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Analyzing selected risk factors for the development of kidney cancer

Research Article

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Abstract: The aim of this study was to determine influence of selected lifestyle factors on kidney cancer. The study brings data from two centres of international multicentric hospital-based analytical observational case-control studies. Data were obtained from a group of 300 patients newly diagnosed with kidney cancer (ICD-O-2 code C64) and 335 controls from two centres in the Czech Republic. Results showed that smoking increased OR to 1.09 (95% CI 0.77–1.55) and 1.06 (95% CI 0.73–1.52), but the results were not statistically significant. Obesity (BMI≥30) created adjusted OR 1.71 (95% CI 1.11–2.66) and 1.44 (95% CI 0.91–2.28), showing a minor, statistically insignificant, effect of obesity on the development of kidney cancer. For hypertension, adjusted OR was 1.73 (95% CI 1.25–2.40), suggesting a minor to moderate effect of hypertension on kidney cancer. The analysis results showed a positive association between hereditary predisposition and the development of kidney cancer with an OR of 1.97 (95% CI 1.41–2.76) and 1.97 (95% CI 1.40–2.77) depending on the model of adjustment. The reasons for the high incidence of kidney cancer are not fully understood. Genetic polymorphisms, together with other lifestyle and environmental factors, are likely to contribute to various rates of kidney cancer incidence throughout the world.

Keywords: *Kidney cancer • Smoking • Obesity • Hypertension • Hereditary predisposition*

1. Introduction

The main risk factors reported to be linked to the development of kidney cancer are smoking, obesity and hypertension, contributing to as many as 60% of cases. Another important risk factor is hereditary predisposition. In addition to the above factors, the development of kidney cancer is contributed to by the use of analgesics, antihypertensives and oestrogens, nutritional factors, occupational factors (asbestos, polychlorinated biphenyls, tetrachlorethylene, petrol and other petroleum products etc.), haemodialysis, ionizing radiation, socioeconomic factors and environmental factors [1-8]. The risk factors may act individually or they may combine and potentiate each other.

Kidney cancer is one of the ten most common cancers both worldwide and in the Czech Republic. Moreover, both the incidence and mortality rates of kidney cancer in the Czech Republic are the highest in the world [9-11]. Therefore, understanding the risk factors and assessing their effect as the disease develops is crucial for proposing preventive measures. In 2007, a total of 1,756 males and 1,039 females developed the condition and 668 males and 398 females died of it. The highest incidence rates were observed in the age ranges of 65–69 years in males and 70–74 years in females. The male to female ratio of kidney cancer incidence is 1.8–2 : 1 [9-11].

Smoking is considered to be one of the most important causal risk factors for kidney cancer, accounting for 20–30% of cases in males and 10–20% of cases in fe-

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males [7,12]. Although the results of case-control studies are inconclusive, a significant correlation between cigarette smoking and kidney cancer was found [13]. This association was also confirmed by results of cohort studies [14,15]. Most frequently, the risk for smokers ranges from 1.2 to 2.3, being considered moderate [16] and independent of gender [14]. Epidemiological studies confirmed the impact smoking has on the development of kidney cancer with respect to smoking duration and number of cigarettes smoked. In heavy smokers, i.e. those smoking 21 or more cigarettes a day, the risk ranges from 2.0 to 3.0 [7,17,18]. Contrary to opinions published earlier, smoking has been proven to be a risk factor, either acting individually or influencing other risk factors [14]. Cigarette smoking is the most serious causal carcinogenic factor for the development of kidney cancer [6].

Obesity has been consistently reported as a risk factor for kidney cancer. The effect seems to be more prominent in females who are at up to 3 times higher risk [15,19,20]. However, other epidemiological studies did not confirm the difference between males and females [21,22]. According to Scélo and Brennan, obesity and being overweight account for as many as 25% of kidney cancer cases in both genders [12].

The association between hypertension and the risk of kidney cancer has been mentioned by numerous epidemiological studies. Hypertension is seen in as many as 40% of adults with adenocarcinoma of the kidneys. Based on the published results, hypertension has been considered a risk factor for kidney cancer [23]. However, the strength of this association was significantly reduced after adjustment for the use of diuretics and other antihypertensives [24]. Many case-control studies found a link between hypertension and kidney cancer, with an OR of 1.4 to 3.2, even after adjustment for the most frequent influencing factors such as age, smoking and BMI [25]. These findings were also confirmed by cohort studies showing a RR ranging from 1.12 to 2.2. It has not been clearly established whether the real risk is due to hypertension or hypertension treatment. However, a European prospective study supports the hypothesis of hypertension rather than the use of antihypertensives being the risk factor, even after adjustment for gender and administration of antihypertensives [26].

Kidney cancer is rarely determined by hereditary predisposition. Most such cases are sporadic diseases resulting from acquired genetic changes in tumour tissue [27]. Apart from hereditary predisposition, there are families that do not meet the criteria for the monogenic type of inheritance and yet show higher rates of cancer (familial incidence), probably due to a certain lifestyle or unknown low-penetrance genes or genetic polymorphism [28]. In the case of hereditary kidney cancer, the condition is always a part of a syndrome. In their multicentre case-control study of 2,652 subjects that also included centres in the Czech Republic, Hung *et al*. showed a risk of the disease development in the family by finding a positive association even after adjustment for other risk factors [29].

The presented work is aimed at explaining the association between the main risk factors (smoking, obesity, hypertension, hereditary predisposition) and the development of kidney cancer.

2. Materials and methods

The study was carried out as a part of a multicentre study led by the International Agency for Research on Cancer (IARC) in Lyon and performed in seven centres in European countries including the Czech Republic to elucidate the relationship between lifestyle and its risks and health disorders. A hospital-based analytical observational case-control study was designed to determine selected lifestyle factors in a group of patients newly diagnosed with kidney cancer (ICD-O-2 code C64) and a control group of the same size. The study was approved by the Research Ethics Committee of Faculty Hospital and Palacky University in Olomouc and informed consent was obtained from all participants before participating in the study. The study lasted from August 1999 through January 2003. The response rates were 90–98.6% for cases and 90.3–96.1% for controls.

The group enrolled in the presented study comprised 635 subjects of which 300 were kidney cancer cases and 335 were controls from the University Hospital Olomouc and České Budějovice Hospital. Each case or control was interviewed using a standardized questionnaire to obtain information about the individual's smoking status, family history of cancer in first-degree relatives (parents, offspring, siblings), height and weight, hypertension and its therapy, alcohol consumption, dietary habits and demographic characteristics. The interview was conducted by a trained interviewer. The inclusion criteria for the control group were age (a possible deviation of 3 years), gender and health status, with the condition that the subjects had no malignancies, were hospitalized for reasons unrelated to the studied disease and had no other life-threatening diseases. The controls were recruited within 3 months from the diagnosis made in kidney cancer patients. The average age of kidney cancer patients was 60.2 years, with a standard deviation of 10.1 and a range of 26–83 years. The case group comprised 184 males and 116 females. The average age of females was 62 years, with the minimum and maximum ages of 26 and 83 years, respectively. The males were 59 years of age on average, with the minimum age of 32 years

and the maximum age of 79 years. The average age of controls was 60.8 years, with a standard deviation of 9.9 and a range of 27–82 years. The control group was made up of 220 males and 115 females. In females, the average age was 61 years, with the minimum age of 27 and the maximum age of 79 years. The average age of male controls was 60 years, with the minimum age being 31 and the maximum age being 82 years. The male to female ratio in the presented study was 1.5 : 1.

Statistical analysis was performed using the STATA 10 software. The assessment was carried out using OR (odds ratio) with 95% confidence intervals (CI) and adjusted for age and gender (Table 1, Analysis 1) and OR adjusted for age, gender, smoking, BMI, hypertension and familial incidence (Table 1, Analysis 2).

3. Results

The analysis of whether smoking is a risk factor for kidney cancer was carried out by comparing exposed subjects (smokers) with those who had never smoked or smoked only up to 99 cigarettes per life. In the group of kidney cancer cases were 45.3% non-smokers and 54.7% smokers, while 72.6% of these smokers belonged to the category of moderate and heavy smokers (smoked per life 200 000, respectively 300 000 or more cigarettes per life). In the control group, 45.7% were non-smokers and 54.3% were smokers, while 72.5% of smokers in control group were moderate and heavy smokers. The age- and gender-adjusted OR was 1.09 (95% CI 0.77–1.55) and was not statistically significant. Similar values were found even after adjustment for the studied risk factors, with the OR being 1.06 (95% CI 0.73–1.52). Thus, smoking was not confirmed to be a risk factor in this study.

In the study group, obese subjects with a BMI≥30 were compared with those with normal weight and a BMI≥18.5<25. The age- and gender-adjusted OR was 1.71 (95% CI 1.11–2.66), showing a minor effect of obesity on the development of kidney cancer. After adjustment for other studied factors (smoking, hypertension, familial incidence, age and gender), the OR was 1.44 (95% CI 0.91–2.28), a statistically insignificant result.

When comparing hypertensive and normotensive subjects in the entire group, the age- and gender-adjusted OR was 1.73 (95% CI 1.25–2.40), suggesting a minor to moderate effect of hypertension on kidney cancer. After adjustment for other studied factors (smoking, obesity, familial incidence), the OR was 1.69 (95% CI 1.20–2.38). The result was statistically significant even after adjustment for other most important risk factors. Only hypertensive patients receiving treatment were included in the analysis. Those accounted for 96% of all subjects who stated that they had hypertension.

The presented study also analyzed the familial incidence of cancer in first-degree relatives in both kidney cancer patients and controls. The analysis results showed a positive association between hereditary predisposition and the development of kidney cancer. Positive association was found in the overall incidence of cancer, with the age- and gender-adjusted OR of 1.97 (95% CI 1.41–2.76). After adjustment for not only age and gender but also smoking, BMI and hypertension, the OR was 1.97 (95% CI 1.40–2.77). Both results suggested moderately statistically significant association. Table 1 shows distribution of the group according to the studied characteristics and results of the analyses.

Table 1. Association between smoking, obesity, hypertension, familial incidence and the risk of the development of kidney cancer. Analysis 1 – age- and gender-adjusted OR; Analysis 2 – OR adjusted for age, gender, smoking, BMI, hypertension and familial incidence.

Risk factors	Category	Kidney cancer		Total number	Analysis 1		Analysis 2	
		yes	no		OR	95% CI	OR	95% CI
Gender	male	184	220	404	1+		1+	
	female	116	115	231	1.22	0.87–1.70	1.25	0.86–1.81
Age	under 50	47	43	90	1+		1+	
	50–64	144	166	310	0.80	0.50–1.28	0.65	0.30–1.06
	65–74	90	96	186	0.84	0.51–1.39	0.70	0.41–1.19
	75–84	19	30	49	0.56	0.28–1.14	0.44	0.21–0.94
Smoking	no	136	153	289	1+		1+	
	yes	164	182	346	1.09	0.77–1.55	1.06	0.73–1.52
BMI	≥18.5<25	68	94	162	1+		1+	
	≥25<30	136	165	301	1.13	0.76–1.67	1.03	0.67–1.55
	≥30	96	76	172	1.71	1.11–2.66	1.44	0.91–2.28
Hypertension	no	149	206	355	1+		1+	
	yes	151	129	280	1.73	1.25–2.40	1.69	1.20–2.38
Familial incidence	no	176	244	421	1+		1+	
	yes	124	90	214	1.97	1.41–2.76	1.97	1.40–2.77

4. Discussion

Our study and also previous case–control studies in Cancers, including kidney cancer, are multifactorial diseases. Factors most associated with kidney cancer are smoking, obesity, hypertension and especially hereditary predisposition. Cigarette smoking and obesity are clear risk factors for the development of kidney cancer, meeting all the necessary criteria such as consistent results in numerous cohort studies and meta-analyses, a confirmed dose-effect relationship and the strength of association [3,6,12,30]. Cigarette smoking plays a role after approximately 20 person-years of exposure. The association between smoking and kidney cancer is weaker than association between smoking and lung cancer. It is a low to moderate risk factor increasing the risk by 1.2–2.3 and, in severe smokers, by 2.0–3.0, as compared with non-smokers. The risk drops with increasing years from smoking cessation. After 10–15 years from smoking cessation, the risk decreases by 15–30% [6]. As a preventive measure, the elimination of smoking may decrease the incidence of kidney cancer by 16–28% in adults [1,3]. In 2005, Hunt *et al*. published a meta-analysis of 19 case-control studies and 5 cohort studies. This large review also showed a relative risk of 1.38 (95% CI 1.27–1.50), suggesting only weak association [18]. A small effect of smoking was confirmed by McLaughlin *et al*. in an international study performed in Australia, Denmark, Germany, Sweden and the USA, reporting an OR of 1.4, and Yuan *et al*. (OR 1.35) [7,23]. Identical results were found by Hu *et al*. in both active and passive smoking in males as well as females in Canada [30].

In the presented study, the OR irrespective of gender was 1.09. Due to the OR value and statistically insignificant results, no association between smoking and a higher risk of the development of kidney cancer was found in this study. After adjustment, the OR was 1.06. Once again, the result was not statistically significant. The detected association is consistent with results of other epidemiological studies. Given the moderate effect of smoking as a risk factor for kidney cancer, more subjects than the number in the presented study are needed to confirm the association. A high proportion of smokers in the study is worth mentioning, both among kidney cancer patients (73.9%) and controls (67.7%). The fact that the presented results suggested negative association may be explained by the study design using hospital controls (a hospital-based study). Therefore, the result might have been underestimated since the prevalence of smokers among hospitalized persons is higher than in the general population [31].

Kidney cancer is one of the most strongly associated with obesity [32]. Obesity is a risk factor with linear dependence, with an increase in BMI raising the risk of kidney cancer [1,3]. The risk ranges from 1.1 to 4.6 [3,23,33–35]. In presented study, obesity, but not being overweight, showed to be risk factor for kidney cancer. The age- and gender-adjusted OR was 1.71 (95% CI 1.11-2.66), suggesting a moderate effect of obesity on the development of kidney cancer. After adjustment for the main risk factors for kidney cancer, the OR for obesity was found to be 1.44 but the result was not statistically significant. In the study, being overweight was not demonstrated to be a risk factor, probably due to a high proportion of obese persons in the control group. In obese patients, many other factors may influence kidney cancer risk. In the presented study it was particularly family history of cancer. Our results are consistent with the literature data suggesting an increased risk of kidney cancer in obese subjects in both case-control and cohort studies [22]. Studies from the USA [38], Denmark [39] and Italy [40] showed a higher risk for females than for males, suggesting a role of different fat distribution and hormone levels, in particular oestrogens [3]. In their study of 2 million Norwegian males and females, Bjørge *et al.* found a positive association for both genders [41]. In a recently published meta-analysis of 11 studies, Bergstrom *et al.* stated that each 1-point increase in BMI is accompanied by an increase of the risk of kidney cancer by 6-7% [32]. Most studies performed in Europe, the USA and other regions are consistent in finding approximately a double risk of kidney cancer in obese males and females when compared with normal-weight persons, which corresponds with the result of our analysis. After adjustment for the studied risk factors (gender, age, hypertension, smoking, familial incidence), however, no statistically significant association between BMI and kidney cancer was confirmed.

Adipose tissue is established as an endocrine organ [36]. Obesity thus presents with several hormonal changes, such as increased oestrogens, insulin and insulin-like growth factor [37]. In addition, alterations in the immune response, oxidative stress and peroxidation are common in obesity [37]. Increased oestrogen levels were in many studies put into context with increased risk of kidney cancer, but its level was not measured in this study. Oestrogen level measurement would need further studies. According to studies by Renehan and Paz Fiho, kidney cancer risk would be influenced not only by oestrogen, but also by other pathophysiological mechanisms. The products of adipose tissue pathways (insulin like-growth factor, tumor necrosis factor and others) may also play a role [36,37].

Numerous epidemiological case-control studies consider hypertension a risk factor, with the risk ranging from 1.4 to 3.2. This association was confirmed by cohort stud-

ies reporting a relative risk of 1.1–2.2. Other studies, with an OR of 1.9 for males and 3.2 for females [3,42] pointed to a potential interaction with obesity and did not consider hypertension a separate risk factor. McLaughlin *et al.* reported a relative risk of hypertension as a risk factor for kidney cancer of 1.3–2.0. They noted, however, that hypertension may be due to preclinical kidney disease or undiagnosed kidney cancer [7]. As a risk factor, hypertension may be influenced by simultaneous use of diuretics and other antihypertensives. This suggests that drug therapy of hypertension may be the primary risk factor. Hypertension may also be related to metabolic or functional changes in renal tubules and thus increase susceptibility to carcinogenesis [7]. Both furosemide and hydrochlorothiazide are known as suspected risk factors for kidney cancer in animals. This association was also suggested by some epidemiological studies showing a risk of 2.3-4.0 which was significant even after adjustment for hypertension [3]. According to Dhôte *et al*., hypertension and its therapy are only risk markers since the relationship between the dose and duration of exposure needed for the development of the disease is not fully elucidated [3]. In the presented study, the comparison of hypertensive and normotensive patients after adjustment for age and gender showed an OR of 1.73, i.e. a minor, statistically significant effect of hypertension on kidney cancer. The statistically significant result was confirmed even after adjustment for the main risk factors, with an adjusted OR of 1.69. In the presented study, hypertension was confirmed to be a moderate risk factor. Given the fact that 96% of subjects claimed to have hypertension which was treated and only 4% had untreated hypertension, the impact of untreated hypertension could not be assessed. As diuretic and antihypertensive drug use may influence the hypertension risk factor [2,43], its impact was analyzed only in the form of treated hypertension-normotension. But use of both drug groups was not analyzed separately in the presented study.

Although hereditary predisposition has a less important role in kidney cancer than in breast or colon cancer, there is a spectrum of predisposing genes contributing to hereditary forms of kidney cancer [27]. The incidence of kidney cancer is particularly high in Central Europe, namely in the Czech Republic. Yet, there are no available data on the familial incidence or genetic predisposition. In their study involving 7 centres in Central European countries including the Czech Republic, Hung *et al*. reported an increased risk for persons having at least one first-degree relative with kidney cancer. After adjustment for smoking, BMI and treated hypertension, the risk was 1.4. This association was more prominent especially in siblings and offspring [29]. In the presented study, 214 subjects reported a history of cancer in their first-degree relatives. There was a positive association with the development of cancer, with an age- and gender-adjusted OR of 1.97. After adjustment for other studied risk factors, a moderate, statistically significant positive association was revealed, once again with an OR of 1.97 and statistically significant results. The results are suggestive of genetic predisposition to cancer in persons with kidney cancer. Our results are consistent with those from a study performed in Central and Eastern Europe and a large Swedish study and confirm the association between hereditary predisposition and the risk of the development of kidney cancer [28,44,45]. Familial incidence of cancer in first-degree relatives suggested moderate, statistically significant association with kidney cancer. It may be the explanation for the higher genetic susceptibility of our population [29,45].Genetic polymorphisms, together with other lifestyle and environmental factors, are likely to contribute to various rates of kidney cancer incidence throughout the world. Rather than genetic screening, prevention should focus more on elimination of risk factors in people with higher risk.

Analysis by age and gender showed no statistically significant results and only suggested a rise in the risk with an increasing age. Similarly, no statistically significant difference was found by gender analysis, with a less favourable trend being noted in females. The results of the presented study revealed no significant difference in the risk of the disease between genders.

Globally, another increase in the incidence of kidney cancer by 2-3% per decade is expected [46].

5. Conclusions

Kidney cancer is one of the most frequent types of cancer both in the Czech Republic and worldwide. The reasons behind the first place are not fully understood since the role of individual potential risk factors has not been completely elucidated. Results of the presented study attempt to elucidate the aetiology of kidney cancer. Smoking was not confirmed to be a risk factor of kidney cancer in the presented study. Obesity, but not being overweight, was elucidated as a risk factor for kidney cancer. Analysis of familial incidence of cancer in first-degree relatives suggested a moderate, statistically significant association with kidney cancer. Hypertension showed a minor to moderate effect on kidney cancer risk. Further studies should focus on oestrogen level, antihypertensive treatment and diuretic use analyses.

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