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A prospective study of body mass index, hypertension, and smoking and the risk of renal cell carcinoma (United States)

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Abstract

Objective: We prospectively investigated the independent association of hypertension, thiazide use, body mass index, weight change, and smoking with the risk of renal cell carcinoma among men and women using biennial mailed questionnaires.
Methods: The study population included 118,191 women participating in the Nurses' Health Study and 48,953 men participating in the Health Professionals Follow-up Study
Results: During 24 years of follow-up for women and 12 years for men, 155 and 110 incident cases of renal cell carcinoma were confirmed, respectively. In multivariate models including age, body mass index (BMI), smoking and hypertension, higher BMI was confirmed as a risk factor for women and smoking as a risk factor for men and women. After adjusting for age, updated BMI and smoking, an updated diagnosis of hypertension was associated with renal cell carcinoma (RCC); the relatve risk (RR) was 1.9 (95% CI 1.4–2.7) for women and 1.8 (95% CI 1.2–2.7) for men. Based on limited data regarding the use of thiazide diuretics, we did not observe a risk associated with their use, independent of the diagnosis of hypertension.
Conclusions: Diagnosis of hypertension, higher BMI, and increasing pack-years of smoking appear to independently increase the risk of renal cell carcinoma.

Introduction

Body mass index (BMI) and smoking are accepted risk factors for renal cell carcinoma (RCC). Hypertension and anti-hypertensive medications have also been implicated. However, the independent contribution of each factor is not well-defined. While many studies have reported these as individual risk factors in univariate analyses, fewer have evaluated the independent association of each risk factor in multivariate analyses [1–7].

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The majority of published studies used a case-control design, with information on exposures collected after the diagnosis of RCC. Recall bias can particularly confound analyses that include BMI and smoking. The available prospective studies have been based on fatal cases of RCC [8–12], with the exception of two [13, 14]. As early stage renal cell carcinoma can be cured with surgery in the vast majority of cases, an important subset of cases would be excluded.

Elevated body mass index (BMI) has consistently been found to be a risk factor for RCC in women but less so in men [3–6, 9, 11–25]. Cigarette smoking has been consistently identified as a risk factor for RCC in men, but not in women [1–4, 15–20, 26–29]. In the one prospective study that included men and women, the

relative risk among cigarette smokers was significantly elevated for men, but not for women [9]. Hypertension has been variably associated with risk of RCC [1, 4, 5, 7–9, 13, 14, 16, 20, 23, 30–34], with some studies finding an association only among women and others only among men. The risk of RCC in users of thiazide diuretics remains unclear [3].

Given that relatively few studies have been conducted with prospective data and incident cases of RCC among both men and women, we sought to determine if our cohorts could contribute to the understanding of the apparent gender discrepancy among the previously reported risk factors. We also wanted to investigate the independent association of hypertension with RCC, as it is strongly associated with obesity. Therefore, we studied the association between hypertension, thiazide use, BMI, weight change, and smoking and risk of RCC in two large cohorts: the Nurses' Health Study and the Health Professionals Follow-up Study.

Materials and methods

Study population

The Nurses' Health Study (NHS) cohort was established in 1976 and is constituted of 121,700 female nurses aged 30–55 years. The Health Professionals Follow-up Study (HPFS) cohort was established in 1986 with 51,529 male dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians aged 40–75 years. Questionnaires collected information on a variety of life-style factors and health conditions. Every two years, follow-up questionnaires requested updated information on risk factors and major medical events.

Participants were excluded from the present analysis if they reported a history of cancer, other than non-melanoma skin cancer, at baseline. The present analysis is based on 118,191 women and 48,953 men who provided information including height, weight, cigarette smoking habits and if they had ever been diagnosed with hypertension by a physician on the baseline and at least one subsequent biennial questionnaire. On each questionnaire, participants were asked to report any cancer diagnosed in the previous two years. The follow-up through 1998 in HPFS and 2000 in NHS was greater than 90%. We also used the National Death Index and the Postal Service to identify fatalities from RCC that may not been reported on questionnaires; we estimate that more than 98% of deaths were ascertained [35].

Assessment of BMI, hypertension and smoking

Information on height was obtained from the baseline questionnaire, while weight was updated on each biennial questionnaire. These values are highly correlated with actual measurement [36]. Women were asked to record their weight at the age of 18 and men at age 21. These values have been previously validated [37].

Participants were asked to report physician-diagnosed hypertension, which has been shown to be reliably reported [38, 39]. Thiazide use was asked on the 1980 questionnaire and was updated every 2–4 years.

Information on smoking initiation, cessation, and number of cigarettes smoked was queried at baseline and updated biennially.

Identification of renal cell carcinoma cases

A new history of kidney cancer or cancer of the urinary tract, not including bladder cancer, was self-reported or obtained from a death certificate from 289 NHS women between 1976 and 2000 and from 236 HPFS men between 1986 and 1998. Pathologic subtypes were confirmed by review of the medical record by a physician blinded to the exposure data. Medical records were obtained for 257 of 289 women (89%) and 190 of 236 men (81%). We confirmed 214 (83%) cancers of the urinary tract, not including bladder cancer among women, and 162 (85%) among men. We were unable to confirm the remaining reported cases due to either inadequate information regarding a histologic diagnosis or an error in the reported diagnosis. Subjects were considered cases if they had a biopsy, nephrectomy or autopsy showing any of the histologic subtypes of carcinoma of the kidney recognized by the workgroup organized by the World Health Organization in conjunction with the Union Internationale Contre le Cancer and American Joint Committee on Cancer in 1997, including: clear cell, papillary, chromophobe, collecting duct and renal cell carcinoma not otherwise classified [40]. There were 166 female and 118 male incident cases of histologically confirmed renal cell carcinoma. After further excluding participants with a history of another cancer prior to the diagnosis of RCC, there were 156 female and 110 male cases included in our analyses.

Statistical analysis

The primary analysis examined incidence rates with person-years of follow-up as the denominator. For each participant, person-years of follow-up were counted from the date of return of the baseline questionnaire until a diagnosis of RCC or death or the end of

follow-up (31 May 2000 for NHS and 31 January 1998 for HPFS).

The study subjects were grouped according to five categories of BMI. We first analyzed BMI based on the weight from the baseline questionnaire. We repeated the analysis updating BMI every two years using the most recent weight. To minimize the potential for an effect of the cancer diagnosis on current weight, we also considered the weight provided on the questionnaire two years earlier. The effect of weight change was examined subtracting the weight at age 18 from the weight at baseline or an updated value, as we have done in previous studies [41]. We created five categories of weight change: loss of greater than 10 kg, loss of 4–10 kg, loss or gain of less than 4 kg (referent group), gain of 4–10 kg, and gain of greater than 10 kg. The same analysis was performed for men, using weight at age 21.

The incidence of RCC was compared between participants who had ever reported physician-diagnosed hypertension and those who never reported the diagnosis. The association with duration of hypertension was examined by comparing those who had reported a duration of physician-diagnosed hypertension less than 5, 5–10, 11–15, and 16–20 years, or more than 20 years before the time of updated information on hypertension. Because RCC may cause hypertension, we also performed analyses using a two-year lag for a diagnosis of hypertension.

Current thiazide diuretic use was first asked in 1980 in NHS and in 1986 for HPFS. We compared the incidence of RCC among those who reported current thiazide use in 1980 for women or 1986 for men with those who did not.

To evaluate the risk associated with cigarette smoking, we compared the incidence of RCC among current, former and never smokers. Former and current smokers were further subdivided by pack-years: 1–19, 20–39, and 40 or more.

We used the relative risk (RR) as the measure of association defined as the incidence rate of RCC among the participants in each exposure category divided by the corresponding rate in the reference category. Individuals with missing information on the exposure of interest were excluded from the relevant analysis; thus, the total number of cases may differ. We used pooled multivariate logistic regression to adjust simultaneously for the other risk factors for RCC [42]. When appropriate, we used the Mantel-Extension test for linear trend across categories of exposures and reported the two-tailed p values [43].

Results

At baseline in the NHS, the average age was 42.4 years, 11.4% reported a history of hypertension, 23.2% of the women were former smokers, and 33.1% were current smokers. The BMI was ≥25 kg/m^2 in 28.0% of the participants and ≥30 kg/m^2 in 8.1%. At baseline in the HPFS, the average age was 54.0 years, 22.2% reported a history of hypertension, 41.8% of the men were former smokers, and 9.6% were current smokers. The BMI was ≥25 kg/m^2 in 52.5% of the participants and ≥30 kg/m^2 in 7.8%.

We confirmed the diagnosis of renal cell carcinoma in 156 women and 110 men The incidence of RCC in the NHS cohort appears to be lower than the age-adjusted incidence reported in the SEER data [44]. This may indicate that this cohort has an inherently lower risk of RCC than the general population. Alternatively, our stringent requirement for pathology reports may have excluded a number of true cases that were reported, but not confirmed. The average age at diagnosis was 60.0 years for women and 65.4 years for men. Overall, the majority of cases were described as clear cell type (60%) or renal cell carcinoma, "not further classified" (28%). The remaining 12% were reported as papillary,

Table 1. Age-adjusted relative risks of renal cell carcinoma in NHS and HPFS according to body mass index (BMI) at baseline

	< 22.0	22.0–24.9	25.0–27.9	28.0–29.9	30.0 +	p for trend
Baseline BMI – women						
No. of cases	40	47	27	14	26	
Person-years	1,096,199	849,189	391,559	146,728	215,463	
Age-adjusted RR			1.5 (0.9–2.5)	2.1 (1.2–3.9)	2.7 (1.6–4.4)	< 0.001
Multivariate RR[a]	1.0	1.3 (0.9–2.0)	1.6 (0.9–2.5)	2.2 (1.2–4.1)		< 0.001
Baseline BMI – men						
No. of cases	4	37	45	12	10	
Person-years	49,169	196,786	189,044	53,696	41,726	
Age-adjusted RR		2.1 (0.8–6.0)	2.7 (1.0–7.6)	2.5 (0.8–7.8)	2.8 (0.8–9.0)	0.06
Multivariate RR[b]	1.0	2.1 (0.7–5.9)	2.4 (0.9–6.8)	2.1 (0.7–6.6)	2.1 (0.7–6.8)	0.19

[a] Adjusted for age, hypertension and pack-years of smoking in 1976.
[b] Adjusted for age, hypertension and pack-years of smoking in 1986.

chromophobe, collecting duct, and spindle cell carcinomas. We suspect that a portion of the unspecified RCC tumors were likely clear cell type as the standards for pathologic assessment of RCC evolved during the interval of this study.

In NHS, after adjusting for age, hypertension and pack-years of cigarette smoking, the highest category of BMI (≥30 kg/m^2) in 1976 was associated with an increased risk of RCC compared with women in the lowest category of BMI (< 22.0 kg/m^2) (RR = 2.7; 95% CI = 1.6–4.6) (Table 1). There was no significant increase in risk for women in the highest category of BMI at age 18, updated BMI with a two-year lag, weight change from age 18 to baseline or to updated weight (data not shown).

Among men, the age-adjusted and multivariate relative risks were all above 2.0 for baseline BMI in 1986, compared to the referent category, but none was significant (Table 1). Given the small number of cases in the top two categories of BMI, we also assessed the relative risk for men in the top two BMI categories combined, but the results remained non-significant (RR: 2.1; 95% CI: 0.7–6.2). Of note, the number of cases in the referent group was small ($n = 4$). However, the non-significant trend across categories corroborated a lack of dose response. Updated BMI, BMI at age 21, weight change from age 21 to baseline or updated values were also unassociated with increased risk (data not shown).

Smoking was modestly related to increased risk (Table 2). For men, there was a non-significant increase in the risk of RCC for former smokers and current smokers, and those with ≥40 pack-years of exposure. There was a significant trend across the three categories of pack-years for men ($p = 0.003$). For women, none of these categories was associated with a significant risk.

After adjusting for age, pack-years and BMI, a history of hypertension at baseline was not associated with increased risk of RCC among women (RR: 1.1; 95% CI: 0.7–1.7); however, an updated diagnosis of hypertension with a two-year lag was associated with risk (RR: 1.9;

Table 2. Age adjusted and multivariate relative risk (RR) of renal cell carcinoma in NHS and HPFS according to smoking history & updated pack-years with two-year lag.

	Never	Former	Current	Pack-years			
				1–19	20–39	≥40	*p* for trend
Women							
No. of cases	60	68	22	30	29	24	
Person-years	1,175,497	950,558	570,627	728,108	421,269	270,790	
Age-adjusted RR	1.0	1.3 (0.9–1.9)	0.9 (0.6–1.5)	0.9 (0.6–1.4)	1.4 (0.9–2.2)	1.4 (0.8–2.2)	0.08
Multivariate RR[a]	1.0	1.3 (0.9–1.8)	0.9 (0.6–1.5)	0.9 (0.6–1.4)	1.4 (0.9–2.2)	1.3 (0.8–2.2)	0.09
Men							
No. of cases	34	62	8	21	23	25	
Person-years	242,598	238,211	43,095	118,852	91,932	56,527	
Age-adjusted RR	1.0	1.5 (1.0–2.3)	1.3 (0.6–2.9)	1.2 (0.7–2.1)	1.5 (0.9–2.6)	2.1 (1.2–3.6)	0.002
Multivariate RR[a]	1.0	1.4 (0.9–2.2)	1.3 (0.6–2.9)	1.2 (0.7–2.0)	1.4 (0.8–2.5)	2.0 (1.2–3.5)	0.003

[a] Adjusted for age, updated BMI and hypertension (two-year lag).

Table 3. Age-adjusted multivariate relative risk of renal cell carcinoma in NHS and HPFS according to hypertension (HTN)

	− HTN at baseline	+ HTN at baseline	Two-year lag	
			− HTN updated	+ HTN updated
Women				
No. of cases	129	27	82	74
Person-years	2,426,807	300,124	2,057,947	668,983
Age-adjusted RR	1.0	1.3 (0.9–2.0)	1.0	1.9 (1.4–2.7)
Multivariate RR	1.0	1.1 (0.7–1.7)[a]	1.0	1.9 (1.4–2.7)[b]
Men				
No. of cases	60	49	51	58
Person-years	426,523	116,258	371,376	171,406
Age-adjusted RR	1.0	2.2 (1.5–3.2)	1.0	1.8 (1.3–2.7)
Multivariate RR	1.0	2.1 (1.4–3.1)[a]	1.0	1.8 (1.2–2.7)[b]

[a] Adjusted for age, BMI and pack-years in 1976 (NHS) or BMI and pack-years of smoking in 1986 (HPFS).
[b] Adjusted for age, updated BMI (2 year lag) and pack-years of smoking.

Table 4. Age-adjusted and multivariate relative risk of renal cell carcinoma in NHS and HPFS according to thiazide diuretic use at baseline

	Women		Men	
	No use	Current use in 1980	No use	Current use in 1986
No. of cases	134	22	89	20
Person-years	2,500,076	226,855	493,424	49,357
Age-adjusted RR	1.0	1.5 (1.0–2.4)[a]	1.0	1.5 (0.9–2.5)
Multivariate RR[b]	1.0	1.4 (0.9–2.3)	1.0	0.8 (0.5–1.5)

[a] $p = 0.08$.
[b] Adjusted for age, hypertension at baseline and updated BMI.

95% CI: 1.4–2.7) (Table 3). To address the possibility that the hypertension was caused by RCC, we also examined a four-year lag and the magnitude of the association was unchanged (RR: 1.9; 95% CI: 1.3–2.7). There was no increasing association according to duration of hypertension (data not shown). Among men, the risk was significantly increased when using the diagnosis of hypertension at baseline or after updating with a two-year lag (Table 3). Among men, the risk did appear to increase slightly with longer duration of hypertension (data not shown). Thus, hypertension appears to be independently associated with RCC risk in both women and men.

Among women and men, there was no increased risk of RCC associated with thiazide use in the age-adjusted or multivariate analyses (Table 4). This result was not altered by updating thiazide use (data not shown). While our data regarding thiazide use were not as complete as the hypertension data, we did not find an independent risk associated with their use. Our analysis of this factor is limited by the same issue present in other studies, namely the coexistence of hypertension in the vast majority of patients prescribed thiazides.

Discussion

There are few reports of hypertension and the risk of RCC independent of BMI and smoking. The value of prospective data, such as the current study, is the ability to analyze the contribution of each risk factor at multiple timepoints. Significant risks could manifest at one interval but not another, as risk factors may have variable latency with respect to the clinical appearance of cancer. Previous reports have suggested that the risk associated with BMI and smoking may have different magnitudes among men and women. Our data is consistent with that possibility; however, the number of cases included in our study was too small to make definitive comparisons across gender.

In our study, BMI was associated with a significantly increased risk in women, but a non-significant risk was observed in men. There was a clear dose–response with pack-years of smoking in men, but no significant association with smoking was observed in women. Hypertension was associated with an increased risk of RCC among both men and women. While the preponderance of published prospective data regards risk factors in men, our study contributes more prospective data regarding these risk factors in women.

In our cohorts, a diagnosis of hypertension was independently associated with a significantly increased risk of RCC in both men and women, after adjusting for BMI and pack-years of smoking. For both cohorts, risk was increased for a diagnosis of hypertension proximate to the diagnosis of RCC. Considering that follow-up has been considerably longer in the NHS cohort, it is not clear that the association of baseline HTN with RCC risk in men, but not women, represents a true difference in the temporal contribution of this factor. These findings contrast with those from the Iowa Women's Health Study in which a history of hypertension was not associated with risk of RCC [13]. An updated analysis of this cohort was recently published [45]. In the only other prospective study to report on the risk of RCC and hypertension in both men and women, the risk of RCC was increased two-fold for women being treated for hypertension, but not for men [9].

Previous reports have implicated antihypertensive medications as causal agents in the carcinogenesis of RCC [9, 13]. This issue has been difficult to resolve, as the prevalence of exposure to these medications is so high among hypertensive individuals. In particular, thiazide diuretics have been reportedly associated with an increased risk of RCC. We did not have detailed information on dose or duration of thiazide therapy. Therefore, we limited our analyses to the use of thiazides at the time participants were first queried and updated use. There was no significant association between thiazide use and risk of RCC among males or females. While our study may have been underpowered to detect a significant relation, the data from both cohorts do not support a risk from thiazides comparable in magnitude to that observed for hypertension.

The mechanism by which hypertension might play a causal role in RCC is poorly understood. The renin–angiotensin axis might act as a promoter in preneoplastic lesions by favoring cellular proliferation, as angiotension II has been shown to do in the coronary vasculature [46]. The fact that we did not see an increase in risk of RCC with increasing duration of hypertension suggests that hypertension may contribute to carcinogenesis only in the later stages of the disease. It is possible, though unlikely, that HTN led to an increase in detection of RCC. The prevalence of humorally mediated hypertension due to RCC is not well-described. In one series of RCC cases with hypertension, renin secretion from the tumor was demonstrated in 15% of cases [47].

We found that elevated BMI at baseline was independently associated with a significantly increased risk of RCC for women but not men after adjusting for hypertension and smoking. This risk was attenuated when BMI was updated. This is in agreement with findings from the Iowa Women's Health Study [13]. This attenuation may result from the weight reduction that some women experience in the years preceding the diagnosis of RCC. Our data suggest that the highest risk of RCC may be associated with elevated BMI, present for years before the occurrence of disease, but not necessarily from youth. The lack of association between BMI and RCC risk among men is in contrast to the findings of the two largest prospective studies of men [12, 14]. Our study may not have had sufficient power to detect a true difference in risk among men as the relative risk we observed was similar to that found in the studies with more cases [12, 14]. The small number of cases in the referent group limits our confidence in the risk estimates for the higher categories. The lack of dose–response, however, suggests that BMI is not a strong risk factor in our male cohort.

Elevated levels of circulating growth factors may promote tumor growth in obese individuals. Kellerer *et al.* [48] examined the expression levels of the insulin and insulin-like growth factor 1 receptors (IGF-R) in renal cell carcinomas and adjacent normal renal parenchyma from biopsy material from 8 patients. They found that both receptors were two- to four-fold overexpressed in RCC cells compared to normal tissues. In the few samples that did not have increased levels of expression, there was evidence of increased receptor autophosphorylation, suggesting that this may be an important signal transduction pathway in RCC. Higher circulating levels of IGF-R ligands in obese individuals could plausibly promote tumor growth, but we know of no reason why such a mechanism would differ among men and women.

Smoking has been reported to be a risk factor for RCC in prospective studies [8–10, 13, 14] and is listed as a consistent factor by both the International Agency for Research on Cancer and the U.S. Surgeon General. Taken together, our data suggest a weak association between smoking and RCC among women. These same assessments of exposure for men point to a stronger relation between smoking and RCC risk. The apparent gender disparity is consistent with previous studies. The data from this and other studies are conflicting with regard to the relative importance of current smoking *versus* cumulative exposure. Our data suggest that smoking has an early carcinogenic effect among men. The mechanism by which smoking affects RCC pathogenesis may be similar to that proposed for bladder cancer, where cigarette smoking has been implicated in mutations in p53 [49].

Our study was limited by the number of incident cases. We performed multiple analyses, allowing the possibility that some of the associations were related to chance. The agreement of our univariate risk estimates with published univariate analyses suggests that our findings were not due to chance. Furthermore, a careful analysis of exposure and dose duration is not easily done with retrospective data. Thus, we planned multiple analyses regarding these variables to take advantage of the available data. In light of the apparent differences in risk factors for RCC among men and women, we chose not to combine the male and female cohorts. Furthermore, the sample size limited the statistical power to directly compare the relative risks between genders or to investigate the potential interaction between risk factors. It is possible that risk factors vary according to the histologic subtype of RCC. However, we have neither the statistical power nor the complete histologic classification necessary to perform such analyses. Future studies would be strengthened by central pathologic review.

Our study is among the largest, prospective analyses to date of the independent associations of hypertension, thiazide use, obesity, and smoking among fatal and nonfatal cases of RCC in men and women. With assessment of exposure prior to the diagnosis of carcinoma, the prospective design of this study avoids recall bias. By requiring histologic evidence of RCC, we avoided some of the misclassification of cases that may occur in studies that are limited to fatal cases and data from death certificates. In addition, studies that did not segregate renal pelvis from parenchymal tumors may have been influenced by the differences in risk factors for cancer of the renal pelvis [23, 28].

In summary, we found that hypertension was associated with increased risk of renal cell carcinoma in men

and women. Thiazide use did not appear to account for this risk. BMI was associated with a significantly increased risk only in women and increasing pack-years of smoking was associated with increased risk only in men. The increasing incidence of RCC may be due, in part, to increases in the prevalence of these modifiable risk factors. The mechanisms by which these factors influence the development of RCC require further investigation.

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References

1. Yuan J-M, Castelao JE, Gago-Dominguez M, Yu MC, Ross RK (1998) Tobacco use in relation to renal cell carcinoma. *Cancer Epidemiol Biomarkers prev* **7**: 429–433.
2. Benichou J, Chow W-H, Mclaughlin JK, Mandel JS, Fraumeni JFJ (1998) Population attributable risk of renal cell cancer in Minnesota. *Am J Epidemiol* **148**: 424–430.
3. Hiaatt AH, Tolan K, Quesenberry CPJ (1994) Renal cell carcinoma and thiazide use: a historical, case-control study (California, USA). *Cancer Causes Control* **5**: 319–325.
4. Kreiger N, Marrett LD, Dodds L, Hilditch S, Darlington GA (1993) Risk factors for renal cell carcinoma: results of a population-based case-control study. *Cancer Causes Control* **4**: 101–110.
5. Yuan J-M, Castelao JE, Gago-Dominguez M, Ross RK, Yu MC (1998) Hypertension, obesity and their medications in relation to renal cell carcinoma. *Br J Cancer* **77**: 1508–1513.
6. Chow W-H, Mclaughlin JK, Mandel JS, Wacholder S, Niwa S, Fraumeni JFJ (1996) Obesity and risk of renal cell cancer. *Cancer Epidemiol Biomarkers Prev* **5**: 17–21.
7. Mellemgaard A, Niwa S, Mehl ES, Engholm G, McLaughlin JK, Olsen JH (1994) Risk factors for renal cell carcinoma in Denmark: role of medication and medical history. *Am J Epidemiol* **23**: 923–930.
8. Couglin SS, Neaton JD, Randall B, Sengupta A (1997) Predictors of mortality from kidney cancer in 332,547 men screened for the multiple risk factor intervention trial. *Cancer* **79**: 2171–2177.
9. Heath CWJ, Lally CA, Calle EE, McLaughlin JK, Thun MJ (1997) Hypertension, diuretics, and antihypertensive medications as possible risk factors for renal cell cancer. *Am J Epidemiol* **145**: 607–613.
10. McLaughlin JK, Hrubec Z, Heineman EF, Blot WJ, Fraumeni JFJ (1990) Renal cancer and cigarette smoking in a 26-year follow-up of U.S. veterans. *Public Health Rep* **105**: 535–537.
11. Whittemore AS, Paffenbarger RSJ, Anderson K, Lee JE (1985) Early precursors of site-specific cancers in college men and women. *JNCI* **74**: 43–51.
12. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ (2003) Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* **348**: 1625–1638.
13. Prineas RJ, Folsom AR, Zhang ZM, Sellers TA, Potter J (1997) Nutrition and other risk factors for renal cell carcinoma in postmenopausal women. *Epidemiology* **8**: 31–36.
14. Chow WH, Gridley G, Fraumeni JF, Jarvholm B (2000) Obesity, hypertension, and the risk of kidney cancer in men. *N Engl J Med* **343**: 1305–1311.
15. Stefani EDe, Fierro L, Mendilaharsu M, *et al*. (1998) Meat intake, 'mate' drinking and renal cell cancer in Uruguay: a case-control study. *Br J Cancer* **78**: 1239–1243.
16. Muscat JE, Hoffman D, Wynder EL (1995) The epidemiology of renal cell carcinoma. *Cancer* **75**: 2552–2557.
17. McLaughlin JK, Gao Y-T, Gao R-N, Zheng W, Ji B-T, Blot WJ (1992) Risk factors for renal-cell cancer in Shanghai, China. *Int J Cancer* **52**: 562–565.
18. Maclure M, Willett W (1990) A case-control study of diet and risk of renal adenocarcinoma. *Epidemiology* **1**: 430–440.
19. Goodman MT, Morgenstern H, Wynder EL (1986) A case-control study of factors affecting the development of renal cell cancer. *Am J Epidemiol* **124**: 926–941.
20. McLaughlin JK, Mandel JS, Blot WJ, Schuman LM, Mehl ES, Fraumeni JFJ (1984) A population-based case-control study of renal cell carcinoma. *JNCI* **72**: 275–284.
21. Shapiro JA, Williams MA, Weiss NS (1999) Body mass index and risk of renal cell carcinoma. *Epidemiology* **10**: 188–191.
22. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH (1994) Risk factors for renal-cell carcinoma in Denmark. III. Role of weight, physical activity and reproductive factors. *Int J Cancer* **56**: 66–71.
23. McCredie M, Stewart JH (1992) Risk factors for kidney cancer in New South Wales, Australia. II. Urologic disease, hypertension, obesity, and hormonal factors. *Cancer Causes Control* **4**: 323–331.
24. Talamini R, Baron AE, Barra S, *et al*. (1990) A case-control study of risk factors for renal cell cancer in northern Italy. *Cancer Causes Control* **1**: 125–131.
25. Asal NR, Risser DR, Kadamani S, Geyer JR, Lee ET, Nehemiah C (1988) Risk factors in renal cell carcinoma. *Cancer Detect Prev* **11**: 359–377.
26. Mclaughlin JK, Lindblad P, Mellemgaard A, *et al*. (1995) International renal-cell cancer study. I. Tobacco use. *Int J Cancer* **60**: 194–198.
27. Mellemgaard A, Engholm G, McLaughlin JK, Olsen JH (1994) Risk factors for renal cell carcinoma in Denmark. I. Role of socioeconomic status, tobacco use, beverages, and family history. *Cancer Causes Control* **5**: 105–113.
28. McCredie M, Stewart JH (1992) Risk factors for kidney cancer in New South Wales. I. Cigarette smoking. *Eur J Cancer* **28**: 2050–2054.
29. La Vecchia C, Negri E, D'Avanzo B, Franceschi S (1990) Smoking and renal cell carcinoma. *Cancer Res* **50**: 5231–5233.
30. Weinmann S, Glass AG, Weiss NS, Psaty BM, Siscovick DS, White E (1994) Use of diuretics and other antihypertensive medications in relation to the risk of renal cell cancer. *Am J Epidemiol* **140**: 792–804.
31. Shapiro JA, Williams MA, Weiss NS, Stergachis A, LaCroix AZ, Barlow WE (1999) Hypertension, antihypertensive medication use, and risk of renal cell carcinoma. *Am J Epidemiol* **149**: 521–530.
32. Mclaughlin JK, Chow W-H, Mandel JS, *et al*. (1995) International renal-cell cancer study. VIII. Role of diuretics, other antihypertensive medications and hypertension. *Int J Cancer* **63**: 216–221.
33. Chow W-H, Mclaughlin JK, Mandel JS, Wacholder S, Niwa S, Fraumeni JFJ (1995) Risk of renal cell cancer in relation to

diuretics, antihypertensive drugs, and hypertension. *Cancer Epidemiol Biomarkers Prev* **3**: 327–331.
34. Finkle WD, McLaughlin JK, Rasgon SA, Low JE (1993) Increased risk of renal cell cancer among women using diuretics in the United States. *Cancer Causes Control* **4**: 555–558.
35. Stampfer MJ, Willett WC, Speizer FE, *et al*. (1984) Test of the National Death Index. *Am J Epidemiol* **119**: 837–839.
36. Willett WC, Stampfer MJ, Bain C, *et al*. (1983) Cigarette smoking, relative weight and menopause. *Am J Epidemiol* **117**: 651–658.
37. Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Willett WC (1995) The validity of recalled weight among younger women. *Int J Obes Relat Metab Disorder* **19**: 570–572.
38. Colditz GA, Martin P, Stampfer MJ, *et al*. (1986) Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* **123**: 894–900.
39. Ascherio A, Rimm EB, Giovannucci EL, *et al*. (1992) A prospective study of nutritional factors and hypertension among US men. *Circulation* **86**: 1475–1484.
40. Storkel S, Eble JN, Adlakha K, *et al*. (1997) Classification of renal cell carcinoma. Workgroup No. 1. *Cancer* **80**: 987–989.
41. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Stampfer MJ, Fuchs CS (2001) Physical activity, obesity, height, and the risk of pancreatic cancer. *JAMA* **286**: 921–929.
42. D'Agostino RB, Lee ML, Belanger AJ, Cupples LA, Anderson K, Kannel WB (1990) Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. *Stat Med* **9**: 1501–1515.
43. Mantel N (1963) Chi-square tests with one degree of freedom: extension of the Mantel-Haenszel procedure. *J Am Stat Assoc* **58**: 690–700.
44. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. (1999) Rising incidence of renal cell cancer in the United States. *JAMA* **281**: 1628–1631.
45. Nicodemus KK, Sweeney C, Folsom AR (2004) Evaluation of dietary, medical and lifestyle risk factors for incident kidney cancer in postmenopausal women. *Int J Cancer* **108**: 115–121.
46. Duff JL, Marrero MB, Paxton WG, Schieffer B, Bernstein KE, Berk BC (1995) Angiotensin II signal transduction and the mitogen-activated protein kinase pathway. *Cardiovasc Res* **4**: 511–517.
47. Steffens J, Bosck R, Braedel HU, Isenberg E, Buhrle CP, Ziegler M (1992) Renin-producing renal cell carcinomas – Clinical and experimental investigations on a special form of renal hypertension. *Urol Res* **20**: 111–115.
48. Kellerer M, Eye Corleta Hvon, Muhlhofer A, *et al*. (1995) Insulin- and insulin-like growth-factor-I receptor tyrosine-kinase activities in human renal carcinoma. *Int J Cancer* **62**: 501–507.
49. LaRue H, Allard P, Simoneau M, *et al*. (2000) P53 point mutations in initial superficial bladder cancer occur only in tumors from current or recent cigarette smokers. *Carcinogenesis* **21**: 101–106.