IARC HANDBOOKS

ABSENCE OF EXCESS BODY FATNESS

VOLUME 16

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Cancer-Preventive Interventions, which met in Lyon, 5–12 April 2016

LYON, FRANCE - 2018

IARC HANDBOOKS OF CANCER PREVENTION

International Agency for Research on Cancer

World Health Organization

2.2.16 *Cancer of the kidney (renal cell carcinoma)*

Cancer of the kidney accounts for about 2% of all cancers diagnosed. Established epidemiological risk factors for kidney cancer include tobacco smoking, which can double the risk of the disease in smokers compared with non-smokers. Other established risk factors, which are closely associated with obesity, are high blood pressure and pre-existing diabetes mellitus.

The two most common types of kidney cancer are renal cell carcinoma (RCC) and transitional cell carcinoma (also known as urothelial cell carcinoma) of the renal pelvis. About 90% of kidney cancers are RCCs. Histological subtypes of RCC include clear cell tumours (about 70% of RCCs), papillary tumours (also called chromophilic RCC; about 10% of RCCs), and chromophobe RCC (about 5% of RCCs). Various rarer types of RCC exist, each representing less than 1% of RCCs.

In 2001, the Working Group of the *IARC Handbook* on weight control and physical activity (IARC, 2002) concluded that there was *sufficient evidence* for a cancer-preventive effect of avoidance of weight gain for RCC. The 2007 WCRF review concluded that there was convincing evidence of a positive association between body fatness and kidney cancer risk (WCRF/AICR, 2007). In 2015, the WCRF Continuous Update Project reaffirmed the 2007 conclusions (WCRF/AICR, 2015).

(a) Cohort studies

Since 2000, 19 cohort studies of anthropomorphic measures and risk of kidney cancer have been published (excluding analyses that were later updated and analyses based on fewer than 100 incident cases). Table 2.2.16a shows those findings by BMI at baseline, with comments on findings according to other anthropometric measures of body fatness and weight changes over the life-course.

The findings are remarkably consistent across studies, showing increasing risk of kidney cancer with increasing BMI. The association is approximately linear with increasing BMI. A meta-analysis of 21 cohort studies concluded that there was consistency of the association across sexes and world regions, with a relative risk for obesity compared with normal weight of 1.63 (95% CI, 1.50–1.77) in men and 1.95 (95% CI, 1.81–2.10) in women (Wang & Xu, 2014).

Some investigators have assessed the association between BMI at different ages and subsequent risk of kidney cancer (Nicodemus et al., 2004; van Dijk et al., 2004; Adams et al., 2008). In general, the strong positive association between baseline BMI and kidney cancer risk was also seen for BMI in middle adulthood, but much less so for BMI in early adulthood (ages 18–20 years).

Five cohort studies reported on the association between measures of waist circumference and kidney cancer risk (Nicodemus et al., 2004; Pischon et al., 2006; Adams et al., 2008; Sanfilippo et al., 2014; Kabat et al., 2015). In all of the studies, measures of waist circumference were associated with kidney cancer risk similarly to BMI.

(b) Case–control studies

Since 2000, a total of nine case–control studies in China, Europe, and North America have reported on the association of BMI with risk of RCC (Table 2.2.16b). In all of the studies except one (Wang et al., 2012), BMI was assessed through self-reports by patients with RCC and control subjects, with reference to a variable time frame before cancer diagnosis and an equivalent time frame for the controls. Of the nine studies, seven adjusted for smoking and two did not. Other possible confounding factors considered and adjusted for in some studies included use of artificial sweeteners, pre-existing diabetes mellitus, use of anti-hypertensive drugs, and

exposures to pesticides, herbicides, or certain industrial exposures.

Most of the studies showed an increased risk of RCC with higher BMI, in men, women, or both sexes, although this positive association was not statistically significant in all studies. In all the larger studies, including the earlier studies, there was a statistically significant trend of increasing RCC risk with increasing BMI, up to an approximately 2–3-fold increased risk for the highest versus the lowest BMI categories, both in men and in women. In several studies, RCC risk was also found to be positively associated with BMI at younger ages (20–40 years) (Brock et al., 2007; Dal Maso et al., 2007; Beebe-Dimmer et al., 2012).

Purdue et al. (2013) combined the data from a large case–control study in the USA (Beebe-Dimmer et al., 2012) and a multicentre study in central and eastern Europe (Brennan et al., 2008) to examine the association of BMI with different histological subtypes of RCC and found a positive association of BMI with risk of clear cell RCC (n = 1524; OR per 5 kg/m^2, 1.2; 95% CI, 1.1–1.3) and chromophobe RCC (n = 80; OR per 5 kg/m^2, 1.2; 95% CI, 1.1–1.4), but not papillary RCC (n = 237; OR per 5 kg/m^2, 1.1; 95% CI, 1.0–1.2) or RCC not otherwise specified (n = 367; OR per 5 kg/m^2, 1.0; 95% CI, 0.7–1.4).

(c) Meta-analyses

Several meta-analyses of cohort and/or case–control studies assessed the association between BMI and kidney cancer risk (Table 2.2.16c). Bergström et al. (2001) combined data from 14 studies in men and 14 studies in women, and reported a summary relative risk of RCC of 1.07 per 1 kg/m^2 increase in BMI in both men and women. Two more recent meta-analyses reported summary relative risks for cohort studies and case–control studies separately, for women (Mathew et al., 2009) and for men (Ildaphonse et al., 2009) respectively, all in the range of 1.05 to 1.07.

(d) Mendelian randomization study

There has been one Mendelian randomization study, which used the *FTO* rs9939609 SNP, robustly associated with BMI (Frayling et al., 2007; Scuteri et al., 2007; Peeters et al., 2008), to estimate the causal association between BMI and kidney cancer, among other cancer types (Brennan et al., 2009; Table 2.2.16d). Those with the *FTO* AA genotype had a higher BMI than controls with the TT genotype (difference, 1.14 kg/m^2; 95% CI, 0.66–1.61; P < 0.00001). Mendelian randomization analyses showed that each 1 kg/m^2 increase in BMI was weakly associated with an increased risk of kidney cancer (OR, 1.11; 95% CI: 0.91–1.37; P = 0.31), which was more pronounced in those younger than 50 years (OR, 1.90; 95% CI, 1.16–2.27; P = 0.0002).

Table 2.2.16a Cohort studies of measures of body fatness and cancer of the kidney

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Calle et al. (2003) Population-based cohort USA 1982–1998	404 576 Men Mortality	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 [P_{trend}]	 305 437 81 14 	 1.00 1.18 (1.02–1.37) 1.36 (1.06–1.74) 1.70 (0.99–2.92) [0.002]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin, fat intake, vegetable intake	
	495 477 Women Mortality	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40 [P_{trend}]	 243 153 55 12 10 	 1.00 1.33 (1.08–1.63) 1.66 (1.23–2.24) 1.70 (0.94–3.05) 4.75 (2.50–9.04) [< 0.001]	Age, education level, smoking, physical activity, alcohol consumption, marital status, aspirin, fat intake, vegetable intake, HRT	
Bjørge et al. (2004) Population-based cohort Norway 1963–2001	1 037 788 Women Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 1061 977 568 	 1.00 1.32 (1.21–1.45) 1.85 (1.66–2.06) [< 0.001]	Age	Association weaker in current and former smokers than in never-smokers
	963 442 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 1908 1638 267 	 1.00 1.18 (1.11–1.26) 1.55 (1.36–1.76) [< 0.001]	Age	Association weaker in current and former smokers than in never-smokers
Nicodemus et al. (2004) Iowa Women's Health Study USA 1986–2000	34 637 Women Incidence	BMI < 22.9 22.9–25.0 25.0–27.4 27.4–30.6 > 30.6 [P_{trend}]	 16 13 24 31 40 	 1.00 0.80 (0.38–1.65) 1.46 (0.77–2.74) 1.87 (1.02–3.41) 2.49 (1.39–4.44) [< 0.0001]	Age	Postmenopausal women. Weight at ages 30 yr, 40 yr, and 50 yr (but not at 18 yr) associated similarly. WC also associated

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
van Dijk et al. (2004) Netherlands Cohort Study The Netherlands 1986–1995	120 852 Women and men Incidence	BMI 23–24.9 25–26.9 27–29.9 ≥ 30 [P_{trend}] per 1 kg/m²	 83 54 62 16 	 1.00 0.92 (0.61–1.38) 1.46 (0.97–2.21) 1.04 (0.54–1.99) [0.04] 1.07 (1.02–1.12)	Age, sex	No association with BMI at age 20 yr
Flaherty et al. (2005) Nurses' Health Study USA 1976–2000	118 191 Women Incidence	BMI < 22.0 22.0–24.9 25.0–27.9 28.0–29.9 ≥ 30 [P_{trend}]	 40 47 27 14 26 	 1.0 1.3 (0.9–2.0) 1.6 (0.9–2.5) 2.2 (1.2–4.1) 2.7 (1.6–4.4) [< 0.001]	Age, hypertension, smoking	RR for BMI ≥ 30 adjusted for age only
Flaherty et al. (2005) Health Professionals Follow-Up Study USA 1986–1998	48 953 Men Incidence	BMI < 22.0 22.0–24.9 25.0–27.9 28.0–29.9 ≥ 30 [P_{trend}]	 4 37 45 12 10 	 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]	Age, hypertension, smoking	
Rapp et al. (2005) Population-based cohort Austria 1985–2002	67 447 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 46 70 21 	 1.00 1.19 (0.82–1.74) 1.46 (0.87–2.46) [0.14]	Age, smoking, occupation	
	78 484 Women Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 32 44 12 	 1.00 1.81 (1.13–2.89) 1.14 (0.58–2.24) [0.3]	Age, smoking, occupation	

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Pischon et al. (2006) EPIC cohort Europe 1992–2004	218 889 Women Incidence	BMI, quintiles < 21.8 21.8–23.7 23.8–25.9 26.0–28.9 > 29.0 [P_{trend}]	 12 22 24 37 37	 1.00 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]	Smoking, education level, alcohol consumption, physical activity	WC also associated
	129 660 Men Incidence	BMI, quintiles < 23.6 23.6–25.3 25.4–27.0 27.1–29.3 > 29.4 [P_{trend}]	 29 35 23 28 40	 1.00 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]		
Samanic et al. (2006) Swedish Construction Worker Cohort Sweden 1971–1999	362 552 Men Incidence	BMI 18.5–24.9 25–29.9 ≥ 30 [P_{trend}]	 444 448 94	 1.00 1.23 (1.08–1.42) 1.61 (1.27–2.04) [< 0.001]	Age, year, smoking, hypertension	
Reeves et al. (2007) Million Women Study United Kingdom 1995–2005	1.2 million Women Incidence	BMI < 22.5 22.5–24.9 25.0–27.4 27.5–29.9 ≥ 30 per 10 kg/m^2	 119 165 155 106 178	 0.95 (0.79–1.14) 1.00 (0.86–1.17) 1.10 (0.94–1.28) 1.19 (0.99–1.44) 1.52 (1.31–1.77) 1.53 (1.27–1.84)	Age, region, SES, reproductive history, smoking, alcohol consumption, physical activity, HRT use	Association slightly weaker in never-smokers
Setiawan et al. (2007) Multiethnic Cohort USA 1993–2002	85 964 Women Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 38 52 37	 1.00 2.03 (1.31–3.15) 2.27 (1.37–3.74) [0.001]	Age, ethnicity, smoking, alcohol consumption, hypertension, physical activity	
	75 172 Men Incidence	BMI < 25 25–29.9 ≥ 30 [P_{trend}]	 77 93 50	 1.00 1.14 (0.84–1.55) 1.76 (1.20–2.58) [0.005]		

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Adams et al. (2008) NIH-AARP cohort USA 1995–2003	214 906 Women Incidence	BMI 18.5–22.5 22.5–24.9 25–27.5 27.5–29.9 ≥ 30 [P_{trend}]	 17 33 46 27 64	 1.00 1.66 (0.92–2.98) 2.44 (1.39–4.26) 2.27 (1.23–4.20) 2.67 (1.53–4.66) [0.002]	Age, smoking, physical activity, protein intake, diabetes, hypertension	Similar association with BMI at age 50 yr; no association at age 18 yr or 35 yr. WC also associated
	312 500 Men Incidence	BMI 18.5–22.5 22.5–24.9 25–27.5 27.5–29.9 ≥ 30 [P_{trend}]	 28 88 169 127 152	 1.00 1.12 (0.73–1.72) 1.51 (1.01–2.26) 1.74 (1.15–2.63) 1.87 (1.24–2.82) [< 0.0005]		Similar association with BMI at age 50 yr; no association at age 18 yr or 35 yr. WC also associated
Jee et al. (2008) Cohort from National Health Insurance Corporation Republic of Korea 1992–2007	443 273 Women Incidence	BMI < 20 20–22.9 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 22 95 100 100 14	 0.48 (0.28–0.82) 0.70 (0.49–0.99) 1.00 0.92 (0.64–1.31) 1.21 (0.58–2.53) [0.0042]	Age, smoking	
	770 556 Men Incidence	BMI < 20 20–22.9 23–24.9 25–29.9 ≥ 30 [P_{trend}]	 97 430 425 392 16	 0.64 (0.49–0.84) 0.67 (0.56–0.79) 1.00 1.11 (0.93–1.31) 1.38 (0.76–2.52) [< 0.0001]	Age, smoking	Association weaker in ever-smokers than in non-smokers
Song et al. (2008) Korean medical insurance cohort Republic of Korea 1993–2003	170 481 Women Incidence	BMI 21.0–22.9 23.0–24.9 25.0–26.9 27.0–29.9 ≥ 30.0 [P_{trend}]	 18 34 29 14 7	 1.00 1.74 (0.94–3.22) 1.74 (0.92–3.29) 1.37 (0.66–2.84) 2.61 (1.06–6.41) [< 0.05]	Age, height, smoking, alcohol consumption, physical activity, pay grade	

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Wilson et al. (2009) ATBC cohort Finland 1985–2002	27 111 Men Incidence	BMI < 23.7 23.7–26.0 26.0–28.5 ≥ 28.5 [P_{trend}]	 41 70 65 69	 1.00 1.8 (1.3–2.7) 1.8 (1.2–2.7) 2.1 (1.4–3.1) [< 0.001]	Age, energy intake	
Sawada et al. (2010) Population sample of Japan Japan 1990–2006	46 837 Men Incidence	BMI < 21 21.0–22.9 23.0–24.9 25.0–26.9 ≥ 27.0	 22 20 21 18 20	 1.86 (1.01–3.45) 1.16 (0.62–2.16) 1.00 1.39 (0.73–2.63) 1.99 (1.04–3.81)	Age, area, tobacco use, alcohol consumption, physical activity, hypertension, diabetes	Analysis of data in women (n = 52 625) was based on very small number of cases; association unclear
Häggström et al. (2013) 3 cohorts Austria, Norway, Sweden 1994–2006	281 468 Women Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 24 28 61 66 84	 1.00 0.95 (0.52–1.74) 1.84 (1.08–3.13) 1.74 (1.02–2.94) 2.21 (1.32–3.70) [0.0002]	Age, time of measurement	
	278 920 Men Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	 89 108 100 139 156	 1.00 1.11 (0.81–1.52) 0.94 (0.68–1.29) 1.28 (0.95–1.73) 1.51 (1.13–2.03) [0.001]		
Macleod et al. (2013) Population-based cohort USA 2000–2009	77 260 Women and men Incidence	BMI < 25 25–29.9 30–34.9 ≥ 35	 59 104 47 28	 1.00 1.23 (0.88–1.72) 1.20 (0.81–1.78) 1.71 (1.06–2.79)	Age, sex, race, smoking, alcohol consumption, hypertension, diabetes	
Bhaskaran et al. (2014) Clinical Practice Research Datalink United Kingdom 1987–2012	5.24 million Women and men Incidence	BMI per 5 kg/m^2	1906 total	 1.25 (1.17–1.33)	Age, year, sex, diabetes, SES, alcohol consumption, tobacco use	Similar findings for never-smokers

Table 2.2.16a (continued)

Reference Cohort Location Follow-up period	Total number of subjects Sex Incidence/ mortality	Exposure categories	Exposed cases	Relative risk (95% CI)	Covariates	Comments
Sanfilippo et al. (2014) Women's Health Initiative cohort USA 1993–1998	156 774 Women Incidence	BMI 18.5–24.9 25–29.9 30–34.9 35–39.9 ≥ 40	 108 144 83 45 27	 1.00 1.32 (1.03–1.70) 1.47 (1.10–1.96) 1.91 (1.33–2.75) 2.48 (1.61–3.80)	Age, race/ethnicity, diastolic blood pressure	(See also Kabat et al., 2015) WC also associated with increased risk
Kabat et al. (2015) Women's Health Initiative cohort USA 1992–2013	143 901 Women Incidence	BMI, quintiles Q1 Q2 Q3 Q4 Q5 [P_{trend}]	376 total	 1.00 0.89 (0.61–1.28) 1.21 (0.86–1.71) 1.36 (0.96–1.91) 1.73 (1.24–2.42) [< 0.0001]	Age, alcohol consumption, smoking, physical activity, age at menarche, age at first birth, parity, HRT use, family history of kidney cancer, ethnicity, education level	WC also associated with risk

ATBC, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; BMI, body mass index (in kg/m^2); CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; HRT, hormone replacement therapy; NIH-AARP, National Institutes of Health–AARP Diet and Health Study; RR, relative risk; SES, socioeconomic status; WC, waist circumference; yr, year or years

Table 2.2.16b Case–control studies of measures of body fatness and cancer of the kidney

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Shapiro et al. (1999) USA (western Washington state) 1980–1995	238 (155 men, 83 women) 616 (261 men, 355 women) Population	Median BMI	Women:		Age, diabetes mellitus, hypertension Median BMI calculated using median weight recorded in medical records during the 5-yr period immediately before the reference date (2 yr before date of diagnosis and corresponding index date for controls)
		< 22.20	5	1.0	
		22.20–24.85	16	3.3 (1.1–9.7)	
		24.86–28.25	20	3.6 (1.3–10.3)	
		> 28.25	29	4.1 (1.5–11.8)	
		Top 10% (> 32.99)		6.0 (1.9–18.8)	
		Median BMI	Men:		
		< 24.59	23	1.0	
		24.59–26.39	27	1.1 (0.5–2.1)	
		26.40–28.88	26	1.0 (0.5–2.0)	
		> 28.88	45	1.8 (0.9–3.5)	
		Top 10% (> 31.85)		2.2 (1.0–5.0)	
Hu et al. (2003) Canada (8 provinces) 1994–1997	1279 (691 men, 588 women) 5370 (2696 men, 2674 women) Population	BMI 2 yr before study entry	Women:		10-year age group, province, education level, pack-years of smoking, alcohol consumption, total intake of meat, vegetables, and fruit
		< 18.5–24.9	221	1.0	
		25.0–29.9	200	1.5 (1.20–1.90)	
		30.0–34.9	100	2.5 (1.90–3.40)	
		35.0–39.9	31	2.7 (1.70–4.40)	
		≥ 40.00	33	3.8 (2.30–6.40)	
		BMI 2 yr before study entry	Men:		
		< 18.5–24.9	147	1.0	
		25.0–29.9	369	2.20 (1.70–2.70)	
		30.0–34.9	144	2.80 (2.20–3.80)	
		35.0–39.9	21	1.90 (1.10–3.30)	
		≥ 40.00	8	3.70 (1.50–9.40)	

Table 2.2.16b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Chiu et al. (2006) USA 1986–1990	406 (261 men, 145 women) 2434 (1601 men, 833 women) Population	BMI in 60s	Men:		All respondents: age, total energy intake, intake of red meat, intake of vegetables, hypertension, education level, smoking, family history of kidney cancer, proxy status; women only: marital status Analyses for BMI at age 20 yr and age 40 yr gave very similar results to BMI at age 60 yr
		≤ 23.48	49	1.0	
		23.49–25.17	33	0.6 (0.3–1.1)	
		25.18–27.35	34	0.6 (0.3–1.1)	
		27.36–30.07	27	0.8 (0.4–1.7)	
		≥ 30.08	20	0.4 (0.2–1.0)	
		[P_{trend}]		[0.2]	
		BMI in 60s	Women:		
		≤ 22.20	23	1.0	
		22.21–24.32	18	0.5 (0.2–1.4)	
		24.33–27.31	20	1.0 (0.4–2.5)	
		27.33–30.13	13	0.7 (0.3–2.1)	
		≥ 30.14	21	2.3 (0.9–6.0)	
		[P_{trend}]		[0.1]	
Brock et al. (2007) USA (Iowa) 1985–1989	406 (261 men, 145 women) 2434 (1601 men, 833 women) Population	BMI at age 20 yr			Age, sex, proxy status, pack-years of smoking Analysis also reported for men and women separately
		< 25	271	1.00	
		25–30	62	1.54 (1.10–2.17)	
		≥ 30	21	2.75 (1.51–5.01)	
		BMI at age 40 yr			
		< 25	180	1.00	
		25–30	130	1.36 (1.04–1.79)	
		≥ 30	51	2.08 (1.39–3.12)	
		BMI at age 60 yr			
		< 25	111	1.00	
		25–30	93	1.12 (0.81–1.55)	
		≥ 30	39	1.46 (0.94–2.28)	
Dal Maso et al. (2007) Italy 1992–2004	767 (494 men, 273 women) 1534 (988 men, 546 women) Hospital	BMI at age 30 yr			Calendar period of interview, years of education, smoking habits, family history of kidney cancer
		< 25	492	1.00	
		25– < 30	194	1.17 (0.95–1.45)	
		≥ 30	38	1.46 (0.95–2.25)	
		[P_{trend}]		[0.04]	
		BMI at age 50 yr			
		< 25	256	1.00	
		25– < 30	265	1.17 (0.94–1.45)	
		≥ 30	89	1.48 (1.07–2.03)	
		[P_{trend}]		[0.02]	

Table 2.2.16b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Dal Maso et al. (2007) (cont.)		BMI 1 yr before diagnosis			
		< 25	281	1.00	
		25– < 30	347	0.95 (0.78–1.16)	
		≥ 30	136	1.29 (0.99–1.69)	
		[P_{trend}]		[0.16]	
		By smoking status			
		Never-smokers:			
		< 25	39	1.00	
		25– < 30	62	1.25 (0.74–2.09)	
		≥ 30	82	1.83 (1.10–3.04)	
		Ever-smokers:			
		< 25	87	1.00	
		25– < 30	93	0.96 (0.66–1.41)	
		≥ 30	112	1.37 (0.95–1.98)	
		By histological type			
		Clear cell subtype:			
		< 25	71	1.00	
		25– < 30	89	0.99 (0.68–1.44)	
		≥ 30	121	1.40 (0.98–1.99)	
		Other subtype:			
		< 25	23	1.00	
		25– < 30	38	1.30 (0.73–2.30)	
		≥ 30	41	1.62 (0.92–2.85)	
Brennan et al. (2008) Czech Republic, Poland, Romania, Russian Federation (7 centres) 1998–2003	1097 (648 men, 449 women) 1476 (952 men, 524 women) Hospital	BMI 2 yr before interview	Men:		Age, smoking, history of hypertension, country
		< 25	191	1.00	
		25–27.5	166	1.19 (0.91–1.56)	
		27.5–29.99	125	1.32 (0.98–1.79)	
		30–35	133	1.70 (1.25–2.31)	
		> 35	32	1.72 (1.01–2.94)	
		[P_{trend}]		[0.001]	
		BMI 2 yr before interview	Women:		
		< 25	136	1.00	
		25–27.5	87	0.86 (0.60–1.25)	
		27.5–29.99	98	1.16 (0.80–1.70)	
		30–35	98	0.95 (0.66–1.38)	
		> 35	30	0.85 (0.49–1.48)	
		[P_{trend}]		[0.68]	

Table 2.2.16b (continued)

Reference Study location Period	Total number of cases Total number of controls Source of controls	Exposure categories	Exposed cases	Relative risk (95% CI)	Adjustment for confounding Comments
Beebe-Dimmer et al. (2012) USA 2002–2007	1214 (720 men, 494 women) 1234 (689 men, 545 women) Population	BMI 5 yr before interview			Age, education level, hypertension, family history of renal cancer, smoking history, study centre Analysis of BMI at age 21 yr gave similar results
		< 25.0	240	1.0	
		25.0–29.9	436	1.2 (0.9–1.5)	
		30.0–34.9	298	1.5 (1.2–2.1)	
		≥ 35	230	1.6 (1.1–2.2)	
		per 1 kg/m²		1.02 (1.01–1.04)	
		[P_{trend}]		[0.0013]	
Wang et al. (2012) China 2007–2009	250 299 Hospital	Current BMI			Univariate analysis
		< 25	157	1.00	
		≥ 25	93	1.94 (1.34–2.81)	
Purdue et al. (2013) USA (Detroit and Chicago; USKC study) and Europe (Czech Republic, Poland, Romania, Russian Federation; CEERCC study) 2002–2007	2314 2711 Population (USKC), hospital (CEERCC)	BMI a few years before interview			Study centre, age, sex, race, education level, BMI, smoking status, history of diagnosed hypertension, family history of kidney cancer Time before interview: 5 yr (USKC), 2 yr (CEERCC)
		Clear cell:	1524		
		per 5 kg/m²		1.2 (1.1–1.3)	
		Papillary:	237		
		per 5 kg/m²		1.1 (1.0–1.2)	
		Chromophobe:	80		
		per 5 kg/m²		1.2 (1.1–1.4)	
		Other/NOS:	367		
		per 5 kg/m²		1.0 (0.7–1.4)	

BMI, body mass index (in kg/m²); CEERCC, Central and Eastern European Renal Cell Cancer Study; CI, confidence interval; NOS, not otherwise specified; USKC, United States Kidney Cancer; yr, year or years

Table 2.2.16c Meta-analyses of measures of body fatness and cancer of the kidney

Reference	Total number of studies Sex	Exposure categories	Relative risk (95% CI)	Heterogeneity values
Bergström et al. (2001)	28 studies (6 cohort studies, 22 case–control studies; 16 population-based, 6 hospital-based) Men: 14 studies Women: 14 studies	BMI, per 1 kg/m^2 All Men Women	 1.07 (1.05–1.09) 1.07 (1.04–1.09) 1.07 (1.05–1.09)	 $P_{heterogeneity}$ = 0.03 $P_{heterogeneity}$ = 0.08 $P_{heterogeneity}$ = 0.24
Mathew et al. (2009)	28 studies (15 cohort studies, 13 case–control studies) Women	BMI, per 1 kg/m^2 Cohort studies Case–control studies	 1.06 (1.05–1.07) 1.07 (1.06–1.08)	 $P_{heterogeneity}$ = 0.081 $P_{heterogeneity}$ = 0.0643
Ildaphonse et al. (2009)	27 studies (13 cohort studies, 14 case–control studies) Men	BMI, per 1 kg/m^2 Cohort studies Case–control studies	 1.05 (1.04–1.06) 1.08 (1.06–1.09)	 $P_{heterogeneity}$ = 0.78 $P_{heterogeneity}$ = 0.4238
Wang & Xu (2014)	21 cohort studies Men and women	BMI, vs normal weight All: Pre-obesity Obesity Men: Pre-obesity Obesity Women: Pre-obesity Obesity	 1.28 (1.24–1.33) 1.77 (1.68–1.87) 1.22 (1.17–1.28) 1.63 (1.50–1.77) 1.38 (1.29–1.47) 1.95 (1.81–2.10)	BMI in adults was classified as follows: normal weight, 18.50–24.99; pre-obesity, 25.00–29.99; obesity, ≥ 30.00

BMI, body mass index (in kg/m^2); CI, confidence interval

Table 2.2.16d Mendelian randomization studies of measures of body fatness and cancer of the kidney

Reference	Characteristics of study population	Sample size	Exposure (unit)	Outcome	Odds ratio (95% CI); *P* value (with each unit increase in exposure) of the association between the exposure and outcome
Brennan et al. (2009)	Men and women from 15 centres in 6 countries in central and eastern Europe (Czech Republic, Hungary, Poland, Romania, Russian Federation, and Slovakia)	7067 (4015 cases and 3052 controls)	BMI (kg/m^2)	Kidney cancer	All subjects: 1.11 (0.91–1.37); $P = 0.31$ Subjects aged < 50 yr: 1.90 (1.16–2.27); $P = 0.0002$

BMI, body mass index (in kg/m^2); CI, confidence interval; OR, odds ratio; yr, year or years

References

Adams KF, Leitzmann MF, Albanes D, Kipnis V, Moore SC, Schatzkin A, et al. (2008). Body size and renal cell cancer incidence in a large US cohort study. *Am J Epidemiol*, 168(3):268–77. PMID:18544571

Beebe-Dimmer JL, Colt JS, Ruterbusch JJ, Keele GR, Purdue MP, Wacholder S, et al. (2012). Body mass index and renal cell cancer: the influence of race and sex. *Epidemiology*, 23(6):821–8. doi:10.1097/EDE.0b013e31826b7fe9 PMID:23007040

Bergström A, Hsieh CC, Lindblad P, Lu CM, Cook NR, Wolk A (2001). Obesity and renal cell cancer – a quantitative review. *Br J Cancer*, 85(7):984–90. doi:10.1054/bjoc.2001.2040 PMID:11592770

Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L (2014). Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet*, 384(9945):755–65. doi:10.1016/S0140-6736(14)60892-8 PMID:25129328

Bjørge T, Tretli S, Engeland A (2004). Relation of height and body mass index to renal cell carcinoma in two million Norwegian men and women. *Am J Epidemiol*, 160(12):1168–76. doi:10.1093/aje/kwh345 PMID:15583369

Brennan P, McKay J, Moore L, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, et al. (2009). Obesity and cancer: Mendelian randomization approach utilizing the *FTO* genotype. *Int J Epidemiol*, 38(4):971–5. doi:10.1093/ije/dyp162 PMID:19542184

Brennan P, van der Hel O, Moore LE, Zaridze D, Matveev V, Holcatova I, et al. (2008). Tobacco smoking, body mass index, hypertension, and kidney cancer risk in central and eastern Europe. *Br J Cancer*, 99(11):1912–5. doi:10.1038/sj.bjc.6604761 PMID:19034282

Brock KE, Gridley G, Lynch CF, Ershow AG, Cantor KP (2007). Obesity and hypertension interact to increase risk of renal cell carcinoma in Iowa, USA. *Obes Res Clin Pract*, 1(2):I–II. doi:10.1016/j.orcp.2007.02.004 PMID:24351456

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(17):1625–38. doi:10.1056/NEJMoa021423 PMID:12711737

Chiu BC, Gapstur SM, Chow WH, Kirby KA, Lynch CF, Cantor KP (2006). Body mass index, physical activity, and risk of renal cell carcinoma. *Int J Obes*, 30(6):940–7. doi:10.1038/sj.ijo.0803231 PMID:16446746

Dal Maso L, Zucchetto A, Tavani A, Montella M, Ramazzotti V, Talamini R, et al. (2007). Renal cell cancer and body size at different ages: an Italian multicenter case-control study. *Am J Epidemiol*, 166(5):582–91. doi:10.1093/aje/kwm108 PMID:17591592

Flaherty KT, Fuchs CS, Colditz GA, Stampfer MJ, Speizer FE, Willett WC, et al. (2005). A prospective study of body mass index, hypertension, and smoking and the risk of renal cell carcinoma (United States). *Cancer Causes Control*, 16(9):1099–106. doi:10.1007/s10552-005-0349-8 PMID:16184476

Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. (2007). A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*, 316(5826):889–94. doi:10.1126/science.1141634 PMID:17434869

Häggström C, Rapp K, Stocks T, Manjer J, Bjørge T, Ulmer H, et al. (2013). Metabolic factors associated with risk of renal cell carcinoma. *PLoS One*, 8(2):e57475. doi:10.1371/journal.pone.0057475 PMID:23468995

Hu J, Mao Y, White K; Canadian Cancer Registries Epidemiology Research Group (2003). Overweight and obesity in adults and risk of renal cell carcinoma in Canada. *Soz Praventivmed*, 48(3):178–85. doi:10.1007/s00038-003-2046-2 PMID:12891869

IARC (2002). Weight control and physical activity. Lyon, France: IARC Press (IARC Handbooks of Cancer Prevention, Vol. 6). Available from: http://publications.iarc.fr/376.

Ildaphonse G, George PS, Mathew A (2009). Obesity and kidney cancer risk in men: a meta-analysis (1992–2008). *Asian Pac J Cancer Prev*, 10(2):279–86. PMID:19537897

Jee SH, Yun JE, Park EJ, Cho ER, Park IS, Sull JW, et al. (2008). Body mass index and cancer risk in Korean men and women. *Int J Cancer*, 123(8):1892–6. doi:10.1002/ijc.23719 PMID:18651571

Kabat GC, Xue X, Kamensky V, Lane D, Bea JW, Chen C, et al. (2015). Risk of breast, endometrial, colorectal, and renal cancers in postmenopausal women in association with a body shape index and other anthropometric measures. *Cancer Causes Control*, 26(2):219–29. doi:10.1007/s10552-014-0501-4 PMID:25430815

Macleod LC, Hotaling JM, Wright JL, Davenport MT, Gore JL, Harper J, et al. (2013). Risk factors for renal cell carcinoma in the VITAL study. *J Urol*, 190(5):1657–61. doi:10.1016/j.juro.2013.04.130 PMID:23665301

Mathew A, George PS, Ildaphonse G (2009). Obesity and kidney cancer risk in women: a meta-analysis (1992–2008). *Asian Pac J Cancer Prev*, 10(3):471–8. PMID:19640194

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(1):115–21. doi:10.1002/ijc.11532 PMID:14618625

Peeters A, Beckers S, Verrijken A, Roevens P, Peeters P, Van Gaal L, et al. (2008). Variants in the *FTO* gene are associated with common obesity in the Belgian population. *Mol Genet Metab*, 93(4):481–4. doi:10.1016/j.ymgme.2007.10.011 PMID:18055244

Pischon T, Lahmann PH, Boeing H, Tjønneland A, Halkjaer J, Overvad K, et al. (2006). Body size and risk of renal cell carcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*, 118(3):728–38. doi:10.1002/ijc.21398 PMID:16094628

Purdue MP, Moore LE, Merino MJ, Boffetta P, Colt JS, Schwartz KL, et al. (2013). An investigation of risk factors for renal cell carcinoma by histologic subtype in two case-control studies. *Int J Cancer*, 132(11):2640–7. doi:10.1002/ijc.27934 PMID:23150424

Rapp K, Schroeder J, Klenk J, Stoehr S, Ulmer H, Concin H, et al. (2005). Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. *Br J Cancer*, 93(9):1062–7. doi:10.1038/sj.bjc.6602819 PMID:16234822

Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D; Million Women Study Collaboration (2007). Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*, 335(7630):1134. doi:10.1136/bmj.39367.495995.AE PMID:17986716

Samanic C, Chow WH, Gridley G, Jarvholm B, Fraumeni JF Jr (2006). Relation of body mass index to cancer risk in 362,552 Swedish men. *Cancer Causes Control*, 17(7):901–9. doi:10.1007/s10552-006-0023-9 PMID:16841257

Sanfilippo KM, McTigue KM, Fidler CJ, Neaton JD, Chang Y, Fried LF, et al. (2014). Hypertension and obesity and the risk of kidney cancer in 2 large cohorts of US men and women. *Hypertension*, 63(5):934–41. doi:10.1161/HYPERTENSIONAHA.113.02953 PMID:24637660

Sawada N, Inoue M, Sasazuki S, Iwasaki M, Yamaji T, Shimazu T, et al.; JPHC Study Group (2010). Body mass index and subsequent risk of kidney cancer: a prospective cohort study in Japan. *Ann Epidemiol*, 20(6):466–72. doi:10.1016/j.annepidem.2010.03.008 PMID:20470974

Scuteri A, Sanna S, Chen W-M, Uda M, Albai G, Strait J, et al. (2007). Genome-wide association scan shows genetic variants in the *FTO* gene are associated with obesity-related traits. *PLoS Genet*, 3(7):e115. doi:10.1371/journal.pgen.0030115 PMID:17658951

Setiawan VW, Stram DO, Nomura AM, Kolonel LN, Henderson BE (2007). Risk factors for renal cell cancer: the Multiethnic Cohort. *Am J Epidemiol*, 166(8):932–40. doi:10.1093/aje/kwm170 PMID:17656615

Shapiro JA, Williams MA, Weiss NS (1999). Body mass index and risk of renal cell carcinoma. *Epidemiology*, 10(2):188–91. doi:10.1097/00001648-199903000-00019 PMID:10069258

Song Y-M, Sung J, Ha M (2008). Obesity and risk of cancer in postmenopausal Korean women. *J Clin Oncol*, 26(20):3395–402. doi:10.1200/JCO.2007.15.7867 PMID:18612154

van Dijk BA, Schouten LJ, Kiemeney LA, Goldbohm RA, van den Brandt PA (2004). Relation of height, body mass, energy intake, and physical activity to risk of renal cell carcinoma: results from the Netherlands Cohort Study. *Am J Epidemiol*, 160(12):1159–67. doi:10.1093/aje/kwh344 PMID:15583368

Wang F, Xu Y (2014). Body mass index and risk of renal cell cancer: a dose-response meta-analysis of published cohort studies. *Int J Cancer*, 135(7):1673–86. doi:10.1002/ijc.28813 PMID:24615287

Wang G, Hou J, Ma L, Xie J, Yin J, Xu D, et al. (2012). Risk factor for clear cell renal cell carcinoma in Chinese population: a case-control study. *Cancer Epidemiol*, 36(2):177–82. doi:10.1016/j.canep.2011.09.006 PMID:22000673

WCRF/AICR (2007). Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington (DC), USA: American Institute for Cancer Research. Available from: http://www.aicr.org/assets/docs/pdf/reports/Second_Expert_Report.pdf.

WCRF/AICR (2015). Continuous Update Project Report. Diet, nutrition, physical activity and kidney cancer. Washington (DC), USA: American Institute for Cancer Research. Available from: http://wcrf.org/kidney-cancer-2015.

Wilson RT, Wang J, Chinchilli V, Richie JP, Virtamo J, Moore LE, et al. (2009). Fish, vitamin D, and flavonoids in relation to renal cell cancer among smokers. *Am J Epidemiol*, 170(6):717–29. doi:10.1093/aje/kwp178 PMID:19651663