

Trends in the kidney cancer incidence and mortality in the Slovak and Czech republics in 1980-2005 – in the context of an international comparison

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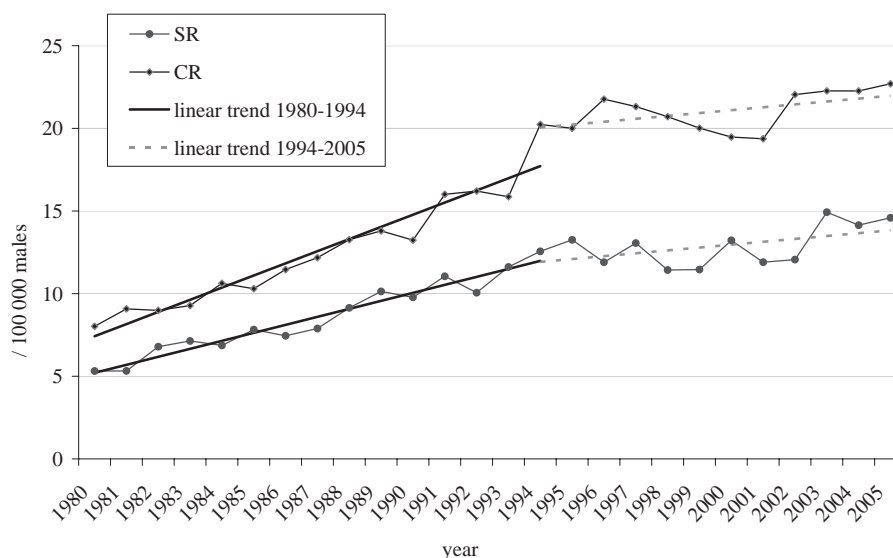
Incidence rates of kidney cancer vary in global standards more than tenfold, the highest worldwide rates are repeatedly registered in the Czech Republic (hereafter CR) and in other geographically neighbouring countries in Central Europe, including the Slovak Republic (hereafter SR). The aim of the study was to analyse the changes in time trends of incidence and mortality from kidney cancer in two geographically close countries (CR and SR) and to compare detected differences with the worldwide data. In spite of high rates of incidence and its global growth in analyses in 1980 – 2005, the character of its progress in time was changed in both countries. While in 1980 – 1994 the incidence of kidney cancer in males and females in both analysed countries increased significantly, after 1994 (to 2005) stagnation in males in SR and significant slowdown of its growth in males in CR were reported. In females in SR after 1994 significant slowdown of the incidence growth was reported and in CR there was even its non-significant fall. Mortality trend in both sexes in both countries in 1980-2005 was slower than the incidence. After 1994 (to 2005) in males in SR statistically non-significant slowdown of mortality growth was reported, in CR it was statistically significant fall of mortality rates. In women after 1994 (to 2005) statistically non-significant decrease was reported, in CR the decrease was significant. The increase of total incidence of the disease is not explained only by the growth of asymptomatic localized tumors due to high quality diagnostic methods, but it likely reflects actual growth of new cases of the disease. Assumed partial cause of the mortality stabilization and slowdown of the incidence growth after its previous culmination in 1994 is the decline of smoking and obesity prevalence in the last decades in men, although this fact does not reflect situation in women. More striking mortality decrease in CR in comparison with SR might be influenced by potentially more radical surgical therapy (rate of the amount of surgery within primary therapy according to the data in National Cancer Registry CR raises, in SR the data are not available) and by more significant increase of the disease rate in the clinical stages I and II in CR (in SR only short-time data are available).

Key words: kidney cancer – epidemiology, incidence, mortality, time trends

Kidney cancer represents nowadays a serious diagnosis in epidemiology, primarily due to increasing values of their incidence in the majority of countries worldwide and relatively high mortality [1, 2]. Latest estimates for 2008 indicate worldwide 167 947 new cases of kidney cancer in males (world standardized rates /hereafter WSR/ of incidence 5.2/100 000) and 103 401 new cases in females (WSR incidence 2.8/100 000). Deaths number estimates in the same year in males are 72 030 (WSR mortality 2.2/100 000) and 44 279 in females (WSR mortality 1.1/100 000) [2]. Out of malignant tumours of the urologic localization the kidney cancers are the third in the scale of incidence rates (after the prostate cancer and

bladder cancer), whereas 85 – 90 % of all histological types make up renal cell carcinomas (RCC) and 2 – 6% childhood tumours (Wilms' tumor as the most frequent).

The purpose of this study is to analyse the incidence of kidney cancer and resulting mortality and the possible reasons for any differences discovered in two neighbouring countries in the Central Europe (the Slovak and the Czech Republics), both of which have national, population-based cancer registries. When the global WSR incidence is compared, the Czech Republic (hereafter CR) is a country with the highest incidence of the disease in the world. However, the Slovak Republic (hereafter SR) as well as some other countries of



Graph 1. Trends of the age-adjusted (to the World standard population) kidney cancer incidence in males in the Czech and Slovak Republics

the Central and Eastern Europe achieve very high incidence rates worldwide. This paper compares the results of detected analyses of time progress of kidney cancer incidence and mortality in the CR and SR, discusses possible causal factors of their highest global incidence and compares the results with selected world countries.

Patients and methods

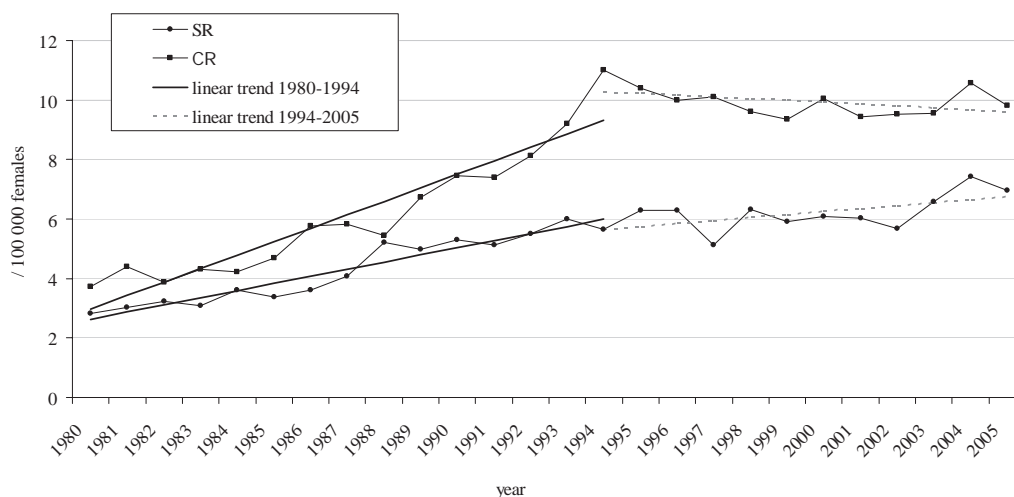
The data concerning the incidence of kidney cancer used in this analysis were obtained from the pre-processed data portals of the National Cancer Registry (hereafter NCR) SR [3] (www.nor-sk.org) and the NCR CR [4] (www.svod.cz) valid until the end of July 2009 as well as from the standard outcomes and annual reports of the NCR SR and the NCR CR. These registries are national population-based cancer registries with high quality data [5]. Analyses of the overall incidence and mortality take into account the period 1980-2005 in which both countries have validated data. Corresponding national mortality data were obtained from the Statistical Office of the SR and from the NCR CR. The values of incidence and mortality are presented in the form of crude rates in the last statistically closed year 2005. The comparison with other countries is only possible after correction of different age structure in the population. The standardisation to the world standard population was performed [6] and the standardised rates in the CR and SR have been compared. The trends in incidence and mortality have been extracted using linear regression model separately for each gender and country in time periods 1980-2005 and then individually the periods 1980-1994 and 1994-2005 and the trends are presented with corresponding 95% Confidence Intervals (CI) and p-value with null hypothesis being constant with time. Increase of incidence and its culmination in 1994

in both countries correlates with introduction of high-quality imaging diagnostic methods into urologic practice [7], on that score the trends of incidence and mortality were compared not only for the entire period of 1980-2005, but also the character of their changes before and after incidence culmination in 1994 was compared.

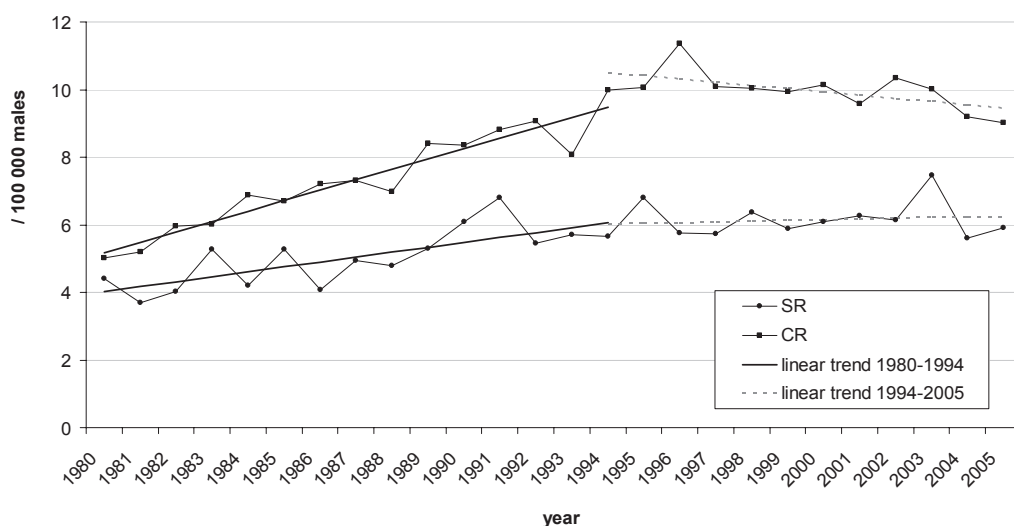
Results

In SR 484 kidney cancers were diagnosed in 2005 in males (crude rates –18.5/100 000, standardised (WSR) – 14.6/100 000) and 299 in females (crude rates 10.8/100 000, WSR 7/100 000). Of this number 83.4% of cases in males and 80.9% cases in females were microscopically verified. In 1980-2005 – the period compared with CR – the average annual increase of standardised incidence was 0.35/100 000 in males (CI 95% = 0.29-0.40, $p < 0.0001$) and 0.16/100 000 in females (CI 95% = 0.13-0.19, $p < 0.0001$). Steep increase of the disease incidence in both sexes and its culmination in 1994 in both countries correlates with introduction of high-quality imaging diagnostic methodology into urologic practice [7]. In analysis of incidence trends before and after its culmination in 1994 in males there was found out the average growth of standardised incidence 0.48/100 000 (CI 95% = 0.41-0.55, $p < 0.0001$) in 1980-1994, in the following period 1994-2005 stagnation of incidence at the average year-on-year growth 0.17/100 000 (CI 95% = -0.03-0.37, $p = 0.08$) (Graph 1). In females average annual growth of incidence in 1980-1994 was 0.24/100 000 (CI 95% = 0.19-0.28, $p < 0.0001$), after 1994 (to 2005) the growth of incidence slowed down significantly to 0.10/100 000 (CI 95% = 0.005-0.198, $p = 0.041$) (Graph 2).

In 2005, 207 males (crude rates 7.9/100 000, WSR 5.9/100 000) and 130 females (crude rates 4.7/100 000, WSR 2.7/100 000) died



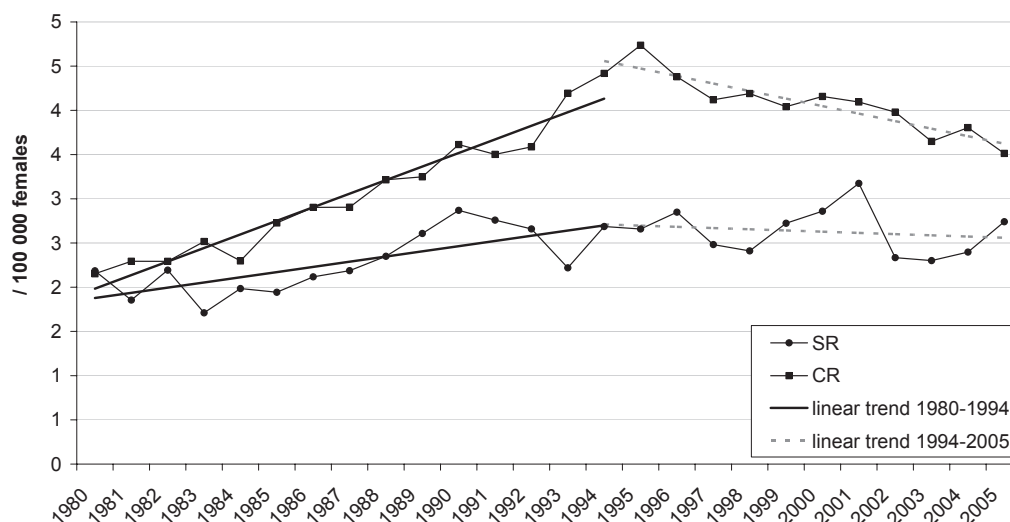
Graph 2. Trends of the age-adjusted (to the World standard population) kidney cancer incidence in females in the Czech and Slovak Republics



Graph 3. Trends of the age-adjusted (to the World standard population) kidney cancer mortality in males in the Czech and Slovak Republics

from kidney cancer in Slovakia. Mortality in both sexes has slower increasing trend than incidence. Expected average annual increase of standardised mortality in 1980-2005 was 0.06/100 000 in males (CI 95% = 0.06-0.13, $p < 0.0001$) and 0.02/100 000 in females (CI 95% = 0.01-0.04, $p = 0.001$). Average annual increase of standardised mortality in 1980-1994 in males was 0.14/100 000 (CI 95% = 0.07-0.22, $p = 0.001$) and after 1994 (to 2005) it was 0.02/100 000 (CI 95% = -0.08-0.12, $p = 0.680$), therefore statistically insignificant slowdown of the mortality growth occurred (Graph 3). In women average annual growth of WSR mortality in 1980-1994 represented 0.06/100 000 (CI 95% = 0.03-0.09, $p = 0.002$), in 1994-2005 statistically non-significant decrease of mortality with average annual values -0.01/100 000 (CI 95% = -0.06-0.04, $p = 0.555$) was reported (Graph 4).

In 2005 in the Czech Republic 1 760 kidney cancers in males (crude rates - 35.18/100 000, WSR - 22.6/100 000) and 1 028 in females (crude rates - 19.6/100 000, WSR - 9.8/100 000) were diagnosed. 80.5% of male's cancers and 76.9% of female's cancers were microscopically verified. The incidence in CR has steeply increasing tendency. Estimated average annual growth of incidence in 1980-2005 was 0.59/100 000 in males (CI 95% = 0.56-0.71, $p < 0.0001$) and 0.24/100 000 in females (CI 95% = 0.24-0.35, $p < 0.0001$). Analysing the development of the disease incidence in 1980-1994 average growth of standardised incidence in males 0.74/100 000 (CI 95% = 0.61-0.86, $p < 0.0001$) was detected, in 1994-2005 statistically significant slowdown of the incidence growth with the average annual rates 0.18/100 000 (CI 95% = -0.02-0.37, $p = 0.075$) was



Graph 4. Trends of the age-adjusted (to the World standard population) kidney cancer mortality in females in the Czech and Slovak Republics

reported (Graph 1). In females on average in 1980-1994 statistically significant increase of the incidence rates was discovered (average annual increase = 0.45/100 000, CI 95% = 0.36-0.55, $p < 0.0001$), however in 1994-2005 non-significant decrease of incidence (average annual decrease = -0.06/100 000, CI 95% = -0.15-0.03, $p = 0.165$) was detected (Graph 2).

In 2005 720 males (crude rates – 14.4/100 000, WSR – 9.1/100 000) and 432 females (crude rates – 8.6/100 000, WSR – 5.1/100 000) died from kidney cancer in CR. Mortality trend in males in CR increases slower compared with the incidence and also compared with the mortality in SR. Expected annual increase of standardised mortality was in 1980-2005 in males 0.19/100 000 (CI 95% = 0.15-0.25, $p < 0.0001$) and in females 0.08/100 000 (CI 95% = 0.05-0.11, $p < 0.0001$). Average annual increase of mortality rates in 1980-1994 was in males 0.31/100 000 (CI 95% = 0.25-0.37, $p < 0.0001$), in 1994-2005 statistically significant mortality decrease with annual value -0.096/100 000 (CI 95% = -0.188 to -0.004, $p = 0.043$) was registered (Graph 3). During the period of 1980-1994 statistically significant mortality increase in females was reported (average annual growth = 0.15/100 000, CI 95% = 0.13 -0.18, $p < 0.0001$), however in 1994-2005 mortality decreased significantly (average annual decrease = -0.09/100 000, CI 95% = -0.11 to -0.06, $p < 0.0001$) (Graph 4).

Discussion

Incidence rates of kidney cancer vary in global standards more than tenfold, higher average rates are reported in developed countries (WSR incidence in males in about 2002 was 10.4/100 000, in females 4.6/100 000) compared with the developing countries (WSR incidence males 2.1/100 000, females 1.2/100 000 in about 2002) [8]. The incidence increase of this disease is slightly steeper in women than in men and

in the blacks compared with the whites [9, 10]. The highest WSR incidence rates have been reported repeatedly from several central European countries, where kidney cancer has been among the tumors with the highest upward trend in incidence, than in Scandinavian countries, Northern America and Australia. Intermediate rates of the WSR incidence have been observed in Southern Europe and Japan, and low elsewhere in Asia, Africa and Pacific. These observations provide indirect evidence that the risk of developing kidney cancer may be higher in the whites than Asians, but may also relate to differences in the prevalence of lifestyle associated risk factors. The lowest incidence rates have been reported from African countries, but on the contrary, the incidence rates are highest among African-Americans in the USA [11]. Primacy in measured rates in the disease incidence worldwide especially in the last years in both sexes has the Czech Republic (CR) (WSR incidence in males 21.1/100 000 and 10.2/100 000 in females in about 2002 according to IARC WHO data), but among the countries with high or intermediate rates of the disease incidence in men were at the same time also Estonia (17.3/100 000), Iceland (16.5/100 000), Lithuania (14.7/100 000), Hungary (14.7/100 000), the Slovak Republic (SR) (13.7/100 000) and Poland (13.7/100 000). Lithuania (8.4/100 000), Iceland (8.1/100 000), Estonia (7.1/100 000), Austria (6.8/100 000), Finland (6.7/100 000), SR (6.6/100 000), Hungary (6.6/100 000) and Australia (6.5/100 000) were about the year of 2002 among the countries with high and intermediate incidence rates of the disease in women [8, 12, 13].

Time trends in kidney cancer incidence have been changed in some countries, after previous upward trend the decline of the rates in both sexes has been reported in the last 15 years, e.g. in Sweden and in other northern countries except England and Scotland. In Eastern Europe, on the contrary, the increase of the incidence is reported in both sexes, excepting a short

period in females in about 2000 [14, 15]. In CR also in 2005 high rates of WSR incidence of the disease were reported (22.6/100 000 in males and 9.8/100 000 in females). Together with SR (WSR incidence 14.6/100 000 and 7/100 000 in males and females respectively in 2005) and some other geographically neighbouring countries (Hungary, Poland) CR is for many years among the countries with the highest incidence rates [8, 14]. Trends analysis of total WSR disease incidence in CR in 1980-2005 points out on rising trends in both sexes. In males more striking increase of the disease incidence is observed, compared with females, whereas in 1994 culmination and successive reduction of the incidence growth occurred. After 1994 in CR the incidence increase slowed down significantly in males (from the rates of the average annual incidence growth 0.74/100 000 in 1980-1994 to 0.18/100 000/year in 1994-2005), in females even after the initial incidence increase (0.45/100 000/year in 1980-1994) non-significant decrease of its rates was reported (-0.06/100 000/annually) in 1994-2005. In SR the progress of the disease incidence is similar as in CR. In analysis of the overall incidence in 1980-2005 its increase was reported which is significantly more striking in males (average annual growth of standardised incidence was 0.35/100 000) than in females (0.16/100 000/year). However, similarly as in CR, to 1994 statistically significant increase and culmination of the incidence rates in both sexes occurred (0.48/100 000/year in males and 0.24/100 000/year in females), whereas subsequently up to 2005 stagnation of its rates to 0.17/100 000/year was reported in males and in females significant slowdown of the increase to the rates 0.10/100 000/year occurred.

The growth of the disease incidence which is reported in more cancer registries and the highest increase of the number of diseases in Central European countries is not interpreted only by the increase (up to 60 %) of the asymptomatic localized tumours due to the high quality of diagnostic methodologies, but it likely reflects even actual increase in the number of new diseases [1, 16]. Incidence culmination could have been in a short-time standard caused by detection of prevalent cases of the disease in population, by more sensitive diagnostic imaging methods and – in long-term standard – also detection of occult tumours which should not have been manifested [17]. Increasing trend of the disease incidence is accompanied in both CR and SR also by the migration in clinical stages, i.e. rising proportion of the disease in earlier clinical stages whereas in CR striking increase of the disease in the clinical stages I and II is reported from 1982 (in SR only data from 2000 are available) [3, 4]. Within localized stages the tendency to reduction of the growth of primarily diagnosed tumors is apparent. These facts reflect effectiveness of modern diagnostics and are probably linked to the increase and availability of modern investigating modalities, particularly ultrasound. Introducing of these techniques to the clinical practice correlates with the beginning of the increase and culmination of the kidney cancer incidence in 1988-1993 [7].

Character of mortality from kidney cancers has been changed in the last years. Kidney cancer death rate in Europe

enhanced from the half of 1950s to the end of 1980s or the beginning of 1990s, the average mortality increase from this disease in Europe was 73% in men and 48% in women. Consequently stabilization or decline of its rates was reported, particularly in the countries of Western Europe. The decline was the most striking in some Scandinavian countries. Despite the reported decrease the rates of overall mortality in the countries of Central and Eastern Europe (e.g. in CR, Hungary, Poland, Baltic countries) are still high [14, 18]. In analysis of mortality in CR its slower increasing tendency was observed in comparison with incidence (in both sexes) and also in comparison with the development in SR. In 1980-2005 on average, significant mortality increase in both sexes was reported (average annual growth of standardised mortality in men was 0.19/100000 and in women 0.08/100 000), but its progress was changed in time. To 1994 statistically significant mortality increase was reported in both sexes (0.31/100 000/year in men and 0.15/100 000/year in women), after 1994 (to 2005) both in males and females significant mortality decrease was reported (in men by -0.096/100 000/year and in women -0.09/100 000/year). In SR the mortality development was slightly different than in CR. In analysis of overall mortality in 1980-2005 statistically significant increase of its rates was reported (average annual growth in males was 0.06/100 000 and in females 0.02/100 000), mortality culminates as well as in CR in about 1994, however consequently in men the growth of its rates continued (even statistically non-significant) by 0.02/100 000/year. In women its non-significant decrease with the average annual rates -0.01/100 000 (in analysed period 1994-2005) was reported. Therefore mortality in CR after 1994 has more striking decreasing trend than in SR, where in men its insignificant increase continues. Generally the mortality decrease is the highest in middle-aged men and in western countries [14]. Assumed partial, although not unequivocal cause of this phenomenon which also relates to the slowdown of the incidence increase, is the decrease of smoking prevalence in the last decades in men in some countries of the Western Europe, e.g. in SR according to the CINDI programme [19] it was a significant decrease by -6.5 % in 1993-2002, in women non-significant decrease by -0.8 % (in CR data on smoking prevalence time-trends are missing), which geographically corresponds with the reported slowdown of the incidence increase. However, this fact does not reflect the situation in women as smoking prevalence and also mortality from other oncologic disease related to smoking in women in the majority of European countries including both SR and CR rises in the last years [14, 18, 19]. Smoking is an established risk factor for kidney cancer, although the increase in risk is weak [20, 21]. Hunt et al. [22] reported the increased risk for ever smokers compared to never smokers and also a strong dose-dependent increase with increasing tobacco consumption. The influence of other risk factors on the mortality decrease and slowdown of the incidence growth of kidney cancer in men is similarly not unequivocal, as far as e.g. prevalence of overweight and obesity in Europe rises, although slower than in the USA [18]. On the

other hand according to the CINDI programme results in SR [19] in 1993–2002 it was reported the decrease of the number of males with overweight and obesity by 5.3 %, in females by 1.4 %, which might correlate with the mentioned incidence and mortality development (in CR data on obesity development are not available). Brennan et al. [20] confirmed that BMI and a history of hypertension are risk factors for renal cell carcinoma (RCC) in central Europe, but these are unlikely to explain fully the highest incidence currently reported, indicating that there may be other important causes. In SR according to the CINDI programme the increase of the number of hypertension in men by 6.7 % was reported, but in women the fall was 2.7 % [19] (similar data are missing in CR), therefore hypertension itself insufficiently explains time progress of incidence and mortality from kidney cancer in SR. There is strong evidence that VHL (von Hippel-Lindau) alteration is a common, early event in clear cell (cc)RCC carcinogenesis [23]. In both familial and sporadic ccRCC, allelic inactivation of VHL gene occurs through mutation, methylation and/or chromosomal loss. Recently, Nickerson et al. [24] have confirmed that the vast majority of ccRCC possessed genetic (mutations) or epigenetic (promoter hypermethylation) alteration of VHL gene. Specific types of VHL mutations may be associated with aetiologic factors, disease progression and prognosis [25]. However, VHL mutations are rare in other types of kidney cancer [26]. Among other genetic factors that could influence molecular mechanisms underlying RCC development, mutations in TP53, EGFR and KRAS have been studied by Szymanska et al. [27], but were not confirmed as major contributors to the RCC development even in the absence of VHL inactivation. Lately, several studies investigated associations between RCC risk, various occupational exposures (pesticide, UV) and their modification by gene polymorphisms. Karami et al. [28] suggested that occupational pesticide exposures may increase RCC risk and observed that this risk was exclusive to individuals with active GSTM1/T1 genotypes. Thus glutathione S-transferase polymorphisms can modify occupational RCC risk associated with pesticide exposure. Similarly, common variants in VDR (vitamin D receptor) and RXRA (retinoid-X-receptor) genes were shown to modify associations between RCC risk and occupational UV exposure as well as consumption frequency of vitamin D and calcium rich foods [29]. Although there is strong inverse association with high vegetable intake and RCC risk, common variation in some folate metabolism (MTHFR and TYMS) genes may be associated with RCC risk, particularly when vegetable intake is low [30]. With regard to the absence of validating data on incidence of the mentioned risk factors in SR and CR population we are not able to explain reliably the cause of high rates of incidence and mortality in this region so far, although the decrease of smoking and obesity prevalence reported in SR may to some extent explain the character of the changes in incidence and mortality. Since the progress of incidence and mortality from kidney cancer in the last years in several countries has the similar tendency as in SR and CR it is not presupposed that the changes in diagnostic

methods and the way of tumour classification as well as earlier established diagnosis of the disease play the most important role in explanation of mortality decrease from this disease [11, 12, 31] and thus this is a question for further discussion. The difference in character of mortality from kidney cancer in SR and CR in both sexes (significant decline in CR) might be potentially affected by more radical surgical therapy, which corresponds to the continually enhancing trend of the number of operations within primary treatment registered in NCR CR (however reciprocal data in SR are not available).

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