Obesity and renal cancer incidence and mortality – a systematic review of prospective cohort studies

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▌**Abstract**

Introduction and objective. There have been many studies published recently on obesity and the risk of renal cancer; however, the epidemiological evidence for such an association has not been consistent. Therefore, a systematic review was conducted of the prospective cohort studies to assess the association between obesity and the risk of renal cancer incidence and death.

Materials and methods. A search was conducted of the PubMed database and references to published studies from inception until May 2013. Guidelines for Assessing Quality in Prognostic Studies on the Basis of Framework for Potential Biases were followed for quality assessment of studies included in the systematic review.

Results. Twenty eligible studies were identified and included in the systematic review. Among the 20 selected studies, overall study quality was high. Although the evidence from the prospective cohort studies, linking obesity with renal cancer incidence, has not been entirely consistent, there is a convincing body of data for a positive relationship. Moreover, cumulative data is compelling for a strong positive association between obesity and fatal renal cancer.

Conclusions. There is a relatively consistent amount of evidence that obesity increases the risk of renal cancer and fatal renal cancer. Further research is needed as better understanding of mechanisms by which obesity may influence renal cancer development and progression will aid the fostering of strategies for prevention and treatment of one of the most lethal human malignancies.

▌**Key words**

obesity, renal cancer, incidence, mortality, systematic review

INTRODUCTION

Being overweight and obese have become major public health challenges worldwide [1, 2, 3]. It has recently been estimated that overweight (body mass index (BMI) ≥25 kg/m²) affects more than one billion people, and more than 300 million of them are considered obese (BMI ≥30 kg/m²) [4]. The trend has been continuing to escalate over the last 20 years, both in the United States and Europe, where the prevalence of obesity among adults has doubled [5, 6].

Being overweight and obese are recognised risk factors for many chronic medical conditions and several types of cancer, including colorectal, endometrial and prostate [7, 8, 9, 10, 11, 12]. Their potential link to renal cancer, which represents 2–3% of all cancers in the developed countries, with 88,400 new cases of renal cell carcinoma and 39,300 kidney cancer-related deaths in the European Union in 2008, has attracted the attention of many clinicians [13, 14, 15, 16, 17]. As a result, a large number of studies have been published recently, with three-quarters of the world's publications written over last decade.

The evidence for an association between obesity and renal cancer incidence and mortality, however, has not been consistent. This may result, in part, from the nature of epidemiologic studies, particularly case-controlled or retrospective, which are more prone to a number of biases. In the absence of randomised trials of weight-change interventions, large well-constructed prospective cohort analyses would instead provide the highest level of evidence.

Therefore, to address the issues described above, a systematic review was carried out of the prospective cohort studies on body weight and the risk of renal cancer incidence and mortality.

OBJECTIVE

This review sought to answer the question: 'What evidence is there for an association between obesity and renal cancer incidence and mortality?'

MATERIALS AND METHOD

A systematic review of prospective cohort studies was undertaken in order to accurately identify, evaluate and

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summarise the findings of all relevant studies. To ensure the complete and transparent reporting of this systematic review, the Preferred Reporting Items for Systematic Review and Mata-Analyses (PRISMA) checklist was used as a tool to guide the structure of the review [18].

Search strategy. A comprehensive search strategy was used on the Medline/PubMed electronic database from its inception until May 2013. Additionally, the search was complemented by scanning the reference lists of the identified studies and the reference lists of previous systematic reviews [19, 20, 21].

All human research articles published in English were taken into consideration, not classified as review, meta-analysis, editorial, comment, letter, guideline, or news. The search strategy included the following terms: obesity, overweight, BMI, nutrition disorder, diet, nutrition assessment, risk, incidence, mortality, kidney cancer, renal cancer, renal cell cancer, renal carcinoma and renal cell carcinoma.

To be included in the review, studies had to fulfill the following criteria:
1) have a prospective design;
2) be a cohort study;
3) exposure of interest was weight or BMI at baseline and/or at the end of follow-up;
4) the outcome of interest was a renal cancer and/or fatal renal cancer;
5) hazard ratio (HRs) estimates with 95% confidence intervals (CIs) or, alternatively, continuous relative risk (RR) estimates (with 95% Cls), or alternatively, RR estimates (with 95% Cls).

Data extraction. The following data was extracted from each study: last name of the first author, publication year, country where the study was conducted, cohort size, duration of follow-up, how BMI or body weight was assessed, age at baseline, per cent of overweight and obese subjects, number of renal cancer and fatal renal cancer cases, HRs or RR estimates with corresponding 95% Cls and p values.

Quality assessment. Guidelines for Assessing Quality in Prognostic Studies on the Basis of Framework for Potential Biases were followed for quality assessment of studies included in the systematic review [22]. The potential risk for bias was evaluated within the 6 following domains:
(i)   study participation;
(ii) study attrition;
(iii) prognostic factors measured;
(iv) outcome measurement; confounding measurement and account;
(v)   analysis.

Two authors performed quality assessment independently. There was no disagreement between the two assessments.

RESULTS

Study selection. A flow chart of the selection of eligible studies is given in Figure 1.

Eligibility assessment was performed independently by 2 reviewers, in duplicate. The search strategy yielded 15,185

Records identified through electronic database searching = 1,5175

Additional records identified through manual searches of the bibliographies of selected publications=10

218 studies for analysis of title and abstracts after duplicates removed

170 studies excluded based on title and/or abstract

48 full-text articles assessed for eligibility

28 full-text articles excluded:
Not a prospective cohort study=19
Overlapping studies=5
Relation of weight with cancer not provided=4

20 studies included in qualitative synthesis

Figure 1. Flow diagram of studies identified

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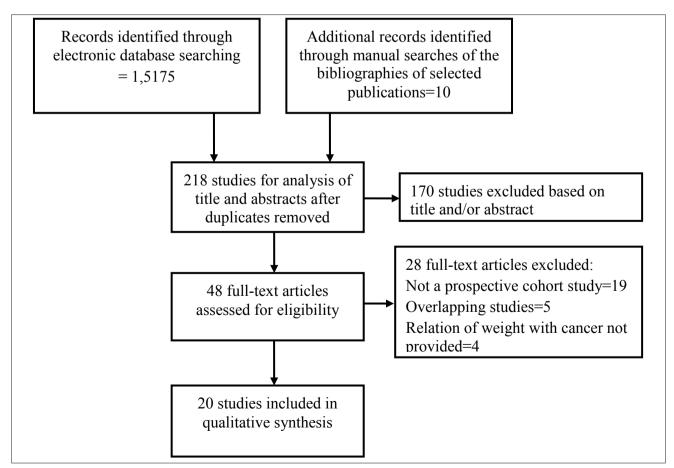
citations, of which 218 were considered potentially relevant. 170 of these were excluded after screening titles and abstracts. The full text of the remaining 48 studies was assessed; of those, 19 were rejected, as the study was not a prospective cohort, and 4 studies did not report on the relation of weight and/or BMI with renal cancer and/or fatal renal cancer. To avoid duplicate information from overlapping studies, 5 studies we removed because their results were pooled or updated. The remaining 20 studies were included in the presented review [23–42]. A chronological overview of the eligible studies is provided in Table 1.

Table 1. Characteristics and results of prospective cohort studies of the association between anthropometric measures and renal cancer incidence and mortality

First author	Year	Study location	Cohort size and gender	Follow-up	BMI Measured or Self-reported	Age range	Percent overweight and obese at baseline	No of cases	Reported HRs(a) or RR (b) for renal incidence	Reported (95%CI) and p value	Reported HRs (a) or RR (b) for renal cancer death	Reported (95%CI) and p value
Leiba	2013	Israel	1,110,835 (M)	15.9	Measured	16-19	12.1% BMI>25	274(I) ?(D)	1.16 for **a** BMI=25.0-27.4 2.43 for BMI≥27.5	(0.72-1.87) P=0.54 (1.54-3.83) p<0.001	?	?
Joh	2011	USA	118,177 (W)	32	Self-reported	30-55	?	330(I) ?(D)	**a** 1.00 for BMI<30 1.22 for BMI≥30	?	?	?
Sawada	2010	Japan	99462 (M+W)	13.5	Self-reported	40-69	27.4% BMI≥25	139(I) ?(D)	Men: **a** 1.39 for BMI=25-26.9 1.99 for BMI≥27 Women: 1.55 for BMI≥25	(0.73-2.63) (1.04-3.81) (0.76-3.18) p=?	?	?
Adams	2008	USA	320,618 (M+W)	8.2	Self-reported	50-71	?	1022(I) (M) 344(I) (W) ?(D)	1.49 for **b** BMI=25-<27.5 1.67 for BMI=27.5-<30 1.97 for BMI=30-<35 2.56 for BMI≥35	(1.19-1.88) (1.32-2.12) (1.56-2.50) (1.95-3.36) p<0.0005	?	?
Song	2008	Korea	152,772 (W)	8.75	Measured	40-64	?	111(I) ?(D)	1.74 for **a** BMI=23.0-24.9 1.74for BMI=25.0-26.9 1.37 for BMI=27.0-29.9 2.61 for BMI≥30	(0.94-3.22) (0.92-3.29) (0.66-2.84) (1.06-6.41) p=?	?	?
Reeves	2007	UK	1,222,630 (W)	5.4 (I) 7.0 (D)	Self-reported	50-64	35.6% (ov) 17.9%(ob)	723(I) 382(D)	1.10 for **b** BMI=25-<27.5 1.19 for BMI=27.5-<30 1.52 for BMI≥30	(0.94-1.28) (0.99-1.44) (1.31-1.77) p=?	1.14 for **b** BMI=25-27.4 1.30 for BMI=27.5-29.9 1.71 for BMI≥30	(0.92-1.42) (1.01-1.68) (1.39-2.09) p=?
Luo	2007	USA	140,057 (W)	7.7	Measured	50-79	?	269(I) ?(D)	1.2 for **b** BMI=25-29.9 1.5 for BMI=30.0-34.9 1.6 for BMI≥35	(0.9-1.7) (1.0-2.1) (1.1-2.4) p =0.01	?	?
Setiawan	2007	Hawaii	75,162 (M) 85,964 (W)	8.3	Self-reported	45-75	Men: 42.5%(ov) 13.8(ob) Women: 30.1%(ov) 18.0%(ob)	220(I) (M) 127(I) (W) ?(D)	Men: **b** 1.14(ov) 1.76(ob) Women: 2.03(ov) 2.27(ob)	(0.84-1.55) (1.20-2.58) p=0.005 (1.31-3.15) (1.37-3.47) p=0.001	?	?
Samanic	2006	Sweden	362,552 (M)	19	Measured	?	?	734(I) ?(D)	1.28(ov) **b** 1.82(ob)	(1.10-1.49) (1.41-2.35)	?	?

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Table 1. Characteristics and results of prospective cohort studies of the association between anthropometric measures and renal cancer incidence and mortality (Continuation)

First author	Year	Study location	Cohort size and gender	Follow-up	BMI Measured or Self-reported	Age range	Percent overweight and obese at baseline	No of cases	Reported HRs(a) or RR (b) for renal incidence	Reported (95%CI) and p value	Reported HRs (a) or RR (b) for renal cancer death	Reported (95%CI) and p value
Pischon	2006	8 European countries	348,550 (M+W)	6.0	Measured and for part self-reported	25-70	25.1% BMI≥26.0	155(I) (M) 132(I) (W)	Men: **b** 0.67 for BMI=25.4-27.0 0.84 for BMI=27.1-29.3 1.22 for BMI≥29.4	(0.39-1.18) (0.49-1.43) (0.74-2.03) p=?	?	?
									Women: 1.99 for BMI=26.0-29.0 2.25 for BMI≥29.1	(1.03-3.88) (1.14-4.44) p=?		
Lukanova	2006	Sweden	33,424 (M) 35,362 (W)	8.2	Measured	29-61	Men: 46%(ov) 11%(ob) Women: 31% (ov) 13% (ob)	25(I) (M) 20(I) (W)	Men: **b** 1.30(ov) 3.63(ob) Women: 0.92(ov) 1.79 (ob)	(0.51-3.56) (1.23-10.66) p=0.02 (0.31-2.58) (0.55-5.27) P=0.37	?	?
Flaherty*	2005	USA	48,953 (M)	12	Self-reported	40-75	52.5%(ov) 7.8%(ob)	110(I)	2.4 for **b** BMI=25.0-27.9 2.1 for BMI=28.0-29.9 2.1 for BMI≥30	(0.9-6.8) (0.7-6.6) (0.7-6.8) p=0.19	?	?
Oh	2005	Korea	781,283 (M)	10	Measured	≥20	?	562(I)	1.31 for **b** BMI=25.0-26.9 1.82 for BMI=27.0-29.9 1.42 for BMI≥30	(1.02-1.67) (1.37-2.52) (0.59-3.46) p<0.001	?	?
Bjørge	2004	Norway	2,001,230 (M+W)	23	Measured	14-74	?	3821(I) (M) 2632(I) (W)	Men: **b** 1.18(ov) 1.55(ob) Women: 1.32(ov) 1.85(ob)	(1.11-1.26) (1.36-1.76) p<0.001 (1.21-1.45) (1.66-2.06) p<0.001	?	?
Van Dijk	2004	Netherlands	120,852 (M+W)	9.3	Self-reported	55-69	?	275(I)	0.92 for **b** BMI=25-26.9 1.46 for BMI=27-29.9 1.04 for BMI≥30	(0.61-1.38) (0.97-2.21) (0.54-1.99) P=0.04	?	?
Niko-demus	2004	USA	34,637 (W)	15	Self-reported	55-69	?	124(I)	1.46 for **b** BMI=25.0-27.4 1.87for BMI=27.4-30.6 2.49 for BMI≥30.6	(0.77-2.74) (1.02-3.41) (1.39-4.44) p=0.0001	?	?
Calle	2003	USA	900,053 (M+W)	16	Self-reported	≥30	?	?(I) 837(D) (M) 473(D) (W)	?	?	Men: **b** 1.18 for BMI=25.0-29.9 1.36 for BMI=30-34.9 1.70 for BMI=35.0-39.9 Women: RR=1.33 for BMI=25.0-29.9 1.66 for BMI=30-34.9 1.70 for BMI=35.0-39.9 4.75 for BMI≥40.0	91.02-1.37) (1.06-1.74) (0.99-2.92) P=0.002 (1.08-1.63) (1.23-2.24) (0.94-3.05) (2.50-9.04) p<0.001

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Table 1. Characteristics and results of prospective cohort studies of the association between anthropometric measures and renal cancer incidence and mortality (Continuation)

First author	Year	Study location	Cohort size and gender	Follow-up	BMI Measured or Self-reported	Age range	Percent overweight and obese at baseline	No of cases	Reported HRs(a) or RR (b) for renal incidence	Reported (95%CI) and p value	Reported HRs (a) or RR (b) for renal cancer death	Reported (95%CI) and p value
Møller	1994	Denmark	43,965 (M+W)	1-4.8	Measured	>0	?	79(I)	Men: 1.2 (ob) Women: 2.0(ob)	**b** (0.7-1.8) (1.5-2.6) p=?	?	?
Whittemore	1985	USA	51,477 (M+W)	16-50	Measured	college	?	Men: 77(I) 31(D) Women 0(I) 0(D)	1.2 for lbs	**b** BW>180 (1.0-1.3) p=?	?	?
Lew	1978	USA	750,000 (M+W)	13	Self-reported	>30	?	?(I) ?(D)	?	?	Men: **b** 1.63 for RBW=110-119% 1.39 for RBW120-129 1.51 for RBW=130-139 Women: 1.09 for RBW=110-119% 1.30 for RBW-120-129 1.85 for RBW=130-139 2.03 for RBW>140%	?

Key: BMI=body mass index; HRs= hazard ratios; RR=relative risk; CI=confidence interval; p=p value;
M=men; W=women; I= renal cancer incidence; D= renal cancer death; Ov=overweight (BMI 25-29.9 kg/m²); Ob=obese (BMI ≥30kg/m²); BW=body weight; RBW=actual weight/average weight;
a= reported hazard ratios; b=reported relative risk;
Follow-up time is given in years; Subjects' age range is given in years and refers to age at the time of study entry (baseline)
*=only male cohort evaluated as female subjects' data is updated in the study by Joh HK et al.

Study characteristics. The selected 20 prospective cohort studies on renal cancer were published between 1978 – 2013 and involved a total of 8,716,689 subjects. In 15 studies, the source of population was the general population [25, 26, 27, 28, 29, 30, 32, 33, 35, 36, 37, 38, 39, 40, 42]; one population was a cohort of university students [41]; one was military recruits [23] and 3 were professional groups [24, 31, 34]. Three studies analysed a potential relationship between weight and renal cancer in men only [23, 31, 35], while 5 limited their investigation solely to women [24, 27, 28, 29, 38]. Almost all populations were more than 90% Caucasian; 3 studies included only Asians [25, 27, 35] and 2 multiethnic populations [23, 30].

In one out of the 20 studies only weight and no BMI analysis was performed [41]. Anthropometric variables were measured in 9 studies [23, 27, 29, 31, 33, 35, 36, 40, 41]; in 10 studies they were self-reported [24, 25, 26, 28, 30, 34, 36, 37, 38, 39, 42]; and in one they were measured or self-reported [32]. A relationship between body weight and the risk of renal cancer and fatal renal cancer was analysed in one study [28]. In 17 studies, only incidence of renal cancer in relation to body weight was evaluated [23, 24, 25, 26, 27, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, 41] and 2 studies examined solely the association between body weight and the risk of fatal renal cancer [39, 42]. The ascertainment of incidental renal cancer was made through linkage to cancer registries in 11 studies [23, 26, 28, 30, 31, 33, 35, 36, 37, 38, 40]. One study relied on self-reported diagnosis [41]. In 4 studies, self-reported diagnosis was verified by linkage with the cancer register or medical records [24, 26, 29, 34]. A mixed system of linkage to cancer and pathology registers, health insurance records and self-reported diagnosis, depending on the study centre considered, was used in one study [32]. The ascertainment of fatal renal cancer cases was made through linkage to death register in 1 study [28]. One study relied on personal enquires successively verified by linkage with death registers [42], and personal enquires or death registers, depending on the length of follow-up period considered, were used in one study [39].

Study synthesis and analysis. Among the 20 selected studies, the overall study quality was high. Assessment of the risk of bias across the studies is presented in Table 2.

A marked positive relationship between anthropometric variables and renal cancer risk in men was reported in 9 studies [23, 25, 26, 30, 31, 33, 35, 36, 41], whereas in women

Table 2. Methodological quality of studies included in the systematic review

First author	Risk of potential bias detected					
	Study participation	Study attrition	Prognostic factors measured	Outcome measurement	Confounding measurement and account	Analysis
Leiba	No	No	No	No	Partly **e**	No
Joh	No	No	Yes **a**	Yes **c**	Partly **f**	Unsure **h**
Sawada	No	No	Yes **a**	Yes **c**	No	No
Adams	No	No	Yes **a**	No	No	No
Song	No	No	No	No	No	No
Reeves	No	No	Yes **a**	No	No	No
Luo	No	No	No	Yes **c**	No	No
Setiawan	No	No	Yes **a**	No	No	No
Samanic	No	No	No	No	No	No
Pischon	No	No	No	No	No	No
Lukanova	No	No	No	No	No	No
Flaherty	No	No	Yes **a**	Yes **c**	no	No
Oh	No	No	No	Yes **c**	No	No
Bjørge	No	No	No	No	Partly **e,g**	No
Van Dijk	No	No	Yes **a**	No	No	No
Nikodemus	No	No	Yes **a**	No	Partly **e,g**	No
Calle	No	No	Yes **a**	No	No	No
Møller	No	No	Yes **b**	No	Partly **e,g**	No
Whitemore	No	No	No	Yes **c,d**	Partly **e,g**	No
Lew	No	No	Yes **a**	Yes **c**	Partly **e,g**	Unsure **h**

Unsure= unable to assess for a potential risk for bias due to lack of data; a= anthropometric variables self-reported; b= obesity measurements not standardized and based on patient appearance; c= possible incompleteness of data; d= possible misclassification of data; e=smoking not included in the multivariate analysis; f= BMI<30 served as a reference level; g=hypertension not included in multivariate analysis; h= confidence interval and p value not reported;

in 10 studies [25, 26, 27, 28, 29, 30, 32, 36, 38, 40]. A modest association between kidney cancer and increased BMI in male and female subjects was found in one study [37]. There was no association, between baseline anthropometric variables and total renal cancer incidence in women in 3 studies [24, 33, 41], whereas obese males were found to have a similar risk for developing renal cancer as individuals with normal weight in 3 studies [32, 34, 40].

A positive relationship between anthropometric variables and fatal renal cancer in men was observed in 2 studies [39, 42], whereas 3 studies reported on a higher risk for kidney cancer death in obese women, when compared with female subjects with normal BMI [28, 39, 42].

DISCUSSION

This systematic review presents epidemiological evidence on the potential role of abnormal body weight in the etiology of renal cancer. In order to provide more conclusive data, and reduce the risk of selection and information bias, the presented assessment was restricted to prospective cohort studies only, and excluded case-control studies. In all, there were 20 studies included in this review. The overall study quality was high. In one study, the cohort size was greater than 2,000,000 subjects, in 2 – >1,000,000 individuals and

in 3 – > 700,000. Their follow-up period varied from 5.4 – 23 years.

The abundance of data gathered in this systematic review supports the hypothesis that obesity may increase the risk of both renal cancer and fatal renal cancer, suggesting an important role for obesity in the initiation and progression of this neoplasm. The pathology underlying the association between obesity and increased risk of renal cancer, however, remains unclear. To-date, several mechanisms have been proposed, one of which suggests the involvement of insulin and insulin-like growth factor-1 (IGF-1), known to have potent cancer-promoting effects [43]. Moreover, oestrogens, as well as polymorphism and genotypic changes of the oestrogen receptor alpha gene, may also play a role [44].

In addition, lipid peroxidation, which is elevated in obese people, has been proposed to be involved in renal cancer development in experimental models; lipid peroxidation of the proximal renal tubules has also been demonstrated to be a necessary mechanistic pathway in chemically-induced renal carcinogenesis [45]. Byproducts of lipid peroxidation have been shown to react with renal DNA to form adducts, which subsequently can damage DNA [46]. This, in turn, may lead to mutations in proto-oncogenes and/or tumor suppressor genes, and result in changing a normal cell into one with a malignant phenotype [47].

Adipose tissue not only stores energy, but also functions as an endocrine organ [48]. Adiponectin, leptin and resistin are adipocyte-secreted peptide hormones that may influence renal cancer development through their demonstrated effects on inflammation, insulin resistanc, cell growth and proliferation [49].

Finally, obesity is related to an increased risk of hypertension, which has been shown to be a risk factor for renal cancer development, most likely independent from increased weight [50].

Strengths and limitations of the review. The presented study has several methodological strengths, namely:
   1) the focused review question;
   2) a comprehensive and systematic literature search;
   3) the collaboration of a multidisciplinary team of urologists, endocrinologist and health researchers, who used explicit and reproducible eligibility criteria and duplicate reproducible eligibility decisions and data extractions;
   4) inclusion of prospective cohort studies only.

This systematic review did not provide a quantitative evaluation of data. Moreover, epidemiological data, even if obtained from prospective cohort studies, may not be completely deprived of selection and surveillance bias. Particularly, studies that failed to use cancer and/or death registries to obtain relevant data, would be more prone to these types of systematic error.

CONCLUSIONS

In conclusion, there is a relatively consistent amount of evidence that obesity increases the risk of renal cancer and fatal renal cancer. Further research is needed for better understanding of the mechanisms by which obesity may influence renal cancer development and progression, and will be an aid to the fostering of strategies for the prevention and treatment of one of the most lethal human malignancies.

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