

Short Communication

Tobacco smoking, body mass index, hypertension, and kidney cancer risk in central and eastern Europe

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In a case–control study of kidney cancer in four central European countries, with 1097 incident cases and 1476 controls, we found an increased risk for self-reported hypertension and for obesity. Additional unknown risk factors are likely to be responsible for the high rates of kidney cancer in this region.

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Kidney cancer accounts for 1.9% of all malignancies, with approximately 189 000 new cases diagnosed globally each year and the incidence varying more than 10-fold around the world, with the highest rates generally observed in central European countries and among blacks in the United States (Murai and Oya, 2004). Smoking is an established risk factor, although the increase in risk is moderate (IARC, 2004). Other possible risk factors are hypertension and obesity, with potentially differing risks for men and women (Shapiro *et al*, 1999; Bergstrom *et al*, 2001). To examine the risk factors for kidney cancer in central Europe, we conducted a large multicenter case–control study in Czech Republic, Poland, Russia, and Romania. We present here data on the role of smoking, hypertension, and body mass index (BMI) in this high-risk population.

MATERIALS AND METHODS

This hospital-based case–control study was conducted in seven centres (Moscow (Russia), Bucharest (Romania), Lodz (Poland), and Prague, Olomouc, Ceske Budejovice, and Brno (Czech Republic)). A total of 1097 newly diagnosed, histologically confirmed, renal parenchymal cancers (ICD-O-2 code C64) between 20 and 79 years of age were recruited during August 1999 and January 2003. Trained medical staff reviewed medical records to extract relevant diagnostic information, including date and method of diagnosis, histological type, tumour location, stage, and grade. Eligible controls ($n = 1476$) were admitted to the same hospitals as the cases for conditions unrelated to smoking or genitourinary disorders (except for benign prostatic hyperplasia) between August 1998 and March 2003. No single disease made up

more than 20% of the control group. Both cases and controls had to be residents of the study areas for at least 1 year. The response rate for cases ranged from 90 to 98.6% and for the controls, 90.3–96.1%.

Trained interviewers used standardised questionnaires at all centres to elicit information on demographic background, smoking, alcohol drinking, dietary practices, height, weight, medical history, family history of cancer, residential history, and occupational history.

Smoking status (never smoker, former smoker, current smoker) was defined as status 2 years before interview. Packyears were used as a measure of cumulative tobacco smoking and were calculated by the number of cigarettes smoked per day multiplied by years of smoking and divided by 20. History of hypertension was self-reported and a positive history was restricted to patients who reported being treated for hypertension. The weight in kilograms was ascertained for 2 years before the interview. Body mass index was calculated by dividing the weight by the square of the height in metres.

Kidney cancer risks were estimated by odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression analysis, with adjustment for age (5-years interval), smoking (current, former, and never smokers), BMI in five categories (< 25 , 25–27.4, 27.5–29.9, 30–34.9, ≥ 35), history of hypertension treatment (no vs yes), and country, where appropriate. Heterogeneity tests were used to evaluate differences among countries by including country–exposure interaction terms in the logistic models, and likelihood ratio tests to evaluate the statistical significance of the interaction terms.

RESULTS

The study population consisted of 1097 kidney cancer cases (648 men and 449 women) and 1476 controls (952 men and 524 women) (Tables 1 and 2). Among cases, tumour stage at diagnosis was

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similar for both sexes, with 9.2% of men and 6.9% of women having M1 stage and 10.3% of men and 8.8% of women having \geq N1 stage, 83% of cases were clear cell carcinoma and 6% papillary carcinoma.

Smoking was not associated with an increased risk of kidney cancer, and no dose-response was seen with increasing levels of

cigarette consumption. The findings were similar for all patients combined or in men and women separately. In addition, no significant heterogeneity between the four countries was observed.

Increasing BMI was positively associated with kidney cancer overall (test for linear trend, $P=0.011$; Table 3). Compared to those with BMI <25 , the OR among those with BMI 30–35 was 1.38 (95% CIs: 1.09, 1.75), and among those with BMI ≥ 35 was 1.29 (95% CIs: 0.88, 1.89). The excess risks, however, were restricted to men, risk nearly doubling among those in the highest category of BMI (OR = 1.72; (95% CIs: 1.01, 2.94)). For women, no increase in risk was observed either overall or in any of the four countries separately. Approximately 14% of cases were estimated to be attributable to a BMI of greater than 25 (95% CI 3–23%).

An increased risk was observed for patients who reported having been treated for hypertension more than 2 years before interview compared to those who did not (OR = 1.25 (95% CIs: 1.06, 1.49)) (Table 4). The effect was more prominent among women (OR = 1.47 (95% CIs: 1.11, 1.95)) than men. The results were largely unaltered when hypertension was defined as ever having been diagnosed with hypertension regardless of treatment status. Approximately 9% of cases were estimated to be attributable to hypertension (95% CIs 2–16%).

Our analysis included all histological types of carcinoma of the renal parenchyma, including 17% of cases who had an histology other than clear cell type, excluding these cases had little influence on the results.

Table 1 Descriptive characteristics of cases and controls

| Variables | Men | | | | Women | | | |
|-----------------------------------|-------|------|----------|------|-------|------|----------|------|
| | Cases | | Controls | | Cases | | Controls | |
| | N | % | N | % | N | % | N | % |
| <i>Country</i> | | | | | | | | |
| Romania | 63 | 9.7 | 109 | 11.4 | 32 | 7.1 | 51 | 9.7 |
| Poland | 56 | 8.6 | 112 | 11.8 | 43 | 6.6 | 86 | 16.4 |
| Russia | 163 | 25.4 | 305 | 32.0 | 154 | 34.3 | 158 | 30.2 |
| Czech Republic | 366 | 56.4 | 426 | 44.8 | 220 | 49.0 | 229 | 43.7 |
| Total | 648 | 100 | 952 | 100 | 449 | 100 | 524 | 100 |
| <i>Age (years)</i> | | | | | | | | |
| <40 | 25 | 4.1 | 25 | 2.6 | 14 | 3.1 | 18 | 3.4 |
| 40–49 | 91 | 14.0 | 152 | 16.0 | 53 | 11.8 | 60 | 11.5 |
| 50–59 | 227 | 35.0 | 320 | 33.6 | 122 | 27.2 | 153 | 29.2 |
| 60–69 | 187 | 28.9 | 289 | 30.4 | 150 | 33.5 | 170 | 32.4 |
| >70 | 118 | 18.0 | 166 | 17.4 | 110 | 24.4 | 123 | 23.5 |
| <i>Tumour stage</i> | | | | | | | | |
| <i>T-stage</i> | | | | | | | | |
| T1 | 117 | 18.8 | | | 90 | 20.5 | | |
| T2 | 275 | 44.1 | | | 209 | 47.5 | | |
| T3 | 210 | 33.6 | | | 126 | 28.6 | | |
| T4 | 22 | 3.5 | | | 15 | 3.4 | | |
| <i>M-stage</i> | | | | | | | | |
| M0 | 486 | 90.8 | | | 363 | 93.1 | | |
| M1 | 49 | 9.2 | | | 27 | 6.9 | | |
| <i>N-stage</i> | | | | | | | | |
| N0 | 505 | 89.7 | | | 371 | 91.2 | | |
| N1 | 31 | 5.5 | | | 24 | 5.9 | | |
| N2 | 24 | 4.3 | | | 10 | 2.4 | | |
| N3 | 3 | 0.5 | | | 2 | 0.5 | | |
| <i>Histology</i> | | | | | | | | |
| (Clear cell) Renal cell carcinoma | 538 | 83.0 | | | 370 | 82.4 | | |
| Papillary renal cell carcinoma | 51 | 7.9 | | | 20 | 4.5 | | |
| Other | 59 | 9.1 | | | 59 | 13.1 | | |

Table 2 Odds ratio of kidney cancer for tobacco smoking

| Smoking | Men | | | | Women | | | | Total | | | |
|-----------------|-------|----------|------------------------|------------------|-------|----------|------------------------|------------|-------|----------|------------------------|------------|
| | Cases | Controls | OR ^a | 95% CI | Cases | Controls | OR ^a | 95% CI | Cases | Controls | OR ^a | 95% CI |
| | N | N | | | N | N | | | N | N | | |
| Never smokers | 170 | 232 | 1.00 | Ref ^b | 340 | 368 | 1.00 | Ref | 510 | 600 | 1.00 | Ref |
| Former smokers | 204 | 302 | 0.89 | 0.68, 1.17 | 47 | 51 | 1.07 | 0.69, 1.67 | 251 | 353 | 0.88 | 0.71, 1.11 |
| Current smokers | 273 | 416 | 0.99 | 0.76, 1.29 | 60 | 105 | 0.70 | 0.48, 1.02 | 333 | 521 | 0.87 | 0.71, 1.07 |
| Never smokers | 170 | 232 | 1.00 | Ref | 340 | 368 | 1.00 | Ref | 510 | 600 | 1.00 | Ref |
| <17 packyears | 150 | 221 | 0.94 | 0.70, 1.26 | 62 | 97 | 0.76 | 0.52, 1.11 | 212 | 318 | 0.85 | 0.67, 1.06 |
| 17–31 packyears | 161 | 234 | 1.00 | 0.75, 1.34 | 32 | 39 | 0.99 | 0.59, 1.65 | 193 | 273 | 0.95 | 0.74, 1.21 |
| >31 packyears | 165 | 261 | 0.89 | 0.67, 1.19 | 13 | 19 | 0.85 | 0.40, 1.78 | 178 | 280 | 0.85 | 0.66, 1.09 |
| | | | P-value for trend 0.49 | | | | P-value for trend 0.34 | | | | P-value for trend 0.19 | |

^aAdjusted for age, body mass index, history of hypertension and country. ^bRef = reference category.

Table 3 Odds ratio of kidney cancer for BMI

| BMI | Men | | | | Women | | | | Total | | | |
|------------|-------------------------|---------------|-----------------|------------------|------------------------|---------------|-----------------|------------|-------------------------|---------------|-----------------|------------|
| | Cases N | Controls N | OR ^a | 95% CI | Cases N | Controls N | OR ^a | 95% CI | Cases N | Controls N | OR ^a | 95% CI |
| <25 | 191 | 363 | 1.00 | Ref ^b | 136 | 169 | 1.00 | Ref | 327 | 532 | 1.00 | Ref |
| 25–27.5 | 166 | 248 | 1.19 | 0.91, 1.56 | 87 | 115 | 0.86 | 0.60, 1.25 | 253 | 363 | 1.09 | 0.88, 1.35 |
| 27.5–29.99 | 125 | 167 | 1.32 | 0.98, 1.79 | 98 | 90 | 1.16 | 0.80, 1.70 | 223 | 257 | 1.31 | 1.04, 1.65 |
| 30–35 | 133 | 139 | 1.70 | 1.25, 2.31 | 98 | 111 | 0.95 | 0.66, 1.38 | 231 | 250 | 1.38 | 1.09, 1.75 |
| 35+ | 32 | 32 | 1.72 | 1.01, 2.94 | 30 | 37 | 0.85 | 0.49, 1.48 | 62 | 69 | 1.29 | 0.88, 1.89 |
| | P-value for trend 0.001 | | | | P-value for trend 0.68 | | | | P-value for trend 0.011 | | | |

^aAdjusted for age, smoking, history of hypertension and country. ^bRef = reference category.

Table 4 Odds ratio of kidney cancer for history of hypertension

| History of treated hypertension | Men | | | | Women | | | | Total | | | |
|---------------------------------|------------|---------------|-----------------|------------------|------------|---------------|-----------------|------------|------------|---------------|-----------------|------------|
| | Cases N | Controls N | OR ^a | 95% CI | Cases N | Controls N | OR ^a | 95% CI | Cases N | Controls N | OR ^a | 95% CI |
| No | 385 | 607 | 1.00 | Ref ^b | 215 | 299 | 1.00 | Ref | 600 | 906 | 1.00 | Ref |
| Yes | 262 | 344 | 1.12 | 0.90, 1.40 | 234 | 225 | 1.47 | 1.11, 1.95 | 496 | 569 | 1.25 | 1.06, 1.49 |

^aAdjusted for age, smoking, BMI and country. ^bRef = reference category.

and inhibits apoptosis, which could have a profound impact on tumour growth (Yu and Rohan, 2000).

An association between hypertension and kidney cancer has also been previously reported (McLaughlin *et al*, 2006). Hypertension is hypothesised to cause renal damage directly or cause metabolic or functional changes within the renal tubules, thus increasing the kidney's susceptibility to carcinogens or promoting agents (Cowley and Roman, 1996). The relationship between kidney cancer and hypertension is complex. McCredie and Stewart (1992) showed that kidney cancer in hypertensive patients was related to the duration of hypertension, suggesting that hypertension contributes is aetiologically relevant rather than being a consequence of the tumour (McCredie and Stewart, 1992). Also, in this connection, cohort studies may stratify by follow-up time, several findings that have found that the effect of hypertension is the same in the first years of follow-up as later (Fraser *et al*, 1990; Coughlin *et al*, 1997; Chow *et al*, 2000). These findings support the hypothesis that hypertension is a risk factor for kidney cancer. Further, an increased risk has been reported with mild hypertension that would usually go untreated, and a decreasing risk of among those who have experienced lowered blood pressure levels over time (Chow *et al*, 2000).

Smoking is an established risk factor for kidney cancer, although the increase in risk is weak (IARC, 2004). In a comprehensive meta-analysis, we have recently estimated that the increased risk for ever smokers compared to never smokers

was 38% (RR = 1.38 (95% CI: 1.28, 1.49) (Hunt *et al*, 2005)). There was also a strong dose-dependent increase with increasing tobacco consumption. However, the OR for smoking obtained from the meta-analysis in hospital-based studies was 1.17 (95% CIs: 1.03, 1.34), whereas in population-based studies, it was 1.49 (95% CIs: 1.34, 1.66). Our current study had a 97% power of detecting an increased risk of 40% associated with smoking, although only about a 50% power of detecting a 20% increase in risk. One possible conclusion is that smokers were over-represented in hospital controls resulting in a reduced power to detect a real effect of smoking on kidney cancer. We did compare the smoking prevalence between the major control groups and did not detect any heterogeneity, although a small amount of bias could not be excluded.

Our study confirms that BMI and a history of hypertension are risk factors for kidney cancer in central Europe, a region with the highest incidence currently reported, but these are unlikely to explain fully the high incidence, indicating that important causes remain to be discovered.

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