Siguiendo el concepto de personalización del tratamiento propuesto por GesEPOC, nuestro planteamiento podría cobrar especial relevancia en aquellos individuos de AR-SpO_2 <92% en los que la terapia de inicio recomendada fuera un β2-agonista de acción prolongada-corticoide inhalado, hecho que ocurre en el fenotipo EPOC-asma. Dichos sujetos podrían beneficiarse de un inicio precoz de una doble broncodilatación, al margen del impacto clínico que pudiera alcanzarse con el corticoide inhalado. Por otro lado, sin ser un objetivo del análisis, debemos destacar que en el grupo de BR existían enfermos con SpO_2 <92% (9 pacientes). Si bien era un porcentaje muy bajo de pacientes, consideramos que podrían ser necesarios futuros estudios que profundicen en su caracterización para así evaluar su relevancia clínica.

El trabajo actual tiene limitaciones, y sirve esencialmente para generar debate. Es un estudio retrospectivo y está realizado en un único centro. El número de pacientes de BR fue muy bajo, no pudiendo emplear la variable SpO_2 en estos sujetos. No podemos descartar que a lo largo del seguimiento a muchos de estos enfermos se le prescribiera OCD, lo que podía haber influido en las cifras de mortalidad descritas. Con intención de no restar potencia estadística, no fue posible estratificar a los pacientes según los rangos de valores de SpO_2. A pesar de dichas limitaciones, consideramos que nuestros resultados podrían ser un punto de partida para estudios adecuadamente diseñados que valoren el hecho de añadir la variable SpO_2 a los clásicos criterios de AR.

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Bibliografía

1. Miravitlles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Guía española de la enfermedad pulmonar obstructiva crónica (GesEPOC) 2017. Tratamiento farmacológico en fase estable. Arch Bronconeumol. 2017;53:324–5.
2. Cabrera López C, Casanova Macario C, Marín Trigo JM, de-Torres JP, Torres RS, González JM, et al. Prognostic validation using GesEPOC 2017 severity criteria. Arch Bronconeumol. 2019;55:409–13.
3. Golpe R, Suárez-Valor M, Castro-Añón O, Pérez-de-Llano LA. Risk stratification in chronic obstructive pulmonary disease. Can the Spanish guidelines be improved? Arch Bronconeumol. 2018;54:533–5.
4. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: A clinical trial. Nocturnal Oxygen Therapy Trial Group. Ann Intern Med. 1980;93:391–8.
5. Lee WW, Mayberry K, Crapo R, Jensen RL. The accuracy of pulse oximetry in the emergency department. Am J Emerg Med. 2000;18:427–31.
6. Garcia-Gutierrez S, Unzurrunzaga A, Arostegui I, Quintana JM, Pulido E, Gallardo MS, et al. The use of pulse oximetry to determine hypoxemia in acute exacerbations of COPD. COPD. 2015;12:613–20.
7. Global strategy for the diagnosis, management and prevention of COPD. Global initiative for chronic obstructive lung disease. 2019 Report [consultado 31 Ago 2020]. Disponible en: https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf.
8. Kim V, Benditt JO, Wise RA, Sharafkhaneh A. Oxygen therapy in chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5:513–8.
9. Gibson GJ. Clinical Tests of Respiratory Function. 3rd ed London: Hodder Arnold; 2009.
10. Flenley DC, Franklin DH, Millar JS. The hypoxic drive to breathing in chronic bronchitis and emphysema. Clin Sci. 1970;38:503–18.
11. Macrea MM, Owens RL, Martin T, Smith D, Oursler KK, Malhotra A. The effect of isolated nocturnal oxygen desaturations on serum hs-CRP and IL-6 in patients with chronic obstructive pulmonary disease. Clin Respir J. 2019;13:120–4.
12. Gologanu D, Ionita D, Daha I, Barbu M, Croitoru A, Bogdan M. Benefits of pulmonary rehabilitation on exercise desaturation in COPD patients. Eur Respir J. 2014;44:629.
13. Lehmann S, Ringbæk T, Løkke A, Grote L, Hedner J, Lindberg E. A randomized trial to determine the impact of indacaterol/glycopyrronium on nighttime oxygenation and symptoms in patients with moderate-to-severe COPD: The DuoSleep study. Int J Chron Obstruct Pulmon Dis. 2019;14:199–210.
14. Sposato B, Franco C. Short term effect of a single dose of formoterol or tiotropium on the isolated nocturnal hypoxemia in stable COPD patients: A double blind randomized study. Eur Rev Med Pharmacol Sci. 2008;12:203–11.
15. Canto ND, Ribeiro JP, Neder JA, Chiappa GR. Addition of tiotropium to formoterol improves inspiratory muscle strength after exercise in COPD. Respir Med. 2012;106:1404–12.

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Sleep Duration and Cutaneous Melanoma Aggressiveness. A Prospective Observational Study in 443 Patients

Duración del sueño y agresividad del melanoma cutáneo. Un estudio observacional prospectivo con 443 pacientes

Dear Editor,

Both short and long sleep duration have been associated with an increased prevalence and incidence of cancer,[1,2] but its relationship with cancer aggressiveness remains unknown. We have previously described an association between cutaneous melanoma and sleep-disordered breathing based on a prospective multicentric cohort.[3] In the present paper, we describe the results of a post-hoc analysis aiming to evaluate the association between subjective sleep duration and objective parameters of melanoma aggressiveness.

This is an observational, cross-sectional, multicenter study that included 443 consecutive patients with a diagnosis of melanoma from 29 Spanish hospitals. Patients were excluded if they had in situ melanoma or had received previous treatment with continuous positive airway pressure. The study was approved by the ethics committees of all the hospitals, and all the patients gave their informed consent. Each patient completed a clinical questionnaire which included anthropometric measurements, relevant antecedents, medication, sleep apnea symptoms, presence of insomnia and somnolence (Epworth Sleepiness Scale).
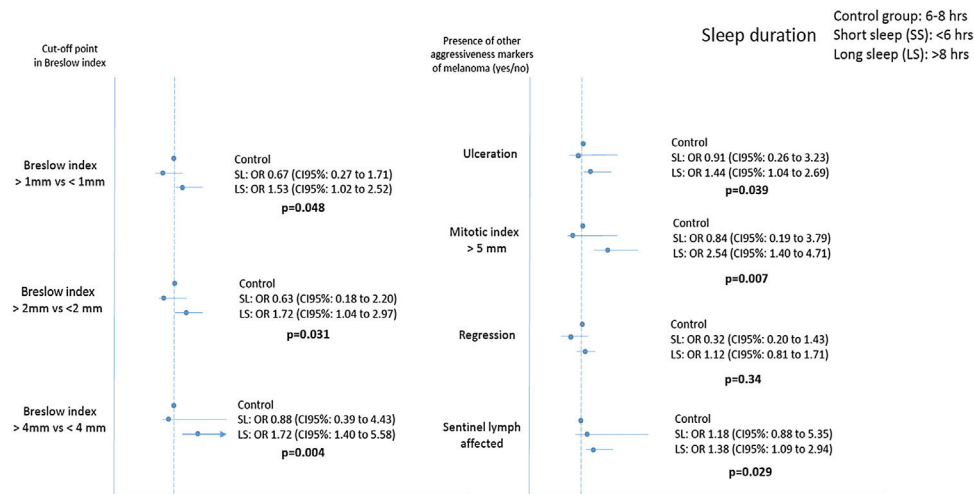
Fig. 1. Relationship between sleep duration and commonly used clinical markers of tumor aggressiveness in cutaneous melanoma. *p* values refer to sleep duration > 8 h versus control group (sleep duration between 6 and 8 h). Results were adjusted for age, sex, apnea-hypopnea index, body mass index, presence of insomnia and intake of hypnotics. SL: Short sleep; LS: Long Sleep.

Sleep duration was assessed by asking the patients the following question: How many hours of sleep (including naps) have you had on average in a 24-h period during the last year (year prior to the diagnosis of melanoma)? Participants estimated habitual sleep duration using full hour units. Snoring time was also quantified in the sleep study records.

All patients underwent a sleep study by means of a home respiratory polygraphy and a peripheral blood test. Patients were divided into three groups depending on their daily sleep duration: appropriate sleep duration (between 6 and 8 h), short sleepers (<6 h) and long sleep duration (>8 h). The independent relationship between melanoma aggressiveness factors and sleep duration was determined by introducing into a multivariate logistical regression analysis those variables which could, in the opinion of the researchers, also have clinical importance as confounders: age, sex, AHI, BMI and hypnotics intake. This relationship was evaluated by Hazard Ratio (CI95%), considering the group of patients with appropriate sleep duration as the control group. The degree of melanoma aggressiveness was measured by histological variables such as the Breslow thickness, the tumor mitotic rate ($\geq$5 vs. <5 mitoses per mm^2), the histological presence of ulceration and regression and positive sentinel lymph node (SLN) involvement. The cut-off points for the Breslow thickness were established at 1, 2 and 4 mm, according to international guidelines.[4]

443 patients were finally included in the study. Mean age was 55.9 ± 15.3 years, and 50.6% were male. The mean BMI was 27.3 ± 4.5 kg/m^2 and the median Epworth score was 6 (IQR: 3–8). The median of the Breslow thickness was 0.85 mm (IQR: 0.49–1.80). A Breslow thickness above 1, 2 and 4 mm was found in, respectively, 44, 22.3 and 8.8% of the patients. Ulceration was present in 16%, regression in 23.3%, and SLN was positive in 10.6% of patients. The median AHI was 8.6 (IQR: 2.8–20.2). The mean sleep duration was 7.4 ± 1.27 h, with 4.7% sleeping <6 h, 77.9% between 6 and 8 h and 17.4% > 8 h. 8.4% of the patients presented insomnia and 12% were taking hypnotic drugs. The sleep study time was 7.2 h (IQR: 6.6–8) and the snoring study time was 6.9 h (IQR: 6.5–7.7). The correlation between subjective sleep duration and snoring study time was $r = 0.86$, $p < 0.0001$.

There was a statistically significant correlation between sleep duration and the Breslow index (r: 0.26; $p = 0.001$). Those patients with more aggressive melanoma (Breslow $\geq$ 2 mm vs <2 mm, and Breslow $\geq$ 4 mm versus <4 mm) presented longer sleep duration (8.1 vs. 7.1 h; $p = 0.0001$ and 8.3 vs. 6.9 h; $p = 0.0001$, respectively).

Long sleepers presented, in comparison with those patients who slept less than 8 h, a significant increase in various systemic markers of inflammation like high-sensitivity C-reactive protein (hs CRP) (2.35 [2.3] vs 1.33 [2.5] mg/L; $p = 0.03$), fibrinogen concentration (392 [97.1] vs.335 [92.7] mg/dL; $p = 0.01$) and erythrocyte sedimentation rate (ESR) (17.4 [13.9] vs. 11.2 [9.1] mm1 h; $p = 0.01$), as well as a higher AHI (19.8 [17.9] vs. 15.1 [16.1]; $p = 0.02$).

Fig. 1 shows that long sleepers were 1.53, 1.72 and 2.84 times more likely to present a more aggressive melanoma (Breslow index above 1, 2 and 4 mm) compared to the control group, after adjustment for age, gender, BMI, AHI, intake of hypnotic drugs and presence of insomnia. Similarly, long sleepers had an increased risk of SLN positive, presence of tumor ulceration and a high tumor mitotic rate.

As far as we know, this is the first study to analyze the relationship between longer sleep duration and the aggressiveness of a cancer. Of note, this association was not caused by the presence of confounders such as obesity, sleep apnea, age, gender, hypnotics intake or insomnia. Various mechanisms have been postulated to explain this relationship, including various deregulations of the immune system (especially reductions in natural killer cell activity),[5] increased sleep fragmentation[3] and increased systemic inflammation.[6,7] In fact, our study shows that long sleepers presented greater systemic inflammation (increased levels of US-CRP, ESR and fibrinogen).

The main limitation of our study was the fact that the evaluation of sleep duration was subjective, as is the case in most of the similar studies published to date on this topic. However, there was a very strong correlation between the subjective sleep duration and the snoring study time (while the patients are supposed to be sleeping). Moreover, some authors[8] have observed in large series that those patients with self-reported sleep > 7 h per night overestimated their real sleep duration by an average of 0.3 h, while this overestimate was even higher (1.3 h) in patients who slept < 5 h. These circumstances would minimize any error derived from our analysis since, even assuming this situation, the vast majority of the patients in our study would remain in the same analysis group. Moreover, the percentage of patients with abnormal sleep time was 22%, which could affect the conclusions. Finally, we did not include the presence of anxiety or depression as a covariate, but we did include the intake of hypnotics and other psychotropic medication, which is closely associated with anxiety and depression.

In conclusion, we found for the first time a positive relationship between a long sleep duration and some markers of melanoma aggressiveness. Future studies are needed to investigate the main pathophysiological mechanisms that could explain this association and the prognostic relevance of this finding.

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Conflict of interest

The authors declare that they have no conflict of interest.

Bibliografía

1. Kakizaki M, Kuriyama S, Sone T, Ohmori-Matsuda K, Hozawa A, Nakaya N, et al. Sleep duration and the risk of breast cancer: the Ohsaki Cohort Study. Br J Cancer. 2008;99:1502–5.
2. Zhang X, Giovannucci EL, Wu K, Gao X, Hu F, Ogino S, et al. Associations of self-reported sleep duration and snoring with colorectal cancer risk in men and women. Sleep. 2013;36:681–8.
3. Martinez-Garcia MA, Campos-Rodriguez F, Nagore E, Martorell A, Rodriguez-Peralto JL, Riveiro-Falkenbach E, et al. Sleep-disordered breathing is independently associated with increased aggressiveness of cutaneous melanoma: a multicenter observational study in 443 patients. Chest. 2018;154:1348–58.
4. -Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer Eighth edition cancer staging manual. CA Cancer J Clin. 2017;67:472–92.
5. Born J, Lange T, Hansen K, Molle M, Fehm HL. Effects of sleep and circadian rhythm on human circulating immune cells. J Immunol. 1997;158:4454–64.
6. Irwin MR, Olmstead R, Carroll JE. Sleep disturbance, sleep duration, and inflammation: a systematic review and meta-analysis of cohort studies and experimental sleep deprivation. Biol Psychiatry. 2016;80:40–52.
7. Patel SR, Zhu X, Storfer-Isser A, Mehra R, Jenny NS, Tracy R, et al. Sleep duration and biomarkers of inflammation. Sleep. 2009;32:200–4.
8. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Sleep duration: how well do self-reported reflect objective measures? The CARDIA Sleep Study. Epidemiology. 2008;19:838–45.

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Comparing Probe-Based Confocal Laser Endomicroscopy With Histology. Are We Looking at the Same Picture?

Comparando endomicroscopía confocal con histología. ¿Estamos mirando la misma imagen?

Dear Editor,

Probe-based confocal laser endomicroscopy (pCLE) provides real-time vision of respiratory tissues at the cellular level through a flexible bronchoscope. This technique might guide sampling of pulmonary nodules,[1–4] lymph nodes[5] or pleural biopsies.[6] First studies of the respiratory tract were performed with a 488 nm wavelength probe that allows elastin visualization without adding fluorophores in the tissue. Because cells are not visualized, lung cancer pattern descriptions were limited to changes on the stromal component.[1,7–9] Later studies used fluorophores like methylene blue or fluorescein that could be excited at a 488 or a 660 nm wavelength, respectively, to visualize cell nuclei.[2,4,10] In these studies, different imaging patterns were described. In particular, healthy tissue was described as having homogeneous architecture with bright, partially overlapping nuclei. Inflammation was considered when heterogeneous tissue architecture without overlapping nuclei but expanded cytoplasms were observed, and neoplasia was reported as a chaotic distribution of dark cells with heterogeneous nuclei.[2,8,9,11,12] Although pictures of these patterns were frequently presented together with pictures of histology samples, none of the studies correlated the measurements performed in pCLE images to those of histology samples. In this pilot study, we aimed to explore

Table 1
Measurements Performed in the Histological Samples (Optical Microscopy) and pCLE Images.

	Final Diagnosis	Optical Microscopy (H&E Stain, 40× Magnification)	Probe-based Confocal Laser Endomicrosocopy	*P*-Value
Number of nuclei	Normal ($n = 6$)	28.8 (5.78)	35.3 (4.13)	.1025
Mean (SD)	Pathological ($n = 9$)	33.8 (16.2)	27.8 (16.6)	.8946
Mean size of nuclei (μm^2)	Normal ($n = 6$)	103 [90.8;129]	36.5 [31.7;40.9]	<.05
Median [Q1;Q3]	Pathological ($n = 9$)	127 [114;155]	29.5 [27.9;59.0]	<.05
Relative area occupied by nuclei (μm^2)	Normal ($n = 6$)	60.6 (18.2)	26.5 (10.8)	<.05
Mean (SD)	Pathological ($n = 9$)	80.1 (13.4)	38.9 (14.3)	<.05

Pathological refers to inflammation or malignancy.
H&E: haematoxylin–eosin, SD: standard deviation.