RESEARCH COMMUNICATION

Obesity and Kidney Cancer Risk in Men - a Meta-analysis (1992-2008)

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Abstract

We conducted a quantitative summary analysis to evaluate the recent evidence of kidney cancer risk according to body mass index (BMI) among men. The studies included in this quantitative review were all cohort and case-control studies, which provided information on kidney cancer risk associated with obesity/overweight, published between 1992 and 2008. The details of studies have been identified through searches on the MEDLINE database. We first estimated the risk associated with a unit increase in BMI (1 kg/m^2) for individual studies using logit-linear model. After deriving the natural logarithm of the risk per unit of BMI for all studies, we calculated a pooled estimate and corresponding 95% confidence interval (CI) as a weighted average of the risk obtained in individual studies, by giving a weight proportional to its precision. A total of 27 studies (13 cohort studies and 14 case-control studies) that provided kidney cancer risk according to BMI in men were included in the present analysis. The strength of association was almost similar in most of the cohort studies [relative risk (RR) ranged from 1.04-1.06 per unit increase in BMI] and in one study RR was 1.08. There was no heterogeneity across studies (p-value=0.164). The pooled risk was 1.05 (95% CI=1.04-1.06) per unit increase in BMI based on the cohort studies. The present analysis confirmed the evidence of kidney cancer risk with increased BMI in men and obesity may be responsible at least in part for the rising incidence rates.

Key Words: Obesity - kidney cancer risk - meta-analysis

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Introduction

Kidney cancers the third most common malignancy of the genitourinary system account for 2 to 3 percent of all cancers in men worldwide, with 130,000 new cases and 63,000 deaths from the disease occurring annually (Ferlay et al., 2004). More than 80% of kidney cancers are renal cell carcinomas (RCC) originating from the renal parenchyma. The remainder is mainly transitional cell carcinomas originating from the renal pelvis (Chow et al., 1999). Kidney cancer incidence and mortality rates are more than twice in men compared to women. These rates vary more than 10-fold over the world and are highest in North America and Europe and lowest in Asian and Latin American countries (Curado et al., 2007). Incidence and mortality rates of this disease, particularly RCC, have been reported to be rising in several countries worldwide (Mathew et al., 2002; Perez-Farinos et al., 2006; Falebita et al., 2008) except in a few countries in Europe (Levi et al., 2008).

It is reported that the rising incidence of renal parenchyma cancer is due both to an increased prevalence of risk factors and to improvements in diagnosis (Falebita et al., 2008). Cigarette smoking, obesity and hypertension (Lipworth et al., 2006) are well-established risk factors for kidney cancer. Per capita cigarette consumption among men decreased in many countries such as USA, Canada, Europe, and New Zealand (Monteiro et al., 2007; Ahacic et al., 2008; Duval et al., 2008; Edwards et al., 2008). Further it is reported that antihypertensive drug use has risen sharply in some countries and thereby prevalence of hypertension has remained stable or declined (Mosterd et al., 1999). However, the prevalence of obesity has increased to epidemic proportion in recent decades in many populations (Abubakari et al., 2008; Chen et al., 2008; Lilja et al., 2008; Matsushita et al., 2008; Wildman et al., 2008) and this increasing prevalence might therefore, at least, explain the increasing incidence of kidney cancer.

In a quantitative summary analysis by including mostly case-control studies and a few cohort studies-in principle more valid study design among the observational studies - which were published between 1966 and 1998, it is reported that 7% increased risk for kidney cancer per unit of increase in body mass index (BMI) (corresponding to 3 kg body weight increase for a subject of average height) in men (Bergstrom et al., 2001). However, during the past decade, more than 10 cohort studies reported on such associations. Hence we conducted a quantitative summary analysis to evaluate the recent evidence of kidney cancer risk according to BMI among men by including all cohort and case-control studies, which were published during the past one and a half decades.

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Materials and Methods

The studies included in this quantitative review were all cohort and case-control studies, which provided information on kidney cancer risk and obesity/overweight, published between 1992 and 2008. The details of studies have been identified through searches on the MEDLINE database, using keywords "kidney cancer", "renal cell carcinoma", "body mass index", "obesity" and "anthropometric factors". Papers were also searched among those quoted as references in the retrieved studies. We also identified previously published quantitative reviews to compare the present results. We considered mostly the studies of kidney parenchyma (ICD-10: C64). A description of the main characteristics such as the authors, year of publication, country, categories of BMI, the relative risk (RR) for cohort studies, the odds ratio (OR) for case-control studies and the corresponding 95% confidence intervals (CI), for different categories of BMI were obtained. We used the estimates adjusted for smoking and other confounding factors. If the RR or OR was expressed in more than one way, the estimate with greatest degree of controlling for confounders was used.

We first estimated the OR or RR associated with a unit increase in BMI (1 kg/m^2) for individual studies where the results were reported in categories of BMI. To treat BMI as a continuous exposure variable, its value was set at the midpoint of each category. For open-ended categories of BMI (e.g., <25 or >35), we assigned a value following the algorithms suggested by II'yasova et al., (2005). For the upper open-ended category, we assigned the value of its lower bound plus the width of the previous (second-to-highest) interval. For example, if the upper open-ended BMI category is >30, and the previous category is 25-30, we assigned a value of 30 + (30-25) = 35. For the lower open-ended BMI category we assigned the value of its upper bound minus half the width of the next (second-to-lowest) interval. For example, if the lower open-ended category is <25 and the next category is 25-30, we assigned the value of 25-0.5 (30-25) = 22.5.

The OR associated with a unit increase in BMI was estimated using logit-linear (linear-logistic) model: $\phi(x, z) = \alpha + \beta x + \chi' z$; where 'x' is BMI, 'z' is the vector of confounders, and 'ϕ' is the log odds of being a case in the study versus being a control.

The estimate (β) [OR=exp (β)] is computed as follows: Initially we subtracted the midpoint BMI of reference category from the midpoint BMI of all other categories and thus BMI reference category is set to '0'. The log odds ratio for the corresponding reference category was also set to zero (corresponding to a relative risk of 1).

Let Nx=the total number of subjects at each BMI category 'x'; N=the vector of Nx; M1=the total number of cases; Lx=the adjusted log odds ratio estimate for category 'x' ($x \neq 0$) versus the reference category (x=0); L=the vector of Lx ($x \neq 0$); vx=the estimated variance for Lx; v=the vector of vx ($x \neq 0$). Variance for Lx is estimated using the method provided by Greenland (1987).

We fitted cell counts (which have margins Nx and M1) such that (AxB0)/ (A0Bx) = exp (Lx), where Ax and Bx (Bx=Nx–Ax) are the fitted number of cases and non-cases at category 'x'. The algorithm is based on Newton's method (Seber and Wild, 1989) for solving the vector of fitted number of cases (Ax) at each non-zero categories. For $x \neq z$, we estimated the asymptomatic correlation of Lx and Lz by rxz = (1/A0+1/B0)/(SxSz), where Sx^2 =crude variance estimate = 1/Ax + 1/Bx + 1/A0 + 1/B0, and the asymptotic covariance (C) of Lx and Lz by cxz = rxz $(vx\ vz)^{1/2}$. We estimated 'β' by weighted least squares as b*=vb* x' C-1L, where vb*= var (b*)= (x'C-1x)-1, 'x' is the vector of observed non-zero exposure levels, 'C' is the covariance of 'L' and 'L' is the vector of 'Lx'. 'C' has diagonal elements 'vx', and off-diagonal elements 'cxz' (Greenland and Longnecker 1992). The estimation was carried out using SAS programming language.

Cohort studies where rate ratios were reported, 'β' becomes the coefficient in a log-linear (exponential) Poisson regression, Nx becomes the total person-time observed at exposure level 'x'; the Lx's become adjusted log rate ratios; cell counts are fitted such that (AxN0)/ (A0Nx) = exp (Lx); and rxz becomes 1/(A0SxSz), where Sx^2 =M1/(AxA0) and for the analysis of risk ratios (as in a cohort study with Nx persons, rather than person-time), these formulas are applied with Sx^2=M1/(AxA0) -1/N0 - 1/Nx and rxz = (1/A0–1/N0)/(SxSz) (Greenland and Longnecker 1992).

After deriving the natural logarithm of the risk per unit of BMI for all studies, we calculated a pooled estimate RRsum (and corresponding 95% CI) as a weighted average of the RRs (RRi), by giving a weight proportional to its precision (i.e., to the inverse of the variance of the RRi) [i.e. RRsum=sum (weighti x ln RRi)/ sum (weighti)]. To assess the consistency of findings among studies, we calculated test for heterogeneity using general variance-based method. i.e. Q= sum[(weighti x(ln RRsum–ln RRi)^2]. Q is referred to the chi-square distribution with degrees of freedom equal to the number of studies minus 1. When the chi-square p-value is less than 0.1, we excluded studies with a high value of weighti x (ln RRsum– ln RRi)^2 and then calculated RRsum and the corresponding 95% CI assuming a fixed-effect model (Petiti 2000). Separate and combined estimates based on cohort and case-control studies were computed.

The results of the meta analysis along with the individual studies were presented graphically (forest plot), plotting RR and the respective 95% CI.

Results

A total of 27 studies (13 cohort studies and 14 case-control studies) that provided kidney cancer risk according to BMI in men during 1992-2008 were included in the present analysis. The majority of the cohort studies were based on incident cases of kidney cancer (Hiatt et al., 1994; Chow et al., 2000; Bjorge et al., 2004; Flaherty et al., 2005; Oh et al., 2005; Lukanova et al., 2006; Pischon et al., 2006; Samanic et al., 2006; Setiawan et al., 2007; Adams et al., 2008) and a few studies are based on mortality due to kidney cancer (Heath et al., 1997; Calle et al., 2003). The majority of the case-control studies are population–based (McCredie and Stewart 1992; McLaughlin et al., 1992; Kriger et al., 1993; Lindblad et

al., 1994; Mellengaard et al., 1995; Chow et al., 1996; Yuan et al., 1998; Shapiro et al., 1999; Hu et al., 2003; Chiu et al., 2006; Pan et al., 2006) and a few studies are hospital-based (Benhamou et al., 1993; Maso et al., 2007). All case-control studies are based on incident cases of kidney cancer.

In the majority of the cohort studies, height and weight for calculating BMI were obtained using questionnaire method (Heath et al., 1997; Calle et al., 2003; Flaherty et al., 2005; Lukanova et al., 2006; Pischon et al., 2006; Setiawan et al., 2007; Adams et al., 2008) except in a few studies where these variables were obtained through measurements (Chow et al., 2000; Bjorge et al., 2004; Oh et al., 2005; Samanic et al., 2006). Height and weight were assessed using questionnaire method in most of the case-control studies (McCredie and Stewart 1992; Mclaughlin et al., 1992; Lindblad et al., 1994; Mellengaard et al., 1995; Chow et al., 1996; Yuan et al., 1998; Hu et al., 2003; Chiu et al., 2006; Pan et al., 2006; Maso et al., 2007) and in a few studies, these were obtained from the medical records (Shapiro et al., 1999). In all the studies, these details from the cases were collected at least 1 year before cancer diagnosis. The ages of kidney cancer cases were between 20 and 75 in most of the studies (McCredie and Stewart 1992; McLaughlin et al., 1992; Lindblad et al., 1994; Mellengaard et al., 1995; Chow et al., 1996; Heath et al., 1997; Yuan et al., 1998; Shapiro et al., 1999; Bjorge et al., 2004; Oh et al., 2005; Chiu et al., 2006; Pan et al., 2006; Pischon et al., 2006; Samanic et al., 2006). A few studies limited their ages between 40-75 years (Hu et al., 2003; Flaherty et al., 2005; Lukanova et al., 2006; Setiawan et al., 2007; Adams et al., 2008). Some studies provided only the mean age among cases and the same was between 44-50 years (Mclaughlin et al., 1992; Hiatt et al., 1994; Chow et al., 2000; Calle et al., 2003).

An increased kidney cancer risk among overweight/obese men was reported in majority of the studies. There was no heterogeneity across studies (p=0.164). The pooled risk was 1.06 (95% CI=1.05-1.07) for unit increase in BMI based on all the cohort and case-control studies combined.

Cohort studies

Of the 13 cohort studies that investigated the association between BMI and kidney cancer risk after adjusted for age, smoking and other confounding factors, 5 studies reported a significant increased risk (RR ranged from 1.05 to 1.08) (Heath et al., 1997; Chow et al., 2000; Bjorge et al., 2004; Oh et al., 2005; Adams et al., 2008), and 7 studies reported increased risk with borderline significance (RR ranged from 1.02 to 1.06) (Hiatt et al., 1994; Calle et al., 2003; Flaherty et al., 2005; Lukanova et al., 2006; Pischon et al., 2006; Samanic et al., 2006; Setiawan et al., 2007). Kidney cancer risk according to unit increase in BMI could not be estimated in one study, as BMI category was not specified (Moller et al., 1994) and thus excluded the study for assessing the heterogeneity between studies. Significant association was observed in all the 8 studies that reported dose-response relationship between BMI and kidney cancer risk (Chow et al., 2000; Calle et al., 2003; Bjorge et al., 2004; Oh et al., 2005; Lukanova et al., 2006; Samanic et al., 2006; Setiawan et al., 2007; Adams et al., 2008). There was no evidence of heterogeneity between the cohort studies (p=0.78). The pooled risk estimate was 1.05 (95% CI: 1.04-1.06) per unit increase in BMI (Figure 1 and Table 1).

Case-control studies

Of the 14 case-control studies that investigated the association between BMI and kidney cancer risk after adjusted for age, smoking and other confounding factors, 9 studies reported a significant increased risk (OR ranged from 1.05 to 1.15) (McCredie and Stewart 1992; McLaughlin et al., 1992; Benhamou et al., 1993; Mellengaard et al., 1995; Yuan et al., 1998; Shapiro et al., 1999; Hu et al., 2003; Chiu et al., 2006; Pan et al., 2006) and the remaining studies also reported increased risk but borderline significance (OR ranged from 1.03-1.08) (Kriger et al., 1993; Lindblad et al., 1994; Chow et al., 1996; Maso et al., 2007). Kidney cancer risk according to unit increase in BMI could not be estimated in one study, as BMI category was not specified (Benichou et al., 1998) and thus excluded the study from pooled analysis. Of the 3 studies (McCredie and Stewart 1992; Pan et al., 2006; Maso et al., 2007) that reported dose-response relationship between the BMI and kidney cancer risk, significant association was observed in one study (Pan et al., 2006). There was no evidence of heterogeneity between the case-control studies (p=0.424). The pooled risk estimate was 1.08 (95% CI: 1.06-1.09) per unit increase in BMI (Table 2 and figure 1).

Assessment of validity of the Greenland and Longnecker (1992) method

Three studies have provided kidney cancer risks according to BMI as a continuous as well as categorical variable (VanDijk et al., 2004; Pischon et al., 2006; Lou et al., 2007) . The validity of the above method is assessed by comparing the empirical values of kidney cancer risk according to BMI as a continuous variable which were provided by the above three studies with the values estimated using the above method based on the risks according to BMI categories (Table 3). In one study, same risk was obtained according to BMI as a continuous as

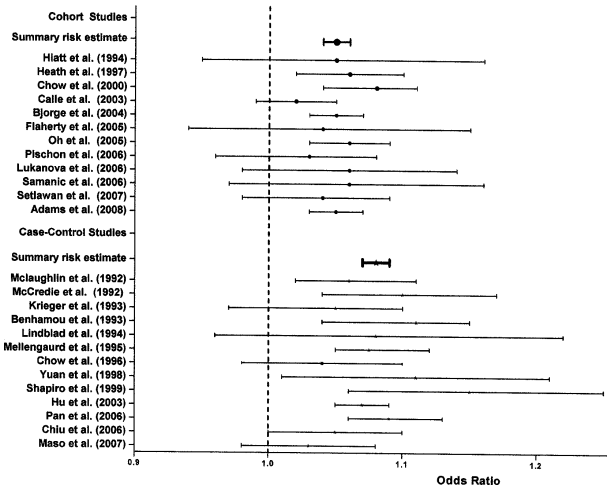

Figure 1. Results of the Summary Analysis of Published Studies on theAssociation between Body Mass Index and Kidney Cancer Risk in Men

Table 1. Association Between Body Mass Index and Kidney Cancer Risk in Men (Cohort Studies)

Author/Country	Category comparison	BMI[1] as a Category		BMI[1] as a Continuous Variable	
		RR	95% CI	RR	95% CI
Adams et.al., 2008	22.5-25.0 vs. 18.5-22.5	1.15	0.85-1.57	1.05	1.03-1.07
USA	25.0-27.5 vs. 18.5-22.5	1.43	1.07-1.92		
	27.5-30.0 vs. 18.5-22.5	1.64	1.22-2.22		
	30.0-35.0 vs. 18.5-22.5	1.87	1.38-2.53		
	>35.0 vs. 18.5-22.5	2.47	1.72-3.53		
Setiawan et.al., 2007	25.0-30.0 vs. <25.0	1.14	0.84-1.56	1.04	0.98-1.09
USA	>30.0 vs. <25.0	1.76	1.20-2.58		
Samanic et.al., 2006	25.0-29.9 vs. 18.5-24.9	1.23	1.08-1.42	1.06	0.97-1.16
Sweden	> 30.0 vs. 18.5-24.9	1.61	1.27-2.04		
Lukanova et al., 2006	24.2-26.7 vs. 18.5-24.1	2.86	0.87-12.8	1.06	0.98-1.14
Sweden	>26.8 vs. 18.5-24.1	3.20	1.01-14.1		
Pischon et al., 2006	23.6-25.3 vs. <23.6	1.07	0.65-1.77	1.03	0.96-1.08
Europe	25.4-27.0 vs. <23.6	0.67	0.39-1.18		
	27.1-29.0 vs. <23.6	0.84	0.49-1.43		
	>29.4 vs. <23.6	1.22	0.74-2.03		
Oh et.al., 2005	23.0-24.9 vs. 18.5-22.9	1.11	0.89-1.38	1.06	1.03-1.09
Korea	25.0-26.9 vs. 18.5-22.9	1.31	1.02-1.67		
	27.0-29.9 vs. 18.5-22.9	1.82	1.37-2.52		
	>30.0 vs. 18.5-22.9	1.42	0.59-3.46		
Flaherty et al., 2005	22.0-24.9 vs. <22.0	2.10	0.70-5.90	1.04	0.94-1.15
USA	25.0-27.9 vs. <22.0	2.40	0.90-6.80		
	28.0-29.9 vs. <22.0	2.10	0.70-6.60		
	> 30.0 vs. <22.0	2.10	0.70-6.80		
Bjorge et al., 2004	25.0-29.9 vs. <24.9	1.18	1.11-1.26	1.05	1.03-1.07
Norway	>30 vs. <24.9	1.55	1.36-1.76		
Calle et.al., 2003	25.0-29.9 vs. 18.5-24.9	1.18	1.02-1.37	1.02	0.99-1.05
USA	30.0-34.9 vs. 18.5-24.9	1.36	1.06-1.74		
	35.0-34.9 vs. 18.5-24.9	1.70	0.99-2.92		
Chow et al., 2000	20.75-21.90 vs. < 20.75	1.20	0.70-1.80	1.08	1.04-1.11
Sweden	21.91-22.85 vs. < 20.75	0.90	0.60-1.50		
	22.86-23.80 vs. < 20.75	1.40	0.90-2.10		
	23.81-24.76 vs. < 20.75	1.60	1.10-2.40		
	24.77-25.95 vs. < 20.75	1.30	0.80-1.90		
	25.96-27.75 vs. < 20.75	1.70	1.10-2.50		
	>27.76 vs. < 20.75	1.90	1.30-2.70		
Heath et al., 1997	24.7-27.7 vs. 20.7-24.6	1.10	0.80-1.60	1.06	1.02-1.10
USA	27.8-31.0 vs. 20.7-24.6	1.60	1.10-2.30		
	>31.1 vs. 20.7-24.6	1.60	0.90-2.70		
Hiatt et al.,1994 USA	> 28.3 vs. < 24.6	1.40	0.70-3.10	1.05	0.95-1.16
Moller et al., 1994,Denmark	Obesity vs. normal[2]	1.20	0.70-1.80		
	Heterogeneity p-value =0.78		Summary RR	1.05	1.04-1.06

[1]BMI, body mass index; [2]Category not specified

well as categorical variable. In the other three studies, the risks estimated based on the Greenland and Longnecker (1992) method slightly overestimated the results.

Discussion

The results of this meta-analysis indicated a moderate excess risk of kidney cancer with increased BMI. The strength of association was almost similar in most of the cohort studies (RR ranged from 1.04-1.06 per unit increase in BMI) and in one study RR was 1.08. A slightly higher risk was observed in most of the case-control studies with a wider variation in the risks (OR ranged from 1.03 to 1.15). Lower value with a narrow confidence interval was observed in the pooled risk based on cohort studies (RR=1.05; 95% CI: 1.04-1.06) compared to the case-control studies (OR=1.08; 95% CI: 1.06-1.09). The variation in the strength of association between kidney cancer risk and BMI could be due to the difference in the confounding variables adjusted for risk estimation. Also, the higher risks in case-control studies point to the presence of selection bias. Moreover, odds ratios always show slightly overestimated figures than risk ratios. These might be the reasons for higher risks reported in case-control studies.

A total of 13 cohort studies were included in the present analysis as against 3 by Bergstrom et al. (2001). In the present analysis we observed slightly a lower pooled risk (RR=1.05) with a narrow 95% confidence interval (95% CI: 1.04-1.06) based on cohort studies as against the previous review (RR=1.07; 95% CI: 1.04-1.09) (Bergstrom et al., 2001). As cohort studies are in principle the most valid study design in observational studies, the results based on cohort studies may be considered as more reliable.

Another strength of the present analysis was that the

Table 2. Association Between Body Mass Index and Kidney Cancer Risk in Men (Case-control Studies)

Author/Country	Category comparison	BMI[1] as a Category		BMI[1] as a Continuous Variable	
		RR	95% CI	RR	95% CI
Maso et al., 2007[2]	25.0-29.9 vs. <25.0	1.14	0.88-1.47	1.03	0.98-1.08
Italy	>30.0 vs. <25.0	1.38	0.79-2.42		
Chiu et al., 2006[3]	22.21-24.25 vs. <22.2	1.30	0.70-2.30	1.05	1.00-1.10
USA	24.26-26.47 vs. <22.2	2.00	1.10-3.50		
	26.48-28.89 vs. <22.2	1.50	0.80-2.80		
	28.90 vs. <22.2	1.70	0.90-3.30		
Pan et al., 2006	25-29.9 vs. 18.5-25.0	2.05	1.55-2.72	1.09	1.06-1.13
Canada	>30.0 vs. 18.5-25.0	2.57	1.80-3.66		
Hu et al., 2003	25.0-29.9 vs. 18.5-24.9	2.20	1.70-2.70	1.07	1.05-1.09
Canada	30.0-34.9 vs. 18.5-24.9	2.80	2.20-3.80		
	35.0-39.9 vs. 18.5-24.9	1.90	1.10-3.30		
	> 40.0 vs. 18.5-24.9	3.70	1.50-9.40		
Shapiro et al., 1999	25.38-27.23 vs.<25.58	1.30	0.70-2.60	1.15	1.06-1.25
USA	27.24-29.48 vs.<25.38	1.20	0.60-2.40		
	>29.48 vs.<25.38	2.30	1.20-4.50		
Benichou et al., 1998[4]	Q2 vs. lowest quartile (Q1)	1.10	0.80-1.70		
USA	Q3 vs. lowest quartile	1.30	0.90-1.80		
	Q4 vs. lowest quartile	1.60	1.10-2.30		
Yuan et. al., 1998	22.0-24.0 vs. <22.0	1.70	1.10-2.50	1.11	1.01-1.21
USA	24.0-26.0 vs. <22.0	1.60	1.10-2.40		
	26.0-28.0 vs. <22.0	2.00	1.30-3.10		
	28.0-30.0 vs. <22.0	2.70	1.70-4.30		
	> 30.0 vs. <22.0	4.60	2.90-7.50		
Chow et al., 1996	23.17-24.41 vs. 23.12	0.80	0.50-1.20	1.04	0.98-1.10
USA	24.68-25.83 vs. 23.12	0.80	0.50-1.40		
	25.84-27.60 vs. 23.12	1.10	0.70-1.70		
	27.80-29.65 vs. 23.12	1.10	0.60-2.00		
	> 29.75 vs. 23.12	1.30	0.70-2.30		
Mellengaardet al.,1995[5]	25.0-27.1 vs. <25.0	1.20	0.90-1.50	1.08	1.05-1.12
Australia, Denmark,	27.1-29.7 vs. <25.0	1.50	1.10-1.90		
Germany, Sweden, USA	>29.7 vs. <25.0	1.40	0.90-1.80		
Lindblad et al., 1994[5]	24.7-26.1 vs. <24.70	0.77	0.42-1.42	1.08	0.96-1.22
Western Europe	26.2-28.7 vs. <24.70	1.58	0.90-2.75		
	>28.7 vs. <24.70	1.08	0.58-2.02		
Benhamou et al., 1993 France	> 27.0 vs. <20.00	2.40	1.00-5.90	1.11	1.04-1.75
Krieger et al., 1993 Canada	> 25.1 vs. <21.50	1.30	0.82-2.20	1.05	0.97-1.10
McCredie et al., 1992	23.05-25.33 vs. <23.05	1.00	0.60-1.50	1.10	1.04-1.17
Australia	> 25.34 vs. <23.05	1.60	1.10-2.50		
Mclaughlin et.al., 1992[6]	19.8-21.9 vs. <19.7	1.40	0.40-5.00	1.06	1.02-1.11
China	22.0-23.3 vs. <19.7	2.70	0.70-10.9		
	>23.3 vs. <19.7	1.70	0.50-5.70		
	Heterogeneity p-value =0.4238		Summary OR	1.08	1.06-1.09

[1]BMI: body mass index; [2]BMI at age 30 years; [3]BMI at age 40 years; [4]Included both gender & OR according to unit change was not calculated, [5]used maximal weight for BMI; [6]BMI at age 50 years

individual studies were controlled for a varying degree of confounders. We included only those studies, which were adjusted for age and smoking. Cigarette smoking is consistently reported with an increased risk of kidney cancer (Lindblad et al., 1994; Chow et al., 1996; Hu et al., 2003; Flaherty et al., 2005; Pischon et al., 2006). Although hypertension and blood pressure are possible confounders of the association between obesity and kidney cancer, only 7 studies (Heath et al., 1997; Shapiro et al., 1999; Chow et al., 2000; Flaherty et al., 2005; Chiu et al., 2006; Samanic et al., 2006; Setiawan et al., 2007) were adjusted for hypertension/ blood pressure. However, since both blood pressure and hypertension could be intermediate steps in the causal pathway, it is not clear if adjustment is desirable. Other factors adjusted in the various studies were alcohol use (Calle et al., 2003; Hu et al., 2003; Pischon et al., 2006; Setiawan et al., 2007), family history of kidney cancer (Chiu et al., 2006; Maso et al., 2007), physical activity (Calle et al., 2003; Pan et al., 2006; Pischon et al., 2006; Setiawan et al., 2007; Adams et al., 2008), energy intake (Calle et al., 2003; Chiu et al., 2006; Pan et al., 2006; Adams et al., 2008), meat intake (Hu et al., 2003; Chiu et al., 2006) and fruits and vegetables intake (Calle et al., 2003; Hu et al., 2003; Chiu et al., 2006; Pan et al., 2006). Thus it is assumed that the bias due to the effect of smoking and other confounders is mostly removed in the pooled risk also.

There can be several arguments in favour of a causal relationship between obesity and the occurrence of kidney cancer. An increased risk was observed in majority of the studies in which we performed a meta-analysis. In addition to the consistency and strength of association, dose-response relationship was observed in most of the studies. Out of 11 studies (McCredie et al., 1992; Chow et al.,

Table 3. Risk Estimation Based on BMI as a Continuous Variable using Categories: Assessment of the Validity of the Method

Author, year & country, gender & type of study	BMI Category	RR (category)	RR[2] (continuous)	RR[3] (continuous)
Pischon et al., 2006, Europe, men, cohort study	23.6-25.3 vs. <23.6	1.07 (0.65-1.77)	1.01 (0.97-1.06)	1.03 (0.96-1.08)
	25.4-27.0 vs. <23.6	0.67 (0.39-1.18)		
	27.1-29.0 vs. <23.6	0.84 (0.49-1.43)		
	>29.4 vs. <23.6	1.22 (0.74-2.03)		
Pischon et al., 2006, Europe, women, cohort study	21.8-23.7 vs. <21.8	1.48 (0.73-3.01)	1.05 (1.01-1.09)	1.06 (1.02-1.15)
	23.8-25.9 vs. <21.8	1.39 (0.69-2.80)		
	26.0-29.0 vs. <21.8	1.99 (1.03-3.88)		
Lou et al., 2007, USA women, cohort study	25.0-29.9 vs. <25.0	1.30 (1.00-1.80)	1.03(1.01-1.05)	1.04(1.02-1.07)
	30.0-34.9 vs.<25.0	1.60 (1.10-2.30)		
	>35.0 vs. <25.0	1.80 (1.20-2.70)		
Van Dijk et.al., 2004 The Netherland, men & women, cohort study				
	23-25 vs <23	0.77 (0.50-1.19)	1.07(1.02-1.12)	1.07(1.02-1.12)
	25-27 vs <23	0.92 (0.61-1.36)		
	27-30 vs <23	1.46 (0.97-2.21)		
	30-33 vs <23	1.04 (0.54-1.99)		

RR[1] based on raw data; RR[2] is estimated based on the Greenland and Longnecker (1992)

2000; Calle et al., 2003; Bjorge et al., 2004; Oh et al., 2005; Lukanova et al., 2006; Pan et al., 2006; Samanic et al., 2006; Maso et al., 2007; Setiawan et al., 2007; Adams et al., 2008) that reported dose-response relationship between BMI and kidney cancer risk, significant association was observed in 9 studies (Chow et al., 2000; Calle et al., 2003; Bjorge et al., 2004; Oh et al., 2005; Lukanova et al., 2006; Pan et al., 2006; Samanic et al., 2006; Setiawan et al., 2007; Adams et al., 2008). Further a biologic plausibility exists, as obesity might be associated with increased risk of kidney cancer through several hormonal mechanisms. Elevated risk associated with obesity included increased levels of estrogens and insulin, a higher concentration of growth factors in the adipose tissue, abnormalities in cholesterol metabolism, and alterations in the immune system (Moyad 2001).

The main limitation of summary analysis concerns the possibility that the included studies are a biased sample of studies in general, since findings of no association are more likely to be unpublished. Another concern is that not all published studies during the period 1992-2008, provided results that could be included in the summary analysis as the specific categories of BMI was not provided (Mellemgaard et al., 1994; Moller et al., 1994; Pan et al., 2004; Van Dijk et al., 2004; Spyridopoulos et al., 2007). However, these studies were also reported increased risk with increased BMI.

Another potential limitation of the present findings is that majority of the studies in the summary analysis used height and weight using self-administered questionnaire. Although such data have been shown to be quite accurate, obese subjects in general under-report, their weight more than non-obese subjects while underweight subjects overestimate their body size. This might lead to non-differential misclassification, which, if anything, only underestimates the true association between obesity and kidney cancer risk and therefore cannot explain the finding of a positive association (Rothman and Greenland 1998). The possibility of differential misclassification (recall bias -i.e. case subjects might report their weight differently than control subjects) may be possibility in the case-control studies, but the consistency of findings from the case-control studies and the cohort studies is a strong argument against recall bias.

Obesity might be associated with increased risk of kidney cancer through several hormonal mechanisms. Increasing BMI is accompanied by elevated levels of fasting serum and free insulin like growth factor-I (IGF-I) (Frystyk et al., 1995). Insulin and IGF-I could both contribute to the growth and proliferation of renal cell cancer (Kellerer et al., 1995). Epidemiological studies indicated that patients with diabetes, which is associated with higher plasma insulin levels, have an increased risk of kidney cancer (Lindblad et al., 1994; Schlehofer et al., 1996).

Obesity also affects the hormonal milieu by increasing levels of free endogenous oestrogen, which may in turn influence renal cell proliferation and growth by direct endocrine receptor-mediated effects, by regulation of receptor concentrations or through paracrine growth factors. However, though potent estrogens have been shown to induce renal tumors in animal models (Stadler and Vogdzang, 1993), there is little epidemiological evidence supporting an association of exogenous estrogens in humans (Mclaughlin and Lipworth, 2000). Obesity could also have other effects on the kidneys. For example, obese individuals have been reported to have higher glomerular filtration rate and renal plasma flow independent of hypertension, which may increase risk for kidney damage (Hall et al., 1994; Ribstein et al., 1995), and therefore make the kidney more susceptible to carcinogens.

In conclusion, the pooled analysis confirmed the evidence of kidney cancer risk with increased BMI in men and obesity may be responsible at least in part for the rising incidence rates. The association may be considered as causal as it supports most of the Hill's (1965) criteria such as consistency, strength of association, dose-response relationship, temporal relationship, and biological plausibility.

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