CHEST

# Sleep-Disordered Breathing Is Independently Associated With Increased Aggressiveness of Cutaneous Melanoma

## A Multicenter Observational Study in 443 Patients

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**BACKGROUND:** Sleep-disordered breathing (SDB) has been associated with a greater incidence and mortality of cancer, although such findings are inconsistent. However, no large studies are currently available to investigate this association in patients with a specific type of cancer. This study seeks to assess potential relationships between SDB severity and aggressiveness markers of cutaneous melanoma.

**METHODS:** Four hundred and forty-three patients with a diagnosis of melanoma underwent a sleep study within 6 months of diagnosis. General demographics were collected, along with melanoma characteristics and polygraphic parameters consisting of the apnea-hypopnea index (AHI) and indices of both continuous and intermittent night-time oxyhemoglobin desaturation (DI4%). An exploration of independent relationships between SDB and various objective melanoma aggressiveness markers (Breslow index, presence of ulceration, presence of regression, mitotic index, stage of severity, damage to the sentinel lymph, and spreading of the melanoma) was performed.

**RESULTS:** Patients in the upper tertiles of AHI or DI4% were 1.94 (95% CI, 1.14-3.32; $P = .022$) and 1.93 (95% CI, 1.14-3.26; $P = .013$) times more likely, respectively, to present with aggressive melanoma (Breslow index $> 1$ mm) than those in the lowest tertiles of these sleep attributes after adjustment for age, sex, tumor location, and BMI. This association was particularly prominent among patients $< 56$ years of age with Breslow index $> 2$ mm. The presence of the additional markers of aggressiveness was also associated with higher AHI and DI4% values.

**CONCLUSIONS:** The severity of SDB was independently associated with greater aggressiveness of cutaneous melanoma, particularly among younger patients. CHEST 2018; 154(6):1348-1358

**KEY WORDS:** Breslow index; melanoma aggressiveness; sleep apnea; sleep-disordered breathing

**ABBREVIATIONS:** AHI = apnea-hypopnea index; CM = cutaneous melanoma; DI = desaturation index; IQR = interquartile range; SDB = sleep-disordered breathing

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Both cancer and sleep-disordered breathing (SDB) are major and challenging public health problems.[1,2] Cutaneous melanoma (CM) is one of the most aggressive neoplastic tumors. There has been an estimated annual increase of 3% to 7% from 1990 to 2015 in the incidence of CM among white men.[3] Although some of the major risk factors have been clearly established, other risk factors remain unknown, particularly those factors that determine the aggressiveness profile of the tumor.[4] SDB affects 9% to 38% of the general population, and is characterized by repetitive collapse of the airway during sleep, leading to intermittent hypoxemia and sleep fragmentation.[5] These two major components of SDB have been related to a higher incidence of traffic accidents and to cardiovascular, neuropsychiatric, and metabolic disease.[6,7]

Emerging evidence has suggested an association between the presence of SDB and higher cancer prevalence, incidence, and mortality.[8-10] This finding has been supported by pathophysiologic and experimental animal studies that have confirmed the biologic plausibility of such putative associations.[11,12] Other authors, however, have failed to identify any significant link between the two conditions.[13,14] Among the multiple possible explanations for these discrepancies, methodologic limitations may have played a key role, particularly when considering that the majority of the studies were retrospective or used databases that were not specifically designed to analyze this association.[15]

We have attempted here to overcome the aforementioned limitations, and examined the relationship between well-established severity measures of SDB and clinical aggressiveness markers of CM in a large cohort of patients receiving diagnoses with this tumor.

## Methods

### Study Design and Participants

This was a cross-sectional study that included consecutive patients who received a diagnosis of CM[16] at 29 Spanish hospitals. Exclusion criteria were as follows: melanoma of an unknown primary site, melanoma in mucosa or melanomas "in situ," pregnant women, and respiratory or cardiac insufficiency. Subjects with previous continuous positive airway pressure treatment were also excluded, since this therapy counteracts the intermittent hypoxia associated with SDB, thereby decreasing the potential association between SDB and our endpoint. The study was approved by the ethics committees of all the hospitals, and all the patients gave their informed consent.

### Data Collection

Every participant completed a standardized protocol including cardiovascular and respiratory history and self-reported symptoms (witnessed apneas, chronic snoring, presence of daytime hypersomnia, sleep duration, and presence of insomnia). The following data were

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also recorded with respect to the melanoma: the histologic type (superficial spreading, nodular, lentigo maligna, acral lentiginous, or others/unspecified); tumoral thickness (Breslow index, in mm); the histologic presence of ulceration, regression, and the mitotic index (number of mitoses per $mm^2$)[17]; and tumoral stage in accordance with the 7th edition of the staging classification system of the American Joint Committee on Cancer.[18] The tumor was subsequently categorized as localized, locoregional, or distant. Tumor location was dichotomized according to its location on the head/neck/trunk (value, 1) or on limbs/acral area (value, 0).

### Procedures

**Sleep Study:** All the patients underwent respiratory polygraphy that was performed in accordance with national guidelines.[19] This sleep study was performed in all cases before 6 months had elapsed from the diagnosis of melanoma. Respiratory polygraphy included continuous recording of oronasal flow and pressure, heart rate, thoracic and abdominal respiratory movements, and oxygen saturation. Polygraphic data were scored manually by skilled staff. Apnea was defined as an interruption of oronasal airflow for > 10 s. Hypopnea was defined as a 30% to 90% reduction in oronasal airflow for > 10 s, associated with an oxygen desaturation ≥ 3%. The apnea-hypopnea index (AHI) was defined as the number of apneas plus hypopneas per hour of recording, while Tsat90% was defined as the percentage of recording night-time with oxygen saturation < 90%. The recording time, desaturation indices (DI) at 3%, and the mean baseline nocturnal, baseline daytime, and minimum nocturnal saturation were also recorded.

**Endpoints:** The primary endpoint was the association between SDB severity and CM aggressiveness as measured by the Breslow index. We used a Breslow index > 1 mm as one of the thresholds to define aggressiveness, according to the American Cancer Association, but also explored other proposed cutoff points (> 2 and > 4 mm).[18] As secondary endpoints, we used other markers of melanoma aggressiveness, such as the presence of ulceration or regression, a mitotic index ≥ 5/mm,[2] damage to the sentinel lymph, and the various stages of melanoma severity.[18]

### Statistical Analysis

The sample size was calculated by assuming an average age of 50 years in the patients with melanoma,[4] a distribution of SDB similar to that of the general population,[5] and 50% of melanomas with Breslow > 1 mm.[20] Accepting an $\alpha$ error < 0.05 and a $\beta$ error < 0.20, and foreseeing recruitment losses of 10%, the minimum number of patients needed was 430.

The SPSS 20.0 statistical package (IBM) was used for all analyses. Data were expressed by using the mean/median and standard deviation/interquartile range according to the distribution of the variables. Qualitative and dichotomous variables were expressed as absolute and relative values. Comparison between the two groups' baseline variables (Breslow index > 1 mm vs ≤ 1 mm) was made by Student *t* test or the Mann-Whitney test, according to the distribution of the quantitative variables, while the $\chi^2$ test was used to compare the two percentages. Factors independently related to the presence of a Breslow index > 1 were determined by introducing into a multivariate logistical regression analysis those variables that, in the opinion of the researchers, could have clinical importance: age, sex, BMI, alcohol consumption, smoking, and tumor location. Both the AHI and DI4% were introduced into each logistic regression analysis as tertiles, with the lower tertile being considered the reference group. In addition, both AHI and DI4% were analyzed as continuous variables, and using the usual clinical cutoff in AHI values (5, 15, and 30 events/h). Various subgroups of patients of clinical interest were also analyzed, based on age, sex, presence of obesity (BMI ≥ 30 $kg/m^2$), and presence of hypersomnia (Epworth Sleepiness Scale ≥ 10). Finally, the association between these polygraphic variables (AHI and DI4% in tertiles) and other markers of melanoma aggressiveness was evaluated by means of the odds ratio (OR) (95% CI), considering the lower tertile of severity as the reference group. $P < .05$ was considered significant in every case.

## Results

### Baseline Characteristics

Of the 476 patients who were initially recruited from October 2012 to September 2015, 443 were finally included (Fig 1). The patients' mean age was 55.9 ± 15.3 years and 50.6% were male. The median Breslow index score was 0.85 (interquartile range [IQR], 0.49-1.80) mm. The median time span between CM diagnosis and sleep recording was 82 (IQR, 49-120) days. Table 1 shows the patients' general and melanoma characteristics, while Table 2 shows the main results of the sleep studies and clinical variables related to sleep. The median AHI was 8.6 (IQR, 2.8-20.2) events/h (65% with an AHI ≥ 5, and 14.7% an AHI ≥ 30), while the median value of DI4% was 4.84 desaturations/h (IQR, 1.1-13.3).

### Comparison of Baseline Characteristics Between Groups According to the Breslow Index

The comparison of baseline characteristics in patients with a Breslow index of ≤ 1 mm vs > 1 mm is shown in Table 3. Higher age, male sex, greater BMI, and melanoma location, and all the measured polygraphic variables, including the desaturation indices, were statistically significantly higher in the group with more aggressive melanoma. However, there were no significant differences between the two groups regarding sleep symptoms.

### Sleep-Disordered Breathing Is Associated With Melanoma Aggressiveness

Table 4 shows the findings of the logistic regression analysis, including both the AHI and the DI4% as tertiles of growing severity. Those patients in an upper AHI tertile (AHI > 15.6 events/h) or DI4% tertile (> 9.3 desaturations/h) exhibited an approximately twofold greater probability of presenting a melanoma with greater aggressiveness (Breslow > 1 mm) compared with the reference group (lower tertile, AHI < 4.5 or DI4% < 2) adjusted by age, sex, BMI, and location of the melanoma. Similarly, both age and location of the melanoma were also independent indicators of greater melanoma aggressiveness. Using AHI and DI4% as

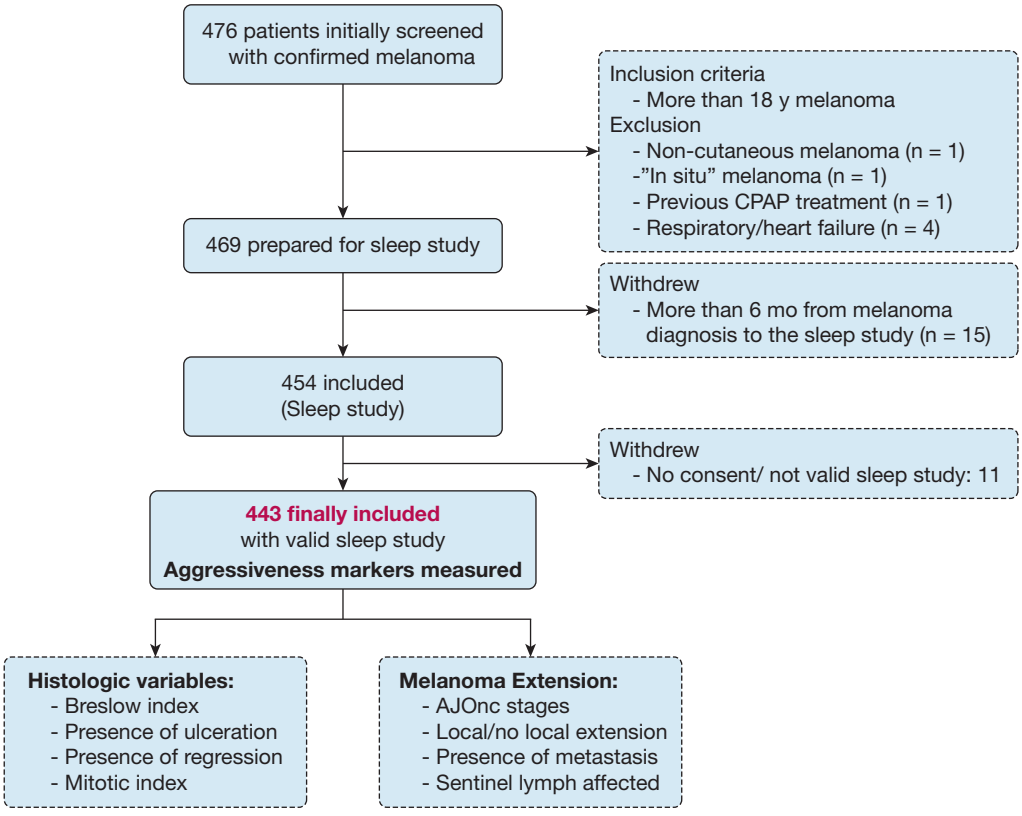



Figure 1 – *Flow chart of the study. AJOnc = American Journal of Oncology; CPAP = continuous positive airway pressure.*

continuous variables, and using standard clinical cutpoints for AHI, yielded similar patterns of association: both AHI (e-Table 1) and DI4% (e-Table 2) remained significantly associated with greater melanoma aggressiveness.

### *Analysis by Age Groups*

In patients $< 56$ years, this association between sleep apnea and melanoma aggressiveness established by the Breslow index increased in robustness as the melanoma exhibited increasing Breslow index, while the opposite pattern emerged in patients $\geq 56$ years. Indeed, among older subjects the association between SDB measures (both the AHI and the DI4%) and Breslow index was significant only in those patients with lower Breslow index values ($\leq 1$) (Table 5).

### *Analysis by Other Clinical Relevant Groups*

The probability of having a Breslow index $> 1$ in those patients with an AHI in the upper tertile compare with the reference group was higher in men (n = 224) than in women (n = 219) and in nonobese (n = 339) than in obese (n = 104) patients. Finally, regarding the presence of daytime hypersomnia (n = 71) or not (n = 372), the ORs were not statistically significant in both cases. The findings were markedly similar when DI4% tertiles were used as the SDB polygraphic variable (e-Table 3).

### *Relationship With Other Melanoma Aggressiveness Markers*

Additional melanoma aggressiveness markers were also significantly associated with the upper AHI and DI4% tertiles (with ORs between 1.4 and 2.6 and between 2 and 2.55, compared with the lower tertiles, respectively). Only the presence of regression did not exhibit a statistically significant association with DI4% (Fig 2).

### *Severity-Dependent Effect Relationship*

Figure 3 shows the presence of a "severity-dependent effect," that is, the more advanced the stage of the CM lesion according to the classification of the American Joint Committee on Cancer[18] the greater the values of both the AHI and the DI4% in a quantitative analysis.

## Discussion

To our knowledge, this study shows for the first time that there is a positive, independent association between

**TABLE 1** ] Patient and Cutaneous Melanoma Characteristics at Baseline

| Parameter | Value |
|---|---|
| Patients, No. (%) | 443 (100) |
| Male sex, No. (%) | 224 (50.6) |
| Age, mean ± SD, y | 55.98 ± 15.3 |
| BMI, mean ± SD, kg/m$^2$ | 27.3 ± 4.5 |
| BMI ≥ 30, No. (%) | 104 (23.5) |
| Breslow index,[a] thickness in mm | 0.85 (0.49-1.80) |
| Ulceration, No. (%) | 71 (16) |
| Regression, No. (%) | 103 (23.3) |
| Mitotic rate, mitoses/mm$^2$, No. (%) | |
| 0-1/mm$^2$ | 278 (64.5) |
| > 5/mm$^2$ | 63 (14.2) |
| Subtype, No. (%) | |
| Superficial spreading melanoma | 312 (70.4) |
| Nodular melanoma | 66 (14.9) |
| Lentigo maligna melanoma | 34 (7.7) |
| Acral lentiginous melanoma | 23 (5.3) |
| Sentinel lymph node affected, No. (%) | 47 (10.6) |
| Anatomical site, No. (%) | |
| Head and neck | 64 (14.4) |
| Trunk | 178 (40.2) |
| Upper limb | 67 (15.1) |
| Lower limb | 113 (25.5) |
| Acral | 20 (4.5) |
| Stage, No. (%) | |
| Localized (I-II) | 387 (87.4) |
| Locoregional (III) | 46 (10.4) |
| Metastatic (IV) | 4 (0.9) |

[a]Breslow index is expressed as median (interquartile range).

**TABLE 2** ] Sleep Characteristics and Other Comorbidities at Baseline

| Parameter | Value |
|---|---|
| Patients, No. (%) | 443 (100) |
| Smoking, pack-years (if > 0)[a] | 17 (8-30) |
| Current, No. (%) | 82 (18.5) |
| Past, No. (%) | 138 (31.2) |
| Never, No. (%) | 221 (49.9) |
| Alcohol, g/d (if > 0)[a] | 15 (10-30) |
| Never, No. (%) | 363 (81.9) |
| Previous cancer, No. (%) | 34 (7.7) |
| Previous chronic respiratory/ heart disease, No. (%) | 33 (7.4) |
| Site of sleep study, No. (%) | |
| Hospital | 123 (27.8) |
| Home | 320 (72.2) |
| Sleep study time, h[a] | 7.2 (6.6-8) |
| Chronic snoring (at least 3 d/wk), No. (%)[b] | 278 (62.8) |
| d/wk, mean ± SD | 3.7 ± 2.96 |
| Witnessed apneas, No. (%)[b] | 88 (19.9) |
| Epworth test[a,b] | 6 (3-8) |
| Epworth test ≥ 10, No. (%) | 71 (16) |
| Neck circumference, mean ± SD, cm | 37.7 ± 4.5 |
| Sleep duration, mean ± SD, h[b] | 7.4 ± 1.27 |
| Less than 6 h, No. (%) | 21 (4.7) |
| Between 6 and 8 h, No. (%) | 354 (77.9) |
| More than 8 h, No. (%) | 77 (17.4) |
| Insomnia, No. (%)[b] | 37 (8.4) |
| Baseline $O_2$ saturation[a] | 97 (96-98) |
| AHI, No. of events/h[a] | 8.6 (2.8-20.2) |
| AHI ≥ 5, No. (%) | 288 (65) |
| AHI ≥ 15, No. (%) | 156 (35.2) |
| AHI ≥ 30, No. (%) | 65 (14.7) |
| Central AHI, events/h[a] | 0 (0-0.6) |
| DI4%, No. of desaturations/h[a] | 4.84 (1.1-13.3) |
| DI3%, No. of desaturations/h[a] | 9 (2.8-21.6) |
| Minimum $O_2$ saturation[a] | 85 (80-89) |
| Nocturnal average $O_2$ saturation[a] | 93 (91-96) |
| Tsat90%[a] | 0.65 (0-5.25) |

AHI = apnea-hypopnea index; DI4% and DI3% = desaturation index at 4% and 3%, respectively; Tsat90% = night time spent with oxygen saturation below 90%.
[a]Smoking, alcohol use, sleep study time, Epworth test, diurnal $O_2$ saturation, AHI, central AHI, DI4%, DI3%, nocturnal average $O_2$ saturation, and Tsat90% are expressed as median (interquartile range).
[b]Self-reported variable.

the number and severity of SDB (measured as both AHI and DI4%), and various commonly used aggressiveness markers of CM in a large series of patients. This association was more robust among younger patients in the context of higher Breslow values. Considering that SDB is a treatable disease, and although further studies are needed to demonstrate the role of SDB and its treatment in the evolution of CM, our results emphasize the need to raise awareness among physicians treating patients with melanoma of the possibility of underlying SDB.

The melanoma model has been used in this study for several reasons: (1) an initial pilot study undertaken by our research group on 56 patients with CM found a significant association between the severity of SDB and melanoma aggressiveness (patients from this pilot study were not included in the present study)[21]; (2) several authors have suggested that melanoma

**TABLE 3** ] Comparison of Sleep-Disordered Breathing Severity Measures in Groups With a Breslow Index > 1 mm and ≤ 1 mm

| Variable | Breslow Index > 1 mm (n = 195) | Breslow Index ≤ 1 mm (n = 248) | *P* Value |
|---|---|---|---|
| Age, mean ± SD, y | 59.52 ± 15.3 | 53.2 ± 14.8 | .0001 |
| Sex, male, No. (%) | 109 (55.9) | 115 (39.9) | .029 |
| BMI, mean ± SD, kg/m$^2$ | 27.9 ± 4.5 | 26.8 ± 4.4 | .015 |
| Smoking, mean ± SD, pack-years | 12.5 ± 19.9 | 9.3 ± 14.8 | .32 |
| Alcohol, mean ± SD, g/d | 4 ± 15 | 4.2 ± 12.6 | .39 |
| Melanoma site, No. (%) | | | .035 |
| Head/neck | 26 (13.3) | 38 (13.2) | |
| Arms | 26 (13.3) | 41 (14.2) | |
| Legs | 55 (28.2) | 58 (20.1) | |
| Trunk | 72 (36.9) | 106 (36.8) | |
| Acral | 15 (7.7) | 5 (1.7) | |
| AHI, No. of events/h[a] | 13 (4.5-25) | 6.4 (2.1-15.6) | .0001 |
| AHI ≥ 5, No. (%) | 144 (73.8) | 144 (50) | .0001 |
| AHI ≥ 15, No. (%) | 89 (45.6) | 67 (23.3) | .0001 |
| AHI ≥ 30, No. (%) | 37 (19) | 28 (9.7) | .017 |
| DI3%, No. of events/h[a] | 12.9 (3.9-24.6) | 7.1 (2.3-17.6) | .001 |
| DI4%, No. of events/h[a] | 7 (2.2-15.5) | 3.4 (0.9-10.7) | .0001 |
| Tsat90%[a] | 1.4 (0.1-5.9) | 0.3 (0-4.3) | .005 |
| Baseline $O_2$ saturation[a] | 96 (95-97) | 96 (95-97) | .22 |
| Minimum $O_2$ saturation[a] | 85 (78-88) | 86 (81-89.3) | .0001 |
| Sleep study time, h[a] | 7.2 (6.5-8) | 7.2 (6.7-8) | .84 |
| Sleep duration, h/d | 7.7 (1.1) | 7.3 (1.3) | .009 |
| Sleep-related symptoms | | | |
| Chronic snoring, No. (%) | 123 (63.1) | 155 (53.8) | .46 |
| Witnessed apneas, No. (%) | 42 (21.5) | 46 (16) | .73 |
| ESS[a] | 6 (3-8.3) | 6 (3-8) | .91 |

ESS = Epworth Sleepiness Scale. See Table 2 legend for expansion of other abbreviations.
[a]AHI, DI3%, DI4%, Tsat90%, baseline and minimum $O_2$ saturations, sleep study time, and ESS values are expressed as median (interquartile range).

could be one of the neoplastic conditions most likely to be associated with SDB[22]; (3) studies on animals injected with melanoma cells and subjected to intermittent hypoxemia showed faster growth of the tumor when compared with mice exposed to normoxic conditions[11]; and, finally, (4) melanoma is a prevalent and clinically significant cancer with well-documented objective markers of aggressiveness, especially the Breslow index.[4,16] Since there is no natural cutoff point in the Breslow index that clearly defines melanoma aggressiveness, we finally used a cutoff point of 1 mm (one of the points defined by the current classification of the American Joint Committee on Cancer[18]), due to the distribution of the Breslow index in our series (median value, 0.85 mm).

The relationship between SDB and cancer remains controversial. Nieto et al[10] observed in a study of the Wisconsin cohort that patients with an AHI ≥ 30 were 4.8 times more likely to die of cancer than those with an AHI < 5, and almost twice as likely if a higher nocturnal desaturation index was chosen as a marker of SDB severity. Similar results were reported by Marshall et al[23] in 393 patients, but both these studies were carried out on individuals of the general population or on patients with sleep apnea, rather than in patients with cancer. Other authors, however, have had different findings. Gozal et al,[22] in an epidemiologic study of case and control subjects, using a health insurance database with more than 1.7 million patients with sleep apnea, found that this type of SDB was related to a higher incidence of some tumors (including melanoma) when compared with a

**TABLE 4** ] Variables Independently Associated With the Presence of a Cutaneous Melanoma Tumor With Greater Aggressiveness (Breslow Index > 1 mm) in a Model Including AHI Tertiles, and a Model Including DI4% Tertiles

| Variables | Nonadjusted OR (95% CI) | *P* Value | Fully adjusted OR (95% CI)[a] | *P* Value |
|---|---|---|---|---|
| Model Including AHI (but not DI4%) | | | | |
| AHI, events/h | | | | |
| Tertile | | | | |
| 0-4.5 | 1 | … | 1 | … |
| 4.6-15.6 | 1.41 (0.88-2.27) | .16 | 1.18 (0.71-1.94) | .52 |
| > 15.6 | 2.76 (1.72-4.42) | .0001 | 1.96 (1.14-3.36) | .014 |
| Age, y | 1.03 (1.02-1.04) | .0001 | 1.02 (1.01-1.03) | .017 |
| Melanoma location | 1.36 (0.93-1.98) | .11 | 1.57 (1.01-2.32) | .049 |
| BMI | 1.05 (1.01-1.10) | .016 | 1.02 (0.97-1.07) | .8 |
| Sex | 1.47 (1.01-2.14) | .096 | 1.33 (0.91-2.15) | .27 |
| Alcohol consumption, g/d | 1.01 (0.99-1.02) | .21 | 1.00 (0.99-1.02) | .45 |
| Smoking, pack-years | 1.01 (0.99-1.02) | .25 | 0.99 (0.99-1.01) | .93 |
| Model Including DI4% (but not AHI) | | | | |
| DI4%, desaturations/h | | | | |
| Tertile | | | | |
| 0-2 | 1 | … | 1 | … |
| 2.1-9.3 | 1.49 (0.92-2.41) | .11 | 1.22 (0.73-2.02) | .45 |
| > 9.3 | 2.71 (1.69-4.34) | .0001 | 1.95 (1.15-3.30) | .013 |
| Age, y | 1.03 (1.02-1.04) | .0001 | 1.02 (1.01-1.04) | .01 |
| Melanoma location | 1.36 (0.93-1.98) | .11 | 1.43 (1.01-2.17) | .047 |
| BMI | 1.05 (1.01-1.10) | .016 | 1.02 (0.97-1.06) | .61 |
| Sex | 1.47 (1.01-2.14) | .096 | 1.21 (0.77-1.90) | .41 |
| Alcohol consumption, g/d | 1.01 (0.99-1.02) | .21 | 1.01 (0.99-1.02) | .42 |
| Smoking, pack-years | 1.01 (0.99-1.02) | .25 | 1.00 (0.99-1.01) | .96 |

OR = odds ratio. See Table 2 legend for expansion of other abbreviations.
[a]Fully adjusted odds ratio: age, sex (0, men; 1, women), BMI, melanoma location, alcohol consumption, smoking, and AHI/DI4% tertiles. Melanoma location: variable dichotomized according to its location on the head/neck/trunk (value, 1) or on limbs/acral area (value, 0).

similar number of control subjects, but also reported a lower incidence of other malignant tumors, with no compelling evidence to suggest that any of the cancer types examined was more aggressive. To our knowledge, our study is the first to assess a sufficient sample size of patients with a specific type of cancer (in this case, CM) to demonstrate a positive and independent association between SDB severity, measured by both the AHI and the ID4%, and melanoma aggressiveness, objectively quantified using various well-established markers, and more particularly the Breslow index.

Among the most salient findings were the dependence of the association between SDB and the markers of melanoma aggressiveness on both age and the actual indicators of tumor aggressiveness. Accordingly, in the group of younger patients (< 55 years old), the SDB-melanoma relationship was significant only in more aggressive melanomas (ie, values > 2 mm on the Breslow index). In contrast, in the older patients, a significant association of melanoma aggressiveness with SDB measures was found only in those melanomas when Breslow indices were < 1 mm at the time of CM diagnosis. This intriguing age-dependent bifurcation in the association with SDB was apparent despite the fact that age per se was a variable independently and linearly associated with greater aggressiveness of the CM lesion. The potential explanation for this phenomenon is unclear. However, other studies investigating the association between cancer and sleep apnea in humans[8,9] and between intermittent hypoxemia and cancer in animals[11] have

**TABLE 5** ] Association Between Aggressiveness of Cutaneous Melanoma at Diagnosis and Severity of SDB as Measured by AHI and DI4%, According to the Breslow Index Cutoff Points Established by the 2010 American Joint Committee on Cancer and According to the Age of the Patients[a]

| AHI, events/h<br>1° tertile (0-4.5) vs 3° tertile (> 15.6) | OR (95% CI) |
|---|---|
| Breslow > 1 mm (n = 195) | < 56 y (n = 215), 1.32 (0.85-3.01; *P* = .44)<br>≥ 56 y (n = 228), 3.18 (1.85-7.23; *P* = .02) |
| Breslow > 2 mm (n = 99) | < 56 y (n = 215), 2.83 (1.12-7.33; *P* = .03)<br>≥ 56 y (n = 228), 1.53 (0.25-3.66; *P* = .58) |
| Breslow > 4 mm (n = 39) | < 56 y (n = 215), 8.01 (1.35-17.55; *P* = .04)<br>≥ 56 y (n = 228), 0.60 (0.19-1.55; *P* = .49) |
| DI4%, desaturations/h<br>1° tertile (0-2) vs 3° tertile (> 9.3) | OR (95% CI) |
| Breslow > 1 mm (n = 195) | < 56 y (n = 215), 1.91 (0.96-4.76; *P* = .11)<br>≥ 56 y (n = 228), 2.14 (0.97-5.11, *P* = .09) |
| Breslow > 2 mm (n = 99) | < 56 y (n = 215), 3.87 (1.33-11.56; *P* = .03)<br>≥ 56 y (n = 228), 1.35 (0.77-3.01; *P* = .34) |
| Breslow > 4 mm (n = 39) | < 56 y (n = 215), 7.94 (1.78-16.45; *P* = .03)<br>≥ 56 y (n = 228), 0.60 (0.18-1.67; *P* = .33) |

SDB = sleep-disordered breathing. See Table 2 and 3 legends for expansion of other abbreviations.
[a]Cutoff point at 56 y.

revealed similar patterns. This may reflect interactions between the highly variable immune deregulation that traditionally occurs with aging and the now well-established alterations in immune responses elicited by sleep apnea.[24] It is also possible that the reduced tumoral immunovigilance resulting from the aging process may hinder any manifestation of the overall effects of sleep apnea, or that these effects may have disappeared altogether due to the inability of sleep apnea to elicit any changes in the susceptible immune pathways of the elderly. It would therefore be anticipated that younger patients with more robust

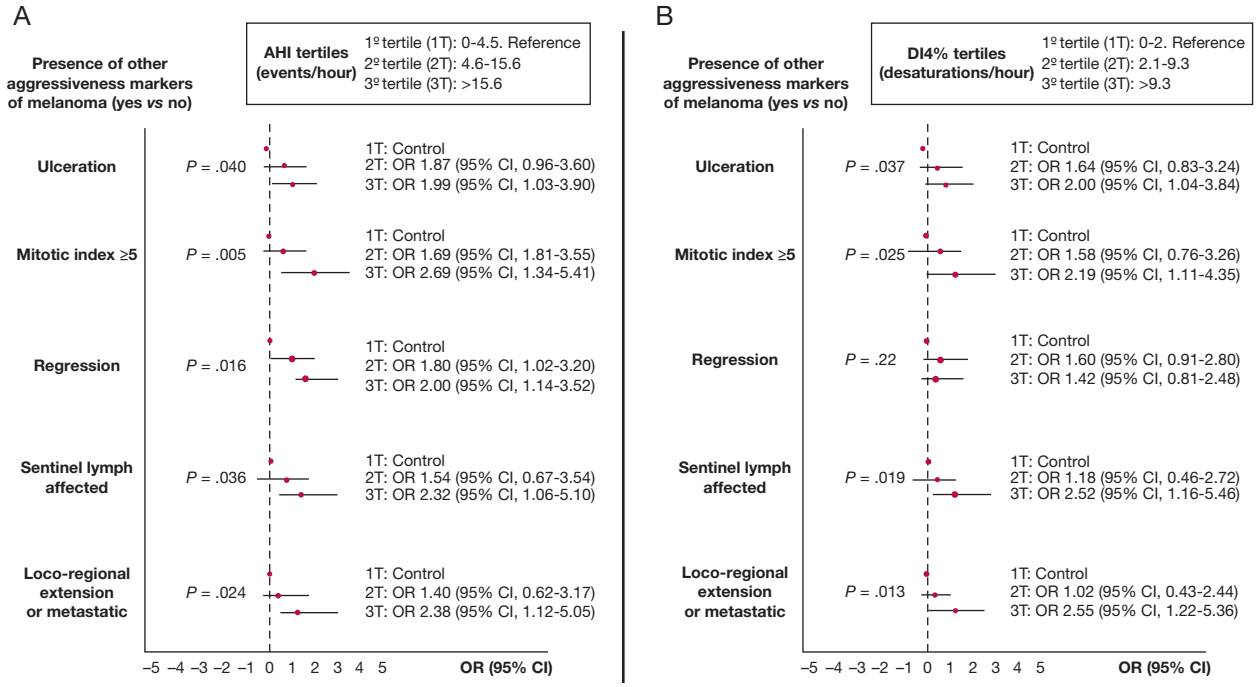
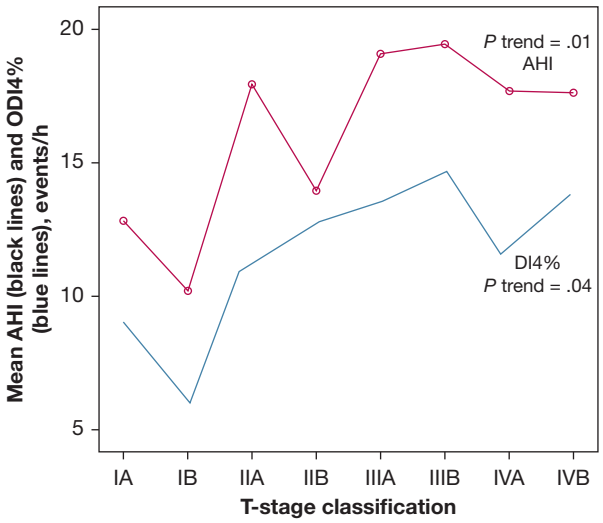



Figure 2 – *A and B, Relationship between (A) AHI and (B) DI4% and other commonly used clinical markers of tumor aggressiveness in cutaneous melanoma. P values refer to upper tertile vs lower tertile. AHI = apnea-hypopnea index; DI4% = desaturation index at 4%.*




| T classification | Breslow Index (Thickness (mm) | Ulceration status/mitosis |
|---|---|---|
| T1 | ≤ 1.0 | A: without ulceration and mitosis < 1/mm2<br>B: with ulceration or mitoses ≥ 1/mm2 |
| T2 | 1.01-2.0 | A: Without ulceration<br>B: With ulceration |
| T3 | 2.01-4.0 | A: Without ulceration<br>B: With ulceration |
| T4 | > 4.0 | A: Without ulceration<br>B: With ulceration |

Figure 3 – *Relationship between AHI (black line) and DI4% (blue line) and T-stage classification of cutaneous melanoma as recommended by the 2010 American Joint Committee on Cancer. See Figure 2 legend for expansion of abbreviations.*

tumoral immunovigilance, and thus a more favorable prognosis of CM, would be more likely to manifest detectable adverse effects when concomitant sleep apnea is present.[25-28]

Beyond the main strength of the study related to the relatively large cohort size that enables appropriate gauging of the potential effects of SDB on a single neoplasia, there are some limitations that are worthy of mention. The absence of full overnight polysomnography as a diagnostic method precludes assessment on the role of sleep fragmentation or duration, both of which have been suggested as being participatory in the possible link between sleep apnea and cancer.[29-31] Our decision to use respiratory polygraphy aimed to ensure a more representative participation by patients from 29 hospitals from all over Spain, since several of the participating centers had no access to polysomnography.

In summary, current findings support the presence of a positive, independent association between sleep apnea and various commonly used clinical markers of melanoma aggressiveness. Such findings were particularly apparent in younger patients with more aggressive melanomas. Future prospective studies are needed to confirm whether the presence and treatment of SDB and its evolution over time are also associated with poor melanoma outcomes, including death, and the pathophysiologic mechanisms underlying this association.

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**Additional information:** The e-Tables can be found in the Supplemental Materials section of the online article.

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