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Original Contribution

Body Size and Renal Cell Cancer Incidence in a Large US Cohort Study

Kenneth F. Adams[1], Michael F. Leitzmann[1], Demetrius Albanes[1], Victor Kipnis[2], Steven C. Moore[1], Arthur Schatzkin[1], and Wong-Ho Chow[1]

[1] Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD.
[2] Biometry Research Group, Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD.

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Renal cell cancer (RCC) incidence has increased in the United States over the past three decades. The authors analyzed the association between body mass index (BMI) and invasive RCC in the National Institutes of Health (NIH)–AARP Diet and Health Study, a large, prospective cohort aged 50–71 years at baseline initiated in 1995–1996, with follow-up through December 2003. Detailed analyses were conducted in a subcohort responding to a second questionnaire, including BMI at younger ages (18, 35, and 50 years); weight change across three consecutive age intervals; waist, hip, and waist-to-hip ratio; and height at age 18 years. Incident RCC was diagnosed in 1,022 men and 344 women. RCC was positively and strongly related to BMI at study baseline. Among subjects analyzed in the subcohort, RCC associations were strongest for baseline BMI and BMI recalled at age 50 years and were successively attenuated for BMI recalled at ages 35 and 18 years. Weight gain in early (18–35 years of age) and mid- (35–50 years of age) adulthood was strongly associated with RCC, whereas weight gain after midlife (age 50 years to baseline) was unrelated. Waist-to hip ratio was positively associated with RCC in women and with height at age 18 years in both men and women.

body height; body mass index; body size; carcinoma, renal cell; obesity; overweight; waist-hip ratio

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

The incidence of kidney cancer, which combines renal parenchyma (renal cell) and renal pelvis cancers, is increasing in the United States, with all of the increase due to renal cell cancer (1). High body mass has been consistently identified as a risk factor (2), which is of concern because a large proportion of the US adult population is overweight and obese (3).

Recent body mass is positively related to renal cell cancer in both men and women (4). A limited number of studies have investigated whether the body mass relation differs according to the age period during which body mass is considered—that is, whether body mass at any stage of adulthood is particularly associated with renal cell cancer—with conflicting results (5–15). Limited evidence suggests that weight gain is related to renal cell cancer risk (11, 12, 15, 16), but, again, whether timing of weight gain matters is not understood. Most analyses report no association between height and renal cell cancer (7–9, 12, 15, 17), although intriguing recent evidence suggests a relation between waist-to-hip ratio, a measure of abdominal adiposity, and renal cell cancer (13, 15–17).

We analyzed the relations of renal cell cancer incidence with body size, including body mass index (BMI) at younger ages, weight change, waist and hip sizes, and height at age 18 years in the National Institutes of Health (NIH)–AARP Diet and Health Study, a large cohort of men and

Correspondence to Dr. Kenneth F. Adams, Health Partners Research Foundation, Mail Stop: 21111R, 8170 33rd Avenue South, PO Box 1524, Minneapolis, MN 55440-1524 (e-mail: kenneth.f.adams@healthpartners.com).

women living in six states and two metropolitan areas across the United States. The availability of several measures of body size and the large number of incident cases of renal cell cancer that have occurred enabled us to consider these associations in detail.

MATERIALS AND METHODS

Study population

Design and maintenance of the NIH–AARP Diet and Health Study cohort have been described previously (18). Briefly, in 1995–1996, a self-administered baseline questionnaire was mailed to 3.5 million AARP members, 50–71 years of age, requesting information on demographic and anthropometric characteristics, dietary intake, and health-related behaviors. A total of 566,402 persons satisfactorily completed the baseline questionnaire. Exclusions were as follows: 719 with a diagnosis of renal cell cancer before study entry, 477 cases for whom only mortality information on kidney cancer was available (excluded because this study specifically evaluated renal cell cancer incidence), 15,760 whose questionnaires were completed by surrogates, and 13,400 for whom information on height or weight was missing. We further excluded 4,637 AARP members whose energy intake estimates were implausible and 2,637 reporting extreme values for weight or height. The baseline analytical cohort, which was used to analyze the relation of baseline BMI and height to renal cell cancer, included 528,772 participants (312,500 men and 214,906 women). In 1996–1997, a second (subcohort) questionnaire was mailed to persons responding to the first one, and responses were received from 334,908 persons. The second questionnaire collected more detailed information on body weight history and baseline waist and hip size. After exclusions similar to those for the baseline questionnaire, the remaining 320,618 participants (185,758 men and 134,860 women) constituted the analytical subcohort.

The study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute. All study participants provided written informed consent.

Case ascertainment

Incident renal cell cancer cases were identified through state cancer registries, linked by name, address, sex, date of birth, and, if available, Social Security number. Renal cell carcinoma was defined as *International Classification of Disease for Oncology* code C260 and incorporating histology codes (8010, 8032, 8140, 8211, 8246, 8260, 8310, 8312, 8320) consistent with renal cell carcinoma. Participants were followed until diagnosis of first renal cell cancer, date they moved out of the registry area, death, or date of last follow-up on December 31, 2003.

Assessment of height, weight, and other exposures

Self-reported height and weight were collected from the baseline questionnaire, and height at age 18 years; weight at ages 18, 35, and 50 years; and waist and hip circumferences were collected from the subcohort questionnaire. Persons whose body size measures were missing or extreme were excluded on a per-analysis basis to conserve sample size. Extreme values were defined as more than three interquartile ranges below the 25th percentile or more than three interquartile ranges above the 75th percentile. As an example, this procedure removed subjects with the lowest 0.07 percent and highest 0.08 percent baseline weights. Baseline BMI was calculated from baseline height and weight as weight (kilograms) divided by height (meters) squared. BMI at ages 18, 35, and 50 years was calculated from the subcohort questionnaire by using height at age 18 years and weight at ages 18, 35, and 50 years. BMI was divided into seven categories for analysis in the full cohort: <18.5, 18.5–<22.5 (referent), 22.5–<25, 25–<27.5, 27.5–<30, 30–<35, and ≥ 35 kg/m^2; in the subcohort, the highest category was ≥ 30 kg/m^2. These categories correspond to or are nested within the World Health Organization classifications for underweight (<18.5 kg/m^2), normal weight (18.5–<25 kg/m^2), overweight (25–<30 kg/m^2), and obesity (≥ 30 kg/m^2). Because participants tended to report much lower weights at ages 18 and 35 years, an alternative categorization was created dividing the normal BMI range into three finer categories: 18.5–<21 (referent), 21–<23, and 23–<25 kg/m^2).

Weight change within 4 kg was defined as stable for analyses of 18–35 years, 35–50 years, and 50 years to baseline age intervals. A wider range of weight gain of -4 kg to 10 kg was considered stable for the longer, 18 years to baseline age interval to achieve a sufficiently large referent group. Height at age 18 years, waist and hip sizes, and waist-to-hip ratio were analyzed as quintiles.

Cigarette smoking was categorized as never smoked, formerly smoked (quit smoking 1–9 years ago or quit smoking ≥ 10 years ago), and currently smoked at baseline or quit for <1 year, and, among smokers, by dose (1–10, 11–20, 21–30, or >30 cigarettes/day), with a separate category assigned to missing values. A three-level physical activity index was created based on two questions addressing sports and non-sports-related activity. Percentage of energy consumed as protein was categorized to quartiles and other anthropometric variables (height, weight) to quintiles. Self-reported physician-diagnosed history of diabetes and hypertension were dichotomous.

Data analysis

Age-adjusted and multivariate relative risks were estimated by using Cox regression analysis with age as the underlying time metric (19). All statistical tests were two sided, with $\alpha = 0.05$ considered statistically significant. Trends were evaluated as grouped linear variables by using BMI category medians. For weight change analyses, the trend reported is for weight stability or gain, excluding persons who lost ≥ 4 kg.

Multivariate models were adjusted for age, smoking, physical activity, percentage of energy consumed as protein, and history of diabetes. Analyses combining men and women were adjusted for gender. Analyses based on the subcohort were adjusted for these variables and, in addition, history of hypertension. Numerous potential confounders

TABLE 1. Baseline characteristics of the NIH*–AARP Diet and Health Study cohort, United States, 1995–1996 through 2003†

	Renal cell cancer cases		Noncases	
	Men	Women	Men	Women
Participants (no.)	1,022	344	312,500	214,906
Age at entry (years)	63.3 (5.1)	63.0 (5.1)	62.3 (5.3)	61.9 (5.4)
Weight (kg)	90.1 (16.2)	76.9 (17.1)	86.7 (14.6)	71.6 (15.7)
Height (cm)	179 (6.9)	164 (6.6)	178 (6.9)	163 (6.6)
Baseline BMI* (kg/m^2)	28.2 (4.5)	28.7 (6.4)	27.3 (4.1)	26.8 (5.6)
Protein intake (g/day)	76.8 (35.2)	59.7 (25.9)	76.2 (33.8)	60.3 (27.2)
Energy intake (kcal/day)	2,026 (869)	1,499 (611)	2,012 (843)	1,569 (652)
Race (% Caucasian)	90.9	88.7	92.8	90.1
Smoking (%)‡				
Never	24.4	39.5	29.0	43.5
Former	59.1	42.4	56.9	38.3
Current	14.3	16.6	12.1	16.1
Physical activity level (%)‡				
Low	27.0	36.3	24.2	31.7
Medium	36.0	36.2	38.4	35.4
High	33.7	23.7	35.5	29.9
Diabetes history (%)	13.5	11.9	10.3	7.5
Hypertension history (%)§	55.5	52.0	40.5	37.2

* NIH, National Institutes of Health; BMI, body mass index.
† Values are expressed as mean (standard deviation) unless indicated otherwise.
‡ Values do not add to 100% because of missing information.
§ Available from the subcohort data only.

were tested but were found to not affect risk estimates appreciably: dietary variables of fat, carbohydrate, fruit and vegetable, and red meat intake (all adjusted for calories) and total calories, and, for women, reproductive variables including number of children, age at first livebirth, menopausal hormone replacement therapy, and multivitamin use. Weight change analyses were also adjusted for BMI at the beginning of the weight change interval (initial BMI) and for height at age 18 years.

Effect modification was evaluated by both tests of interaction and analysis of heterogeneity (stratification according to categories of the third variable, using a single referent group). Potential effect modifiers included age, smoking, protein intake, history of diabetes, history of hypertension, and BMI at a younger age. Statistical interactions involving naturally continuous variables (e.g., BMI, weight change) were modeled as continuous, linear cross-product terms. Statistical significance was evaluated by using the likelihood ratio test, comparing full and reduced models, with $p = 0.05$ considered statistically significant.

RESULTS

A total of 1,366 incident cases of renal cell cancer were observed over the 8.2-year follow-up period, including 1,022 in men and 344 in women. The subcohort included 778 incident cases of disease, 578 in men and 200 in women, with follow-up of 7.2 years. Compared with noncases, renal cell cancer cases had higher BMI and lower physical activity levels, and they were more likely to be smokers and have histories of diabetes and hypertension (table 1).

Relative risks for renal cell cancer increased consistently with BMI at baseline (ages 50–71 years) for both men (p-trend < 0.0005) and women (p-trend < 0.0005) (table 2). Multivariate relative risks were significantly elevated at a BMI of 25–<27.5 kg/m^2 (relative risk (RR) = 1.43, 95 percent confidence interval (CI): 1.07, 1.92 for men and RR = 1.57, 95 percent CI: 1.07, 2.29 for women) relative to the 18.5–<22.5 kg/m^2 referent group. Among participants whose BMI was $\geq$35 kg/m^2, relative risks were 2.47 (95 percent CI: 1.72, 3.53) for men and 2.59 (95 percent CI: 1.70, 3.96) for women.

After confirming that the relation between baseline BMI and renal cell cancer in the subcohort was similar to that in the entire cohort, we undertook detailed analyses using the subcohort data (table 3). Further adjustment for hypertension status, a known risk factor for renal cell cancer, did not alter the relation between baseline BMI and renal cell cancer risk. Body mass at baseline and at age 50 years were both strongly associated with renal cell cancer risk. BMI at age 35 years was less strongly related to renal cell cancer risk, and associations with BMI at age 18 years were further

TABLE 2. Relative risk of renal cell cancer in relation to BMI* at study baseline (1995–1996 through 2003), United States

	Baseline BMI (kg/m^2)							*p*-trend†
	<18.5	18.5–<22.5	22.5–<25	25–<27.5	27.5–<30	30–<35	≥35	
Men								
Age adjusted								
HR*	1.42	1.0	1.13	1.42	1.66	1.92	2.61	<0.0005
95% CI*	0.51, 3.93	Referent	0.83, 1.54	1.06, 1.90	1.23, 2.24	1.42, 2.59	1.83, 3.70	
Multivariate adjusted‡								
HR	1.37	1.0	1.15	1.43	1.64	1.87	2.47	<0.0005
95% CI	0.49, 3.77	Referent	0.85, 1.57	1.07, 1.92	1.22, 2.22	1.38, 2.53	1.72, 3.53	
No. of cases	4	53	166	294	219	210	76	
Women								
Age adjusted								
HR	1.73	1.0	1.14	1.65	1.72	2.36	2.95	<0.0005
95% CI	0.69, 4.37	Referent	0.76, 1.69	1.13, 2.40	1.13, 2.61	1.62, 3.44	1.97, 4.43	
Multivariate adjusted‡								
HR	1.70	1.0	1.11	1.57	1.60	2.16	2.59	<0.0005
95% CI	0.67, 4.30	Referent	0.74, 1.65	1.07, 2.29	1.05, 2.44	1.47, 3.17	1.70, 3.96	
No. of cases	5	43	55	72	45	73	51	
Men and women combined								
Age adjusted								
HR	1.57	1.0	1.16	1.50	1.72	2.06	2.76	<0.0005
95% CI	0.79, 3.11	Referent	0.91, 1.47	1.19, 1.88	1.36, 2.18	1.63, 2.60	2.11, 3.60	
Multivariate adjusted‡								
HR	1.51	1.0	1.17	1.49	1.67	1.97	2.56	<0.0005
95% CI	0.76, 2.99	Referent	0.92, 1.48	1.19, 1.88	1.32, 2.12	1.56, 2.50	1.95, 3.36	
No. of cases	9	96	221	366	264	283	127	

* BMI, body mass index; HR, hazard ratio; CI, confidence interval.
† Linear trend of category medians.
‡ Adjusted for age, smoking status and dose, physical activity, protein intake, and history of diabetes.

attenuated, although, among men, a statistically significant trend persisted ($p = 0.02$). Analysis of BMI at ages 18 and 35 years, using narrower BMI categories to improve the distribution of participants across categories of the normal range (18.5–<21 (referent), 21–<23, 23–<25 kg/m^2), did not change the results (this information is described in supplemental table 1, the first of two supplementary tables posted on the *Journal*'s website (http://aje.oupjournals.org/)). BMI at different ages tended to be highly correlated across proximal age periods but weaker with greater distance over the adult age span (table 3).

We evaluated renal cell cancer associations with weight change across three consecutive age spans of 18–35 years, 35–50 years, and 50 years to baseline age, adjusting for BMI at the beginning of each age interval (table 4). Weight gain in early (18–35 years of age) and mid- (35–50 years of age) adulthood was positively related to renal cell cancer risk, whereas weight gain recalled between 50 years and study baseline was unrelated to risk. Weight loss was not related to risk over any of the three age intervals, although measures were imprecise because of small numbers of cases.

To evaluate whether weight gain per se was associated with renal cell cancer beyond the influence of excess weight at baseline, we added baseline BMI as a covariate to the weight-gain models. The effect was to attenuate many of the weight-gain associations; however, for men, weight gain of ≥20 kg either from ages 18 to 35 years (RR = 1.47, 95 percent CI: 1.02, 2.12) or from ages 35 to 50 years (RR = 1.81, 95 percent CI: 1.21, 2.71) remained associated with renal cell cancer. Similarly, men and women who gained ≥10 kg over both age periods were at increased risk (RR = 1.42, 95 percent CI: 1.04, 1.94) even after consideration of baseline BMI (supplemental table 2). These results suggest an influence of early-adulthood-to-midadulthood weight gain on renal cell cancer risk independent of attained BMI. Furthermore, for men, model fit was marginally improved by incorporating weight gain over the two younger intervals into the statistical models (likelihood ratio test comparing full and reduced models; $p = 0.08$ for inclusion of weight gain between 18 and 35 years of age and $p = 0.04$ for inclusion of weight gain between 35 and 50 years of age).

TABLE 3. Relative risk of renal cell cancer in relation to BMI* at four distinct age periods, United States, 1995–1996 through 2003†

	BMI (kg/m^2)						*p*-trend‡
	<18.5	18.5–<22.5	22.5–<25	25–<27.5	27.5–<30	≥30	
Baseline BMI							
Men§							
HR*		1.0	1.12	1.51	1.74	1.87	<0.0005
95% CI*		Referent	0.73, 1.72	1.01, 2.26	1.15, 2.63	1.24, 2.82	
No. of cases	0	28	88	169	127	152	
Women							
HR	3.65	1.0	1.66	2.44	2.27	2.67	0.002
95% CI	1.23, 10.9	Referent	0.92, 2.98	1.39, 4.26	1.23, 4.20	1.53, 4.66	
No. of cases	4	17	33	46	27	64	
BMI at age 50 years							
Men							
HR	1.24	1.0	1.12	1.49	1.37	1.90	<0.0005
95% CI	0.30, 5.13	Referent	0.78, 1.60	1.06, 2.11	0.94, 2.01	1.31, 2.78	
No. of cases	2	40	111	195	83	107	
Women							
HR	0.49	1.0	1.57	2.02	2.00	2.12	0.001
95% CI	0.07, 3.54	Referent	1.03, 2.40	1.30, 3.14	1.13, 3.53	1.27, 3.53	
No. of cases	1	37	53	46	19	33	
BMI at age 35 years							
Men							
HR	0.40	1.0	1.08	1.36	1.61	1.65	<0.0005
95% CI	0.10, 1.63	Referent	0.85, 1.39	1.07, 1.74	1.19, 2.20	1.16, 2.33	
No. of cases	2	108	150	166	68	49	
Women							
HR	0.61	1.0	1.27	1.46	1.26	1.44	0.06
95% CI	0.22, 1.67	Referent	0.90, 1.80	0.92, 2.31	0.58, 2.76	0.71, 2.93	
No. of cases	4	87	52	24	7	9	
BMI at age 18 years							
Men							
HR	0.83	1.0	0.87	1.28	1.55	1.29	0.02
95% CI	0.63, 1.10	Referent	0.69, 1.09	0.98, 1.67	0.99, 2.42	0.72, 2.31	
No. of cases	59	288	98	67	21	12	
Women							
HR	1.20	1.0	0.89	0.87	2.31	0.78	0.81
95% CI	0.81, 1.78	Referent	0.56, 1.43	0.40, 1.87	1.01, 5.28	0.19, 3.20	
No. of cases	33	105	21	7	6	2	

* BMI, body mass index; HR, hazard ratio; CI, confidence interval.

† Subcohort analysis. Pearson's correlations for BMI at different ages: 18 and 35 years, 0.65; 18 and 50 years, 0.47; 18 years and baseline, 0.34; 35 and 50 years, 0.75; 35 years and baseline, 0.56; 50 years and baseline, 0.78. Participants were 51–72 years of age at baseline. Statistical interactions were observed between BMI at age 18 years and baseline (modeled by continuous variable cross-products; likelihood ratio test *p* values: 0.06 for men, 0.65 for women, <0.05 for men and women combined.

‡ Linear trend of category medians.

§ All analyses were adjusted for age, smoking status and dose, physical activity, protein intake, history of diabetes, and history of hypertension.

TABLE 4. Relative risk of renal cell cancer according to weight change at three consecutive age intervals, United States, 1995–1996 through 2003*

	Weight change (kg) over age interval					*p*-trend†
	Lose ≥4	Stable (<4)	Gain 4–<10	Gain 10–<20	Gain ≥20	
Weight change at age 18–35 years						
Adjusted for BMI at age 18 years‡						
Men						
HR§	0.87	1.0	1.29	1.21	1.71	0.02
95% CI§	0.48, 1.58	Referent	0.98, 1.69	0.90, 1.62	1.21, 2.41	
No. of cases	16	71	237	160	77	
Women						
HR	1.49	1.0	1.41	2.23	1.49	0.01
95% CI	0.78, 2.87	Referent	0.95, 2.11	1.40, 3.55	0.61, 3.60	
No. of cases	15	40	70	41	6	
Adjusted for BMI at age 18 years and baseline BMI¶						
Men						
HR	0.85	1.0	1.21	1.07	1.47	0.19
95% CI	0.46, 1.56	Referent	0.46, 1.56	0.79, 1.46	1.02, 2.12	
Women						
HR	1.55	1.0	1.21	1.68	0.99	0.24
95% CI	0.80, 2.99	Referent	0.79, 1.84	1.01, 2.80	0.37, 2.64	
Weight change at age 35–50 years						
Adjusted for BMI at age 35 years						
Men						
HR	1.11	1.0	1.13	1.21	1.80	0.004
95% CI	0.78, 1.56	Referent	0.92, 1.39	0.93, 1.58	1.23, 2.63	
No. of cases	45	169	214	95	35	
Women						
HR	0.91	1.0	1.17	1.47	1.85	0.02
95% CI	0.42, 1.97	Referent	0.80, 1.70	0.94, 2.28	1.04, 3.27	
No. of cases	8	50	69	39	19	
Adjusted for BMI at age 35 years and baseline BMI						
Men						
HR	1.17	1.0	1.07	1.11	1.81	<0.05
95% CI	0.82, 1.66	Referent	0.86, 1.36	0.83, 1.50	1.21, 2.71	
Women						
HR	0.95	1.0	0.97	1.20	1.41	0.25
95% CI	0.44, 2.07	Referent	0.64, 1.45	0.73, 1.97	0.73, 2.72	
Weight change at age 50 years to baseline						
Adjusted for BMI at age 50 years						
Men						
HR	0.91	1.0	1.16	1.07	0.98	0.77
95% CI	0.68, 1.23	Referent	0.94, 1.42	0.81, 1.41	0.59, 1.62	
No. of cases	63	243	158	70	17	
Women						
HR	1.45	1.0	1.12	1.13	1.26	0.49
95% CI	0.86, 2.45	Referent	0.77, 1.63	0.73, 1.75	0.70, 2.26	
No. of cases	21	62	55	35	15	

* Subcohort analysis. Pearson's correlations for weight change over the three age intervals: 18–35 years and 35–50 years, −0.03; 18–35 years and 50 years to baseline, 0.31; 35–50 years and baseline body mass index (BMI), 0.47.

† Linear trend of category medians.

‡ Adjusted for BMI at the beginning of the age interval (ages 18, 35, or 50 years, as indicated), age, height at age 18 years, smoking status and dose, protein intake, physical activity, history of diabetes, and history of hypertension.

§ HR, hazard ratio; CI, confidence interval.

¶ In addition to the covariates described above, risks were also adjusted for BMI at study baseline, when participants were aged 51–72 years.

TABLE 5. Stratified analyses: relative risk of renal cell cancer in relation to weight change, age 18 years to baseline, in men and women combined, United States, 1995–1996 through 2003*

	Weight change (kg), age 18 years to baseline				
	Lose ≥4	Stable (lose ≥4–gain <10)	Gain 10–<20	Gain 20–<30	Gain ≥30
According to BMI at age 18 years†					
Combined men and women					
BMI, 18–<22.5					
HR‡	1.44	1.0	1.46	1.68	2.02
95% CI‡	0.52, 3.97	Referent	1.08, 1.97	1.24, 2.28	1.47, 2.78
No. of cases	4	61	151	143	116
BMI, 18–≥22.5					
HR	1.78	1.63	1.37	1.53	2.45
95% CI	1.09, 2.90	1.16, 2.29	0.94, 1.99	1.01, 2.31	1.63, 3.69
No. of cases	22	76	52	38	41
According to hypertension status§					
Not hypertensive					
HR	1.29	1.0	1.35	1.62	2.21
95% CI	0.68, 2.42	Referent	0.96, 1.89	1.13, 2.33	1.48, 3.29
No. of cases	13	59	87	65	45
Hypertensive					
HR	2.29	1.94	2.11	2.50	3.17
95% CI	1.22, 4.31	1.35, 2.77	1.52, 2.92	1.80, 3.46	2.27, 4.42
No. of cases	13	65	107	111	108

* Subcohort analysis. Adjusted for age, height, and body mass index (BMI, kg/m^2) at age 18 years; smoking status and dose; physical activity; protein intake; history of diabetes; history of hypertension; and sex.

† Linear interaction of BMI at age 18 years and weight change (modeled by continuous variable cross-products), combined men and women, $p = 0.01$.

‡ HR, hazard ratio; CI, confidence interval.

§ Linear interaction of weight change and hypertension, combined men and women, $p = 0.45$.

We conducted further analyses by combining data for men and women to achieve greater statistical power. Associations between adulthood weight gain (18 years of age to baseline) and renal cell cancer risk differed according to body mass at age 18 years (p-interaction = 0.01) (table 5). Renal cell cancer risk increased consistently with weight gain during adulthood for persons with a low BMI (<22.5 kg/m^2) at age 18 years: The risk doubled (RR = 2.02, 95 percent CI: 1.47, 2.78) for those who had gained ≥30 kg since age 18 years compared with those who maintained a stable weight. In contrast, weight gain conferred no increase in risk for those with a high BMI (≥22.5 kg/m^2) at age 18 years, except when the gain was large (RR = 2.45, 95 percent CI: 1.63, 3.69 for a weight gain of ≥30 kg compared with those with stable weight and a BMI of <22.5 kg/m^2). Adulthood weight gain predicted renal cell cancer regardless of hypertension history (p-interaction = 0.45), with risks particularly elevated in groups with both risk factors (table 5). Risk more than tripled (RR = 3.17, 95 percent CI: 2.27, 4.42) for hypertensives who gained ≥30 kg compared with those who reported neither weight gain nor hypertension. Stratification by other known risk factors for renal cell cancer, including smoking and diabetes, yielded comparable results for the association with baseline BMI across the strata (data not shown).

Height at 18 years of age was associated with an increased renal cell cancer risk for both men and women, with similar strengths of association (table 6). After adjusting for height, waist-to-hip ratio was associated with renal cell cancer in women (quintile 5: RR = 1.77, 95 percent CI: 0.93, 3.36; p-trend 0.04) but not in men.

DISCUSSION

Recent body mass was strongly, positively related to risk of renal cell cancer in this large prospective study. Importantly, risk was elevated for those who were merely overweight, a category that includes a large proportion of Americans. Compared with BMI at younger ages, body mass at older age was more strongly related to subsequent renal cell cancer risk. Weight gain between young adulthood and midlife was strongly associated with increased renal cell cancer risk, with some suggestion that the relation was independent of the effect of BMI per se, whereas weight gain after midlife appeared to be unrelated to risk. We observed

TABLE 6. Relative risk of renal cell cancer according to quintiles of anthropometry measures, United States, 1995–1996 through 2003

	Quintile					*p*-trend
	1	2	3	4	5	
Waist-to-hip ratio*						
Men						
HR†	1.0	1.01	0.94	0.91	1.11	0.69
95% CI†	Referent	0.74, 1.39	0.69, 1.30	0.66, 1.23	0.80, 1.52	
No. of cases	75	84	77	88	81	
Women						
HR	1.0	1.23	1.27	1.76	1.77	0.04
95% CI	Referent	0.61, 2.45	0.65, 2.52	0.93, 3.33	0.93, 3.36	
No. of cases	14	19	21	32	34	
Height at age 18 years‡						
Men						
HR	1.0	1.09	1.10	1.13	1.30	0.04
95% CI	Referent	0.81, 1.46	0.88, 1.38	0.84, 1.54	1.02, 1.68	
No. of cases	153	65	168	60	107	
Women						
HR	1.0	1.17	1.21	1.74	1.52	0.02
95% CI	Referent	0.75, 1.82	0.72, 2.06	1.14, 2.67	0.90, 2.57	
No. of cases	34	46	25	60	27	

* Subcohort analysis. Adjusted for age, height at age 18 years, smoking status and dose, physical activity, protein intake, history of diabetes, and history of hypertension.

† HR, hazard ratio; CI, confidence interval.

‡ Adjusted for age, baseline body mass index, smoking, physical activity, protein intake, history of diabetes, and history of hypertension.

a positive association between waist-to-hip ratio and renal cell cancer in women and between height at age 18 years and renal cell cancer in both men and women.

The positive associations we observed between recent body mass and renal cell cancer confirm findings of several other studies of men (5, 6, 8, 11, 12, 17, 20–26) and women (5, 6, 8–10, 12, 13, 16, 17, 20–24, 26–29). In the current study, the relation between BMI and renal cell cancer was stronger in mid- to older adulthood than at a younger age for both men and women, in agreement with limited previous reports (12, 13, 15). However, other studies have either reported the influence of BMI on renal cell cancer risk at young versus older age to differ by sex (5, 6) (with conflicting results) or not found a particular influence of excess weight in young adulthood (7–11, 14).

BMI at age 18 years modified the relation between adulthood weight gain and renal cell cancer, as indicated by statistically significant interactions and stratified analysis. Among participants who were lean at age 18 years, renal cell cancer risk was low if stable weight was maintained but increased markedly with adulthood weight gain. However, for those who were heavier at age 18 years (BMI $\geq$22.5 kg/m^2), risk was elevated regardless of subsequent weight gain. These results suggest that, although BMI at 18 years of age was only weakly associated with renal cell cancer, body mass in young adulthood is important nevertheless. The interactions we observed may be due to chance and need to be confirmed by others. If valid, they suggest complexity in the relation between weight history and renal cell cancer not previously reported to our knowledge.

We also observed strong associations between weight gain across younger age intervals and renal cell cancer risk, again indicating the influence of weight earlier in life. Regarding men, limited evidence suggested that high weight gain per se during this age period was related to renal cell cancer risk, independent of the influence of weight gain on attained BMI.

Relatively little information is available on associations between weight gain and renal cell cancer risk (11, 12, 15, 16); our results concur with the majority, reporting positive associations (11, 12, 16). A novel contribution is the suggestion that weight gain through midlife, but not later years, is related to renal cell cancer risk. The current study also supports recently reported evidence that waist-to-hip ratio, a measure of abdominal adiposity, is related to renal cell cancer risk in women (13, 15–17). Fewer studies have considered the association between waist-to-hip ratio in men, and it does not appear to be as strong (15, 17). Although height was positively associated with renal cell cancer in this study, we located only a single concurring study (23) and another that was equivocal (26), whereas the majority reported null associations (7–9, 12, 15, 17).

Excess BMI is considered to damage the kidney by a number of mechanisms, including oxidative stress (30), hypertension-induced injury to the renal tubules (31, 32), renal atherosclerosis (33), and altered circulating concentrations of estrogen and other hormones (34). Weight gain is associated with unfavorable changes in cardiovascular risk factors, which overlap with these potential mechanisms, including high density lipoprotein and total cholesterol, blood pressure, triglycerides, and glucose metabolism (35). Among men, weight gain has been reported to be a stronger determinant than BMI of clustering of these metabolic factors (36). Nutrition influences hormones, height, and weight in children and adolescents (37); hormones affecting growth in adolescence may also have a role in cancer risk (38).

Strengths of the study include the prospective design, large sample size, and availability of weight at four different ages and important covariates, albeit not detailed for hypertension or diabetes. We took advantage of these strengths to evaluate body mass and weight change associations in detail. Limitations include availability of important data for only the subcohort (approximately 60 percent of the full cohort), including height and weight at a younger age, waist and hip size, and hypertension status, resulting in reduced statistical power in analyses utilizing these variables, and lack of detailed information on hypertension, which may result in residual confounding. We do not consider these results to be substantially biased by use of self-reported weight. Information on validity of self-reported past weight suggests that recalled and measured weights are quite highly correlated, even for weight in young adulthood (39–41). Although error in recall of body mass at distantly recalled age could explain why associations were weaker at young age and stronger at recent age, other unpublished results in this study population indicate that body mass at age 18 years can strongly predict risk, unlikely if the measure was substantially misclassified.

This study is among the largest to date examining risk of incident renal cell cancer, and it is one of the few to focus on body mass and weight change at younger ages. It confirms previously reported relations of recent body mass with renal cell cancer. The results add support to the limited evidence that body mass associations with renal cell cancer are stronger for BMI at recent age than in young adulthood, and that weight gain, waist-to-hip ratio in women, and height are positively related to renal cell cancer. To our knowledge, we present the novel findings, requiring confirmation, that weight gain between young and middle adulthood is particularly related to renal cell cancer and that body mass in young adulthood modifies the relation between subsequent weight gain and renal cell cancer risk.

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