

Press release, European Association of Urology

[How a bad night's sleep might worsen cancer development](#)

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Recent studies have indicated that patients with sleep apnea may be associated with worse cancer outcomes. Now a new animal study, presented at the Annual Congress of the European Association of Urology in Munich, uncovers a possible mechanism which may underlie this link.

Hypoxia is where a tissue or organ does not get enough oxygen. It is one of the consequences of sleep apnea, which is a common disorder in which you have one or more pauses in breathing or shallow breaths while you sleep. Sleep apnea has been associated with increases in the risk of several conditions, such as high blood pressure or stroke. Recently some evidence has also linked it to worse cancer outcomes, although there is some conflicting evidence on this. The possible mechanism linking apnea to worse outcomes is not known, although it is known that patients suffering from obstructive apnea usually suffer from intermittent hypoxia.

Now a group of Spanish-US researchers have used a mouse model to show that intermittent hypoxia promotes the formation of blood vessels within tumours, probably due to an increased production of Vascular endothelial growth factor (VEGF). VEGF is known to promote blood vessels formation.

A team led by Dr Antoni Vilaseca (Hospital Clínic De Barcelona, Spain) took 12 experimental and 12 control mice with kidney tumours and subjected them to varying oxygen levels to mimic intermittent hypoxia. They found that the mice which had been subjected to intermittent hypoxia showed increases in vascular progenitor cells ($6,1 \pm 0,76$ vs $4,5 \pm 1,1$; $p=0,001$) and endothelial cells ($4 \pm 0,8$ vs $2,5 \pm 1$; $p=0,013$) within the tumours; these cells may later mature to form blood vessels in the tumours. Circulating VEGF was also increased in the mice which had undergone hypoxia (306 ± 93 vs 204 ± 45 pg/mL; $p=0,001$), although other factors such as tumour growth, were not affected.

Lead researcher Dr Vilaseca said:

"Patients suffering from obstructive sleep apnea usually suffer from intermittent hypoxia at night. This work shows that intermittent hypoxia has the potential to promote the formation of blood vessels within tumours, meaning that the tumours have access to more nutrients."

This is of course an early animal study, so we need to be cautious in applying this to humans. Nevertheless, this work indicates a plausible mechanism for just why conditions which restrict oxygen flow to tissues, like sleep apnea, may promote cancers".

Commenting, Professor Arnulf Stenzl (Tübingen), Chair of the EAU Congress Committee, said:

"Although this is an experimental study, it is remarkable, because it demonstrates the influence of oxygen deficiency on the growth of renal cell carcinoma tissue (both primary tumour as well as metastases). It may be postulated that increased oxygenation of the blood may be the underlying mechanism why not smoking or giving up smoking, regular sport activity (especially endurance type

sports), reducing the body mass index and other life style changes that increase tissue oxygenation have a supportive beneficial effect on better outcomes in renal cell cancer as well as other tumour types”.

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Notes for Editors

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Contacts

Dr Antoni Vilaseca Cabo tonivilaseca@hotmail.com

Professor Arnulf Stenzl eau@stenzl.net

EAU Press Officer, Tom Parkhill: tom@parkhill.it telephone +39 349 238 8191

The 31st Annual EAU Congress takes place in Munich from 11th to 15th March. This is the largest and most important urology congress in Europe, with up to 13,000 expected to attend: eau16.org.

Abstract Nr: 218 Intermittent hypoxia increases tumor angiogenesis in a mouse model of kidney cancer

Vilaseca Cabo, A.1, Musquera, M.1, Torres, M.2, Campillo, N.2, Gozal, D.3, Montserrat, J.4, Touijer, K.5, Farré, R.2, Almendros, I.2, Alcaraz, A.1
1Hospital Clínic De Barcelona, Dept. of Urology, Barcelona, Spain, 2Universitat De Barcelona, Dept. of Biophysics and Bioengineering, Barcelona, Spain, 3University of Chicago, Dept. of Sleep Disorders, Chicago, United States of America, 4Hospital Clínic De Barcelona, Dept. of Pneumology, Barcelona, Spain, 5Memorial Sloan-Kettering Cancer Center, Dept. of Urology, New York, United States of America

Introduction & Objectives Intermittent hypoxia (IH), a characteristic feature of obstructive sleep apnea (OSA), has been recently associated with an increased cancer aggressiveness and mortality. Renal cell carcinoma is commonly linked to an increased expression of hypoxia-inducible genes promoting neovascularization, and can result in poorest prognosis. We aim to assess the role of IH on tumor angiogenesis as a marker of malignancy in a mouse model of renal cell carcinoma and to study in vitro the role of isolated tumor cells on promoting angiogenesis under IH.

Material & Methods A subcutaneous kidney cancer was induced in 24 Balb/c mice by injecting 10⁵ RENCA cells in the left flank. Twelve mice were subjected to IH (cycles of 20s at 5% O₂ followed by 40s at 21% O₂, 6h/day) from 15 days before injection until 21 days after injection, when they were sacrificed. A control group (n=12) was kept under normoxia for the same period of time. After sacrifice, tumors were excised and processed to evaluate the presence of endothelial progenitor cells (CD309+Gr1+) and endothelial cells (CD31+) by flow cytometry. Circulating vascular endothelial growth factor (VEGF) was quantified by ELISA. We also tested in vitro the hypothesis that isolated RENCA cells subjected to IH increase VEGF production. We seeded 5x10⁴ RENCA cells/well in two 6-well plates. After 12 hours we kept for 24 hours each 6-well plate under normoxia and IH, respectively. Supernatant VEGF quantification was done by ELISA.

Results Percentage of vascular progenitor cells in tumoral tissue was increased under IH compared to normoxia (6,1 ± 0,76 vs 4,5±1,1; p=0,001). Similarly, the percentage of endothelial cells was also promoted by IH (4±0,8 vs 2,5±1; p=0,013). Plasma VEGF was significantly higher among the IH group (306±93 vs 204±45 pg/mL; p=0,001). Tumor growth was not affected by IH (0,7±0,6 vs 0,8±0,42 gr; p=0,08). In the in vitro experiments, VEGF in the supernatant after 24h of culture did not differ between IH and normoxia (719±63 vs 729±192 pg/mL; p=0,912).

Conclusions In the animal model, IH increases the production of circulating VEGF and the mobilization of vascular progenitor cells, resulting in an increased vascularization of the tumor. In vitro, isolated tumor cells do not increase VEGF production under IH compared to normoxia.