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Original Contribution

Blood Pressure and Risk of Renal Cell Carcinoma in the European Prospective Investigation into Cancer and Nutrition

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Elevated blood pressure has been implicated as a risk factor for renal cell carcinoma (RCC), but prospective studies were confined to men and did not consider the effect of antihypertensive medication. The authors examined

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the relation among blood pressure, antihypertensive medication, and RCC in the European Prospective Investigation into Cancer and Nutrition (EPIC). Blood pressure was measured in 296,638 women and men, recruited in eight European countries during 1992–1998, 254,935 of whom provided information on antihypertensive medication. During a mean follow-up of 6.2 years, 250 cases of RCC were identified. Blood pressure was independently associated with risk of RCC. The relative risks for the highest versus the lowest category of systolic ($\geq$160 mmHg vs. $<$120 mmHg) and diastolic ($\geq$100 mmHg vs. $<$80 mmHg) blood pressures were 2.48 (95% confidence interval: 1.53, 4.02) and 2.34 (95% confidence interval: 1.54, 3.55). Risk estimates did not significantly differ according to sex or use of antihypertensive medication. Individuals taking antihypertensive drugs were not at a significantly increased risk unless blood pressure was poorly controlled. These results support the hypothesis that hypertension, rather than its medications, increases the risk of RCC in both sexes, while effective blood pressure control may lower the risk.

antihypertensive agents; hypertension; kidney neoplasms; risk factors

Abbreviations: CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HIF, hypoxia-inducible factor; RCC, renal cell carcinoma.

The incidence and mortality of renal cell carcinoma (RCC) have increased worldwide over the last 30 years (1), particularly in the Western world where RCC has been among the tumors with the highest upward trend in incidence (2, 3). Rising incidence rates are partly attributable to improvements in diagnostic imaging, but better detection does not explain the continued high number of advanced tumors and the increase in tumor size-specific mortality among RCC patients (3). Although most recent data suggest that mortality rates have leveled off (2, 4) while relative 5-year survival rates have risen (5) in the context of earlier detection, the all-cause mortality among kidney cancer patients in the United States has continued to increase until recently (3).

The temporal trends and geographic variations in incidence and mortality (2, 6) suggest a role of environmental factors associated with Western lifestyle in the etiology of this disease. Hypertension or its treatment has been associated with the risk of RCC in a number of prospective studies (7–14). However, data on sex-specific differences in risk estimates have been inconsistent, and it remains unclear whether the elevated blood pressure or the use of antihypertensive medication determines the increase in risk. Data according to level of blood pressure are particularly useful as the dose-response relation can be investigated. Few adequately powered prospective studies (7, 15), however, have measured blood pressure, and none of those provides data on women or has considered the effect of antihypertensive medication. Data from a case-control study (16) investigating the relation among blood pressure, antihypertensive medication, and RCC suggest that high blood pressure, rather than medication use, is associated with an increased RCC risk.

Within the framework of the European Prospective Investigation into Cancer and Nutrition (EPIC), we examined the relation between blood pressure and risk of RCC, taking into account other important risk factors, such as obesity and smoking, and the use of antihypertensive medication.

MATERIALS AND METHODS

Study population

EPIC is an ongoing, multicenter, prospective cohort study designed to investigate the relations between diet, lifestyle, and various medical and environmental factors and the incidence of various types of cancer. The source populations and methods have been described previously (17–20). Briefly, the total cohort consists of 521,457 men and women recruited from the general population residing in defined geographic areas (i.e., town or province) in each of the participating 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom). Exceptions were the Utrecht cohort in the Netherlands (based on women attending breast cancer screening), the Spanish cohorts and the Ragusa cohort in Italy (based mainly on blood donors and their spouses), and the Oxford health-conscious subcohort (recruited throughout the United Kingdom in order to enroll a large number of vegetarians and healthy eaters). The participants were mostly aged between 25 and 70 years at the time of enrolment (1992–1998). For the present analysis, over 95 percent of the participants were in this age range (mean age: 52 years; range: 20–90 years). Eligible subjects completed standardized questionnaires on their diet, lifestyle, medical history, and the presence of chronic diseases. Information on current use of antihypertensive medications was collected at baseline. Exceptions were the study centers in the United Kingdom, that is, Cambridge and Oxford, where no data on medication use were available. Participants were invited to a study center for an examination that included measurement of anthropometry (21) and blood pressure.

Subjects with prevalent cancer at any site at baseline examination (n = 23,679) and those with missing follow-up or dates of diagnosis (n = 2,361) were excluded a priori, leaving 495,416 participants. Additionally, we excluded the cohorts of Norway (n = 35,956) because of the short

follow-up period and the French cohorts ($n = 69,023$) because of incomplete case identification procedures for this cancer site. Further, the Spanish study centers of Asturias ($n = 8,447$) and Navarra ($n = 7,936$) were excluded, as blood pressure was not measured there. After further exclusion of the 77,414 individuals with missing blood pressure values (systolic, diastolic, or both) and two subjects with incompatible combinations of self-reported smoking status and duration of smoking, 296,638 participants (180,688 women and 115,950 men) were eligible for analysis, among whom 254,935 (86 percent) had information on antihypertensive medication use.

Assessment of blood pressure

Systolic and diastolic blood pressures were measured in millimeters of mercury by trained personnel at baseline (22). Two readings were performed on the right arm in a sitting position (spaced by 1–5 minutes) after an initial resting time of at least 5 minutes by use of a standard mercury manometer or oscillometric device. Exceptions were the Danish and Swedish centers where one single measurement was taken in the supine position. Elevated blood pressure was defined as a systolic pressure of 140 mmHg or above or a diastolic pressure of 90 mmHg or above following the current guidelines for defining hypertension based on office or clinic blood pressure (23, 24).

Assessment of endpoints

Incident kidney cancer cases were identified by population cancer registries in Denmark, Italy, the Netherlands, Spain, Sweden, and the United Kingdom. In Germany and Greece, a combination of methods was used, including health insurance records, cancer and pathology registries, and direct contact with participants or their next of kin. Participants were followed from study entry until date of kidney cancer diagnosis or censoring due to death, emigration, loss to follow-up, or end of follow-up. By the end of May 2004 (follow-up—mean: 6.2 years; median: 6.3 years; range: 0.01–10.8 years), 291 kidney cancer cases eligible for analysis according to the aforementioned criteria had been included in the central EPIC database. After further exclusion of subjects with transitional cell cancer of the renal pelvis ($n = 40$) or other non-RCC tumors (sarcoma: $n = 1$), our final data set included 250 cases of incident RCC among 296,638 participants.

Statistical analyses

The relative risks and 95 percent confidence intervals of RCC were estimated by Cox proportional hazard models with center as the stratum variable to control for center effects. Age was used as the dependent variable, with entry time defined as the subject's age in days at recruitment and exit time defined as the subject's age in days at RCC diagnosis or censoring. Models were adjusted for body mass index (continuous); smoking status defined as never, former (quit $\geq$10 years ago, $<$10 years ago, or unknown), or current ($<$15, 15–24, $\geq$25 cigarettes smoked per day, or unknown); duration of smoking (continuous); and educational attainment (none or primary school, technical/professional school, secondary school, or university).

The categories of systolic and diastolic blood pressures were chosen on the basis of current criteria for the definition of normal and elevated blood pressures (23, 24): $<$120 mmHg, 120–139 mmHg, 140–159 mmHg, and $\geq$160 mmHg for systolic blood pressure and $<$80 mmHg, 80–89 mmHg, 90–99 mmHg, and $\geq$100 mmHg for diastolic blood pressure. To test for trend across categories, we assigned participants a score ranging from 1 to 4 according to the category of systolic or diastolic blood pressure, and this score was used as a continuous variable. Models were run separately for men and women and for both sexes combined. Sex-specific differences in relative risk estimates were further evaluated by use of log-likelihood ratio tests of hierarchical models with and without inclusion of the respective interaction terms. Further, interaction with smoking and body mass index was analyzed. Further, we examined the relation among blood pressure, antihypertensive medication use, and RCC risk in 254,935 participants (including 225 cases). Potential differences in risk estimates for elevated blood pressure among users and nonusers of antihypertensive drugs and interaction with drug use were investigated. In order to analyze the combined effects of blood pressure and body mass index, we cross-classified participants using predefined categories of body mass index ($<$25, 25–$<$30, $\geq$30) and blood pressure. The combined effects of blood pressure and antihypertensive drugs (use vs. nonuse) were examined in a similar fashion.

Because among obese subjects and among individuals taking antihypertensive drugs very few or no cases occurred in the lowest categories of systolic ($<$120 mmHg) or diastolic ($<$80 mmHg) blood pressure, the two lower categories of blood pressure were combined for these analyses (systolic: $<$140, 140–159, $\geq$160 mmHg; diastolic: $<$90, 90–99, $\geq$100 mmHg).

To further examine the dose-response pattern, we used restricted cubic spline regression, a more flexible approach to investigate potential nonlinearity of the relative risk function (25, 26). The following knots were used in this analysis: systolic blood pressure (100, 140, 180, and 220 mmHg) and diastolic blood pressure (60, 80, 100, and 120 mmHg). Spline models were restricted to participants with a systolic blood pressure between 100 and 220 mmHg and those with a diastolic blood pressure between 60 and 120 mmHg to avoid unstable estimates in the tails (26). Tests for nonlinearity were performed by log-likelihood ratio tests of hierarchical models with and without inclusion of spline terms.

All analyses were run with SAS software (SAS Institute, Inc., Cary, North Carolina). All p values presented are two sided, and $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows cohort characteristics according to country. Elevated blood pressure was more common among men

TABLE 1. Description of the study cohort, the European Prospective Investigation into Cancer and Nutrition, 1992–2004

Country	Cohort size (no.)	Female (%)	Mean age (years)*		Person-years (no.)		Renal cell carcinoma cases (no.)		Mean blood pressure (mmHg)*		Prevalence of elevated blood pressure (%)*,†	
			Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Italy	44,728	68.5	50	51	75,398	188,127	15	27	133/84	129/81	42.8	33.2
Spain	6,402	67.4	52	50	12,685	24,803	2	3	132/82	127/80	36.7	30.0
United Kingdom	41,703	63.3	57	53	81,323	151,898	15	10	132/82	127/78	35.5	28.6
Netherlands	38,296	73.6	43	51	51,218	186,589	4	25	130/81	127/77	35.3	27.1
Greece	25,994	58.6	53	53	39,823	56,767	3	3	130/82	127/79	40.6	35.7
Germany	34,245	58.6	52	49	80,091	114,468	24	17	135/87	128/82	48.6	31.6
Sweden	49,115	54.1	52	52	177,092	206,837	33	18	136/84	133/81	48.7	40.6
Denmark	56,155	52.2	57	57	178,689	198,346	28	23	140/84	133/80	50.5	38.7
All	296,638	60.9	53	52	696,317	1,127,844	124	126	134/83	129/80	44.0	33.9

* Values are age adjusted.

† Elevated blood pressure defined as systolic blood pressure of 140 mmHg or more or diastolic blood pressure of 90 mmHg or more.

(44.0 percent) than women (33.9 percent). In the entire cohort, systolic and diastolic blood pressure measurements were positively correlated with age (Spearman's coefficients: 0.45 and 0.24) and body mass index (Spearman's coefficients: 0.30 and 0.30). Further, strong correlations were observed between first and second blood pressure readings with correlation coefficients of 0.91 for systolic and 0.88 for diastolic blood pressures. Table 2 shows the risk factors for RCC and potential confounders by categories of systolic and diastolic blood pressures.

TABLE 2. Distribution of important cohort characteristics* according to categories of systolic and diastolic blood pressure, the European Prospective Investigation into Cancer and Nutrition, 1992–2004

Characteristics	Systolic blood pressure (mmHg)				Diastolic blood pressure (mmHg)			
	<120	120–139	140–159	≥160	<80	80–89	90–99	≥100
No. of participants	82,104	118,792	66,763	28,979	122,950	104,994	50,903	17,791
Age (years)	47.0	52.1	56.8	59.7	50.0	53.3	55.4	56.4
Male gender (%)	26.5	42.8	46.1	43.5	30.0	42.8	48.4	53.2
Body mass index (kg/m^2)	24.3	26.0	27.1	27.7	24.7	26.3	27.4	28.3
Smoking duration (years)	13.2	14.3	15.7	16.5	14.1	14.6	15.0	15.5
Smoking (%)								
Never	44.2	44.2	44.0	44.4	44.4	44.4	44.0	42.8
Former								
≥10 years ago	19.3	23.4	25.9	26.4	20.8	24.0	25.8	26.6
<10 years ago	4.5	4.0	3.9	3.8	4.2	4.0	4.0	4.3
Unknown	1.4	1.6	1.6	1.7	1.5	1.5	1.6	1.9
Current								
<15 cigarettes/day	14.0	11.2	10.1	9.5	13.1	10.8	9.8	9.5
15–24 cigarettes/day	10.1	8.9	8.6	8.8	9.8	8.8	8.5	8.6
≥25 cigarettes/day	3.5	3.4	3.0	3.0	3.2	3.4	3.4	3.4
Unknown	1.3	1.4	1.3	1.1	1.3	1.3	1.4	1.4
Unknown	1.7	1.7	1.5	1.2	1.6	1.7	1.6	1.6
Education (%)								
None, primary school	20.6	28.8	38.4	44.8	24.9	31.8	36.8	35.1
Technical, professional school	27.4	27.7	27.6	26.4	28.0	27.2	27.2	26.5
Secondary school	24.6	20.6	15.3	12.4	22.0	19.5	16.4	14.8
University degree	25.7	20.9	16.6	14.2	23.0	19.5	17.9	17.6

* For continuous variables, values are expressed as the mean; for categorical variables, frequencies are given in percent.

TABLE 3. Relative risks* and 95% confidence intervals of renal cell carcinoma across categories of systolic and diastolic blood pressure, the European Prospective Investigation into Cancer and Nutrition, 1992–2004

	Men				Women				All			
	Person-years (no.)	Cases (no.)	Relative risk	95% confidence interval	Person-years (no.)	Cases (no.)	Relative risk	95% confidence interval	Person-years (no.)	Cases (no.)	Relative risk	95% confidence interval
Systolic blood pressure (mmHg)												
<120	126,920	10	1	Referent	366,482	20	1	Referent	493,401	30	1	Referent
120–139	303,180	51	1.61	0.81, 3.21	428,360	40	1.28	0.73, 2.24	731,539	91	1.43	0.94, 2.19
140–159	188,617	35	1.42	0.69, 2.94	228,786	37	1.73	0.95, 3.14	417,403	72	1.54	0.98, 2.43
≥160	77,601	28	2.42	1.13, 5.19	104,217	29	2.62	1.38, 4.97	181,818	57	2.48	1.53, 4.02
p_{trend}				0.05				0.002				<0.001
$p_{interaction}$†												0.45
Diastolic blood pressure (mmHg)												
<80	219,441	23	1	Referent	532,848	45	1	Referent	752,289	68	1	Referent
80–89	269,920	55	1.68	1.02, 2.76	377,898	41	1.04	0.67, 1.60	647,818	96	1.27	0.93, 1.75
90–99	149,480	20	0.96	0.52, 1.77	165,466	27	1.38	0.84, 2.27	314,945	47	1.10	0.75, 1.63
≥100	57,477	26	3.11	1.72, 5.62	51,632	13	1.87	0.98, 3.57	109,109	39	2.34	1.54, 3.55
p_{trend}				0.01				0.05				0.003
$p_{interaction}$†												0.34

* Multivariable models were stratified for center and age and adjusted for sex (where appropriate), body mass index, education, duration of smoking, and smoking status.

† Based on two-sided likelihood ratio test for interaction with sex.

On average, participants with elevated blood pressure were older, tended to be less educated, had a higher body mass index, smoked longer, and were more frequently men than those with normal blood pressure.

Table 3 depicts the relative risks of RCC by categories of systolic and diastolic blood pressures. For both systolic and diastolic blood pressures, the risk of RCC for participants in the highest category of blood pressure was more than double

TABLE 4. Relative risks* and 95% confidence intervals of renal cell carcinoma across categories of blood pressure in relation to body mass index, the European Prospective Investigation into Cancer and Nutrition, 1992–2004

	Body mass index (kg/m^2)											
	<25				25–<30				≥30			
	Person-years (no.)	Cases (no.)	Relative risk	95% confidence interval	Person-years (no.)	Cases (no.)	Relative risk	95% confidence interval	Person-years (no.)	Cases (no.)	Relative risk	95% confidence interval
Systolic blood pressure (mmHg)												
<140	654,115	52	1	Referent	441,699	51	1.12	0.76, 1.66	129,127	18	1.49	0.86, 2.57
140–159	146,099	26	1.49	0.92, 2.42	184,782	32	1.25	0.79, 1.97	86,522	14	1.34	0.73, 2.44
≥160	55,742	15	1.99	1.10, 3.60	79,646	26	2.14	1.31, 3.45	46,430	16	2.54	1.42, 4.53
Diastolic blood pressure (mmHg)												
<90	725,305	66	1	Referent	515,746	71	1.15	0.82, 1.62	159,055	27	1.50	0.95, 2.37
90–99	102,026	17	1.34	0.78, 2.30	142,390	22	1.07	0.65, 1.74	70,529	8	0.92	0.44, 1.92
≥100	28,624	10	2.50	1.28, 4.91	47,990	16	2.10	1.20, 3.68	32,495	13	2.91	1.59, 5.34

* Multivariable models were stratified by center and age and adjusted for sex, education, duration of smoking, and smoking status.

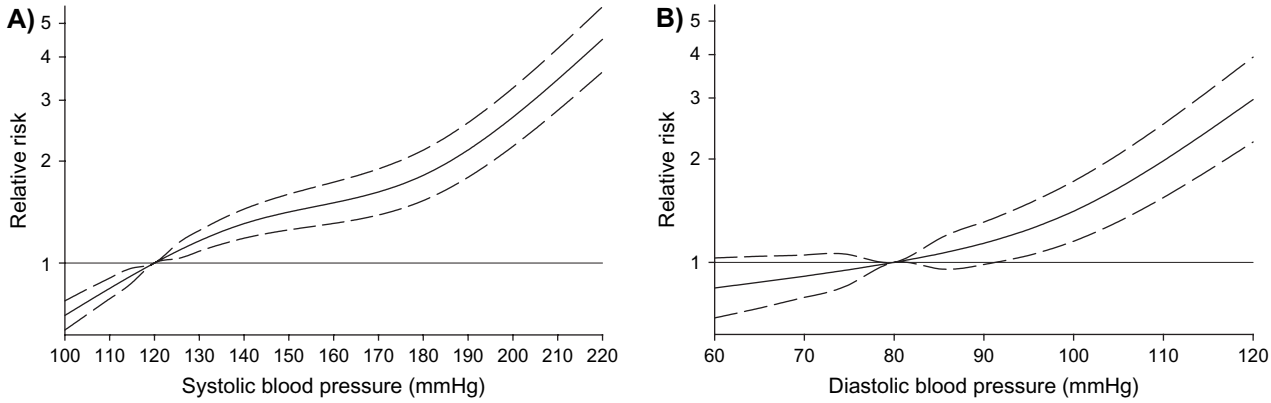

FIGURE 1. Relative risk functions of renal cell carcinoma according to systolic (A) and diastolic (B) blood pressure, the European Prospective Investigation into Cancer and Nutrition, 1992–2004. Functions were calculated from restricted cubic spline regression models stratified for age and center and adjusted for sex, education, body mass index, duration of smoking, and smoking status. Broken lines indicate the 95% confidence interval.

the risk for those in the lowest category. The risk in participants who were in the highest category of either systolic (≥160 mmHg) or diastolic (≥100 mmHg) pressure was 2.56 (95 confidence interval (CI): 1.67, 3.91) compared with those who were in the lowest category for both systolic and diastolic pressures. For systolic pressure, the risk estimates did not differ appreciably between men and women, while somewhat higher risk estimates were observed for men than for women in the highest category of diastolic pressure (table 3). Nonetheless, sex did not substantially modify the associations between blood pressure and risk. Furthermore, no interactions with either smoking or body mass index were observed. Tests for heterogeneity across countries were nonsignificant for both systolic and diastolic blood pressures. It cannot be fully excluded that preclinical renal tumors may lead to increases in blood pressure, but our findings remained essentially the same after excluding the first 2 years of follow-up. For subjects in the highest category, the relative risks were 2.17 (95 percent CI: 1.20, 3.94) for systolic pressure and 2.19 (95 percent CI: 1.29, 3.73) for diastolic pressure as compared with subjects in the lowest category of blood pressure. The dose-response relation remained statistically significant for both systolic and diastolic pressures.

Table 4 shows the combined effects of body mass index and blood pressure on the risk of RCC. Remarkably, the increases in risk related to obesity were mild and nonsignificant unless blood pressure was markedly elevated.

In line with the risk estimates by categories of blood pressure, spline regression (figure 1) suggested a marked increase in risk beyond a systolic pressure of 160 mmHg or a diastolic pressure of 100 mmHg, while below these thresholds risk rose rather mildly but steadily with increasing blood pressure. Positive but nonlinear dose-response relations were confirmed for systolic (p for effect = 0.006; p for nonlinearity = 0.004) and diastolic (p for effect = 0.004; p for nonlinearity = 0.001) pressures, indicating that linear models would not sufficiently represent the relative risk function.

The main analyses by categories of blood pressure were repeated, controlling for use of antihypertensive drugs (n = 254,935), but the results remained essentially the same, indicating that the effect of elevated blood pressure was

TABLE 5. Relative risks and 95% confidence intervals of renal cell carcinoma across categories of systolic and diastolic blood pressure, controlling for use of antihypertensive medication, the European Prospective Investigation into Cancer and Nutrition, 1992–2004*

	Person-years (no.)	Cases (no.)	Relative risk†	95% confidence interval
Systolic blood pressure (mmHg)				
<120	425,229	26	1	Referent
120–139	635,588	80	1.43	0.91, 2.26
140–159	366,821	66	1.54	0.94, 2.51
≥160	163,303	53	2.37	1.40, 4.02
p_{trend}				<0.001
Diastolic blood pressure (mmHg)				
<80	639,055	59	1	Referent
80–89	572,425	85	1.23	0.87, 1.73
90–99	282,689	44	1.07	0.71, 1.63
≥100	96,771	37	2.24	1.43, 3.52
p_{trend}				0.003
Antihypertensive medication				
No	1,368,900	161	1	Referent
Yes	222,041	64	1.34‡	0.97, 1.84
			1.38§	1.0, 1.90

* Restricted to a subgroup of participants (n = 254,935) for whom information on antihypertensive medication use was available.

† Multivariable models were stratified for center and age and adjusted for sex, body mass index, education, duration of smoking, smoking status, and antihypertensive medication use (where applicable).

‡ After adjustment for systolic blood pressure.

§ After adjustment for diastolic blood pressure.

TABLE 6. Relative risks and 95% confidence intervals of renal cell carcinoma across categories of systolic and diastolic blood pressure in relation to use of antihypertensive medication, the European Prospective Investigation into Cancer and Nutrition, 1992–2004*

	Antihypertensive medication use							
	No				Yes			
	Person-years (no.)	Cases (no.)	Relative risk†	95% confidence interval	Person-years (no.)	Cases (no.)	Relative risk†	95% confidence interval
Systolic blood pressure (mmHg)								
<140	984,375	88	1	Referent	76,442	18	1.61	0.95, 2.73
140–159	283,259	46	1.25	0.86, 1.82	83,562	20	1.48	0.89, 2.47
≥160	101,266	27	1.87	1.18, 2.95	62,037	26	2.45	1.53, 3.93
Diastolic blood pressure (mmHg)								
<90	1,102,094	115	1	Referent	109,386	29	1.50	0.97, 2.30
90–99	208,411	31	1.10	0.74, 1.66	74,279	13	1.02	0.56, 1.83
≥100	58,395	15	1.68	0.97, 2.92	38,376	22	3.17	1.96, 5.12

* Restricted to a subgroup of participants ($n = 254,935$) for whom information on antihypertensive medication use was available.

† Multivariable models were stratified by center and age and adjusted for sex, education, body mass index, duration of smoking, and smoking status.

largely independent of its medication (table 5). Use of antihypertensive drugs did not seem to modify the effect of blood pressure, as tests for interaction were nonsignificant. Use of antihypertensive medication alone was associated with a mild increase in risk of RCC only in the sex-adjusted analysis (relative risk = 1.53, 95 percent CI: 1.12, 2.09), but it became weaker and nonsignificant when blood pressure was considered (table 5). After exclusion of all participants who took antihypertensive drugs, elevated blood pressure remained associated with an increased risk of RCC. Among subjects who never used antihypertensive drugs, the relative risks for comparisons of the highest versus the lowest category of blood pressure were 2.42 (95 percent CI: 1.35, 4.33) for systolic and 2.22 (95 percent CI: 1.22, 4.04) for diastolic pressures.

Table 6 shows the combined effect of blood pressure and antihypertensive treatment. The highest risks were observed in the subgroup of subjects who took medication and nonetheless had poorly controlled blood pressure. Although a mild, but nonsignificant increase in risk of renal cell cancer was noted in normotensive medication users, antihypertensive drugs alone did not appear to increase the risk of renal cell cancer unless blood pressure was markedly elevated.

DISCUSSION

In the EPIC cohort study, we observed a positive relation between systolic and diastolic blood pressures and risk of RCC. Elevated blood pressure conferred a two- to threefold increased risk that was independent of sex, body mass index, smoking, and use of antihypertensive medication. For subjects who took antihypertensive medication, risk was not substantially increased unless blood pressure was poorly controlled. The relevance of these observations is underscored by the high prevalence of hypertension in this population and worldwide (27). This risk factor may thus account for a substantial proportion of renal cell cancers (28).

The advantages of our study are the prospective design, the substantial overall heterogeneity of both exposures and cancer incidence across participating centers, the availability of quantitative data according to level of blood pressure, and the opportunity to consider the effect of antihypertensive medication. Limitations are the rather short follow-up and the lack of detailed information on type of antihypertensive medication, duration of high blood pressure, changes in blood pressure over time, and duration of antihypertensive medication use.

Our findings are in line with those of another large cohort study among Swedish male construction workers (7), which, despite the rather homogeneous study population, showed a clear dose-response relation for both systolic and diastolic blood pressures. Although our study had a shorter follow-up, the risk estimates were comparable in magnitude, which supports the validity of our observations. Moreover, results similar to ours were reported in an earlier cohort study that investigated risk factors for kidney cancer mortality in men and found an increased risk with increasing systolic blood pressure (15).

Although these earlier cohort studies (7, 15) provided quantitative data according to level of blood pressure, the effect of antihypertensive medication use was not considered. Our prospective data provide evidence of elevated blood pressure's increasing the risk of RCC independently of antihypertensive treatment, while exposure to antihypertensive medications nonsignificantly increased the risk by

approximately 40 percent. These findings are in contrast to those reported by Grove et al. (11), which, however, were based on only 17 incident cases of kidney cancer. In line with our results, a case-control study (16) found that high systolic and diastolic blood pressures were associated with an increased RCC risk in both sexes even when analyses were restricted to subjects who never took medication.

The effects of blood pressure level and antihypertensive medication have generally been difficult to distinguish, since most investigations were based on a diagnosis of hypertension that is inevitably linked to antihypertensive drug use. In particular, the issue of whether diuretic therapy and hypertension are independent risk factors remains unresolved (29). Recent evidence suggests that use of diuretics is not associated with risk (8, 16), although associations with specific subtypes of RCC have also been reported (14). Unfortunately, our study cannot provide data on this issue.

According to our analyses, untreated or poorly controlled hypertension was associated with an increased risk of RCC, while the risk was markedly lower in hypertensive subjects with adequate blood pressure control at recruitment. These findings are consistent with earlier data published by Chow et al. (7), who demonstrated that the risk is decreased by a reduction of blood pressure over time. Altogether, these observations and recent findings from a Danish cohort study (10) suggest that antihypertensive treatment may not be a risk factor as long as blood pressure is effectively controlled.

Our data provide the first evidence, to our knowledge, of dose-response relations between blood pressure level and risk of RCC in women comparable with those observed in men (7, 11), although the association for diastolic pressure did not reach statistical significance. In support of our observations, previous analyses within large cohort studies found associations between self-reported hypertension and RCC in women (8, 12).

Hypertensive individuals may undergo frequent health examinations that increase the chances of detecting a malignancy. Our analyses excluding the first 2 years of follow-up, in line with previous studies (7, 16, 30), did not confirm such a detection bias. These data also contradict the hypothesis that hypertension secondary to preclinical renal tumors may partly explain the relation between blood pressure and RCC. The biologic mechanisms underlying the observed association have yet to be elucidated. Renal carcinogenesis may be promoted by deregulated lipid peroxidation and the increased formation of reactive oxygen species in hypertensive and obese individuals (31). Elevated levels of lipid peroxidation were observed in hypertensive subjects, but they normalize upon antihypertensive treatment. In animal models, increased lipid peroxidation of the proximal renal tubules has been linked to the chemical induction of renal tumors (32, 33). Moreover, the chronic renal hypoxia accompanying hypertension may potentiate the up-regulation of hypoxia-inducible factors (HIFs) and the vascular endothelial growth factor receptor during renal carcinogenesis (34, 35). Hypoxia-induced up-regulation of HIF-1α has been shown to interfere with tumor suppressor gene function (36, 37) but, in view of opposing functions of HIF isoforms in renal cell carcinomas (38), the precise role of HIF-dependent pathways in carcinogenesis is not fully understood (34). Our findings support further studies into the mechanisms linking hypertension and renal tumorigenesis.

Given that hypertension is a very common risk factor worldwide and its control remains inadequate (27, 39), our findings underscore the relevance of current public health efforts aimed at preventing and effectively controlling hypertension to reduce the incidence of a number of diseases including RCC. Effective blood pressure control may lower the risk of this cancer, but studies with longer follow-up and repeated measurements of blood pressure are necessary.

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