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Body size and risk of renal cell carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC)

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Abstract

Previous studies suggest that obesity is related to increased risk of renal cell carcinoma (RCC); however, only a few studies report on measures of central vs. peripheral adiposity. We examined the association between anthropometric measures, including waist and hip circumference and RCC risk among 348,550 men and women free of cancer at baseline from 8 countries of the European Prospective Investigation into Cancer and Nutrition (EPIC). During 6.0 years of follow-up we identified 287 incident cases of RCC. Relative risks were calculated using Cox regression, stratified by age and study center and adjusted for smoking status, education, alcohol consumption, physical activity, menopausal status, and hormone replacement therapy use. Among women, an increased risk of RCC was conferred by body weight (relative risk [RR] in highest vs. lowest quintile = 2.13; 95% confidence interval [CI] = 1.16-3.90; p-trend = 0.003), body mass index (BMI) (RR = 2.25; 95% CI = 1.14-4.44; p-trend = 0.009), and waist (RR = 1.67; 95% CI = 0.94-2.98; p-trend = 0.003) and hip circumference (RR = 2.30; 95% CI = 1.22-4.34; p-trend = 0.01); however, waist and hip circumference were no longer significant after controlling for body weight. Among men, hip circumference (RR = 0.44; 95% CI = 0.20-0.98; p-trend = 0.03) was related significantly to decreased RCC risk only after accounting for body weight. Height was not related significantly to RCC risk. Our findings suggest that obesity is related to increased risk of RCC irrespective of fat distribution among women, whereas low hip circumference is related to increased RCC risk among men. Our data give further credence to public health efforts aiming to reduce the prevalence of obesity to prevent RCC, in addition to other chronic diseases.

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The incidence of kidney cancer is increasing worldwide.[1] In Europe (including the Eastern European countries), there are about 81,000 new cases of kidney cancer per year, accounting for 2.9% of all cancers, and about 2.3% of all cancer deaths.[2] Renal cell carcinoma (RCC), which is the major type (80-90%) of kidney cancers, is a challenging diagnosis because it remains clinically occult for most of its course. Thus, 25-60% of patients with RCC are asymptomatic and the diagnosis is made incidentally from a radiologic study obtained for other reasons.[3][4] The classical triad of flank pain, hematuria, and flank mass is uncommon (10%) and indicates advanced disease.[5] At time of diagnosis approximately 25-30% of patients have metastatic disease, and the survival rate at advanced disease stage is poor.[5][6] Therefore, primary prevention of RCC is of major importance.

Recent data suggest that the increasing prevalence of obesity may at least partly be responsible for the rising rates of RCC.[7] The relationship between body weight and risk of RCC has been examined in studies based on either a population[8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23] or hospital based[24][25][26][27][28] case-control approach, and in prospective studies.[29][30][31][32][33][34][35][36][37][38][39] Most of these studies, however, used self-reported body weight. Although these data are quite accurate, obese subjects are more likely to under-report whereas underweight subjects are more likely to over-report their body weight.[40] Earlier reviews suggested that the association between body weight and risk of RCC may be stronger in women than in men,[41][42] although a recent meta-analysis found the relationship equally strong in both genders.[43] Differences in body fat distribution between men and women might be among the factors responsible for the differences observed in some studies. Waist and hip circumference measurements are established markers of body fat distribution in clinical and epidemiological settings[44][45] and it has been suggested that waist circumference, as a marker of central adiposity, may be more closely related to disease incidence than body weight as a marker of obesity per se;[45][46] nevertheless, we are aware of only 2 reports on the association of waist and hip circumference with risk of RCC, which have examined this relationship in the Iowa Women's Health Study.[35][36] Similarly, there are only limited data on height as a predictor of RCC risk. Three previous studies found no such association,[17][18][37] whereas 5 other studies found weak positive associations.[20][21][38][39][47]

The aim of our study was to examine the association between anthropometric measures, including waist and hip circumference, and risk of RCC in participants of the European Prospective Investigation into Cancer and Nutrition (EPIC), a large European-wide cohort study. Particularly, we examined whether body fat distribution is related to risk of RCC.

Material and methods

Study population

The European Prospective Investigation into Cancer and Nutrition (EPIC) is an ongoing multicenter prospective cohort study designed primarily to investigate the relationship between nutrition and cancer. The EPIC study consists of sub cohorts recruited in 23 administrative centers in 10 European countries, including Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. The 519,978 eligible male and female participants were between 25-70 years of age at time of enrollment (1992-2000) and recruited from the general population residing in a given geographic area (i.e., town or province). Exceptions were the French cohort (based on female members of a health insurance for school employees), the Utrecht cohort in the

Netherlands (based on women attending breast cancer screening), the Ragusa cohort in Italy (based on blood donors and their spouses) and the Oxford cohort in the United Kingdom (based largely on vegetarian volunteers and healthy eaters). Eligible subjects were invited to participate in the study, and those who accepted gave informed consent and completed questionnaires on their diet, lifestyle and medical history. Subjects were then invited to a center to provide a blood sample and to have anthropometric measurements taken. The methods have been reported in full by Riboli et al.[48][49]

Our present study is based on 495,416 participants without prevalent cancer at any site at baseline, based on the self-reported lifestyle questionnaire or based on information from the cancer registries. We excluded the French cohorts (n = 69,023) because they did not have information about incident kidney cancer status at the time of this analysis. Further, we excluded subjects without measured body height or weight, thus excluding the cohorts from Norway (n = 35,956) and an additional 8,063 participants. We further excluded subjects from the Umeå cohort (n = 24,651) because they did not have information on leisure time physical activity, and an additional 9,134 participants who had not filled out the dietary or nondietary questionnaires, or were in the top or bottom 1% of the ratio of energy intake to estimated energy requirement calculated from body weight, height and age[50] to reduce the impact on the analysis of implausible extreme values; leaving 348,589 participants. For the health-conscious group based in Oxford (UK), linear regression models were used to predict gender- and age-specific values from subjects with measured and self-reported body measures as described previously.[51][52]

Assessment of endpoints

Incident kidney cancer cases were identified by population cancer registries (Denmark, Italy, the Netherlands, Spain, Sweden, the United Kingdom) or by active follow-up (Germany, Greece), depending on the follow-up system in each of the participating centers. Active follow-up used a combination of methods, including health insurance records, cancer and pathology registries, and direct contact of participants or next-of-kin. Mortality data were also obtained from cancer or mortality registries at the regional or national level. Participants were followed from study entry until first kidney cancer diagnosis, death, emigration, or end of follow-up period. Mortality data were coded following the rules of the 10th revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD-10), and cancer incidence data following the 2nd revision of the International Classification of Diseases for Oncology (ICD-O-2). Data were coded according to ICD-10/ICD-O-2 as malignant neoplasm of the kidney except pelvis (C64); and malignant neoplasm of the renal pelvis (C65). By the end of May 2004, 365 cases of kidney cancer had been reported among the 495,416 participants in the common database at the IARC. After applying the aforementioned exclusion criteria, the dataset contained 326 cases of incident kidney cancer. We further excluded 39 subjects with renal pelvis cancer. Our final dataset for analysis included 348,550 participants with 287 cases of incident RCC.

Assessment of anthropometric data and lifestyle factors

Weight and height were measured to the nearest 0.1 kg and 0.1 or 0.5 cm, respectively, with subjects wearing no shoes, in participating centers.[51] Body mass index (BMI) was calculated as weight divided by height squared (kg/m2). Waist circumference was measured either at the narrowest torso circumference (Italy; Utrecht, the Netherlands; Denmark) or at the midpoint between the lower ribs and iliac crest (Bilthoven, the Netherlands; Potsdam, Germany; Malmö, Sweden; Oxford, UK, general population). In Spain, Greece, and Heidelberg

(Germany), a combination of methods was used, although the majority of participants were measured at the narrowest circumference. Hip circumference was measured at the widest circumference (Italy; Spain; Bilthoven, the Netherlands; Greece; Malmö, Sweden) or over the buttocks (the United Kingdom; Utrecht, the Netherlands; Germany; Denmark). Results of the present analyses for waist and hip circumference were similar for the different assessment methods. In our dataset, waist and hip circumference measurements were missing in 3,858 and 6,378 participants, respectively. These participants were excluded for analyses on these variables. For the present study, body weight and waist and hip circumference were corrected to reduce heterogeneity due to protocol differences in clothing worn during measurement, as described in detail elsewhere.[51]

Recreational and household activity was computed as average metabolic equivalent-hours (MET-hr), based on the types and durations of activities separately reported for summer and winter on the baseline questionnaires. The reported activities included walking, cycling, gardening, sports and exercise, housework, do-it-yourself activities, stair-climbing and vigorous recreational activity. Each type of activity was assigned a specific MET-value according to the Compendium of Physical Activities by Ainsworth et al.[53] Occupational activity was coded as sedentary occupation, standing occupation, manual work, heavy manual work, unemployed, or missing, as reported on the questionnaire. To create a variable that encompasses total physical activity subjects were cross-classified based on gender-specific quartiles of recreational and household activity and on categories of occupational work, and coded as inactive, moderately inactive, moderately active, active and missing.

Information on sociodemographic and lifestyle characteristics and medical history was obtained from standardized questionnaires at study entry.[48] Women were classified according to menopausal status at enrollment based on an algorithm that accounts for complete and combined information on menstrual status/history, type of menopause (natural, bi-/unilateral oophorectomy, hysterectomy), use of oral contraceptives and menopausal hormones.[54]

Statistical analyses

We analyzed the association between anthropometric variables and risk of RCC separately for men and women by calculating relative risks as incident rate ratios using Cox proportional hazard models. Age was used as the underlying time variable in the counting process with entry and exit time defined as the subject's age at recruitment and age at RCC diagnosis or censoring, respectively. Subjects were categorized separately into quintiles based on the anthropometric variables over the entire male or female cohort, respectively. We also ran additional analyses by categorizing participants into pre-defined established categories for BMI (<25, 25 to <30 and 30 kg/m2) and waist circumference (<94, 94 to <102 and 102 cm in men; and <80, 80 to <88 and 88 in women).[44] Models were stratified by age at recruitment and by study center to be less sensitive against violations of the proportional hazards assumption. We further adjusted the analysis for smoking status (never, past, current or unknown), education (no school degree or primary school, technical or professional school, secondary school, university degree or unknown), alcohol consumption (g/d, continuously), and physical activity (inactive, moderately inactive, moderately active, active, missing). In women, we also adjusted for menopausal status (premenopausal, perimenopausal, naturally postmenopausal, surgically postmenopausal or missing) and current hormone replacement therapy (no, yes or unknown). Analyses on weight, waist and hip circumference, and waist-hip ratio were also adjusted for body height. In additional models we also adjusted corresponding

models for body weight to examine the association of fat distribution patterns with risk of RCC independent of body weight. We also ran additional models that adjusted for total energy intake; however, because the overall results did not substantially change we decided not to include energy intake in our analysis. To test for linear trend across categories we used the median anthropometric variable within quintiles as a continuous variable. In separate analyses we included the body size measures as continuous variables into the models to estimate the relative risk of RCC per increase in anthropometric variables. We checked the proportional hazard assumption by adding an interaction term of the main exposure variable with time to each model. The interaction term was non-significant at the 5%-level in any of these models, indicating that there is no evidence of an increasing or decreasing trend over time in the hazard ratio. Differences for the associations of body size with risk of RCC between men and women were assessed by 2-test using the heterogeneity statistics based on the inverse variance method.[55]

All p-values presented are 2-tailed and p-values <0.05 were considered statistically significant. Analyses were carried out using SAS 9.1 (SAS Institute, Cary, NC) and STATA 8.2 (STATA Corporation, College Station, TX).

Results

Overall, 348,550 participants were followed for an average 6.0 ± 1.6 years, for a total of 2,089,813 person-years (Table I). During follow-up, 287 incident cases (132 female) of RCC were identified within this cohort. Mean age at inclusion was 51.6 years; 62.8% of participants were female.

Table I. Cohort Characteristics1

Country	Cohort size (*n*)	Age (mean, years)	Follow-up (mean, years)	Person-years	% Women	RCC cases (*n*)
Italy	44,221	50.5	5.9	261,460	68.6	43
Spain	39,609	49.2	6.7	265,020	62.2	24
United Kingdom	73,553	49.3	5.4	396,150	69.3	38
Netherlands	37,378	48.9	6.2	232,079	73.5	29
Greece	25,450	53.1	3.7	94,315	58.6	6
Germany	49,053	50.6	5.8	286,429	56.5	65
Sweden	24,268	58.0	7.6	185,218	57.7	32
Denmark	55,018	56.7	6.7	369,144	52.2	50
Total	348,550	51.6	6.0	2,089,813	62.8	287

1 The European Prospective Investigation into cancer and Nutrition (EPIC).

Tables II and III show the characteristics of the EPIC participants by BMI quintiles for men and women, respectively. Participants in the higher BMI categories were older and reported more frequently a history of hypertension and diabetes. Alcohol consumption was positively related to BMI in men but inversely related in women. Both men and women in the higher BMI categories were less likely to be current smokers and had a lower education level. Among postmenopausal women, the use of hormone replacement therapy was more common among leaner women.

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Table II. Characteristics of Male Study Participants in the EPIC by BMI1

	Quintile of BMI (kg/m²)				
	1	2	3	4	5
BMI, kg/m²					
Range	<23.6	23.6-25.3	25.4-27.0	27.1-29.3	≥29.4
Mean	22.0	24.5	26.3	28.1	32.0
n	25,943	25,953	25,963	25,943	25,943
Age, years	50.4	52.7	53.2	53.8	54.0
Hypertension, %	10.8	15.4	18.9	23.2	32.1
Diabetes, %	2.3	2.6	3.0	4.1	6.4
Alcohol, g/d	20.0	21.2	22.2	23.3	24.7
Weight, kg	68.2	75.5	80.1	85.1	95.6
Height, cm	175.9	175.2	174.5	173.8	172.7
Waist circumference, cm	84.0	89.9	94.0	98.5	107.4
Hip circumference, cm	94.4	98.0	100.4	103.1	108.8
Waist-hip-ratio	0.89	0.92	0.94	0.96	0.99
Smoking status[2], %					
Never	33.4	32.1	30.3	27.9	26.5
Past	29.9	36.0	39.1	41.1	42.0
Current	34.8	30.4	29.0	29.5	30.0
Education[2], %					
No school degree or primary school	21.7	24.8	28.5	35.4	42.6
Technical or professional school	24.4	25.2	25.7	25.2	23.7
Secondary school	15.6	16.0	15.2	13.9	12.9
University degree	34.6	30.8	27.5	22.7	17.8
Physical activity[2], %					
Inactive	19.7	20.4	20.1	20.0	19.9
Moderately inactive	28.8	28.1	28.5	28.9	29.1
Moderately active	35.7	35.0	35.6	35.2	36.2

1 Numbers are means. All values except age, BMI and number of subjects are age-standardized.

2 Numbers do not add up to 100% due to missing values.

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Table III. Characteristics of Female Study Participants in the EPIC by BMI1

	Quintile of Body Mass Index (kg/m²)				
	1	2	3	4	5
BMI, kg/m²					
Range	<21.8	21.8-23.7	23.8-25.9	26.0-28.9	≥29.0
Mean	20.4	22.8	24.9	27.4	32.9
n	43,760	43,760	43,764	43,760	43,761
Age, years	46.0	49.5	51.7	53.4	54.1
Hypertension, %	9.9	12.9	16.4	21.2	31.9
Diabetes, %	1.0	1.1	1.6	2.7	5.3
Alcohol, g/d	9.6	9.4	8.7	7.6	5.8
Weight, kg	54.7	60.8	65.3	71.0	83.6
Height, cm	163.7	163.0	162.0	160.9	159.3
Waist circumference, cm	69.8	74.6	78.9	84.6	95.7
Hip circumference, cm	92.4	96.8	100.2	104.5	113.9
Waist-hip-ratio	0.76	0.77	0.79	0.81	0.84
Smoking status[2], %					
Never	49.9	51.0	52.6	56.5	62.6
Past	23.8	25.7	24.8	22.6	19.6
Current	25.9	22.7	22.0	20.3	16.9
Education[2], %					
No school degree or primary school	16.4	21.1	28.3	37.6	48.3
Technical or professional school	29.3	29.3	28.0	25.6	22.0
Secondary school	20.6	20.3	19.3	17.5	14.2
University degree	28.5	24.1	19.7	14.8	10.4
Menopausal status[2], %					
Premenopausal	35.2	35.1	34.9	34.8	35.0
Perimenopausal	11.9	12.1	11.8	11.8	11.4
Postmenopausal	46.3	45.7	45.7	44.9	44.5
Surgical postmenopausal	2.5	2.8	3.2	3.9	4.7
HRT use among postmenopausal women[2], %					
No	71.7	72.7	75.0	79.1	85.1
Yes	25.8	25.1	22.9	19.2	13.4
Physical activity[2], %					
Inactive	18.7	17.6	15.9	13.4	11.1
Moderately inactive	31.4	30.0	28.1	26.7	25.3
Moderately active	39.3	41.2	44.6	48.9	52.8

1 Numbers are means. All values except age, BMI and number of subjects are age-standardized.
2 Numbers do not add up to 100% due to missing values.

Tables IV and V show the relative risk of RCC by quintiles of anthropometric variables, in men and women, respectively. Height, weight, BMI and waist circumference were not significantly related to risk of RCC in men (Table IV). There was an inverse association between increasing hip circumference and RCC risk, which became stronger after adjusting for body weight, such that the relative risk in the highest vs. lowest quintile of hip circumference was 0.44 (95% CI = 0.20-0.98; p-trend = 0.03). Waist-hip ratio was also positively associated with RCC risk, although this was not significant at the 5% level. The relative risk in the highest vs. lowest quintile of waist-hip ratio was 1.86 (95% CI = 0.97-3.56; p-trend = 0.07) in the multivariable model after accounting for body weight.

Table IV. RR of Renal Cell Carcinoma Across Quintiles of Anthropometric measures in Men of the EPIC

Body measure	Quintile					*p*-trend
	1	2	3	4	5	
Height, cm	<168.0	168.0-172.4	172.5-176.1	176.2-180.4	≥180.5	
No. cases	32	29	27	36	31	
Crude RR (95% CI)[1]	1	0.92 (0.55-1.54)	0.89 (0.52-1.52)	1.27 (0.76-2.10)	1.30 (0.76-2.23)	0.19
MV adjusted RR (95% CI)[2]	1	0.93 (0.56-1.56)	0.91 (0.53-1.55)	1.29 (0.77-2.16)	1.33 (0.77-2.30)	0.17
Weight, kg	<71.0	71.0-76.9	77.0-82.6	82.7-89.9	≥90.0	
No. cases	27	25	37	28	38	
Crude RR (95% CI)[1]	1	0.93 (0.54-1.61)	1.32 (0.80-2.19)	1.01 (0.59-1.73)	1.36 (0.82-2.26)	0.20
MV adjusted RR (95% CI)[3]	1	0.91 (0.53-1.59)	1.29 (0.77-2.18)	0.98 (0.56-1.73)	1.28 (0.73-2.25)	0.35
BMI, kg/m^2	<23.6	23.6-25.3	25.4-27.0	27.1-29.3	≥29.4	
No. cases	29	35	23	28	40	
Crude RR (95% CI)[1]	1	1.05 (0.64-1.73)	0.65 (0.37-1.13)	0.79 (0.46-1.33)	1.12 (0.68-1.84)	0.77
MV adjusted RR (95% CI)[2]	1	1.07 (0.65-1.77)	0.67 (0.39-1.18)	0.84 (0.49-1.43)	1.22 (0.74-2.03)	0.51
Waist, cm	<86.3	86.3-91.9	92.0-96.9	97.0-102.9	≥103.0	
No. cases	23	31	30	30	41	
Crude RR (95% CI)[1]	1	1.11 (0.65-1.92)	0.94 (0.54-1.63)	0.96 (0.55-1.67)	1.24 (0.73-2.11)	0.48
MV adjusted RR (95% CI)[3]	1	1.13 (0.66-1.95)	0.96 (0.55-1.67)	0.96 (0.55-1.69)	1.27 (0.74-2.19)	0.45
MV + body weight adjusted RR (95% CI)[3]	1	1.14 (0.64-2.00)	0.96 (0.52-1.79)	0.97 (0.49-1.94)	1.28 (0.55-3.03)	0.67
Hip, cm	<95.5	95.5-98.9	99.0-101.9	102.0-105.9	≥106.0	
No. cases	37	32	23	26	34	
Crude RR (95% CI)[1]	1	0.77 (0.48-1.23)	0.61 (0.36-1.04)	0.67 (0.40-1.12)	0.89 (0.54-1.45)	0.59
MV adjusted RR (95% CI)[3]	1	0.72 (0.45-1.17)	0.56 (0.32-0.95)	0.60 (0.35-1.02)	0.77 (0.46-1.29)	0.33
MV + body weight adjusted RR (95% CI)[3]	1	0.63 (0.38-1.04)	0.44 (0.25-0.80)	0.43 (0.23-0.81)	0.44 (0.20-0.98)	0.03
WHR	<0.888	0.888-0.922	0.923-0.952	0.953-0.989	≥0.990	
No. cases	19	30	28	32	43	
Crude RR (95% CI)[1]	1	1.23 (0.69-2.20)	1.07 (0.59-1.92)	1.15 (0.65-2.06)	1.53 (0.88-2.67)	0.15
MV adjusted RR (95% CI)[3]	1	1.28 (0.72-2.28)	1.13 (0.62-2.04)	1.25 (0.70-2.24)	1.72 (0.97-3.02)	0.06
MV + body weight adjusted RR (95% CI)[3]	1	1.31 (0.73-2.35)	1.17 (0.64-2.16)	1.32 (0.71-2.44)	1.86 (0.97-3.56)	0.07

1 Crude model is derived from Cox regression using age as the underlying time variable, and stratified by center and age at recruitment.

2 Multivariable models for height and BMI are based on the crude model with additional adjustment for smoking status, education, alcohol consumption and physical activity.

3 Multivariable models for weight, waist, hip and WHR are based on the crude model with additional adjustment for age, smoking status, education, alcohol consumption, physical activity and body height. Test for linear trend across categories is based on the median anthropometric variable within quintiles as a continuous variable.

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Table V. RR of Renal Cell Carcinoma Across Quintiles of Anthropometric Measures in Women of the EPIC

Body measure	Quintile					*p*-trend
	1	2	3	4	5	
Height, cm	<156.0	156.0-159.9	160.0-163.4	163.5-167.6	≥167.7	
No. cases	25	30	29	30	18	
Crude RR (95% CI)[1]	1	1.22 (0.71-2.10)	1.09 (0.62-1.90)	1.22 (0.69-2.14)	0.93 (0.48-1.78)	0.90
MV adjusted RR (95% CI)[2]	1	1.24 (0.72-2.14)	1.13 (0.64-1.97)	1.29 (0.73-2.27)	1.02 (0.53-1.98)	0.85
Weight, kg	<57.4	57.4-62.6	62.7-67.9	68.0-75.5	≥75.6	
No. cases	18	21	21	30	42	
Crude RR (95% CI)[1]	1	1.07 (0.57-2.01)	1.01 (0.53-1.90)	1.36 (0.75-2.46)	1.97 (1.12-3.47)	0.003
MV adjusted RR (95% CI)[3]	1	1.11 (0.59-2.10)	1.07 (0.56-2.05)	1.46 (0.79-2.70)	2.13 (1.16-3.90)	0.003
BMI, kg/m^2	<21.8	21.8-23.7	23.8-25.9	26.0-29.0	≥29.1	
No. cases	12	22	24	37	37	
Crude RR (95% CI)[1]	1	1.48 (0.73-3.00)	1.36 (0.68-2.74)	1.99 (1.03-3.85)	2.26 (1.16-4.41)	0.006
MV adjusted RR (95% CI)[2]	1	1.48 (0.73-3.01)	1.39 (0.69-2.80)	1.99 (1.03-3.88)	2.25 (1.14-4.44)	0.009
Waist, cm	<71.0	71.0-75.9	76.0-81.9	82.0-89.9	≥90.0	
No. cases	19	14	19	35	45	
Crude RR (95% CI)[1]	1	0.67 (0.33-1.34)	0.78 (0.41-1.49)	1.21 (0.68-2.15)	1.73 (0.98-3.04)	0.002
MV adjusted RR (95% CI)[3]	1	0.67 (0.33-1.34)	0.78 (0.41-1.50)	1.19 (0.66-2.13)	1.67 (0.94-2.98)	0.003
MV + body weight adjusted RR (95% CI)[3]	1	0.65 (0.32-1.33)	0.75 (0.38-1.50)	1.11 (0.56-2.22)	1.50 (0.64-3.53)	0.11
Hip, cm	<94.0	94.0-98.0	98.1-102.8	102.9-107.9	≥108.0	
No. cases	15	26	23	31	37	
Crude RR (95% CI)[1]	1	1.72 (0.91-3.26)	1.32 (0.68-2.55)	1.75 (0.93-3.28)	2.24 (1.21-4.15)	0.01
MV adjusted RR (95% CI)[3]	1	1.76 (0.92-3.35)	1.38 (0.71-2.68)	1.81 (0.96-3.43)	2.30 (1.22-4.34)	0.01
MV + body weight adjusted RR (95% CI)[3]	1	1.64 (0.85-3.18)	1.22 (0.60-2.48)	1.50 (0.71-3.17)	1.65 (0.64-4.23)	0.43
WHR	<0.74	0.74-0.76	0.77-0.79	0.80-0.84	≥0.85	
No. cases	19	15	22	36	40	
Crude RR (95% CI)[1]	1	0.64 (0.32-1.27)	0.77 (0.41-1.45)	1.21 (0.68-2.14)	1.37 (0.77-2.43)	0.03
MV adjusted RR (95% CI)[3]	1	0.62 (0.32-1.24)	0.74 (0.39-1.38)	1.14 (0.64-2.02)	1.26 (0.71-2.25)	0.06
MV + body weight adjusted	1	0.60 (0.30-	0.68 (0.36-	0.98 (0.54-	1.01 (0.54-	0.33

1 Crude model is derived from Cox regression using age as the underlying time variable, and stratified by center and age at recruitment.

2 Multivariable models for height and BMI are based on the crude model with additional adjustment for smoking status, education, alcohol consumption, physical activity, menopausal status and HRT use.

3 Multivariable models for weight, waist, hip, and WHR are based on the crude model with additional adjustment for age, smoking status, education, alcohol consumption, physical activity, body height, menopausal status and HRT use. Test for linear trend across categories is based on the median anthropometric variable within quintiles as a continuous variable.

Among women, body weight and BMI were positively related to risk of RCC and women in the highest vs. the lowest quintile of body weight had a 2-fold increased risk after multivariable adjustment (relative risk [RR] = 2.13; 95% confidence interval [CI] = 1.16-3.90; p-trend = 0.003; Table V). The association with BMI was similar to that for body weight; the relative risk of women in the highest vs. lowest quintile of BMI was 2.25 (95% CI = 1.14-4.44; p-trend = 0.009). These associations were only slightly attenuated when the models were further adjusted for waist-hip ratio (RR comparing highest vs. lowest quintile for weight = 1.90; 95% CI = 1.00-3.63; p-trend = 0.02; RR for BMI = 1.99; 95% CI = 0.97-4.07; p-trend = 0.04). Waist and hip circumference were each significantly related to increased risk of RCC, but after adjustment for body weight these associations were attenuated and no longer significant at the 5% level. Height was not related to RCC risk in women.

We further divided participants into established categories for BMI and waist circumference (Figs. 1,2). In these analyses, obese women (BMI = 30 kg/m2) had a 1.68-fold increased risk (95% CI = 1.03-2.75) of RCC compared to non-overweight women (BMI = <25 kg/m2). The RR for women with a waist circumference 88 cm compared to women with a waist circumference <80 cm was 1.80 (95% CI = 1.18-2.75). In contrast, BMI and waist circumference were not associated with RCC risk in men (Figs. 1,2).

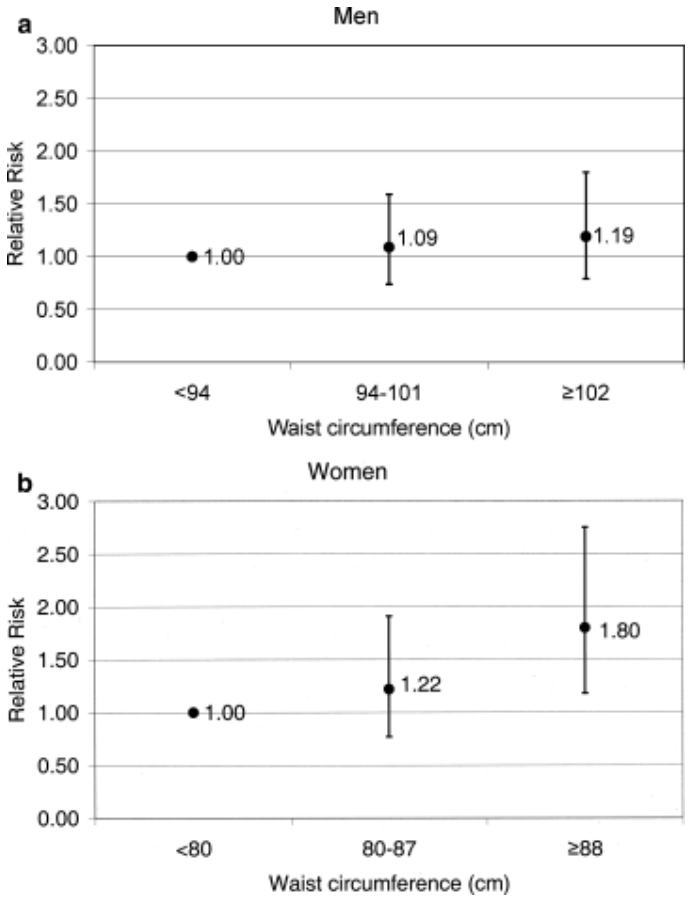

Figure 1. Multivariable adjusted relative risk of renal cell carcinoma across body mass index categories in men (a) and women (b) participating in the European Prospective Investigation into Cancer and Nutrition. Dots and numbers = RR; error bars = 95% CI. RR derived from Cox regression using age as the underlying time variable, stratified by center and age at recruitment, and additional adjustment for smoking status, education, alcohol consumption, and physical activity. In women additionally adjusted for menopausal status and HRT use.

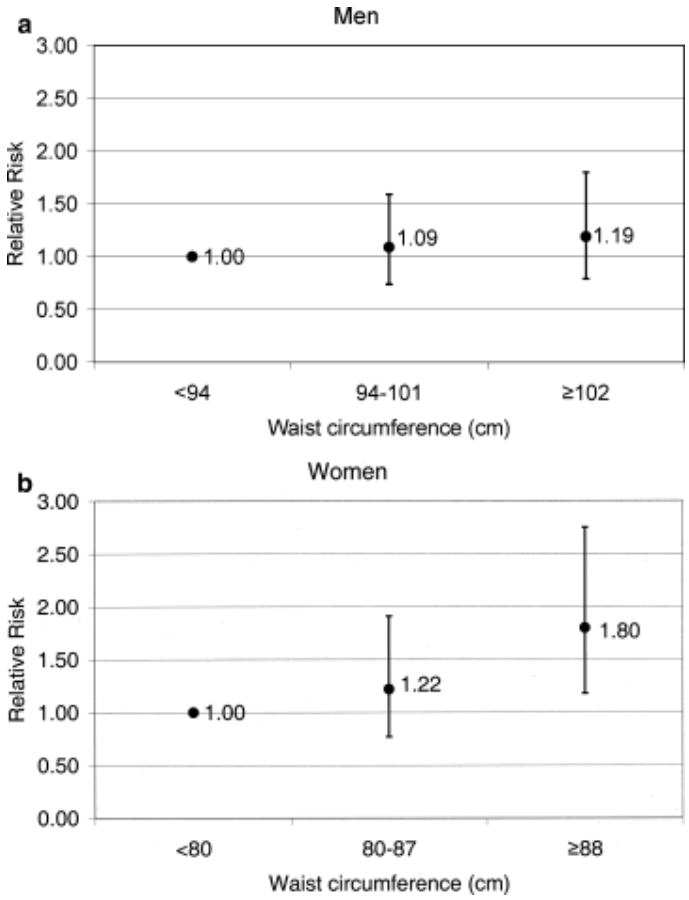

Figure 2. Multivariable adjusted relative risk of renal cell carcinoma across waist circumference categories men (a) and women (b) of the European Prospective Investigation into Cancer and Nutrition. Dots and numbers = RR; error bars = 95% CI. RR derived from Cox regression using age as the underlying time variable, stratified by center and age at recruitment, and additional adjustment for smoking status, education, alcohol consumption, physical activity, and body height. In women additionally adjusted for menopausal status and HRT use.

We also examined the relative risk of RCC in extreme categories of BMI by comparing subjects in the highest 10% of BMI (BMI = 31.2 kg/m2 in men and 31.8 kg/m2 in women, respectively) with those in the lowest 25% (BMI = <24.1 kg/m2 in men and 22.4 kg/m2 in women, respectively). In these analyses, the multivariable adjusted RR of RCC was 1.08 (95% CI = 0.56-2.06) for men and 2.63 (95% CI = 1.19-5.79) for women.

We further evaluated the association of body size with risk of RCC between men and women (Table VI). This analysis suggested differences between both genders, although most p-values for heterogeneity did not reach statistical significance. For example, 5 kg higher weight or 5 cm larger waist circumference were significantly related to 10 or 12% higher risk of RCC, respectively, in women but not in men (p for difference between men and women = 0.15 and 0.10, respectively).

Table VI. Multivariable Adjusted RR of Renal Cell Carcinoma per Increase in Anthropometric Variables in Men and Women of the EPIC1

	Men		Women		
	RR (95% CI)	*p*	RR (95% CI)	*p*	$p_{heterogencity}$
Height, per 5 cm	1.12 (0.99-1.27)	0.08	1.03 (0.89-1.19)	0.70	0.39
Weight, per 5 kg	1.02 (0.95-1.10)	0.55	1.10 (1.02-1.18)	0.009	0.15
BMI, per 1 kg/m^2	1.01 (0.97-1.06)	0.54	1.05 (1.01-1.09)	0.01	0.19
Waist, per 5 cm	1.02 (0.94-1.11)	0.66	1.12 (1.04-1.21)	0.005	0.10
Weight adjusted	0.98 (0.82-1.17)	0.81	1.09 (0.94-1.27)	0.24	0.37
Hip, per 5 cm	0.94 (0.82-1.07)	0.36	1.11 (1.01-1.21)	0.04	0.04
Weight adjusted	0.75 (0.60-0.93)	0.01	0.95 (0.77-1.17)	0.63	0.13
Waist-hip-ratio, per 0.1	1.26 (0.96-1.65)	0.09	1.29 (1.02-1.63)	0.03	0.90

1 Multivariable models are derived from Cox regression using age as the underlying time variable, stratified by center and age at recruitment, and additional adjustment for smoking status, education, alcohol consumption and physical activity. Multivariable models for weight, waist, hip and WHR are also adjusted for height. In women models are additionally adjusted for menopausal status and HRT use.

We did not detect significant differences in the association of anthropometric measures with risk of RCC when we stratified our analysis by geographic regions in Northern (Sweden, Denmark), Central (United Kingdom, Netherlands, Germany), and Southern (Italy, Spain, Greece) Europe, although sample size limited the interpretability of this analysis (data not shown).

When we repeated our analysis with exclusion of RCC cases occurring during the first 2 years of follow-up, leaving 107 cases among men and 83 cases among women, we found similar results compared to those presented in Tables IV and V. In the multivariable-adjusted analysis, the relative risk in the highest compared to lowest quintile for height was 1.44 (95% CI = 0.75-2.75; p-trend = 0.13) among men and 1.30 (95% CI = 0.56-3.05; p-trend = 0.68) among women, for weight was 1.58 (95% CI = 0.80-3.12; p-trend = 0.18) among men and 2.20 (95% CI = 1.00-4.84; p-trend = 0.008) among women, and for BMI 1.46 (95% CI = 0.79-2.68; p-trend = 0.18) among men and 2.17 (95% CI = 0.98-4.80; p-trend = 0.02) among women. Not controlling for body weight the relative risk in extreme quintiles for waist circumference was 1.29 (95% CI = 0.67-2.49; p-trend = 0.42) among men and 1.82 (95% CI = 0.89-3.73; p-trend = 0.003) among women, for hip circumference 0.96 (95% CI = 0.51-1.82; p-trend = 0.95) among men and 2.00 (95% CI = 0.94-4.24; p-trend = 0.009) among women, for waist-hip ratio 1.46 (95% CI = 0.74-2.87, p-trend = 0.23) among men and 1.28 (95% CI = 0.60-2.74; p-trend = 0.11) among women.

Discussion

In this large prospective cohort study of 348,550 Europeans significant associations between body size and risk of RCC were found. Among women, all measures of obesity, including BMI, body weight, waist and hip circumference were related to an increased risk of RCC. In contrast, among men, fat distribution pattern, specifically low hip circumference, was predictive of RCC.

Several previous studies have examined the association between body weight and risk of kidney

cancer;[8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24][25][26][27][28][29][30][31][32][33][34][35][36][37][38][39] however, we are aware of only 2 reports from the Iowa Women's Health Study that examined the relationship of waist and hip circumference with risk of RCC.[35][36]

The pathophysiology underlying the association between obesity and increased RCC risk is unclear although several mechanisms may be possible. Adiposity is related to increased levels of insulin and insulin-like growth factor 1 (IGF-1), which are known to have cancer promoting effects.[56][57][58][59] Obesity is also related to an increased risk of hypertension and diabetes, both of which are risk factors for RCC.[37][60][61] Finally, obesity may also increase risk of RCC through elevation of estrogen levels,[62] or through increased glomerular filtration rate and renal plasma flow.[63] The changes in physiological functions that accompany obesity depend to a certain extent on the regional adipose tissue distribution. In this context, intra-abdominal visceral obesity is related to elevated blood pressure and insulin levels, insulin resistance, and dyslipidemia, and several studies show that upper-body fat distribution is independently associated with a higher risk of developing diabetes and cardiovascular disease (reviewed by Pi-Sunyer).[64] The role of body fat distribution for RCC development is less clear. In the Iowa Women's Health Study,[35][36] the relative risk of kidney cancer in the highest compared to the lowest quintile of body weight was 3.55 (95% CI = 1.92-6.57) whereas for waist-hip ratio it was 3.37 (95% CI = 1.81-627), suggesting an equally strong association for both measurements.

We found measures of obesity, including weight, BMI, and waist and hip circumference to be related to RCC in women. The association between waist and hip circumference and risk were substantially attenuated after controlling for body weight, however, indicating that fat distribution does not predict RCC risk in women beyond adiposity in general. In line with these arguments, waist-hip ratio, as a measure of fat distribution, was only weakly related to RCC risk in women. In contrast, the association of body weight and BMI with risk of RCC was only modestly attenuated when waist-hip ratio was taken into account, suggesting that general adiposity is a more important determinant of risk, irrespective of body fat distribution in women. Among men, hip circumference was inversely related to RCC risk after accounting for body weight, suggesting that in men, the fat distribution pattern, and particularly hip circumference may be more predictive of RCC risk than obesity per se. This may reflect a substitution effect with more subcutaneous peripheral and less visceral abdominal fat; however, waist circumference itself was not significantly related to RCC risk in our analysis. In fact, several recent prospective studies suggest that large hip circumference may independently convey protection toward development of diabetes, cardiovascular disease, and early mortality.[65][66][67] The biological mechanisms are unknown, but may include a larger muscle mass in the gluteofemoral region, which may relate to increased insulin sensitivity and improved metabolic state,[68] or more fat depots in the lower body region (particularly of subcutaneous location), which may protect the liver from fatty acid overload.[69][70] Data on cancer endpoints in relation to hip circumference are scarce.[54][71] Finally, the combination of highly correlated measures may lead to imprecision and instability of the effect estimates; however, the CI in our analysis did not substantially change when we combined hip circumference with body weight.

Height has been related to several types of cancer, including colon, breast, pancreatic and prostate cancer.[54][72] Tallness may reflect exposure to insulin and insulin-like growth factor 1 (IGF-1) in pre-adulthood and may thereby relate to increased cancer risk.[56][57] It was estimated recently that 18% of total cancers are attributable to factors related to tallness.[72] There is only a limited

number of previous studies on height as a predictor of RCC risk. Three previous studies found no such association,[17][18][37] whereas 5 other studies found weak positive associations.[20][21][38][39][47] In our present study, height was not significantly related to increased risk of RCC. In summary, it seems fair to conclude that height is not related to a substantially increased risk of RCC.

Our study has several strengths and limitations. Among the strengths are the prospective design and the large sample size that included several European countries. Further, all body measures were assessed directly at baseline, in contrast to self-reported data used in the majority of previous studies. In contrast to several previous studies the present study distinguished between cancers of the renal parenchyma and the renal pelvis having different etiology and pathophysiology. Residual confounding by geographic differences is unlikely because we found similar results for Northern, Central and Southern Europe (data not shown). RCC is a rare disease compared to other types of cancer, like colorectal, prostate or breast cancer, which limits the number of cases and may thus limit the power to detect associations in our analysis. We found differences in the associations of body size measures and risk of RCC between men and women; however, the tests for heterogeneity between genders did not reach statistical significance. It is not clear whether these differences reflect true biological diversity between men and women or are due to random fluctuation. Several previous studies have found stronger results for the association between weight and risk of RCC in women compared to men.[15][16][17][18][27] In contrast, a meta-analysis suggested that the association between obesity and risk of RCC may be equally strong between genders and argued that the discrepancies may be due to the fact that women tend to be more obese than men, meaning that the highest BMI category for women usually consists of more obese individuals than the highest category for men, resulting in a higher observed RR.[43] However, our risk estimates did not substantially change when we excluded participants with a BMI <20 and >35 from our analysis (data not shown). Further, the gender differences persisted when BMI was used on a continuous scale. Despite exclusion of participants with reported cancers at baseline we cannot exclude the possibility that some subjects had underlying yet undiagnosed RCC. Results did not appreciably change when we excluded subjects with a follow-up time of <2 years.

In conclusion, in this European study measures of obesity were associated with increased risk of RCC irrespective of the fat distribution pattern among women, and measures of abdominal obesity, particularly a low hip circumference, were associated with increased RCC risk among men. Our data give further credence to public health efforts aiming to reduce the prevalence of obesity to prevent RCC, in addition to other chronic diseases.

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