

## OBESITY, HYPERTENSION, AND THE RISK OF KIDNEY CANCER IN MEN

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**ABSTRACT**

**Background** Obesity and hypertension have been implicated as risk factors for the development of renal-cell cancer.

**Methods** We examined the health records of 363,992 Swedish men who underwent at least one physical examination from 1971 to 1992 and were followed until death or the end of 1995. Men with cancer (renal-cell cancer in 759 and renal-pelvis cancer in 136) were identified by cross-linkage of data with the nationwide Swedish Cancer Registry. Poisson regression analysis was used to estimate relative risks, with adjustments for age, smoking status, body-mass index, and diastolic blood pressure.

**Results** As compared with men in the lowest three eighths of the cohort for body-mass index, men in the middle three eighths had a 30 to 60 percent greater risk of renal-cell cancer, and men in the highest two eighths had nearly double the risk (P for trend, <0.001). There was also a direct association between higher blood pressures and a higher risk of renal-cell cancer (P for trend, <0.001 for diastolic pressure; P for trend, 0.007 for systolic pressure). After the first five years of follow-up had been excluded to reduce possible effects of preclinical disease, the risk of renal-cell cancer was still consistently higher in men with a higher body-mass index or higher blood pressure. At the sixth-year follow-up, the risk rose further with increasing blood pressures and decreased with decreasing blood pressures, after adjustment for base-line measurements. Men who were current or former smokers had a greater risk of both renal-cell cancer and renal-pelvis cancer than men who were not smokers. There was no relation between body-mass index or blood pressure and the risk of renal-pelvis cancer.

**Conclusions** Higher body-mass index and elevated blood pressure independently increase the long-term risk of renal-cell cancer in men. A reduction in blood pressure lowers the risk. (N Engl J Med 2000;343:1305-11.)

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**K**IDNEY cancers account for 2 to 3 percent of new cases of cancer in the United States. In more than 80 percent of these cases, the cancer arises from the renal parenchyma and consists of adenocarcinoma (renal-cell carcinoma); most renal-pelvis cancers are transitional-cell carcinomas. In the United States, renal-cell carcinoma is among the most rapidly increasing of all types of tumors in incidence, particularly among black persons, whereas the rates of renal-pelvis cancer have declined during the past two decades.<sup>1</sup>

Obesity increases the risk of renal-cell cancer, although this association has not been consistently observed in men.<sup>2,3</sup> Hypertension is also a risk factor, but quantitative data according to levels of blood pressure are limited.<sup>4</sup> A small case-control study based on medical records found that the risk of renal-cell cancer was higher with higher blood pressures within 5 to 10 years before a diagnosis of renal-cell cancer.<sup>5</sup> Cohort studies with measurements of blood pressure have not distinguished among different types of renal cancer, although a dose-response relation was reported in two studies.<sup>6,7</sup> In general, renal-pelvis carcinoma has not been linked to obesity or hypertension, although an association with hypertension has been suggested.<sup>8</sup> Cigarette smoking increases the risk of both types of kidney cancer, and the increase is greater for renal-pelvis cancer than for renal-cell cancer.<sup>9,10</sup>

To clarify these associations, we conducted a study of newly diagnosed kidney cancer during a follow-up period of as long as 25 years in a large cohort of men in whom measurements of height, weight, and blood pressure were obtained at an initial examination. In a subgroup of the men, who underwent multiple examinations, we also evaluated the effect of changes in body-mass index and blood pressure on the risk of kidney cancer.

**METHODS****The Study Cohort**

In 1968, Bygghälsan, the Swedish Foundation for Occupational Safety and Health of the Construction Industry, was established to coordinate all activities concerning occupational safety and health among construction workers,<sup>11,12</sup> including the provision of preventive medical care to all workers in this industry nationwide. Workers were invited to undergo health examinations at intervals of two to five years. Data from the health examinations, which included measurements of height, weight, and blood pressure, were registered in a central data base beginning in 1971.

Between January 1971 and December 1992, information from 389,135 workers was registered in the data base, after the exclusion of information on 605 workers whose national registration numbers (unique numbers assigned to each Swedish resident) had been entered incorrectly. We then excluded the 19,418 workers who were women, because they constituted only 5 percent of the cohort and because only 5 of them were found to have kidney cancer, and the 5725 men (1.5 percent) who emigrated before the first (base-line) examination or for whom we did not have complete data on weight, height, or blood pressure. Of the 363,992 men included in the study, 234,297 (64 percent) had, in addition to the base-line examination, one or more follow-up visits.

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### Follow-up

The men who were given a diagnosis of kidney cancer were identified with the use of information from the population-based Swedish Cancer Registry, according to the men's national registration numbers. This cancer registry was established in 1958 and has been found to be more than 98 percent complete in its documentation of cases.<sup>13</sup> In addition, dates of death or emigration during the follow-up period were obtained by cross-linkage with the nationwide Mortality Registry and Migration Register. The men were followed from the date of entry into the cohort (defined as the date of the initial examination) until the date of a diagnosis of kidney cancer, emigration, or death or the end of the observation period (December 31, 1995), whichever came first.

### Statistical Analysis

Kidney cancers were classified as renal-cell cancer (codes 180.0 and 180.9 of the *International Classification of Diseases, 7th Revision* [ICD-7]) or renal-pelvis or ureteral cancer (ICD-7 codes 180.1 and 181.1).<sup>14</sup> The relative risks of cancer (with 95 percent confidence intervals) were estimated with Poisson regression analysis, with adjustments for age (as a continuous variable), smoking status (nonsmoker, former smoker, or current smoker at base line), body-mass index (the weight in kilograms divided by the square of the height in meters), and diastolic blood pressure. Body-mass index and blood pressure, as continuous variables, were used for adjustment and for the testing of linear trends. To calculate estimates of risk, body-mass index was divided into eight categories (from  $\leq 20.75$  to  $\geq 27.76$ ), with an approximately equal number of men in each category, and blood pressure was divided into increments of 10 mm Hg (diastolic pressure from  $<70$  to  $\geq 110$  mm Hg and systolic pressure from  $<120$  to  $\geq 160$  mm Hg). Effect modification was assessed by examination of the risk of cancer associated with body-mass index or blood pressure within each level of a second variable, such as age. The significance of interactions between body-mass index and blood pressure was evaluated by adding an interaction term to the model.

The main analysis was based on data from the base-line examination for the entire cohort. To provide more stable information for body-mass index and blood pressure, separate analyses were conducted with the average values from the base-line examination and the first follow-up examination within three years after the base-line examination; in these analyses, person-years were considered to have begun accumulating after the first follow-up visit. The effects of changes over time in body-mass index and diastolic blood pressure were also evaluated with respect to the differences in these values between the base-line examination and the examination conducted during approximately the sixth year of follow-up.

## RESULTS

The workers entered the cohort at an average age of 44.2 years. They were followed for an average of 16 years, for a cumulative total of 5,783,888 person-years of follow-up. At the time of entry, 52 percent of them smoked cigarettes or had smoked in the past (Table 1). They had a mean ( $\pm$ SD) body-mass index of  $24.5 \pm 3.1$ , a mean diastolic blood pressure of  $84 \pm 13$  mm Hg, and a mean systolic blood pressure of  $140 \pm 18$  mm Hg. The mean body-mass index varied little according to age, whereas the mean blood pressure was higher in older men than in younger men.

During follow-up, renal-cell cancer was diagnosed in 759 men and renal-pelvis cancer in 136 men. Men who were current or former cigarette smokers at base line had a significantly higher risk of renal-cell cancer and an even higher risk of renal-pelvis cancer than men who had never smoked (relative risk of renal-cell can-

cer, 1.3 [95 percent confidence interval, 1.0 to 1.6] for former smokers and 1.6 [95 percent confidence interval, 1.3 to 1.9] for current smokers; relative risk of renal-pelvis cancer, 1.6 [95 percent confidence interval, 0.9 to 3.1] for former smokers and 3.5 [95 percent confidence interval, 2.1 to 5.8] for current smokers) (Table 2). Furthermore, the risk of renal-cell cancer was significantly higher among men with a higher body-mass index than among those who were leaner (*P* for trend,  $<0.001$ ); the risk was nearly doubled for men in the highest eighth of the cohort for body-mass index (relative risk as compared with the leanest subgroup, 1.9; 95 percent confidence interval, 1.3 to 2.7) (Table 2). Height was not consistently related to the risk of either type of cancer (data not shown).

Blood pressure was positively related to the risk of renal-cell cancer; the dose-response relation was clearer for diastolic pressure (*P* for trend,  $<0.001$ ) than for systolic pressure (*P* for trend, 0.007). The risk of renal-cell cancer in men with a diastolic pressure of 90 mm Hg or more was more than double the risk in men with a diastolic pressure below 70 mm Hg. The risk of this type of cancer was 60 to 70 percent higher in men with a systolic pressure of 150 mm Hg or more than in those with a systolic pressure below 120 mm Hg. The risks associated with body-mass index and blood pressure were independent of each other. In contrast, the risk of renal-pelvis cancer was not related to body-mass index or blood pressure, either in terms of the relative risks or in terms of a dose-response relation (Table 2).

The risk of renal-cell cancer in relation to body-mass index and blood pressure varied according to age at the time of entry into the cohort; men who were initially less than 50 years old had the highest risks (Table 3). For men who entered the cohort at an age of 60 years or older, the excess risk, if present, was small. Those with a high body-mass index had a significantly higher risk throughout the follow-up period, even more than 15 years after the base-line examination. The association between the risk of renal-cell cancer and diastolic blood pressure, however, was strongest during the first five years of follow-up. Smoking status also appeared to modify the association between this risk and body-mass index, with the highest increases in risk found among nonsmokers. In addition, the association between the risk of renal-cell cancer and body-mass index and the association between this risk and blood pressure were similar for men recruited from 1971 through 1979 and those recruited from 1980 through 1992 (data not shown).

We also examined the combined effect of body-mass index and blood pressure on the risk of renal-cell cancer after excluding the men in whom cancer was diagnosed during the first five years of follow-up and after excluding all the person-years the cohort accumulated during that period (to reduce the possible

OBESITY, HYPERTENSION, AND THE RISK OF KIDNEY CANCER IN MEN

TABLE 1. CHARACTERISTICS OF THE 363,992 MEN IN THE COHORT.\*

AGE AT ENTRY	No. OF MEN (%)	FOLLOW-UP person-yr	CURRENT OR PREVIOUS SMOKING %	BODY-MASS INDEX	BLOOD PRESSURE	
					DIASTOLIC	SYSTOLIC
<30 yr	173,208 (48)	2,466,821	43	24.1±3.2	79±13	138±17
30-39 yr	76,019 (21)	1,327,355	61	24.4±3.1	83±14	138±17
40-49 yr	52,073 (14)	894,554	63	24.6±3.1	86±13	139±18
50-59 yr	45,305 (12)	791,529	61	24.6±3.1	86±13	141±20
≥60 yr	17,387 (5)	303,629	53	24.6±3.1	86±12	144±20
Overall	363,992 (100)	5,783,888	52	24.5±3.1	84±13	140±18

\*Plus-minus values are means ±SD. The cohort included men who underwent at least one physical examination between 1971 and 1992 and who were followed until death or the end of 1995. Body-mass index is the weight in kilograms divided by the square of the height in meters.

TABLE 2. RELATIVE RISK OF RENAL-CELL CANCER AND RENAL-PELVIS CANCER AMONG MEN IN THE COHORT, ACCORDING TO SMOKING STATUS, BODY-MASS INDEX, AND BLOOD PRESSURE.\*

VARIABLE	No. OF MEN IN COHORT (N=363,992)	FOLLOW-UP person-yr	RENAL-CELL CANCER		RENAL-PELVIS CANCER	
			NO. OF MEN WITH CANCER	RELATIVE RISK (95% CI)	NO. OF MEN WITH CANCER	RELATIVE RISK (95% CI)
Smoking status						
Nonsmoker	148,206	2,129,536	180	1.0 (—)	18	1.0 (—)
Former smoker	51,638	909,630	145	1.3 (1.0-1.6)	19	1.6 (0.9-3.1)
Current smoker	138,332	2,289,228	334	1.6 (1.3-1.9)	82	3.5 (2.1-5.8)
Unknown	25,816	455,494	100	1.6 (1.2-2.0)	17	2.6 (1.3-5.0)
Body-mass index						
≤20.75	45,073	705,242	32	1.0 (—)	15	1.0 (—)
20.75-21.90	45,131	707,289	46	1.2 (0.7-1.8)	8	0.4 (0.2-1.0)
21.91-22.85	45,057	710,225	43	0.9 (0.6-1.5)	13	0.6 (0.3-1.3)
22.86-23.80	46,516	741,832	78	1.4 (0.9-2.1)	13	0.5 (0.2-1.1)
23.81-24.76	44,916	720,615	107	1.6 (1.1-2.4)	22	0.8 (0.4-1.5)
24.77-25.95	45,987	744,218	102	1.3 (0.8-1.9)	23	0.7 (0.4-1.3)
25.96-27.75	45,499	735,804	156	1.7 (1.1-2.5)	22	0.6 (0.3-1.1)
≥27.76	45,813	718,663	195	1.9 (1.3-2.7)	20	0.5 (0.2-1.0)
P for trend				<0.001		0.25
Diastolic blood pressure						
<70 mm Hg	40,407	540,097	12	1.0 (—)	6	1.0 (—)
70-79 mm Hg	110,461	1,695,116	96	1.4 (0.8-2.5)	22	0.6 (0.2-1.5)
80-89 mm Hg	139,998	2,317,216	273	1.7 (0.9-3.0)	49	0.6 (0.2-1.4)
90-99 mm Hg	57,060	974,597	272	2.1 (1.2-3.9)	46	0.7 (0.3-1.8)
100-109 mm Hg	11,627	187,114	78	2.3 (1.2-4.4)	10	0.6 (0.2-1.9)
≥110 mm Hg	4,439	69,748	28	2.2 (1.1-4.5)	3	0.6 (0.1-2.4)
P for trend				<0.001		0.74
Systolic blood pressure						
<120 mm Hg	39,010	554,138	28	1.0 (—)	11	1.0 (—)
120-129 mm Hg	100,884	1,561,807	103	1.1 (0.7-1.7)	28	0.8 (0.4-1.7)
130-139 mm Hg	108,165	1,754,399	192	1.5 (1.0-2.2)	29	0.6 (0.3-1.2)
140-149 mm Hg	67,661	1,122,128	168	1.4 (0.9-2.1)	27	0.6 (0.3-1.3)
150-159 mm Hg	27,361	458,505	124	1.6 (1.1-2.4)	20	0.7 (0.3-1.5)
≥160 mm Hg	20,911	332,911	144	1.7 (1.1-2.6)	21	0.7 (0.3-1.5)
P for trend				0.007		0.91

\*All models included age, smoking status, body-mass index (the weight in kilograms divided by the square of the height in meters), and diastolic blood pressure. CI denotes confidence interval.

**TABLE 3.** RELATIVE RISK OF RENAL-CELL CANCER AMONG MEN IN THE COHORT, ACCORDING TO BODY-MASS INDEX AND DIASTOLIC BLOOD PRESSURE, WITH STRATIFICATION ACCORDING TO SELECTED CHARACTERISTICS.\*

VARIABLE	BODY-MASS INDEX			DIASTOLIC BLOOD PRESSURE (mm Hg)		
	≤22.85	22.86–25.95	≥25.96	≤79	80–99	≥100
Age at entry						
<50 yr						
Relative risk (95% CI)	1.0	1.9 (1.4–2.6)	2.5 (1.8–3.5)	1.0	2.2 (1.7–2.9)	4.5 (2.7–7.3)
No. with cancer	61	128	121	68	218	24
50–59 yr						
Relative risk (95% CI)	1.0	1.4 (1.0–2.1)	1.8 (1.2–2.6)	1.0	1.4 (0.9–2.1)	1.5 (0.9–2.5)
No. with cancer	35	108	155	25	222	51
≥60 yr						
Relative risk (95% CI)	1.0	1.0 (0.6–1.6)	1.2 (0.8–1.9)	1.0	1.0 (0.6–1.8)	1.3 (0.7–2.4)
No. with cancer	25	51	75	15	105	31
Length of follow-up						
≤5 yr						
Relative risk (95% CI)	1.0	1.5 (0.8–2.7)	1.6 (0.9–3.0)	1.0	1.9 (1.0–4.0)	3.2 (1.4–7.3)
No. with cancer	14	41	54	9	75	25
6–15 yr						
Relative risk (95% CI)	1.0	1.2 (0.9–1.6)	1.6 (1.2–2.1)	1.0	1.3 (0.9–1.7)	1.4 (0.9–2.1)
No. with cancer	61	130	174	52	263	50
>15 yr						
Relative risk (95% CI)	1.0	1.5 (1.1–2.2)	1.8 (1.3–2.6)	1.0	1.4 (1.0–1.9)	1.6 (1.0–2.6)
No. with cancer	46	116	123	47	207	31
Smoking status						
Nonsmoker						
Relative risk (95% CI)	1.0	3.0 (1.6–5.8)	4.1 (2.1–7.8)	1.0	1.0 (0.6–1.5)	1.5 (0.8–2.6)
No. with cancer	11	69	100	28	117	35
Former smoker						
Relative risk (95% CI)	1.0	1.5 (0.9–2.7)	1.7 (0.9–2.9)	1.0	1.2 (0.8–2.1)	1.7 (0.9–3.2)
No. with cancer	16	58	71	20	102	23
Current smoker						
Relative risk (95% CI)	1.0	1.2 (0.9–1.6)	1.5 (1.1–2.0)	1.0	1.6 (1.1–2.1)	1.3 (0.8–2.1)
No. with cancer	76	127	131	52	256	26
Unknown						
Relative risk (95% CI)	1.0	1.0 (0.6–1.9)	1.3 (0.7–2.3)	1.0	2.2 (1.0–4.7)	3.1 (1.3–7.4)
No. with cancer	18	33	49	8	70	22

\*All models included age, smoking status, body-mass index (the weight in kilograms divided by the square of the height in meters), and diastolic blood pressure. CI denotes confidence interval.

effect of increases in blood pressure due to preclinical cancer) (Table 4). The risk of renal-cell cancer rose consistently with increasing body-mass index at each level of diastolic blood pressure analyzed. Conversely, it tended to rise, though not consistently, with increasing diastolic pressure at each level of body-mass index analyzed.

To increase the stability of the base-line measurements of blood pressure, we averaged the results of the first two examinations for men who had a second examination within three years after the initial examination. Among these men, the risk of renal-cell carcinoma increased steadily with higher average diastolic or systolic blood pressure and was generally higher than the risk for the entire cohort, calculated with data from only the initial examination (data not shown).

We also examined the effects of changes in body-mass index or diastolic blood pressure (actual changes and percent changes) between the base-line examination and the sixth-year follow-up visit (Table 5). The risk of renal-cell cancer was more than doubled in

men whose diastolic pressure rose by more than 14 mm Hg (relative risk, 2.3; 95 percent confidence interval, 1.4 to 3.7) or by more than 19 percent (relative risk, 2.2; 95 percent confidence interval, 1.3 to 3.7) as compared with men who had little change in diastolic blood pressure. In contrast, a decrease in diastolic blood pressure during this period reduced the risk by 40 percent in those whose diastolic pressure decreased by more than 14 mm Hg (relative risk, 0.6; 95 percent confidence interval, 0.3 to 1.3) and in those whose diastolic pressure decreased by more than 9 percent (relative risk, 0.6; 95 percent confidence interval, 0.3 to 0.9). This pattern persisted over each 5-year period of follow-up after the sixth-year examination (0 to 5, 6 to 10, and >10 years after this examination) (data not shown). The risk of renal-cell cancer in relation to changes in body-mass index between the time of the base-line examination and the sixth-year visit was not statistically significant. The risk in men with the largest increases in body-mass index was 1.6 to 2.0 times the risk in men who had little change

**TABLE 4.** COMBINED EFFECT OF DIASTOLIC BLOOD PRESSURE AND BODY-MASS INDEX ON THE RELATIVE RISK OF RENAL-CELL CANCER.\*

BODY-MASS INDEX	DIASTOLIC BLOOD PRESSURE (mm Hg)					
	≤79		80-99		≥100	
	no. with cancer	relative risk (95% CI)	no. with cancer	relative risk (95% CI)	no. with cancer	relative risk (95% CI)
≤22.85	33	1.0 (—)	70	1.3 (0.9-2.0)	4	1.2 (0.4-3.3)
22.86-25.95	40	1.2 (0.8-2.0)	182	1.8 (1.2-2.6)	24	2.3 (1.4-4.0)
≥25.96	26	1.8 (1.1-3.1)	218	2.3 (1.6-3.4)	53	2.7 (1.7-4.2)

\*Men in whom cancer was diagnosed during the first five years of follow-up and the person-years the cohort accumulated during that period were excluded. All relative risks have been adjusted for age and smoking. CI denotes confidence interval.

†Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

**TABLE 5.** RELATIVE RISK OF RENAL-CELL CANCER AMONG MEN IN THE COHORT ACCORDING TO CHANGES IN DIASTOLIC BLOOD PRESSURE AND BODY-MASS INDEX.\*

VARIABLE	NO. OF MEN	FOLLOW-UP person-yr	NO. WITH CANCER	RELATIVE RISK (95% CI)
<b>Diastolic pressure</b>				
Actual change				
More than -14 mm Hg	5,564	65,761	8	0.6 (0.3-1.3)
-14 to -5 mm Hg	25,480	327,037	35	0.7 (0.5-1.0)
-4 to +4 mm Hg	40,883	550,748	76	1.0 (—)
+5 to +14 mm Hg	30,334	403,856	59	1.2 (0.9-1.7)
More than +14 mm Hg	7,994	104,082	24	2.3 (1.4-3.7)
P for trend				<0.001
Percent change				
More than -9%	18,668	232,366	21	0.6 (0.3-0.9)
-9 to -5%	15,855	207,596	24	0.7 (0.4-1.1)
-4 to +4%	33,155	444,512	68	1.0 (—)
+5 to +9%	16,482	219,985	36	1.2 (0.8-1.8)
+10 to +19%	17,927	240,726	34	1.2 (0.8-1.8)
More than +19%	8,168	106,299	19	2.2 (1.3-3.7)
P for trend				<0.001
<b>Body-mass index†</b>				
Actual change				
More than -0.99	8,747	116,331	28	1.3 (0.8-2.0)
-0.99 to -0.50	8,157	109,819	17	1.0 (0.6-1.7)
-0.49 to +0.49	27,409	370,293	54	1.0 (—)
+0.50 to +0.99	18,607	248,801	30	1.0 (0.6-1.5)
+1.00 to +1.49	14,387	190,753	28	1.3 (0.8-2.0)
+1.50 to +1.99	11,746	152,518	13	0.8 (0.5-1.5)
+2.00 to +2.49	7,897	100,808	12	1.3 (0.7-2.4)
More than +2.49	13,094	159,722	20	1.6 (1.0-2.7)
P for trend‡				0.13
Percent change				
More than -4%	7,544	99,943	26	1.5 (1.0-2.3)
-4 to +4%	57,106	769,337	110	1.0 (—)
+5 to +9%	27,872	364,495	43	1.2 (0.8-1.7)
+10 to +14%	11,581	144,902	16	1.5 (0.9-2.6)
More than +14%	5,941	70,369	7	2.0 (0.9-4.2)
P for trend‡				0.06

\*All models included age, smoking status, body-mass index (the weight in kilograms divided by the square of the height in meters), and diastolic blood pressure. Minus signs denote a decrease and plus signs an increase. CI denotes confidence interval.

†Two hundred eleven men did not have measurements of height and weight at the sixth-year examination.

‡P values for trend are for the risk in relation to increases in body-mass index with respect to the reference value.

in body-mass index. The risks related to changes in body-mass index or blood pressure were independent of those associated with the degree of obesity or hypertension at base line.

### DISCUSSION

In this study of Swedish men, we found independent dose-response relations between body-mass index and the risk of renal-cell cancer and between diastolic and systolic blood pressure and the risk of renal-cell cancer, with a greater risk observed in men with an even slightly higher body-mass index or blood pressure than in their counterparts with lower values. Changes in blood pressure over time influenced this risk independently of the effect of hypertension at base line, suggesting that a reduction in blood pressure may help to prevent renal-cell cancer. The specificity of the association between high blood pressure and high body-mass index and the risk of renal-cell cancer, as opposed to renal-pelvis cancer, in this relatively homogeneous population, as well as the persistent increases in this risk during more than 15 years of follow-up, argues against the presence of any confounding factor or other potential source of bias as an explanation for our findings. Furthermore, our study confirmed the results of previous studies<sup>10</sup> that indicated that cigarette smoking increases the risk of both types of renal cancer.

Previous studies of the relation between renal-cell cancer and blood pressure were based on relatively small numbers of subjects.<sup>5-7</sup> In our study, the number of men with renal-cell cancer was sufficient to show a clear dose-response relation over a wide range of blood-pressure levels. Even slightly higher blood pressures conferred some excess risk, whereas increases in blood pressure over time further raised the risk independently of the presence of hypertension at base line. Of special interest was the decrease in risk associated with a reduction in blood pressure over time, although further studies will be needed to confirm this finding.

Whereas the excess risk of renal-cell cancer associated with obesity was consistent throughout the follow-up period, the risk related to hypertension was highest during the first five years of follow-up. Renal tumors in their early stages, before diagnosis, may cause increases in blood pressure<sup>15</sup> and thus contribute to the apparent risk associated with hypertension during the initial years of follow-up. However, even after we excluded the men in whom cancer was diagnosed and the person-years accumulated by the cohort during the first five years of follow-up, the risk of renal-cell cancer still was significantly higher at higher blood pressures, suggesting that the association is not an artifact of routine health examinations.

Epidemiologic studies have not been able to distinguish the effects of hypertension from those of diuretics or other antihypertensive drugs on the risk of renal-cell cancer.<sup>4,5</sup> We did not collect data on the use

of antihypertensive drugs; however, several of our findings — the monotonic, dose-response relation associated with increments in blood pressure, the excess risk seen with only slightly elevated blood pressures (which may not prompt treatment), and the reduced risk associated with decreased blood pressure at subsequent visits — implicate hypertension as a risk factor for renal-cell carcinoma. Indeed, our data indicate that effective control of hypertension may lower the risk of renal-cell cancer.

Several other potential limitations of our study should be considered. Only a subgroup of the men in the cohort had a follow-up visit after the initial, base-line examination. However, the men who had more than one examination were more likely to be active and healthy than those who did not have a follow-up examination. It therefore seems unlikely that increases in the risk of renal-cell cancer associated with worsening hypertension over time were due to selection bias in this subgroup. In addition, although our results provide strong evidence of a dose-response relation with body-mass index and blood pressure in men, they may not apply to the same extent in women.

Our finding that obesity and hypertension independently increase the risk of renal-cell cancer suggests that these factors act to increase this risk through different mechanisms. Obese persons have high serum concentrations of free insulin-like growth factor I,<sup>16</sup> an important mitogen that affects the cell cycle.<sup>17</sup> High serum insulin-like growth factor I concentrations have been linked to an increased risk of several cancers, including cancers of the breast, prostate, lung, and colorectum,<sup>17</sup> but the level of this growth factor has not been reported to be related to the risk of renal-cell cancer. Obesity may also increase the risk by increasing the serum concentrations of free estrogens,<sup>18,19</sup> which have been linked to the risk of renal-cell cancer in studies in animals,<sup>20</sup> but epidemiologic studies of renal-cell cancer among women have found no clear association between the risk of this cancer and the use of exogenous estrogens.<sup>21,22</sup>

As for hypertension, a variety of angiogenic and other growth factors, the levels of which are increased in persons with hypertensive disease, may be involved in renal carcinogenesis.<sup>23,24</sup> Subtle changes in renal function that precede the development of overt hypertension<sup>25,26</sup> may render the kidney susceptible to carcinogens and tumor growth. A long-term cohort study of men who underwent health examinations at the time they entered college<sup>27</sup> revealed a tripling of the risk of kidney cancer among those who had proteinuria.

Our findings underscore the importance of even small excesses in body-mass index and blood pressure in the development of renal-cell cancer and suggest that effective control of weight and hypertension may be useful in the prevention of this increasingly common type of cancer.

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## REFERENCES

1. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. Rising incidence of renal cell cancer in the United States. *JAMA* 1999;281:1628-31.
2. Møller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. *Eur J Cancer* 1994;30A:344-50.
3. Lindblad P, Wolk A, Bergström R, Persson I, Adami HO. The role of obesity and weight fluctuations in the etiology of renal cell cancer: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 1994;3:631-9.
4. Chow W-H, Devesa SS, Fraumeni JF Jr. Epidemiology of renal cell carcinoma. In: Vogelzang NJ, Scardino PT, Shipley WU, Coffey DS, eds. *Comprehensive textbook of genitourinary oncology*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins, 2000:101-10.
5. Shapiro JA, Williams MA, Weiss NS, Stergachis A, LaCroix AZ, Barlow WE. Hypertension, antihypertensive medication use, and risk of renal cell carcinoma. *Am J Epidemiol* 1999;149:521-30.
6. Coughlin SS, Neaton JD, Randall B, Sengupta A. Predictors of mortality from kidney cancer in 332,547 men screened for the Multiple Risk Factor Intervention Trial. *Cancer* 1997;79:2171-7.
7. Grove JS, Nomura A, Severson RK, Stemmermann GN. The association of blood pressure with cancer incidence in a prospective study. *Am J Epidemiol* 1991;134:942-7.
8. Liaw KL, Linet MS, McLaughlin JK, et al. Possible relation between hypertension and cancers of the renal pelvis and ureter. *Int J Cancer* 1997;70:265-8.
9. McCredie M, Stewart JH. Risk factors for kidney cancer in New South Wales. I. Cigarette smoking. *Eur J Cancer* 1992;28A:2050-4.
10. McLaughlin JK, Blot WJ, Devesa SS, Fraumeni JF Jr. Renal cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer epidemiology and prevention*. 2nd ed. New York: Oxford University Press, 1996:1142-55.
11. Östlund E, Englund A. Occupational safety and health in the Swedish construction industry. *Work Environ Health* 1971;8:27-32.
12. Engholm G, Englund A, Fletcher AC, Hallin N. Respiratory cancer incidence in Swedish construction workers exposed to man-made mineral fibres and asbestos. *Ann Occup Hyg* 1987;31:663-75.
13. Mattsson B, Rutqvist LE, Wallgren A. Undernotification of diagnosed cancer cases to the Stockholm Cancer Registry. *Int J Epidemiol* 1985;14:64-9.
14. The Swedish Cancer Registry. *Cancer incidence in Sweden 1995*. Stockholm, Sweden: National Board of Health and Welfare, 1998.
15. Steffens J, Bock R, Braedel HU, Isenberg E, Bührle CP, Ziegler M. Renin-producing renal cell carcinomas — clinical and experimental investigations on a special form of renal hypertension. *Urol Res* 1992;20:111-5.
16. Scacchi M, Pincelli AI, Cavagnini F. Growth hormone in obesity. *Int J Obes Relat Metab Disord* 1999;23:260-71.
17. Giovannucci E. Insulin-like growth factor-I and binding protein-3 and risk of cancer. *Horm Res* 1999;51:Suppl 3:34-41.
18. Hsieh CC, Signorello LB, Lipworth L, Lagiour P, Mantzoros CS, Trichopoulos D. Predictors of sex hormone levels among the elderly: a study in Greece. *J Clin Epidemiol* 1998;51:837-41.
19. Cohen PG. The hypogonadal-obesity cycle: role of aromatase in modulating the testosterone-estradiol shunt — a major factor in the genesis of morbid obesity. *Med Hypotheses* 1999;52:49-51.
20. Hodgson AV, Ayala-Torres S, Thompson EB, Liehr JG. Estrogen-induced microsatellite DNA alterations are associated with Syrian hamster kidney tumorigenesis. *Carcinogenesis* 1998;19:2169-72.
21. Lindblad P, Mellemgaard A, Schlehofer B, et al. International renal-cell cancer study. V. Reproductive factors, gynecologic operations and exogenous hormones. *Int J Cancer* 1995;61:192-8.
22. Gago-Dominguez M, Castela JE, Yuan JM, Ross RK, Yu MC. Increased risk of renal cell carcinoma subsequent to hysterectomy. *Cancer Epidemiol Biomarkers Prev* 1999;8:999-1003.
23. Schena FP, Strippoli GF, Wankelmuth P. Renal growth factors: past, present and future. *Am J Nephrol* 1999;19:308-12.
24. Matsumoto K, Morishita R, Moriguchi A, et al. Prevention of renal damage by angiotensin II blockade, accompanied by increased renal hepatocyte growth factor in experimental hypertensive rats. *Hypertension* 1999;34:279-84.
25. Cowley AW Jr, Roman RJ. The role of the kidney in hypertension. *JAMA* 1996;275:1581-9.
26. Klahr S. Mechanisms of progression of chronic renal damage. *J Nephrol* 1999;12:Suppl 2:S53-S62.
27. Whittemore AS, Paffenbarger RS Jr, Anderson K, Lee JE. Early precursors of urogenital cancers in former college men. *J Urol* 1984;132:1256-61.