



Published in final edited form as:

World J Urol. 2017 January ; 35(1): 51–56. doi:10.1007/s00345-016-1830-6.

## Obstructive sleep apnea and Fuhrman grade in patients with clear cell renal cell carcinoma treated surgically

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### Keywords

clear cell renal cell carcinoma; intermittent hypoxia; sleep apnea syndrome; risk factors

### Introduction

Obstructive sleep apnea (OSA) is a relatively common sleep disorder, with a reported prevalence of 3–7% in the general population [1]. Intermittent hypoxia, a characteristic

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#### Compliance with ethical standards

**Ethical standard:** The creation and retrospective review of the MSKCC Kidney Cancer Database and the Hospital Clínic de Barcelona Database was approved by the Institutional Review Board of each hospital and therefore conforms to the ethical standards laid down in the 1964 Helsinki Declaration and its later amendments. No information with the potential to disclose patient identities was included.

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**Author's contribution:** Vilaseca: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. Nguyen: Data collection or management, Manuscript writing/editing. Vertosick: Data analysis. Corradi: Data collection or management, Manuscript writing/editing. Musquera: Protocol/project development, Data analysis. Pérez: Data collection or management. Fossati: Data collection or management. Sjoberg: Data analysis. Farré: Protocol/project development. Almendros: Data collection or management. Montserrat: Data analysis. Benfante: Data collection or management. Hakimi: Data analysis, Manuscript writing/editing. Skanderup: Data analysis. Russo: Protocol/project development, Manuscript writing/editing. Alcaraz: Protocol/project development, Manuscript writing/editing. Touijer: Protocol/project development, Data analysis.

feature of OSA [2], activates the hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ), a vascular endothelial growth factor (VEGF) regulator and promoter of angiogenesis. It has therefore become a topic of great interest in preclinical cancer research [3]. Recently, a link between OSA and increased cancer incidence [4], aggressiveness [5] and mortality [6] has been described. Biological mechanisms underlying these findings remain incompletely understood.

In a melanoma animal model, intermittent hypoxia was shown to be associated with higher tumor growth [7], metastatic rates [8] and plasma VEGF levels [9] compared to normoxic controls. It was postulated that the resulting hypoxic microenvironment might trigger adaptive cellular mechanisms that largely rely on the transcription of HIF-1 $\alpha$  and its downregulated genes (VEGF, carbonic anhydrase-9 and glucose transporter-1).

Better understanding of the pathophysiology of clear cell RCC (ccRCC) in recent years has shown the important role of HIF-1 $\alpha$  pathways [10,11], which has led to successful application of antiangiogenic drugs targeting VEGF [12] and has promoted the use of other related markers such as carbonic anhydrase-9 as prognostic markers [13]. Thus, HIF-1 $\alpha$  and its downregulated genes have an important role in the pathophysiology of both OSA and ccRCC. Based on these data, a potential link between respiratory disease, hypoxia, and ccRCC is conceivable.

In the present study, we assessed whether patients with ccRCC and OSA had more aggressive disease by assessing the association between OSA and Fuhrman grade and tumor size, two clinical markers of tumor aggressiveness. We then attempted to determine whether OSA affected disease severity, metastasis-free survival (MFS) or cancer-specific survival (CSS).

## Materials and Methods

After obtaining institutional review board approval, we identified 2,997 patients with ccRCC who underwent radical or partial nephrectomy, either at Memorial Sloan Kettering Cancer Center (MSKCC) between 1991 and 2014 (N= 2655) or at Hospital Clínic de Barcelona (HCB) between 1999 and 2012 (N= 342). Patients were excluded if they had metastasis at diagnosis (n=15) or were missing follow-up (n=7), American Society of Anesthesiologists (ASA) score (n=124) or Fuhrman grade (n=272). Our final cohort consisted of 2,579 patients.

Baseline patient characteristics, including age, gender, body mass index (BMI), ASA score, history of smoking, and history of OSA, were collected from a prospectively maintained MSKCC database and a retrospective HCB database. Information on OSA was ascertained from a prior clinical diagnosis in the patient's medical records.

Pathologic data included Fuhrman grade (defined as low [Grade 1 and 2], high [Grade 3 and 4] and intermediate [those who had both Grade 2 and 3 in the pathology report]), tumor size, and stage according to the 2006 American Joint Committee on Cancer TNM classification system [14].

To gain more insight into the biological significance of our results, we applied Gene Set Enrichment Analysis (GSEA) [15] from RNASeq data in 4 patients with OSA compared to 120 without OSA, all of them from the MSKCC cohort profiled in the ccRCC Cancer Genome Atlas (TCGA) cohort [16]. All data were downloaded through the TCGA data portal (<http://tcga-data.nci.nih.gov/tcga/findArchives.htm>) and linked with patient characteristics. All gene sets (MSigDB) of size 15 to 500 genes (n = 5332 gene sets) were used in the GSEA. Student t test was used to quantify differential gene expression between the two groups. To account for gene–gene correlations in the enrichment analysis, gene set enrichment P values were computed with respect to a null distribution obtained from 1000 randomizations of the patient phenotype labels.

### Statistical analyses

Chi-square and Mann-Whitney U tests were used to compare baseline and pathologic variables between patients with and without OSA. Chi-square and linear regression were used to compare baseline characteristics between tumor grades. Univariate linear and logistic regression models were used to assess whether OSA was associated with tumor size or high Fuhrman grade. A non-parametric trend test was used to assess the association between OSA and Fuhrman grades from 1 to 4. To determine whether an association between OSA and disease aggressiveness was driven by behavioral habits/lifestyle factors, cellular changes due to hypoxia, or a combination of both factors, we created multivariable linear and logistic regression models. We assessed whether OSA was associated with tumor size or grade when controlling for factors known to be associated with RCC such as gender and age (per 10-yr increments) and factors we believed represented patient behaviors that may lead to diagnosis with more aggressive disease such as BMI (continuous), ASA score (I/II vs III/IV), and smoking history (yes/no).

In our cohort, only 69 patients were classified as having intermediate grade disease. Since there were so few patients in this group, we assessed both low and intermediate versus high grade, and low versus intermediate and high grade.

MFS and CSS estimate rates were calculated using the Kaplan-Meier method and compared using a log-rank test. To assess whether OSA was associated with survival through a pathway other than an association between OSA and more aggressive disease, we generated multivariable Cox regression models to test whether OSA was independently predictive of oncologic outcome when controlling for tumor size and Fuhrman grade. To test whether OSA is significantly associated with decreased MFS or CSS in intermediate/high grade patients only, an interaction term between Fuhrman grade and OSA was added in the Cox regression model. MFS was modeled for all patients in the cohort. CSS models were based on MSKCC patients only, since information on cause of death was not available for all patients from HCB. All analyses were performed using Stata 13 (StataCorp, College Station, TX, USA).

### Results

Of 2,579 patients, 172 (7%) had OSA, which is in line with the self-reported prevalence of OSA in the general population [17]. They were more likely to be male and to have higher

BMI and ASA score (all  $p < 0.0001$ ) (Table 1). Furthermore, the distribution of Fuhrman grade categories was significantly different between patients with ccRCC who had OSA vs those who did not ( $p = 0.003$ ). OSA was associated with high Fuhrman grade, with a risk difference of 13% (95% confidence interval [CI] 5%–20%). When including patients with intermediate Fuhrman grade in the high-grade group, the association was similar, with a risk difference of 11% (95% CI 3.4%–19%). However, OSA was not associated with either pathologic stage or tumor size (Table 1).

The covariates included in our multivariable model independently associated with Fuhrman grade were gender, age, smoking history, tumor size and ASA scores (Supplemental Table).

OSA was found to be predictive of both intermediate/high Fuhrman grade and high Fuhrman grade alone on univariate analysis ( $p = 0.004$  and  $p = 0.001$ , respectively). When controlling for known risk factors and behavioral risk factors on multivariable analysis, the association between OSA and high Fuhrman grade remained significant (Table 2).

Consistent with these results, we found that the prevalence of OSA was significantly higher in patients with higher grade tumors. The rate of OSA was 4.9% in grade 1 patients, 5.6% in grade 2, 8.4% in grade 3, and 8.7% in grade 4 (non-parametric trend test,  $p = 0.006$ ).

We found no evidence that OSA was a significant predictor of tumor size on either univariate or multivariable analysis ( $p = 0.6$  and  $p = 0.9$ , respectively).

We then compared survival outcomes of patients with ccRCC who had OSA with those who did not have OSA. Median follow-up among all survivors was 4.2 yr (interquartile range [IQR] 1.6–7.3). Overall, MFS and CSS estimates were not significantly different between the two groups ( $p = 0.4$  and  $p = 0.5$ , respectively) (Supplemental Figures 1 and 2). Similarly, Cox regression models failed to show an association between OSA and MFS or CSS ( $p = 0.5$  and  $p = 0.4$ , respectively). Subsequently, we tested whether OSA was associated with poorer oncologic outcomes in intermediate/high-grade patients only, using an interaction term between Fuhrman grade and OSA in the multivariable Cox regression models, and found no evidence that OSA is associated with poorer MFS or CSS in this subgroup ( $p > 0.9$  and  $p = 0.9$ , respectively).

The GSEA analysis to check for biological plausibility showed a trend ( $p = 0.08$ ) towards VEGF pathway enrichment in the OSA group (Supplemental Figure 3).

## Discussion

Fuhrman grade is one of the most accepted prognostic factors in RCC [18]. Our results indicate that a history of OSA is associated with higher Fuhrman grade in patients with ccRCC. To our knowledge this is the first study assessing the association of OSA and adverse pathologic features of ccRCC.

The first indication that OSA may be associated with cancer has come from a multicenter study from Spain that suggested an increased incidence of colorectal, prostate, lung and breast cancer in patients with OSA [4]. Furthermore, cancer mortality has been correlated

with the severity of OSA in a large cohort study from Wisconsin [6]. Along these lines, an association between OSA and aggressive features of cancer has recently been postulated. Martínez-García et al. performed diagnostic sleep tests in 56 patients with cutaneous malignant melanoma in order to evaluate the association of dermatological and pathological features with sleep disorders [19]. This study found a higher incidence of OSA in the subgroup of patients with faster tumor growth rate. Importantly, the authors demonstrated a positive association between the severity of OSA defined by the apnea-hypopnea index and the nocturnal oxygen desaturation indexes (ODI<sub>3%</sub> and ODI<sub>4%</sub>) and markers of aggressiveness of malignant melanoma, namely the Breslow index, tumor growth rate and mitotic index. These results parallel our findings for ccRCC, supporting the notion that OSA may be a risk factor for the development of aggressive cancer phenotypes. We found that a significantly higher proportion of patients with OSA had high Fuhrman grade compared to patients without OSA. For the analyses of both intermediate and high-grade and high-grade alone, the magnitude of effect and confidence intervals were very similar. The more moderate effect seen on multivariable analysis was likely due to confounding between Fuhrman grade, OSA and the covariates included in the multivariable model. Patients with OSA were more likely to be male and more likely to have ASA scores of III or IV, while these characteristics were also associated with a higher likelihood of having a higher-grade tumor [20]. Since these two characteristics are associated with both OSA and grade, controlling for these factors and for lifestyle risk factors (BMI and smoking history) in our multivariable analysis, reduces the strength of the association between OSA and Fuhrman grade in both models. This indicates that while a patient's health habits can be a risk factor for high-grade disease, there may also be an effect of OSA on Fuhrman grade that is unrelated to the correlation between OSA, obesity, and lifestyle risk factors.

On the other hand, we found no independent association between OSA and MFS or CSS. This could be due to the relatively low number of patients with OSA or low number of events (metastasis and death), so the statistical power of larger, prospective studies is required to more definitively test for an independent association between OSA and survival differences. Several hypotheses could influence these results. First, we should take into account the effect of behavioral confounders. OSA is associated with obesity, and obesity is often associated with other unhealthy habits (smoking, high sodium or high fat/cholesterol diets). Thus, these patients could potentially be less health-conscious and present later with more advanced disease, or less likely to follow up after surgery and therefore less likely to be diagnosed with metastases, which could explain why we see an association between OSA and grade but not between OSA and MFS. Another hypothesis is the 'obesity paradox' phenomenon described in ccRCC. This phenomenon means that obesity, a risk factor of kidney cancer, is paradoxically associated with longer survival rates [21]. Obesity is positively associated with OSA, and therefore, an interesting interaction between obesity, hypoxia and tumor behavior should be further explored.

Mouse models and in vitro studies provided experimental correlates to the potential role of OSA in malignant melanoma [7–9, 22]. Almendros et al. created a mouse model of sleep apnea by applying intermittent hypoxia to melanoma-injected mice, while a control group was submitted to normoxic air [7]. Intermittent hypoxia resulted in an almost two-fold increase in tumor weight after 14 days. Using the same model, the authors demonstrated in a

separate study that intermittent hypoxia caused a more than five-fold increase in the number of metastases per lung area after 30 days [8]. Recently, it has been hypothesized that tumor-associated macrophages play a regulatory role on cancer cells under intermittent hypoxia [22] and sleep fragmentation [23].

Similarly, biologically plausible links between OSA, intermittent hypoxia and ccRCC exist. Under normal conditions, the Von Hippel-Lindau protein (VHL) acts as the substrate recognition protein of the E3 ubiquitin ligase complex, and induces the ubiquitination of the HIF- $\alpha$  subunit, leading to proteasomal degradation [24]. In ccRCC, VHL is downregulated, leading to HIF- $\alpha$  accumulation in the cell cytoplasm and translocation to the nucleus, where it activates the hypoxia adaptive response [25]. This pathway triggers the transcription of genes responsible for glycolysis and angiogenesis such as VEGF, thereby promoting tumor growth and survival [26]. Interestingly, the same adaptive response increasing HIF [27] and VEGF [28] levels has been described under conditions of intermittent hypoxia, leading to tumor growth and invasion potential [3]. In a subgroup of patients from our cohort we saw a trend towards VEGF pathway enrichment, although further research with larger patient samples is necessary.

While the present study is the first to investigate the relationship between OSA and aggressive features of ccRCC in a large cohort of patients, several limitations should be discussed. First, the presence of OSA was retrieved from prior clinical diagnosis. Despite the lack of a validated diagnostic tool, however, the prevalence of OSA in our cohort (7%) was in line with the self-reported prevalence of OSA in the general population [17]. A more accurate diagnosis of OSA would include information on its severity, time from diagnosis and treatment received. Observational studies with long-term follow-up find increased risk of all cause mortality compared to those with shorter follow-up. This may be explained by the accumulated effects of OSA [29, 30]. Although there is no evidence of the effect of treatment on cancer incidence, uncontrolled studies suggest that treatment with continuous positive airway pressure is able to reduce the number of cardiovascular events, including arrhythmias, myocardial infarction and stroke [30, 31].

Second, we included only patients undergoing partial or radical nephrectomy. While this design allowed the precise assessment of Fuhrman grade for all patients, it remains to be seen if our findings can be generalized to all patients with ccRCC. Although this type of cohort would include most of the patients diagnosed with localized ccRCC, it may be excluding patients with either advanced disease or low-risk disease that were not considered for surgery. Lastly, the assessment of Fuhrman grade suffers from inter and intraobserver variability and could have biased the results in a long-period study from different institutions.

## Conclusions

In our study OSA was associated with higher Fuhrman grade in patients undergoing radical or partial nephrectomy for ccRCC. Our study offers a clinical correlate to experimental evidence highlighting hypoxia-related pathways in the pathogenesis of ccRCC. If validated in further prospective studies, our findings could help to stimulate future research in this

field that will help understanding etiological mechanisms and maybe delineate novel treatment targets for ccRCC.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We thank Amy Plofker for her reviews on the manuscript and Felisa Alcázar for her help in collecting data.

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Table 1  
Clinicopathologic characteristics of 2,579 patients undergoing surgery for clear cell renal cell carcinoma.

	All N = 2579	No OSA N = 2407 (93%)	OSA N = 172 (7%)	p value
Age, yr Median (IQR)	61 (52–70)	61 (52–70)	59 (52–65)	0.06
Female gender, no. (%)	866 (34)	838 (35)	28 (16)	<0.0001
BMI, kg/m <sup>2</sup> (N = 2460) Median (IQR)	29 (26–33)	29 (26–33)	32 (29–39)	<0.0001
Smoking history	1363 (53)	1276 (53)	87 (51)	0.5
ASA score, n (%)	I	131 (5.1)	128 (5.3)	3 (1.7)
	II	1252 (49)	1207 (50)	45 (26)
	III	1136 (44)	1022 (42)	114 (66)
	IV	60 (2.3)	50 (2.1)	10 (5.8)
Fuhrman grade, n (%)	Low	1498 (58)	1416 (59)	82 (48)
	Intermediate	69 (2.7)	67 (2.8)	2 (1.2)
	High	1012 (39)	924 (38)	88 (51)
Pathologic stage (N = 2575), n (%)	T0	1 (<0.1)	1 (<0.1)	0
	T1	1734 (67)	1623 (68)	111 (65)
	T2	147 (5.7)	141 (5.9)	6 (3.5)
	T3	667 (26)	612 (25)	55 (32)
	T4	20 (0.8)	20 (0.8)	0
	TX	6 (0.2)	6 (0.2)	0
Tumor diameter, cm, median (IQR)	4.0 (2.5–6.0)	4.0 (2.5–6.0)	3.8 (2.5–6.2)	0.9
Institution, n (%)	MSKCC	2324 (90)	2165 (90)	159 (92)
	HCB	255 (10)	242 (10)	13 (7.6)

OSA, obstructive sleep apnea; IQR, interquartile range; BMI, body mass index; ASA, American Society of Anesthesiologists; MSKCC, Memorial Sloan Kettering Cancer Center; HCB, Hospital Clínic de Barcelona.

Univariate and multivariable logistic regression models for the association between OSA and Fuhrman grade. The multivariable model was adjusted for age, female gender, BMI, smoking history, ASA score and tumor size.

**Table 2**

	Intermediate or High Grade			High Grade Only		
	OR	95% CI	p value	OR	95% CI	p value
Univariate						
OSA	1.57	1.15, 2.14	0.004	1.68	1.23, 2.29	0.001
Multivariable						
OSA	1.37	0.97, 1.93	0.077	1.41	1.00, 1.99	0.048

OSA, obstructive sleep apnea; BMI, body mass index; ASA, American Society of Anesthesiologists