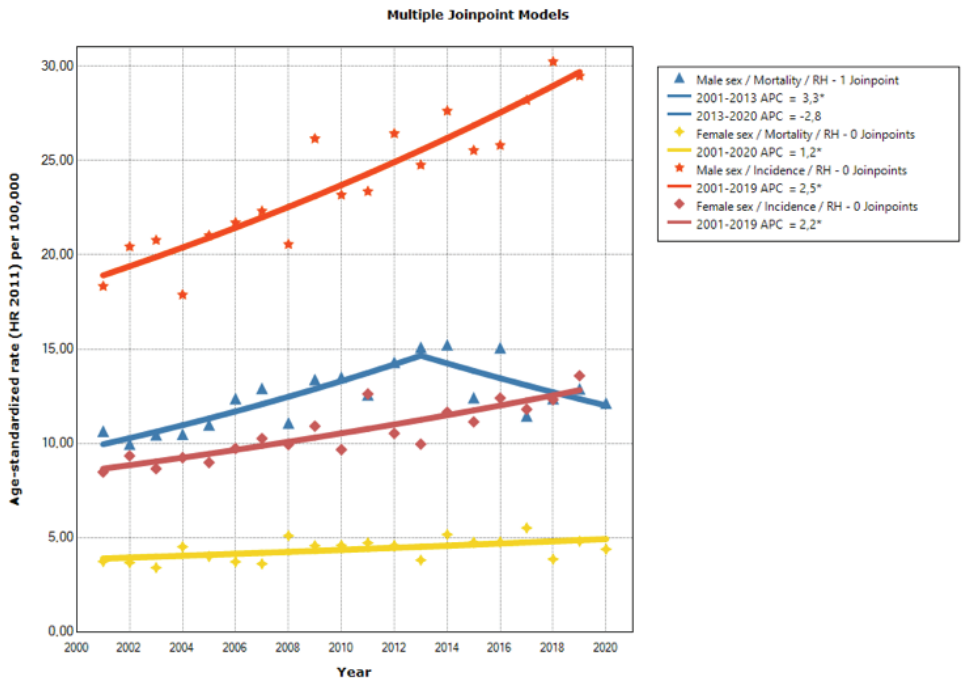

Fig. 2. Joinpoint analysis of kidney cancer incidence and mortality trends in Croatia, 2001–2020, by sex.

from -5.6 to 0.0). In women, there was a significant increase of kidney cancer mortality during the whole period, with no observed changes in trend (APC=1.2%; 95% CI, from 0.2 to 2.3) (Fig. 2).

Discussion

Our analysis suggested a continuous increase in kidney cancer incidence rates from 2001 to 2019, with a downward trend in mortality rates in more recent years (since 2014). While the increase in incidence rates was observed both in men and women throughout the study period, this favorable trend in mortality was due to a statistically significant decrease in mortality rates in men, while the mortality rates in women were still increasing.

There was a significant increase in the incidence in Croatia, both in men and in women. The latest ASIR in men was 21.9 *per* 100 000, while in women it was 9.2 *per* 100 000, which corresponds to the results and estimates for many countries worldwide, where the average ASIRs were also two times higher in men than in women, thus confirming the gender ratio consistency[7]. The Global Burden of Disease 2017 study[14] estimated that in the 1990-2017 period, there had been a 152.4% increase in kidney cancer ASIR in Croatia, with a 186.8% increase in ASMR and 150.1% increase in disability-adjusted life-years (DALYs). In comparison, the respective changes at the global level were +4.7%, +4.4% and -3.6%. There are considerable differences in these trends globally due to different distribution of risk factors and varying levels of diagnostic availability.

There are many possible explanations for incidence trends, with some of them probably closely intertwined. Wong *et al*. took into consideration specific socio-economic factors and confirmed a positive correlation between the incidence of kidney carcinoma and human development index (HDI) and Gross Domestic Products (GDP). Data from 2012 showed a significantly higher incidence in countries with very high HDI[15]. The most prevalent risk factors such as smoking and obesity, as well as sedentary lifestyle and hypertension still play considerable role in the incidence increase, especially in developed countries[15-17]. A more common use of imaging diagnostics is noticed in more developed countries, resulting in incidentally discovering predominantly localized kidney cancer[7]. A previous study also confirmed an increase in the incidence of thyroid cancer in Croatia, probably mediated by the same overuse of diagnostic methods[18].

Mortality trends of kidney cancer are decreasing for most highly developed European countries in the last 30 years, especially in Western Europe and most Northern European countries (average annual percent change (AAPC) -1% to -3%), and in the USA and Australia. In most countries, women's mortality rates are decreasing faster, with a mortality-to-incidence ratio suggesting that men might have higher fatality; it is interesting to notice that we observed a different pattern with a more favorable trend in men, as previously described. Czech Republic had the highest mortality rates (9.1/100 000 for men and 3.6/100 000 for women), and similar patterns were detected in Baltic countries[7]. Brazil (AAPC 2.5% men, 1.1% women) and Ireland (AAPC 1.3% men, 0.7% women) reported significantly increasing mortality trends in both genders. In the 2000s, Croatian mortality trends were increasing for both genders (AAPC 3.0% for men, 1.5% for women), as well as in men in Slovenia, Portugal and Greece (AAPC 1.7%, 1.6%, 1.2%), and in Spanish women (AAPC 0.6%)[7].

Such disparities in kidney cancer mortality trends also greatly depended on the availability of expensive targeted treatments and urologic oncology organization[19]. Our study showed an increase in mortality rates from 2001 to 2014 in total men and women (APC 2.8%) with a joinpoint and a decreasing trend for the rest of the period (APC -2.7%). A change of mortality trends was detected in men (APC 3.3 % 2001-2013, -2.8% 2013-2020), while in women, there was a constant increase in mortality rates (APC 1.2%). This paradox was also observed in other countries when analyzing the trends by sex. Similar trends were observed in Estonia, where female mortality rates showed a plateau since 2002 and in men had significantly decreased[19]. Their age-standardized mortality analysis showed a mortality decrease in all women under 74 years, while in women aged ≥75 a significant increase has been recorded since 2007. They also registered a decreasing trend for more advanced stages in men, but not in women[20].

In conclusion, a significant increasing trend in the incidence of kidney cancer in the Croatian population could also be the result of overdiagnosis and high exposure to recognized risk factors. A decreasing mortality trend could be explained by early detection of the disease in the localized stage, with still localized tumors having more available access to modern therapies. Particularly, considerable gender disparity in mortality trends remains unclear from our current data and confirms the need of further analysis to elucidate the observed differences. Our study lacked data on survival trends, especially the age-specific and

stage-specific survival rates for a more representative information on kidney cancer care in Croatia. Thus, additional evaluation of cancer registry data complemented by medical histories from hospital sources should be obtained. Future studies should consider specific data on age, gender, risk factors, comorbidities, type and time of tumor detection, and treatment information. Health professionals should deliver high-quality and representative data to the population-based cancer registries in order to improve the quality of published indicators.

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Sažetak

RAK BUBREGA U HRVATSKOJ – TRENDOVI INCIDENCIJE I SMRTNOSTI U 21. STOLJEĆU

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Rak bubrega je prema procjenama odgovoran za više od 400.000 novih slučajeva raka i 180.000 smrti uzrokovanih zloćudnim bolestima. Incidencija je u porastu u većini razvijenih zemalja kao rezultat velike učestalosti rizičnih čimbenika: pušenja, konzumacije alkohola i pretilosti, kao i sve većeg broja slučajnih nalaza na slikovnim dijagnostičkim pretragama. Unatoč tome, napredak u liječenju te sve veći udio tumora otkrivenih u lokaliziranom stadiju doveli su do smanjenja smrtnosti u većini europskih zemalja. U ovom smo radu prikazali trendove incidencije i smrtnosti raka bubrega u Republici Hrvatskoj koristeći *joinpoint* regresijsku analizu. Incidencija je u porastu kroz cijelo promatrano razdoblje (2001.-2019.) s godišnjom postotnom promjenom (APC) od 2,5%, pri čemu je porast izraženiji kod muškaraca (APC 2,5%) nego kod žena (APC 2,2%). Smrtnost je rasla od 2001. do 2014. (APC 2,4%) kada počinje pad (APC -2,7%) do 2020. godine. Za razliku od spolnih razlika zabilježenih u europskim zemljama s povoljnijim trendovima smrtnosti zabilježenim kod žena, naši rezultati pokazali su porast smrtnosti kod žena u cijelom razdoblju (AAPC 1,2%), dok je kod muškaraca nakon porasta od 2001. do 2013. godine (APC 3,3%) zabilježen pad u razdoblju od 2013. do 2020. godine (APC -2,8%).

Ključne riječi: *Rak bubrega; Incidencija; Smrtnost; Joinpoint regresijska analiza; Hrvatska*