Obesity and Kidney Cancer

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Abstract

Renal cell cancer (RCC) is the major type of kidney cancer with increasing incidence. Obesity is one of the well-established risk factors for RCC. Meta-analyses including multiple cohort and case–control studies have found a consistent positive association between obesity and RCC. The association appeared to be independent of other RCC risk factors including hypertension and has been often stronger in women, although a positive association has also been observed in men. Obesity has been largely measured as body mass index (BMI). Studies which evaluated other measures of obesity including waist circumference (WC), waist-to-hip ratio (WHR) as well as increase in weight have reported similar positive associations with RCC. Although the mechanisms by which obesity influences renal carcinogenesis have been under-explored, insulin resistance and certain growth factors including insulin-like growth factor (IGF-1), sex steroid hormones, and biochemical markers such as adiponectin may be involved. The positive association with obesity has been observed with

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the clear cell type of RCC, which is the major histological subtype. On the other hand, the association between obesity and RCC survival appears to be much more complex. An apparent inverse association between obesity at time of diagnosis and RCC survival has been observed in some studies, generating speculation of an "obesity paradox" hypothesis. However, this "paradox" may be due to reverse causation, selection bias, or other forms of bias rather than a true biological association.

Keywords
Obesity · BMI · Renal cell carcinoma · Cancer survival · Obesity paradox

1 Introduction

In 2012, there were an estimated 338,000 new cases of kidney cancer worldwide and 144,000 deaths due to kidney cancer [1]. Kidney cancer is made up of renal cell cancer (RCC), which arises from the epithelium of the renal tubules, and cancer of the renal pelvis. Cancers of the renal pelvis appear to have more in common with bladder cancer. Only RCC, which comprises 80–90 % of adult kidney cancers, will be addressed in this chapter.

RCC is itself comprised of multiple histological subtypes including clear cell (75–80 % of cases), papillary (10–15 % of cases), chromophobe, and collecting duct as the most common histological subtypes [2]. While there is some indication that risk factors for these subtypes may differ, few studies have had sufficient case numbers of non-clear cell type RCC to examine them separately.

RCC does not usually show symptoms (pain, hematuria, or constitutional symptoms) until the tumor is relatively large. Locoregional and distant metastatic spread are common at the time of diagnosis. Furthermore, 30–40 % of patients treated with surgery experience relapse with distant metastases. Incidence of RCC has been rising in the USA [3]. Although incidental detection by increased abdominal imaging for many different medical conditions (e.g., hypertension, diabetes) might have contributed to the rising incidence, increase in incidence of all stages of RCC suggests that other factors may also contribute to the increase in incidence [4, 5].

Well-established RCC risk factors include smoking, obesity, and hypertension [6]. Other risk factors relatively recently identified include parity, alcohol consumption, history of diabetes, and use of analgesics. RCC is also more common in men than women [7]. Overweight and notably obesity are well-established risk factors for RCC in both women and men. The proportion of all cases of RCC attributable to overweight and obesity has been estimated to about 40 % in the USA and up to about 30 % in European countries [8, 9].

The majority of epidemiological studies have used body mass index (BMI) as a measure of obesity, though some studies have used WC and/or WHR. Studies have varied in terms of dealing with possible confounding by hypertension and smoking, two other well-established risk factors for RCC; however, the association with obesity appears fairly consistent in spite of differences in study designs and statistical analyses.

The relationship between obesity and survival among RCC patients is much less clear. Many studies have found that obesity measured around the time of diagnosis or treatment is associated with improved survival. The observation of an increased risk of disease but improved survival with obesity has been called an "obesity paradox;" such paradoxes have been described in multiple diseases, including type 2 diabetes [10] and congestive heart failure [11]. However, this "paradox" may be due to reverse causation, selection bias, or other forms of bias rather than a true biological association.

In this chapter, we will review the evidence on obesity and both incidence and survival in RCC and will also discuss possible mechanisms and important methodological issues involved in the study of obesity and RCC.

2 Body Mass Index and Risk of RCC

A 2014 meta-analysis of 21 cohort studies with 15,144 cases and 9,080,052 participants was the most recent and comprehensive meta-analysis of BMI and RCC. The study found increased risks of RCC associated with higher BMI [12]. The pooled relative risk of overweight (BMI 25 kg/m^2 ≤30 kg/m^2) was 1.28 (95 % CI 1.24–1.33) and of obese (BMI ≥ 30 kg/m^2) was 1.77 (95 % CI 1.68–1.87) [12]. There was no evidence of heterogeneity across studies. The Egger's test to test for publication bias showed a possibility of publication bias (p = 0.001), although the Begg's test, another test for publication bias, was not significant (p = 0.16). Relative risks were somewhat stronger for women than for men (RR for obesity of 1.63, 95 % CI 1.50–1.77 for men; 1.95, 95 % CI 1.81–2.10 for women) [12]. The association was also slightly stronger among Asian studies than those conducted in North America or Europe. Although most of the included studies adjusted for age and smoking status, many of the studies did not adjust for some potentially important confounders including hypertension, physical activity, and alcohol consumption. The meta-analysis also omitted a few prospective studies including Rapp et al. (137 cases from Austria) [13], Somanic 2006 (820 cases from Sweden) [14], Kuriyama et al. (5 cases from Japan) [15], and Tulinius et al. (58 cases from Iceland) [16]. An earlier meta-analysis of 17 prospective studies evaluated BMI and incidence of cancer overall. RCC was evaluated as part of it. Many of the studies included overlapped with the 2014 meta-analysis. The three studies omitted in the 2014 meta-analysis were included in this meta-analysis. The meta-analysis found that a 5 unit higher BMI was associated with a 24 % increase in RCC risk for men (95 % CI 15–34 %) and a 34 % increase in risk for women (95 % CI 25–43 %)

[17]. Among the 6 studies that included both men and women, the increase in risk per 5 unit higher BMI was 18 % (95 % CI 8–29 %) in men and 35 % (95 % CI 29–42 %) in women, a statistically significant difference by sex (p value = 0.004) [17]. On the other hand, a dose–response meta-analysis in the American Institute of Cancer Research Continuous Update Project kidney cancer report combined 17 studies (both case–control and cohort) and found a 29 % increased risk for men and a 28 % increase for women associated with a 5 unit higher BMI [18]. Therefore, there was a consistent positive association between BMI and RCC risk in studies conducted in North America, Europe, and Asia in all 3 of the meta-analyses often with dose–response manner. The analyses also consistently reported stronger association in women than in men. The population attributable risks attributable to excess BMI were 11.2 % in men and 17.1 % in women based on data from 30 European countries based on Globocan 2002 [19]. Using the same data, the estimated incident cancer burden attributable to excess BMI (BMI ≥ 25 kg/m^2) was 4520 cases in men and 3786 cases in women.

3 Waist Circumference, Weight Change, and Risk of RCC

WC and WHR provide an estimate of abdominal or central obesity, a powerful contributor to metabolic abnormalities such as insulin resistance and hyperinsulinemia. Several studies have examined WC, WHR, and risk of RCC and found positive associations. [20–24] Four of these studies also examined WC or WHR with adjustment for either BMI or body weight to examine independent effects. In women, two studies found that WHR was significantly associated with RCC risk independent of body weight [20, 23], whereas one study found that WHR was no longer associated with risk upon adjustment for body weight [21]. In men, WHR but not WC was associated with RCC risk in one study, and the WHR associated was independent of body weight [21]. In another study, WC was associated with RCC risk both with and without adjustment for BMI [24]. The AICR Continuous Update Project report meta-analysis combined 3 studies [21, 23, 24] for a relative risk of 1.11 (95 % CI 1.05–1.19) for a 10 cm higher WC [25].

Weight change has been examined in four studies. One study among postmenopausal women found that those who gained weight during the study period were at nonsignificantly increased risk of RCC (adjusted RR 1.3, 95 % CI 0.9–1.8) [23]. In addition, women who gained and lost more than 4.5 kg were at increased risk (adjusted RR 1.5, 95 % CI 1.1–2.0), with increased relative risks for those with more episodes of weight fluctuations [23]. A population-based case–control study also found an association between 2 or more weight loss periods and risk of RCC among women, but not among men [26]. A large cohort study of men and women found that weight gain in early adulthood (18–35 years) and mid-adulthood (35–50 years) was associated with increased risk of RCC, whereas weight gain after age 50 was not related to risk [22]. A population-based case–control study found that weight gain was a risk factor for RCC among women, but not among men [27].

4 Interpretation and Possible Mechanisms for Risk Associations

The findings for BMI and risk of RCC are remarkably consistent. The AICR Continuous Update Project found 21 studies including 30 relative risk estimates for BMI and kidney cancer risk; of these, 28 showed a positive association between BMI and risk, and 14 were statistically significant [25]. The findings for WC and weight change are also quite consistent. While each of these measures has limitations, the consistency across measures suggests a true underlying association between obesity and RCC risk.

It is somewhat difficult to separate the effects of obesity from related risk factors for RCC, particularly hypertension. However, the 2014 meta-analysis found similar associations with obesity among 7 studies that adjusted for hypertension and 14 studies that did not [12]. The relative risk of obesity among studies with adjustment for hypertension was 1.93 (95 % CI 1.74–2.16) and among studies without adjustment was 1.72 (95 % CI 1.62–1.83) [12]. Associations were also consistent across studies with and without adjustment for alcohol intake, smoking, and physical activity. Thus, the association between obesity and RCC appears to be independent of these other RCC risk factors.

The mechanisms by which obesity influences renal carcinogenesis are not clear, but several plausible explanations exist. RCC has been described as a "metabolic disorder" [28]. The genes associated with kidney cancer are all associated with cells' ability to sense oxygen, nutrients, and energy. In addition, type 2 diabetes and hypertension—both of which are also related to metabolic syndrome—are associated with risk of RCC [29]. This suggests a role of insulin along with the interrelated hormonal systems of insulin-like growth factor (IGF) axis, sex hormones, and adipokines.

Obesity is associated with insulin resistance and increased levels of growth factors such as insulin-like growth factor (IGF)-I. It is also related to decreased levels of sex hormone-binding globulin and progesterone and to anovulation in women. The IGF pathway may be especially important for clear cell RCC which is strongly related to the von Hippel–Lindau (VHL) tumor suppressor gene, which in turn helps regulate IGF-I-mediated cell signaling [30]. The VHL tumor suppressor gene leads to an autosomal dominant familial syndrome called VHL syndrome, which is characterized by multiple RCCs. VHL is a critical player in renal carcinogenesis, especially for clear cell type. The VHL gene is directly related to IGF-I-mediated cell signaling, which in turn is inhibited in the presence of the wild-type VHL gene. Sex steroid hormones may affect renal cell proliferation and growth by direct endocrine receptor-mediated effects, by regulation of receptor concentrations, or through paracrine growth factors such as epidermal growth factor. Adiponectin, an adipokine involved in regulating glucose and fatty acid metabolism, has been associated with RCC risk in case–control studies [31, 32] and in a prospective nested case–control study among male smokers [33].

5 Obesity and RCC Subtypes

The association between obesity and histological subtypes of RCC has been examined in only a few studies. An analysis of two case–control studies of RCC, one from the USA and one from Europe, found that BMI was associated with increased risk of clear cell (OR 1.2, 95 % CI 1.1–1.3 per 5 kg/m^2 higher BMI) and chromophobe (OR 1.2, 95 % CI 1.1–1.4) but not papillary RCC (OR 1.1, 95 % CI 1.0–1.2, p value for difference from clear cell = 0.006) [34]. Combined there were 1524 clear cell cases, 207 papillary cases, and 50 chromophobe cases. The US study was a population-based case–control study, and the European study was a hospital-based case–control study. Hospital-based case–control studies of body size measures are difficult due to the wide range of conditions associated with obesity, making selection of controls difficult. However, results were similar when the 2 studies were analyzed separately.

An Italian hospital-based case–control study also found a suggestion that higher BMI at age 30 was more strongly associated with clear cell than with non-clear cell histology (p value for interaction = 0.08) [35]. There were 398 clear cell cases and 147 non-clear cell, of whom 34 % were papillary, 7 % were chromophobe, and 59 % were unclassified. Only 3 of the non-clear cell cases were in the BMI ≥ 30 group at age 30, limiting statistical power in this group. In an analysis of WHR at the time of the study, there were similar positive associations between WHR and RCC risk of both clear cell and non-clear cell subtypes. As this was also a hospital-based case–control study, again the difficulty of appropriately selecting controls for studies of obesity or body size should be noted.

Several clinical cohorts of patients treated surgically for localized RCC have examined the cross-sectional association among cases of obesity at the time of diagnosis and histological subtypes. Among 706 patients surgically treated for localized RCC in Korea, abdominal obesity as measured by visceral adipose tissue percent (VAT%) (measured by CT scan) was associated with relatively more clear cell and chromophobe cases and fewer papillary cases [36]. However, a study of 285 patients found an increased risk associated with higher visceral adiposity of clear cell and papillary, but not chromophobe RCC [37].

Thus, obesity seems to be related to clear cell RCC; this is not surprising given that clear cell is the most common subtype, so it plays a major role in driving the overall association between obesity and RCC risk. The relation of obesity and the less common subtypes is less certain at this point.

6 Obesity and Stage and Grade at Diagnosis of RCC

The American Joint Committee on Cancer (AJCC) TNM staging for RCC, last updated in 2010, stages RCC based on primary tumor size, involvement of adjacent structures (adrenal gland, renal vein, vena cava), involvement of lymph nodes, and distant metastasis for anatomic staging [38]. Stage is a strong predictor of

prognosis; 5-year relative survival is 92 % among those with localized disease, 65 % among those with regional spread, and 12 % with distant metastasis [39].

Multiple grading systems have been suggested in RCC. Fuhrman grade, a four level nuclear grading system put forward in 1982, is the commonly used. It is now used only in clear cell and papillary subtypes and is a prognostic factor for those subtypes independent of stage [40, 41].

Obesity is significantly or suggestively associated with lower stage of disease at diagnosis in most clinical studies that have examined this question [42–50]. While obesity is not always significantly associated with lower T stage, it is almost always associated with less N1 or M1 disease. Several studies also found that obesity was associated with lower risk of presenting with symptoms [42, 45, 48, 49], while only one study found no association between obesity and symptoms at presentation [43], suggesting that obese patients may be more likely to be diagnosed incidentally in the course of other imaging studies.

Obesity is associated with lower grade, though this association is weaker than that seen for stage. Of seven clinical cohorts examining the cross-sectional association between obesity and Fuhrman grade, obesity was associated with significantly lower grade in three studies [42, 45, 47], a suggestive but nonsignificant chance of lower grade disease in three studies [44, 48, 49], and no suggestion of an association with grade in one study [43].

It should be noted that almost all of these studies are of surgically treated patients, so there is some possibility of selection bias if obesity is related to the likelihood of undergoing surgery with curative intent as the primary treatment.

7 Obesity and RCC Survival

Two cohort studies have examined kidney cancer mortality as an outcome, with a combined 1427 deaths [25]. The pooled relative risk per 5 unit higher BMI was 1.32 (95 % CI 1.01–1.71). This was almost identical to the relative risk of kidney cancer incidence of 1.30 found across 21 studies [25]. Unlike these cohort studies of kidney cancer mortality, multiple clinical cohorts of patients treated for RCC have found that in case-only analyses, obesity measured at the time of diagnosis or treatment was associated with improved survival [49, 50]. This has given rise to an "obesity paradox" which stipulates that while obese people are more likely to be diagnosed with RCC, they appear less likely to die of the disease.

A meta-analysis [49] of 15 studies of BMI and cancer-specific mortality found a pooled relative risk of 0.66 (95 % CI 0.53–0.81) for a five unit higher BMI. Almost all of the included studies adjusted for age and stage, and most also adjusted for grade. However, most studies did not adjust for hypertension, and only one adjusted for smoking. There was evidence of significant heterogeneity across studies and evidence of publication bias. The heterogeneity may be partially explained by geographical differences, with a stronger association in Asian compared to European and American studies, and to adjustment for the presence of symptoms at

diagnosis, with a stronger association in studies that adjusted for the presence of symptoms. The association was weaker (less protective) in studies that adjusted for histological subtype. Sex does not appear to have been examined as a source of heterogeneity in the meta-analysis. However, a Japanese study of 435 patients surgically treated for RCC found that obesity was associated with better prognosis in men, but not in women [51].

7.1 Visceral Adiposity

Several clinical studies have assessed survival based on visceral adiposity measured by CT scan around the time of diagnosis. Visceral, or intra-abdominal, fat is more metabolically active and has been associated with poorer health outcomes compared to subcutaneous fat. Two studies of visceral fat area (VFA), an absolute measure of fat mass, found conflicting results. A study of over 2000 patients treated with nephrectomy found that VFA below the median was associated with worse cause-specific and overall survival, independent of stage and grade, among those with stage T3/T4 disease, but not T1/T2 disease [52]. A smaller study of 285 surgically treated non-metastatic RCC patients found that lower VFA was associated with worse survival in T1/T2 disease and in clear cell RCC, but not in the full cohort of T1–T4 disease and across histological subtypes [37]. One other smaller study of 220 clear cell RCC patients found no associations between VFA and overall survival, though as in other studies, BMI was associated with improved survival [53].

A study of 706 surgically treated patients found a U-shaped relation between VAT%—i.e., the proportion of visceral to total adipose tissue—and RCC recurrence, with greater risk among those in the bottom and top quartiles of VAT% [36].

7.2 Histological Subtypes and Survival

A study of 2769 patients surgically treated for non-metastatic RCC in Korea found that higher BMI was associated with significantly improved cancer-specific survival in clear cell RCC, with significantly worse cancer-specific survival in chromophobe RCC, and was not associated with survival in papillary RCC [54]. The lack of association with papillary RCC is consistent with the observations for incidence, as well.

7.3 Interpretation of Associations with Survival Among RCC Patients

It has been hypothesized that obese patients develop a biologically less aggressive disease. Supporting this, a study in a subset of 126 patients from a clinical cohort

surgically treated at Memorial Sloan-Kettering Cancer Center who had data available from The Cancer Genome Atlas Project found significantly lower gene expression of fatty acid synthase (*FASN*) in obese patients [50]. *FASN* expression, in turn, is associated with increased cancer-specific mortality in clear cell RCC. It is worth noting that in this study, obesity was not significantly associated with survival after adjustment for stage and grade at diagnosis. In addition, obese patients in this study and several others were less likely to present with symptoms at the time of diagnosis and were more likely to be diagnosed incidentally (as discussed above). Thus, is it possible that the observed association between obesity and improved survival is because obesity is associated with the increasing trend toward incidental diagnosis of RCC during imaging studies for other medical problems.

In addition, there are several methodological problems that may explain the "obesity paradox," most of which have not been considered in the literature. *Reverse causation* is a major concern, given that the evidence comes from clinical cohorts with measures of obesity at the time of diagnosis or treatment. At that point, there may have been weight loss due to undiagnosed disease, which likely correlates with disease severity. In addition, these clinical cohorts likely suffer from *selection bias*, as they tend to be based among surgically treated RCC patients, rather than among all patients diagnosed with RCC, regardless of treatment strategy. Finally, another form of selection bias is a methodological problem in studies of disease survival when the exposure of interest is also a risk factor for disease incidence. This may arise in case-only survival analysis studying the association between BMI, a risk factor for the disease, and mortality. Because the analysis is done only among people with the disease, this conditioning on disease status can induce a statistical association between BMI and mortality that is not, in fact, a causal association. This form of bias is less intuitive than some of the other possible sources of bias discussed here; it has been explored in the literature with respect to other "obesity paradoxes" in heart disease and type 2 diabetes using methods on causal inference and directed acyclic graphs (DAGs) [55–57].

Given these limitations, the association between obesity and prognosis in RCC should be examined in settings that can include all incident RCC cases, rather than those undergoing a particular primary treatment and with multiple measures of obesity over time. Additional molecular epidemiological studies of tumor markers associated with obesity may also shed light on this issue.

8 Conclusion

Obesity is clearly associated with risk of RCC and particularly with the clear cell subtype. The positive association is seen for both BMI and WC. The association with non-clear cell subtypes is less clear. Possible mechanisms linking obesity and kidney cancer may include IGF-1, sex steroid hormones, and other hormones such as adiponectin. Additional studies of biomarkers and molecular markers in tumors are needed to better understand the relevant mechanisms. An inverse association

between obesity and survival among RCC patients has been observed fairly consistently in clinical cohorts; however, numerous methodological issues make the interpretation of these findings difficult, and more work is needed in this area.

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