2019台灣胸腔暨重症加護醫學會夏季會

2019 Summer Workshop of Taiwan Society of Pulmonary and Critical Care Medicine

The association of sleep apnea and lung cancer

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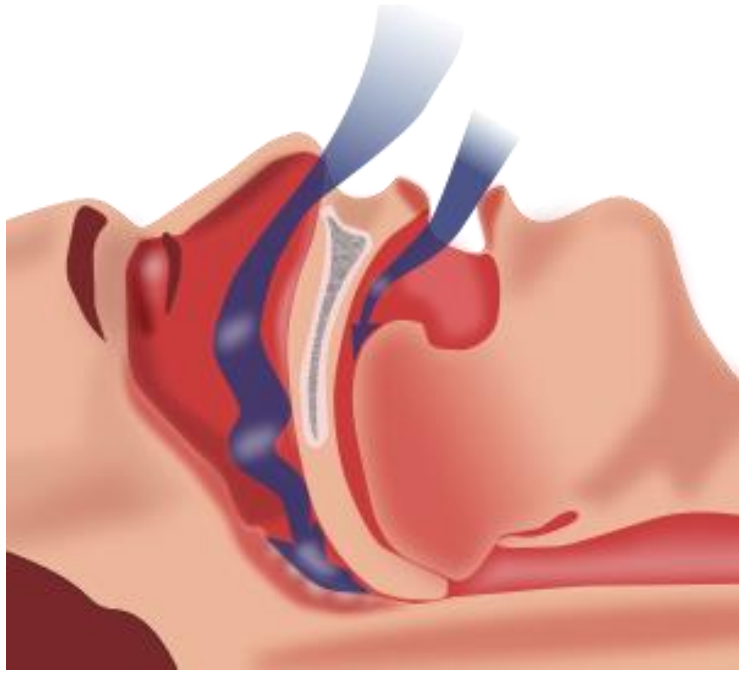
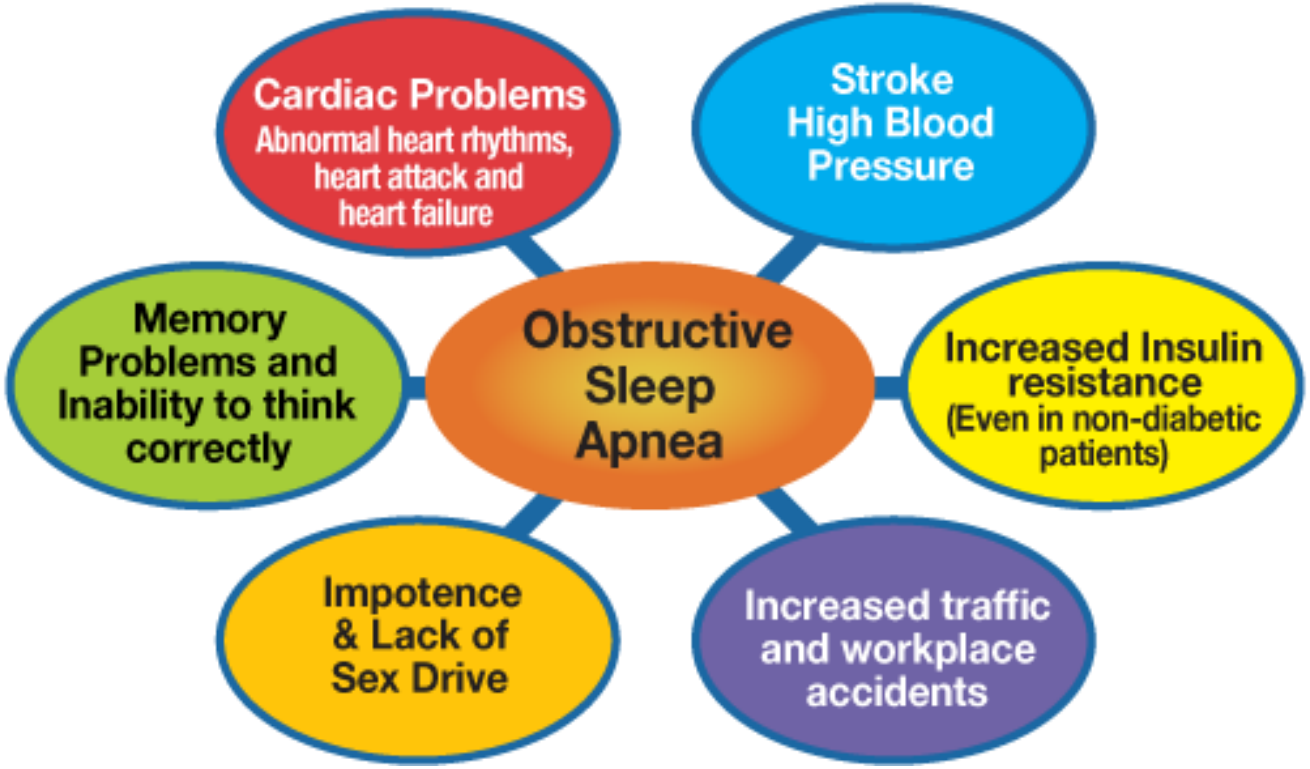
Content

- OSA and comorbidity
- Incidence of lung cancer in OSA
- Outcome of lung cancer in OSA
- Prevalence of OSA in lung cancer
- Possible linkage between lung cancer and OSA
- CGMH cohort result

OSA and comorbidity

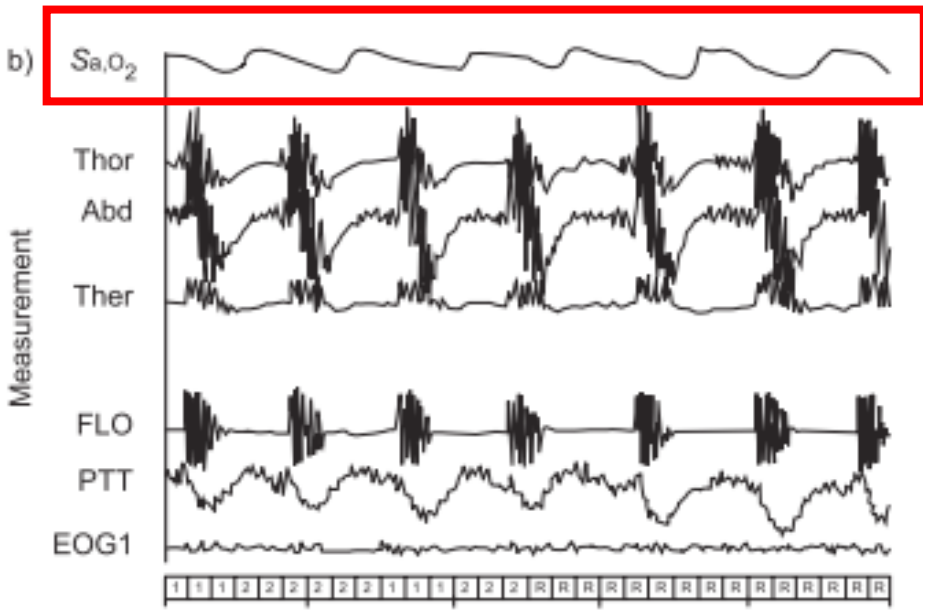
- OSA is characterized by repetitive episodes of apneas and hypopneas associated with recurrent cycles of intermittent hypoxemia



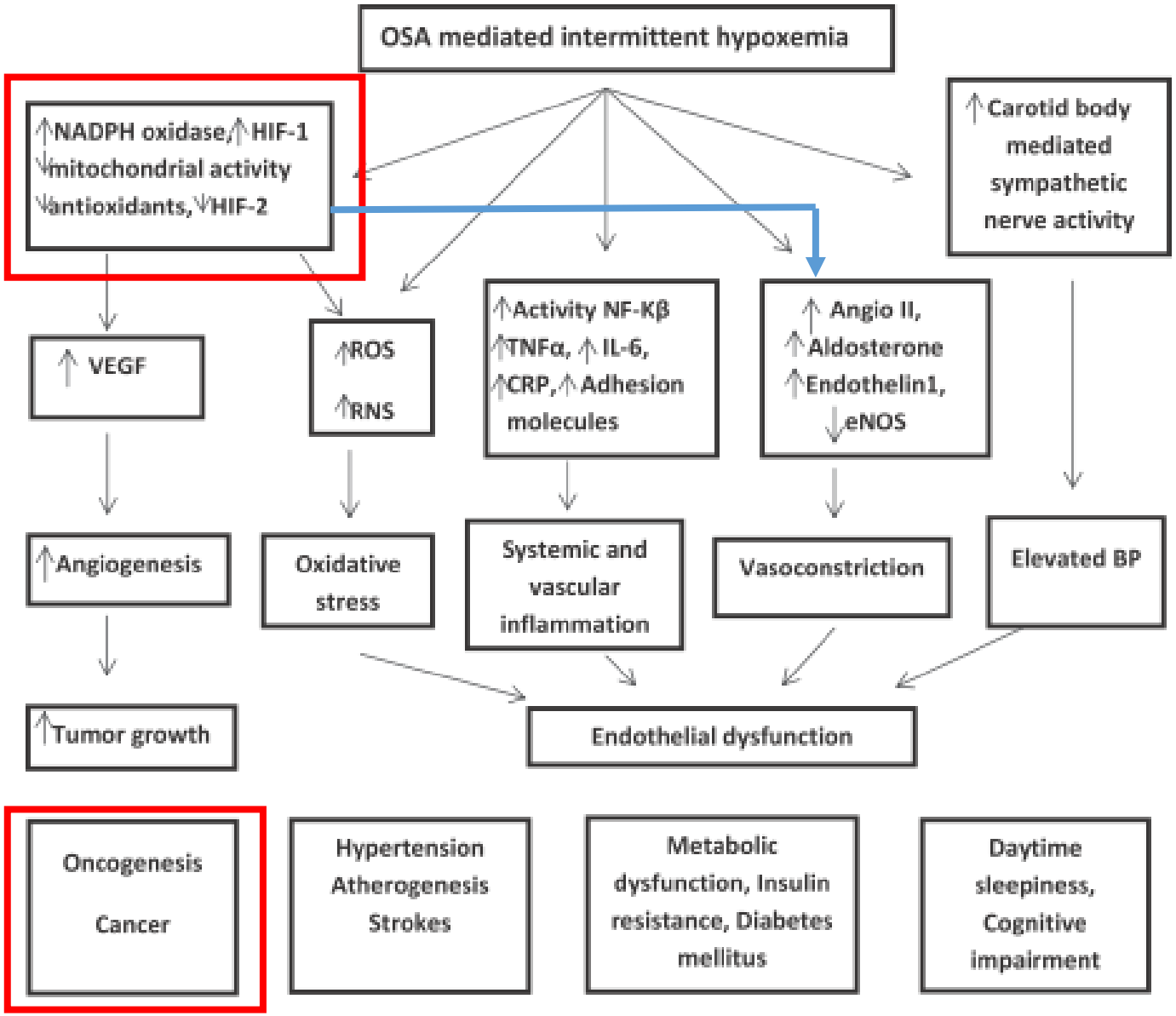


https://www.nswcpap.com.au

Intermittent hypoxia



- Apnea-Hypopnea index, AHI
- Oxygen desaturation index, ODI
- Percentage of sleep time with oxygen saturation <90%, Tsat90%



Dewan et al, Chest 2015

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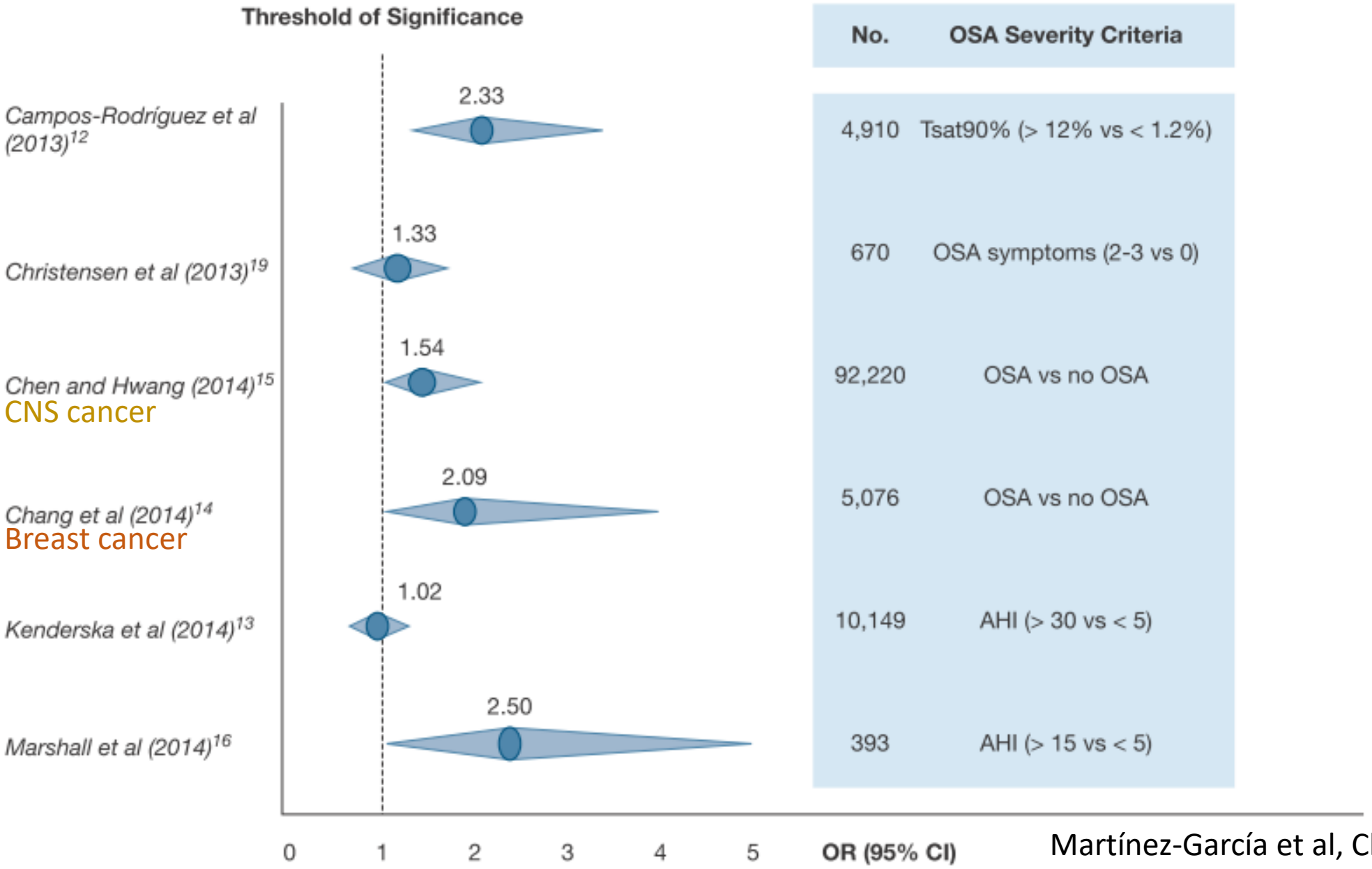
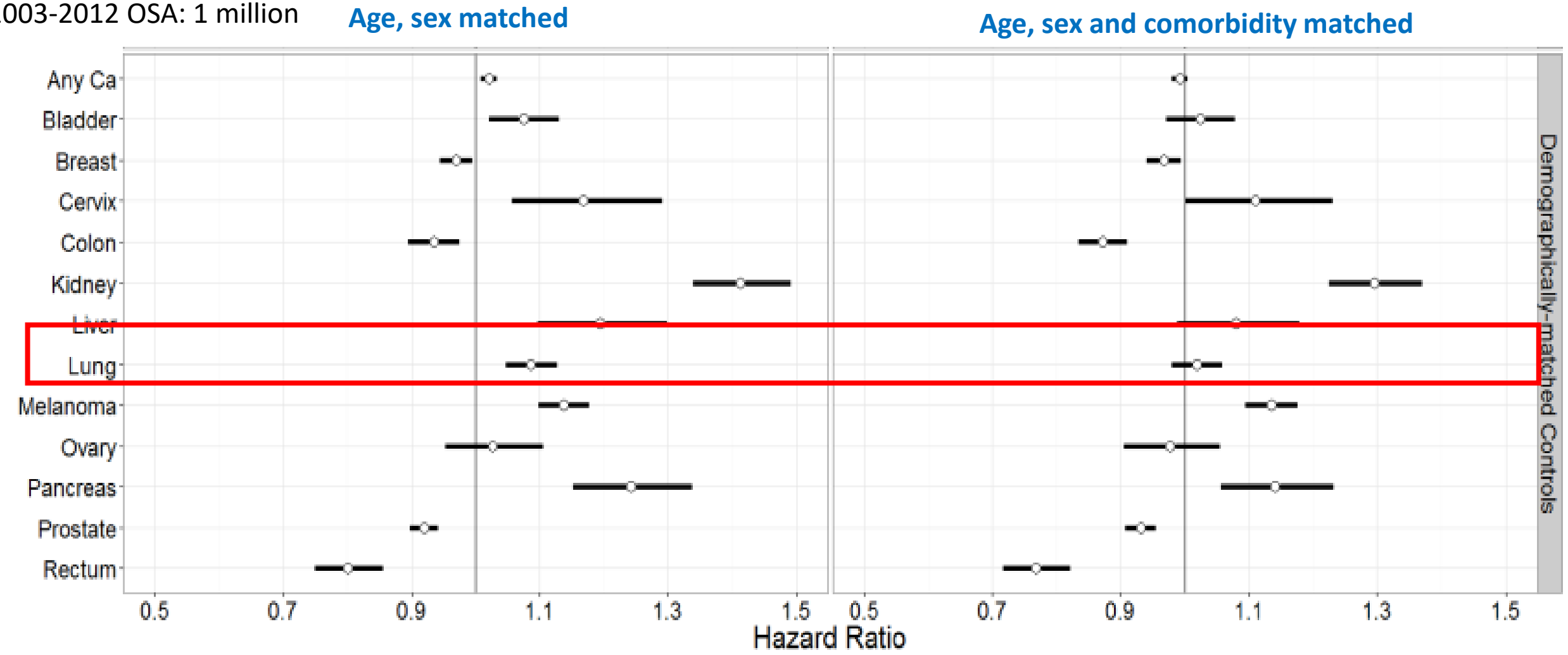
Cancer incidence in patients with OSA



Martínez-García et al, Chest 2016

Lung cancer was not significantly higher among OSA patients when while controlling for age, gender and comorbidity in US insurance cohort

2003-2012 OSA: 1 million



Gozal et al, SLEEP 2016

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Sleep-disordered Breathing and Cancer Mortality Wisconsin Sleep Cohort

		Sleep-disordered Breathing (AHI Range)			
	All	Absent (<5)	Mild (5–14.9)	Moderate (15–29.9)	Severe (≥30)*
No.	1,522	1,157	222	84	59
Age, mean (SD), yr	47.5 (8.1)	46.8 (7.9)	49.8 (8.1)	50.8 (8.6)	49.4 (8.6)
BMI, mean (SD), kg/m^2	29.9 (6.6)	28.7 (5.9)	32.3 (6.5)	34.3 (7.1)	38.6 (8.4)
Alcoholic drinks/wk, mean (SD)	3.9 (6.2)	3.8 (6.1)	4.1 (6.7)	4.7 (6.4)	4.4 (7.3)
Male sex, %	55.1	50.8	64.9	72.6	78.0
Education (≤					
Smoking, %					
Current					
Former					
Self-rated fair/					
Severe daytime sleepiness, %	24.5	23.1	24.9	32.5	39.7
Mortality rate per 1,000 person-yr (95% CI)					
All causes	4.29 (3.54–5.17)	3.24 (2.50–4.12)	6.88 (4.45–10.2)	5.02 (2.02–10.3)	15.57 (8.72–25.7)
Cancer	1.92 (1.42–2.53)	1.54 (1.05–2.19)	1.92 (0.77–3.97)	3.58 (1.16–8,36)	7.27 (2.92–15.0)

Severity of OSA is associated with overall cancer mortality

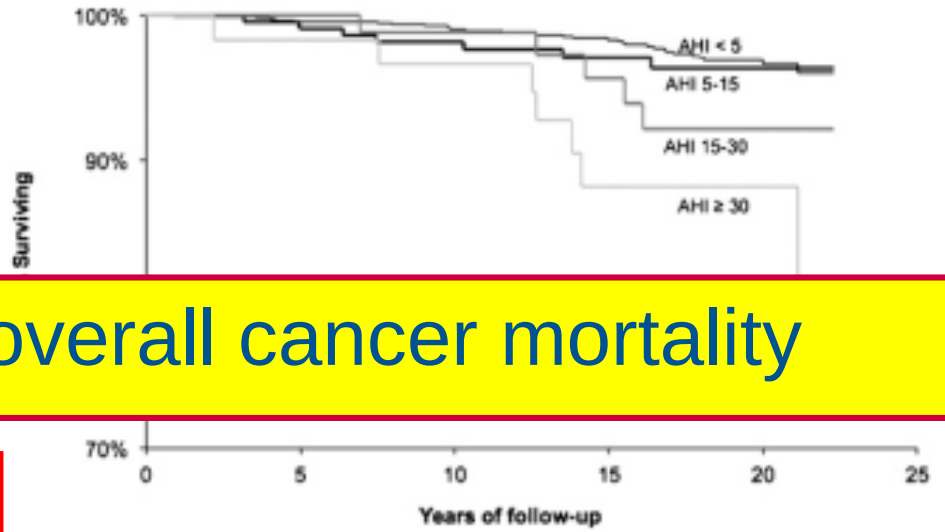


TABLE 2. ADJUSTED RELATIVE HAZARDS OF TOTAL AND CANCER MORTALITY ACCORDING TO SLEEP-DISORDERED BREATHING CATEGORIES

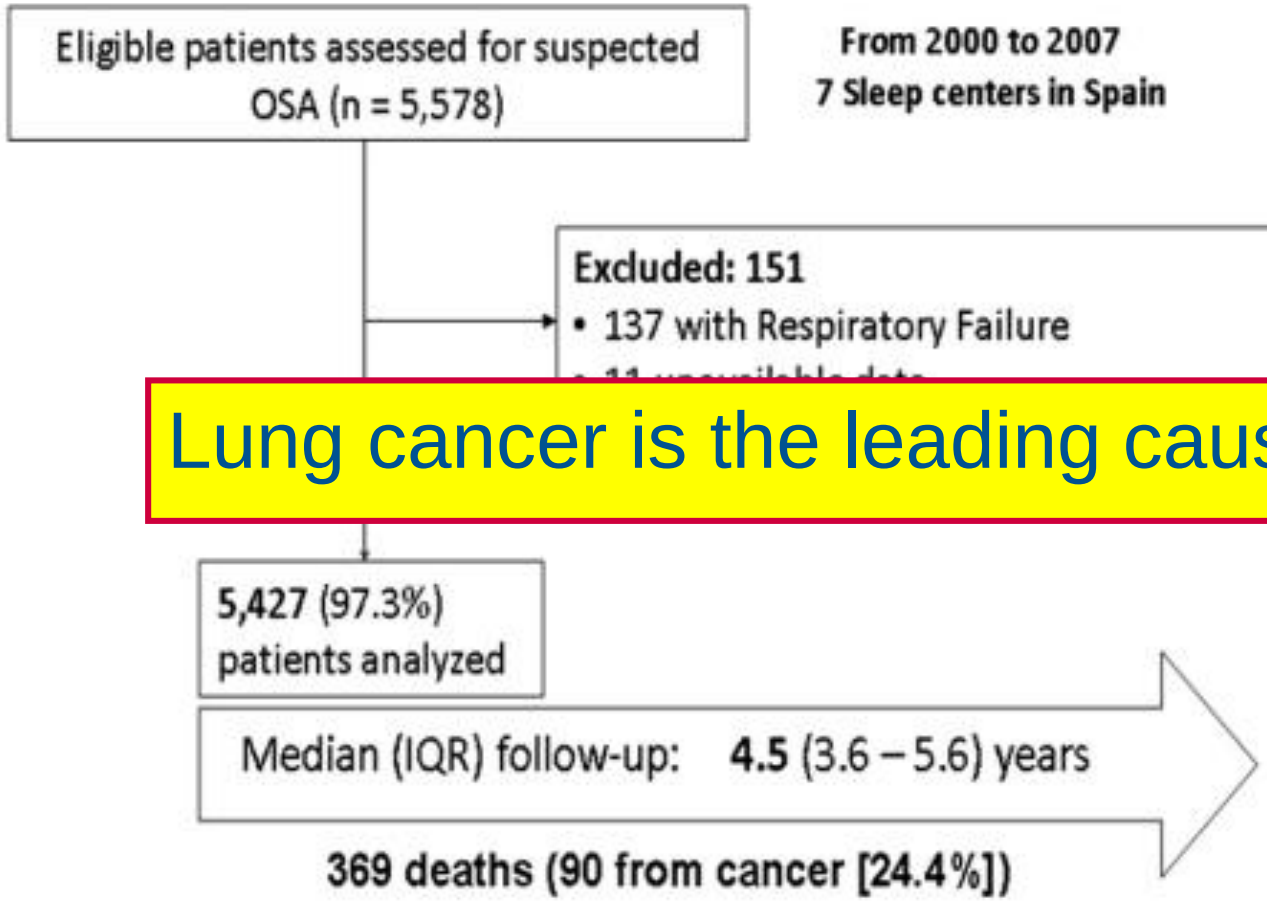
SDB (AHI Range)	All-Cause Mortality	Cancer Mortality
Absent (<5)	1.0	1.0
Mild SDB (5–14.9)	1.8 (1.1–2.8)	1.1 (0.5–2.7)
Moderate SDB (15–29.9)	1.1 (0.5–2.5)	2.0 (0.7–5.5)
Severe SDB (≥30)*	3.4 (1.7–6.7)	4.8 (1.7–13.2)
P for trend	0.0014	0.0052

TABLE 3. ADJUSTED RELATIVE HAZARDS OF CANCER MORTALITY ACCORDING TO HYPOXEMIA INDEX

Hypoxemia Index*	Relative Hazards of Cancer Mortality (95% CI)
Percentile < 73 (<0.8% of the time)	1.0
Percentile 73–89 (0.8–3.6% of the time)	1.6 (0.6–4.4)
Percentile 90–97 (3.6–11.2% of the time)	2.9 (0.9–9.8)
Percentile > 97 (>11.2% of the time)	8.6 (2.6–28.7)
P for trend	0.0008

Nieto et al, AJRCCM 2012

Sleep-disordered Breathing and Cancer Mortality
Spanish Sleep Cohort

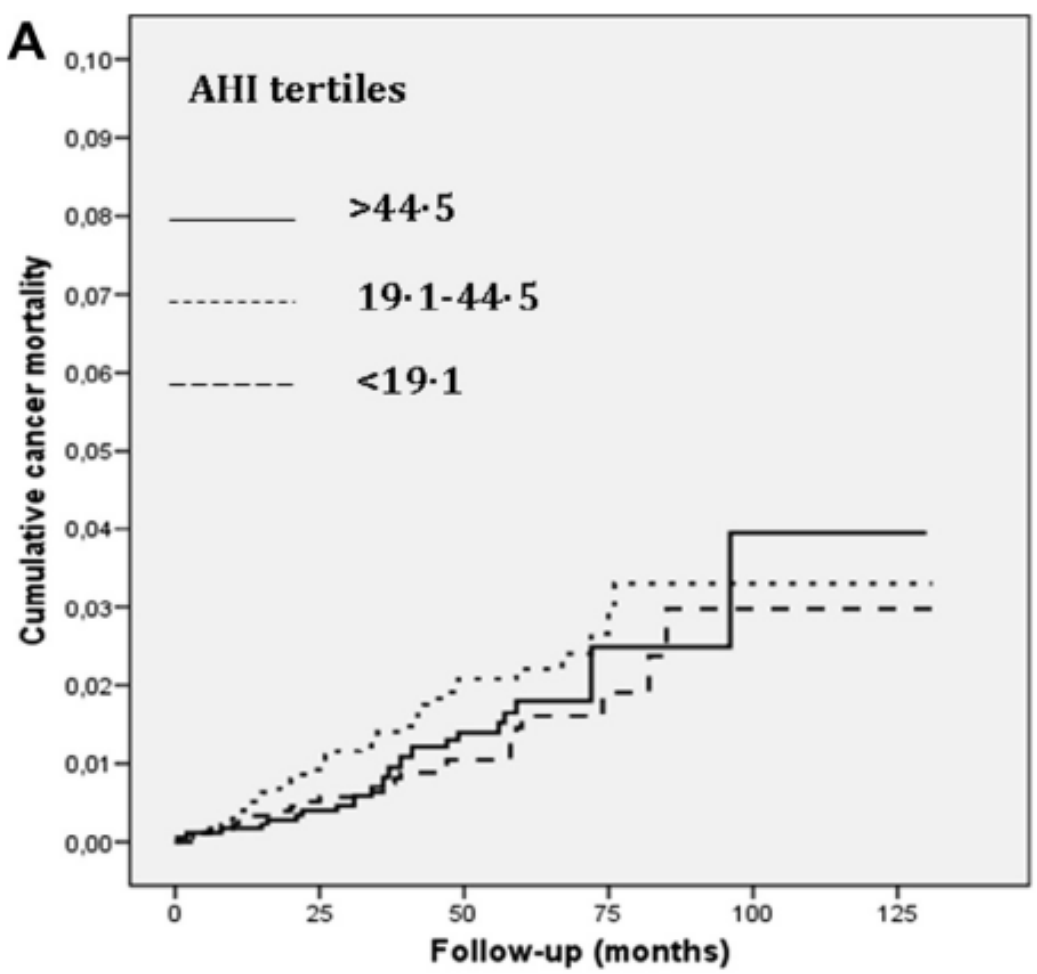


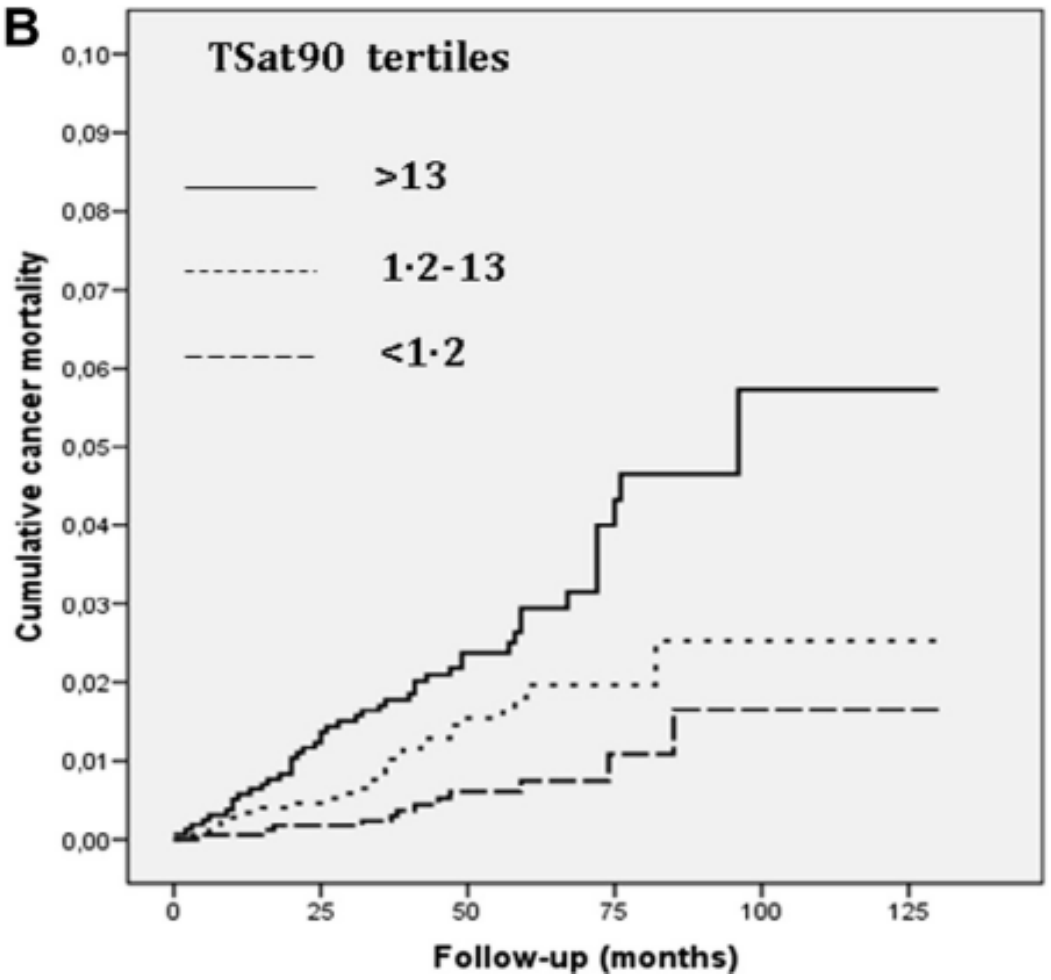
Location	Total deaths from cancer	Deaths from cancer in subgroups studied			
		Age <65 years	Age ⩾65 years	Men	Women
Respiratory tract	24	9	15	23	1
Gastrointestinal tract	20	6	14	12	8
Urinary tract	6	0	6	4	2
Brain	4	1	3	3	1
Pancreatic	3	0	3	2	1
Genital tract	3	1	2	0	3
Thyroid	3	0	3	3	0
Skin melanoma	2	0	2	2	0
Hematological	1	1	0	1	0
Others	7	2	5	6	1
Total	90	25	65	66	24

Lung cancer is the leading cause of cancer mortality in OSA

Martínez-García, Sleep Medicine 2014

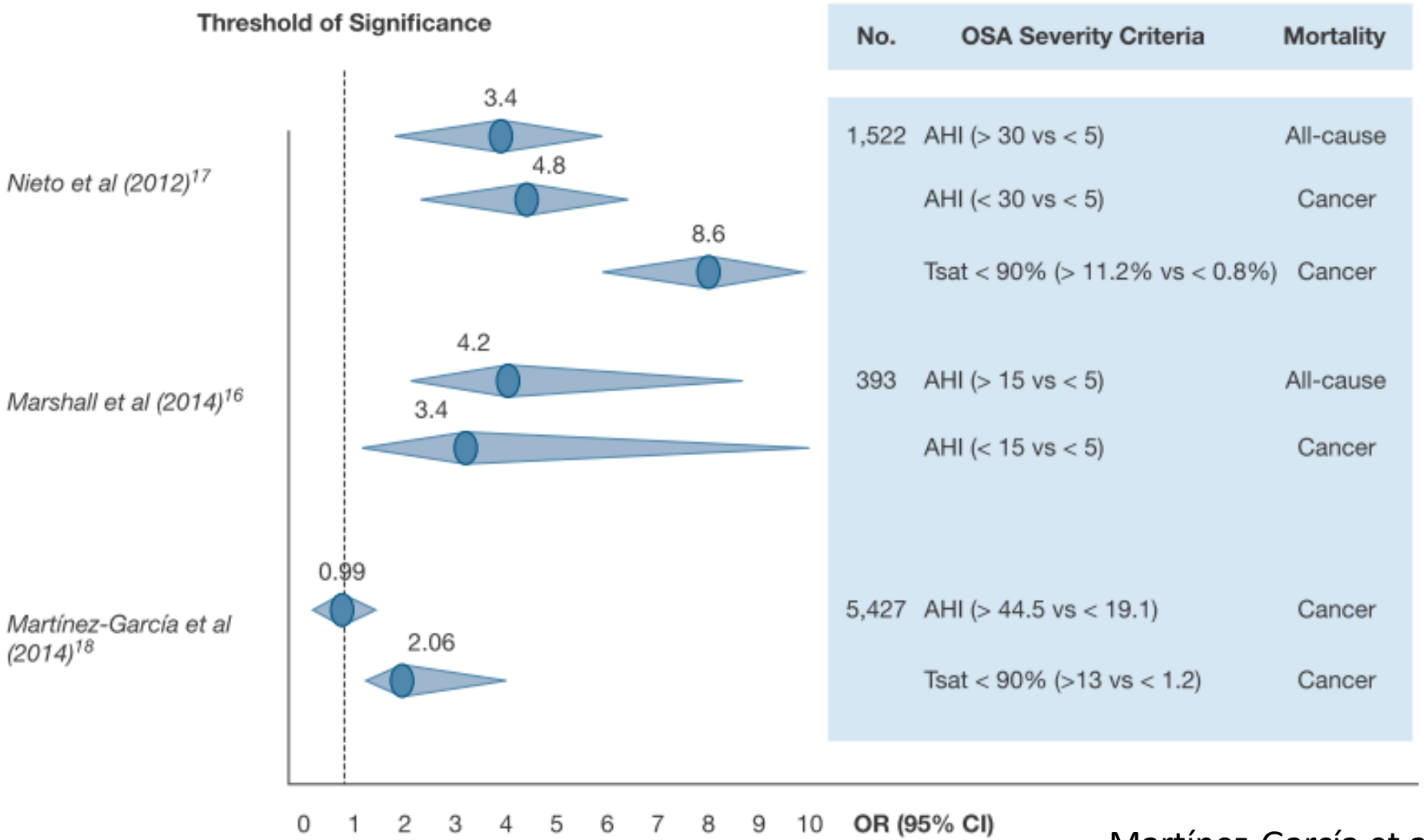
Cumulative cancer mortality increased across TSat90 categories (Spanish Sleep Cohort)





Martínez-García, Sleep Medicine 2014

Increased cancer mortality in patients with OSA



No.	OSA Severity Criteria	Mortality
1,522	AHI (> 30 vs < 5)	All-cause
	AHI (< 30 vs < 5)	Cancer
	Tsat < 90% (> 11.2% vs < 0.8%)	Cancer
393	AHI (> 15 vs < 5)	All-cause
	AHI (< 15 vs < 5)	Cancer
5,427	AHI (> 44.5 vs < 19.1)	Cancer
	Tsat < 90% (>13 vs < 1.2)	Cancer

Martínez-García et al, Chest 2016

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OSA prevalence in lung cancer

	Total no.	Stage III-IV	AdneoCA	SquaCA	Other CA	AHI<5	AHI:5-15	AHI>15
Dreher, 2018	100	78 %	45 %	24 %	31 %	51 %	32 %	17 %
Cabezas, 2019	60	65 %	47 %	17 %	36 %	20 %	30 %	50 %

- Sleep apnea and nocturnal hypoxemia are highly prevalent in patients with lung cancer
- further research is warranted to determine whether SDB influences the outcome of patients with lung cancer

Dreher, BMC Pulmonary Med 2018
Cabezas, Respiration 2019

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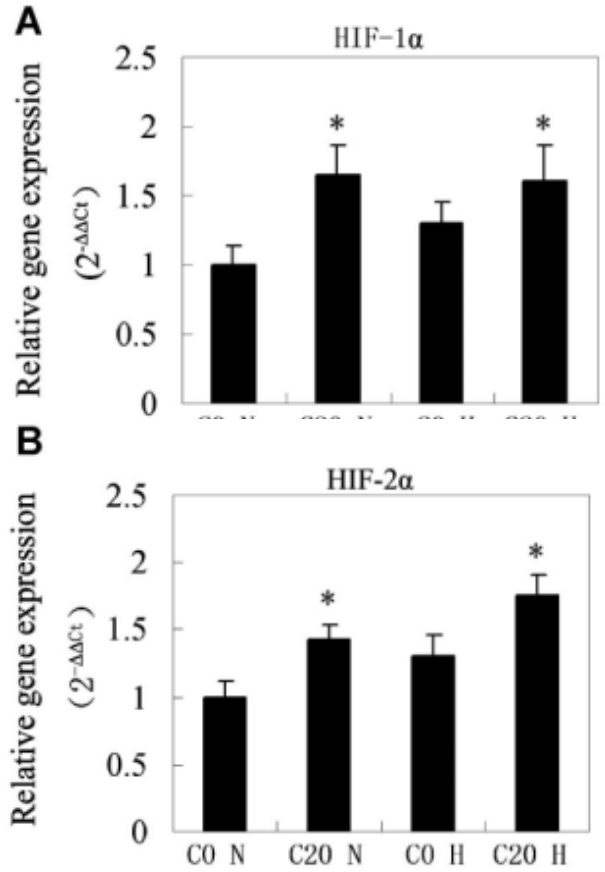
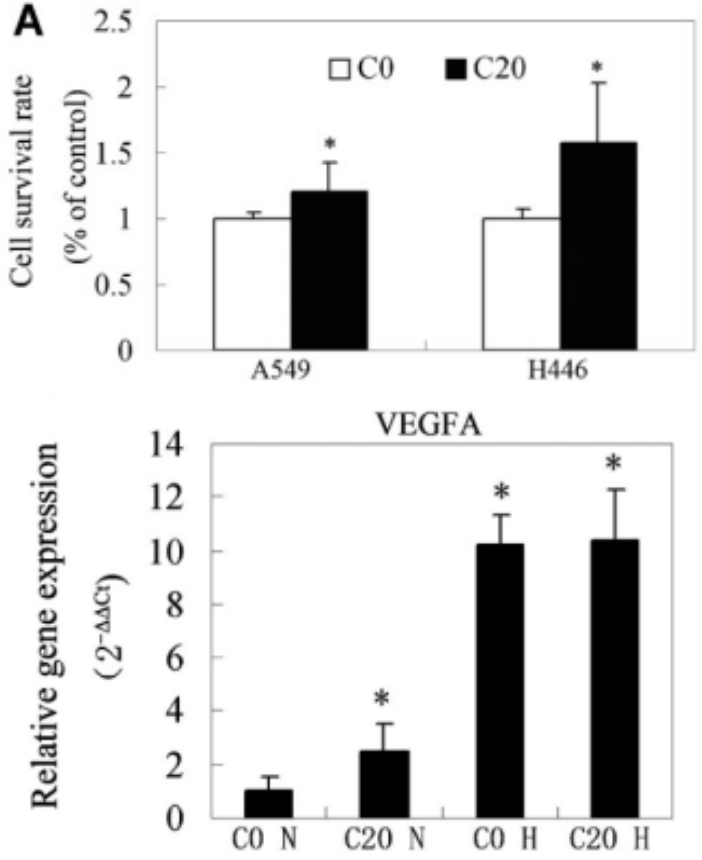
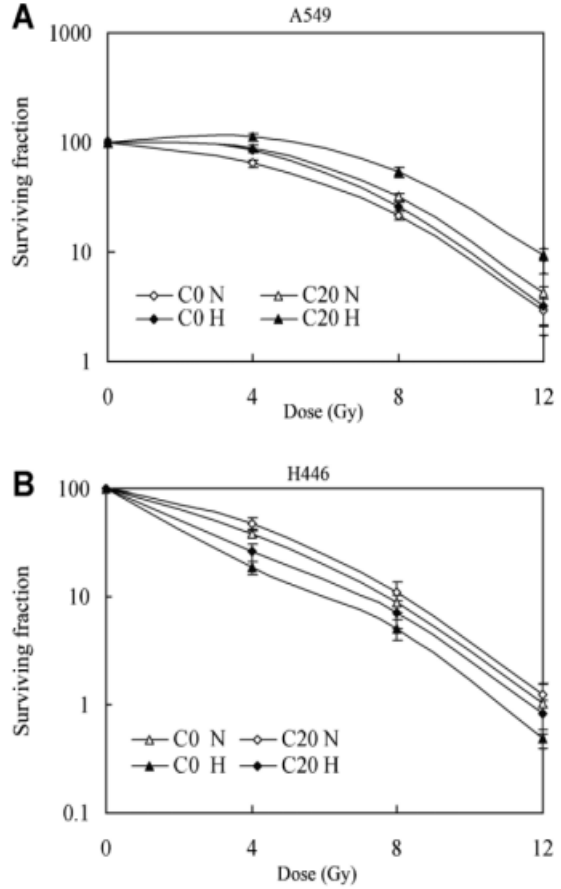
Effect of intermittent hypoxia on lung cancer cells

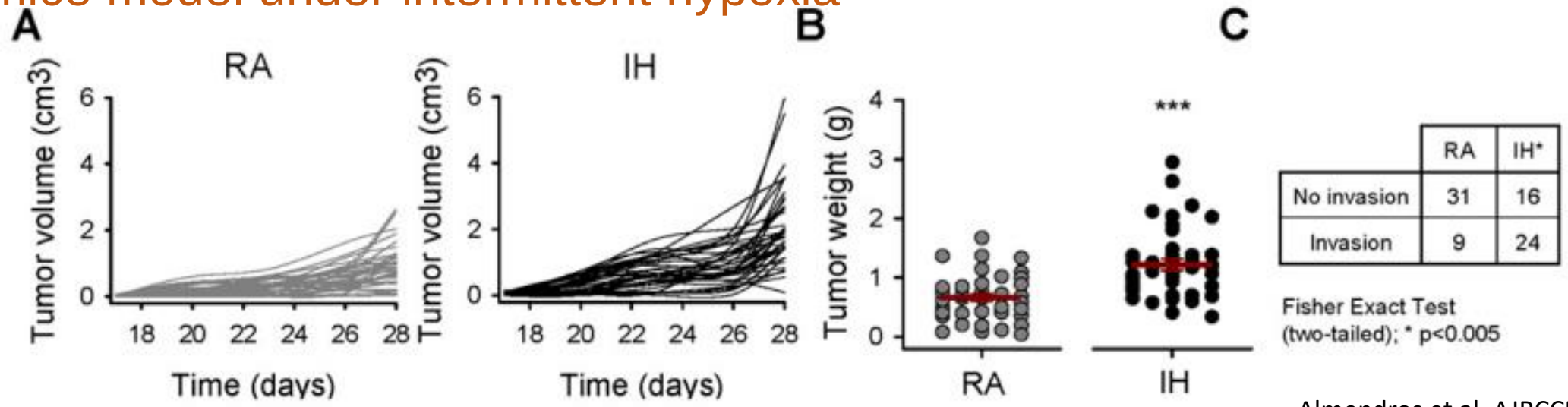






Liu et al, Journal of Cellular Biochemistry 2010

The tumor size, invasiveness,and extent of metastasis increase in mice model under intermittent hypoxia



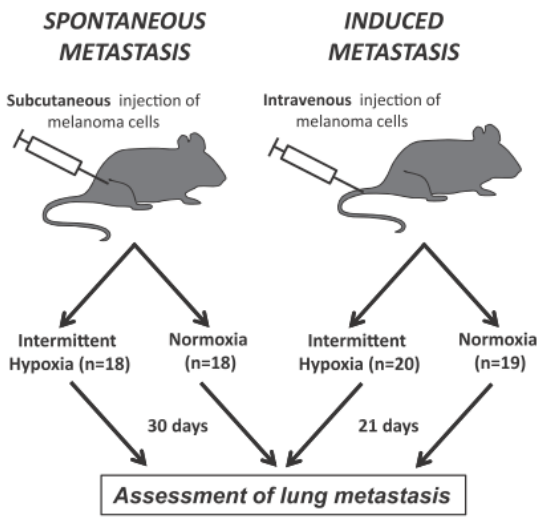
	RA	IH*
No invasion	31	16
Invasion	9	24

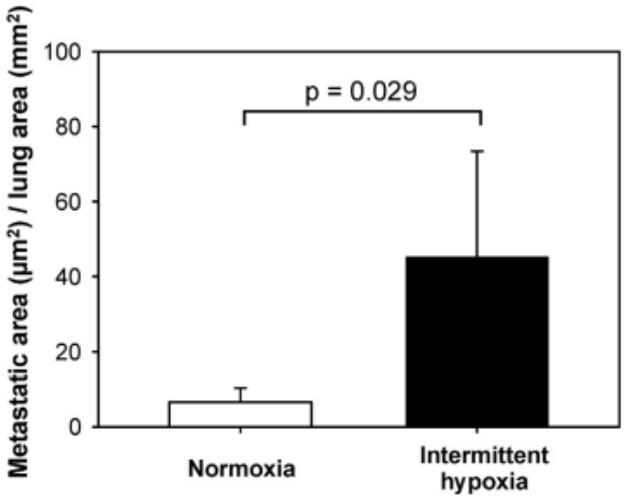
Fisher Exact Test (two-tailed); * p<0.005

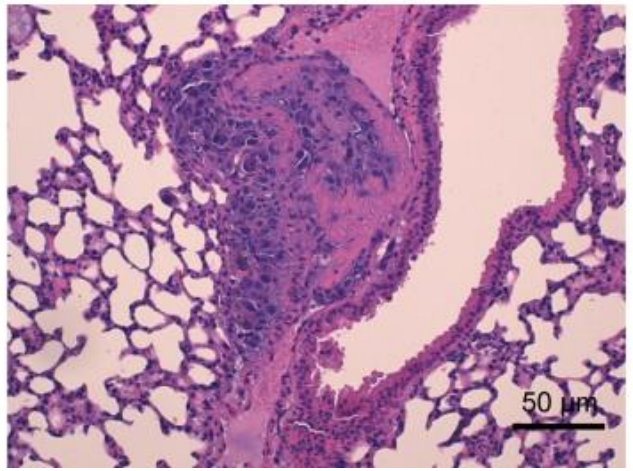
Almendros et al, AJRCCM 2014

Intermittent hypoxia increases melanoma metastasis to the lung

melanoma cells into C57B/6 J mice, intermittenthypoxia (60 times/h and 6 h/day)

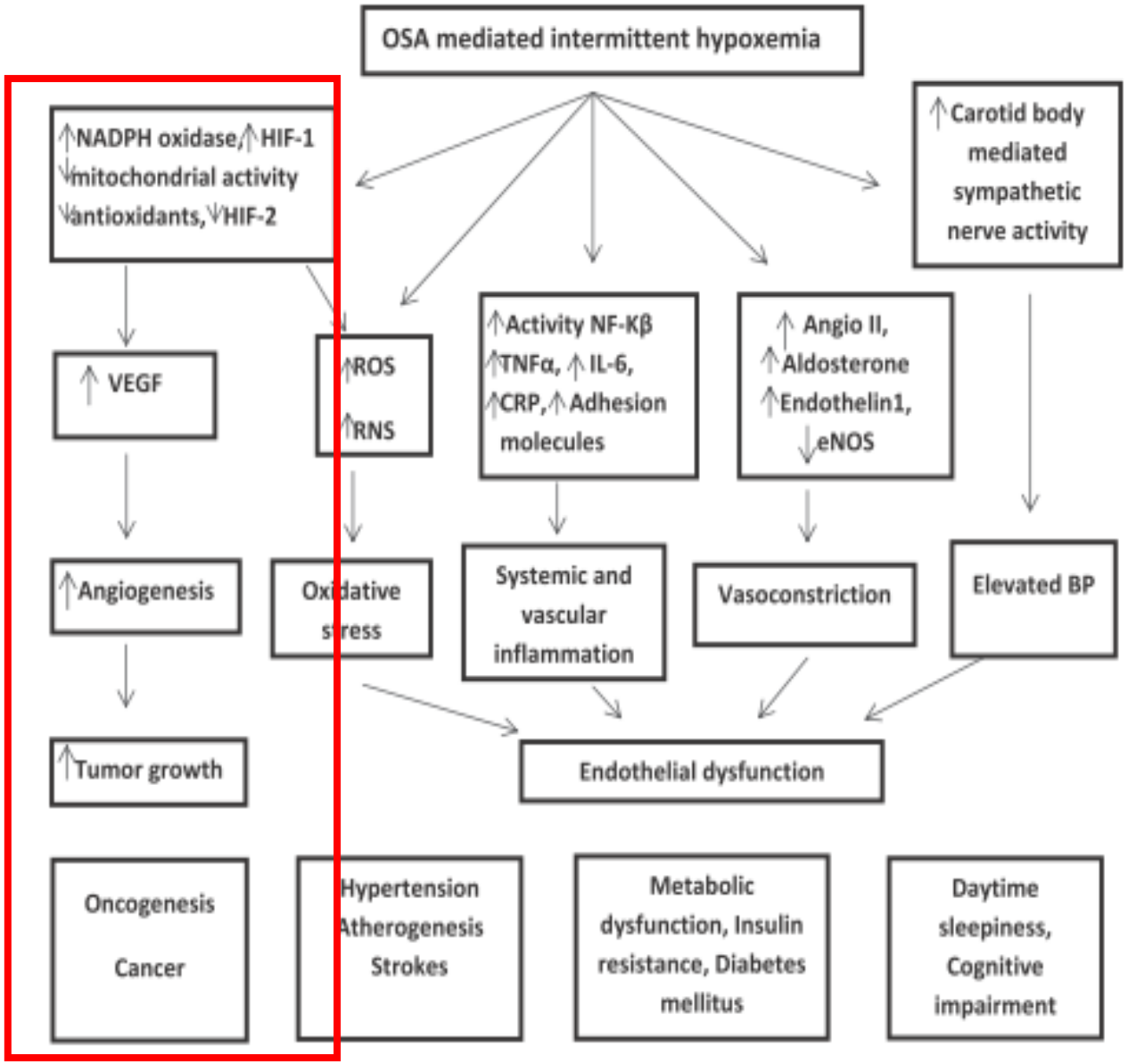




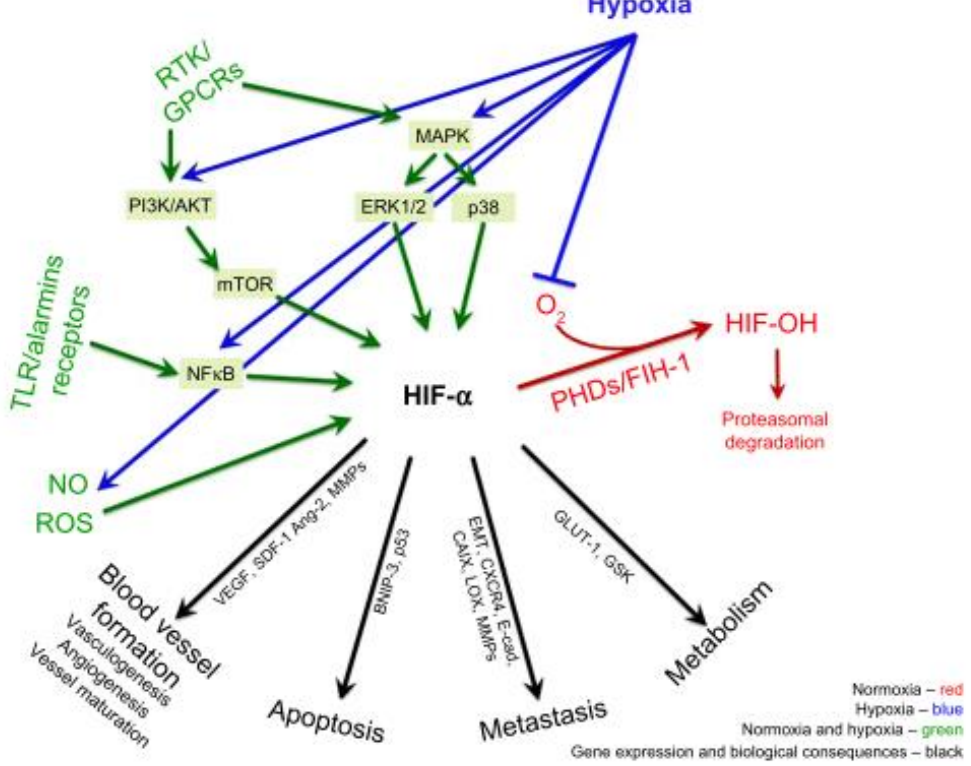


Almendros et al, Respiratory Physiology & Neurobiology 2013

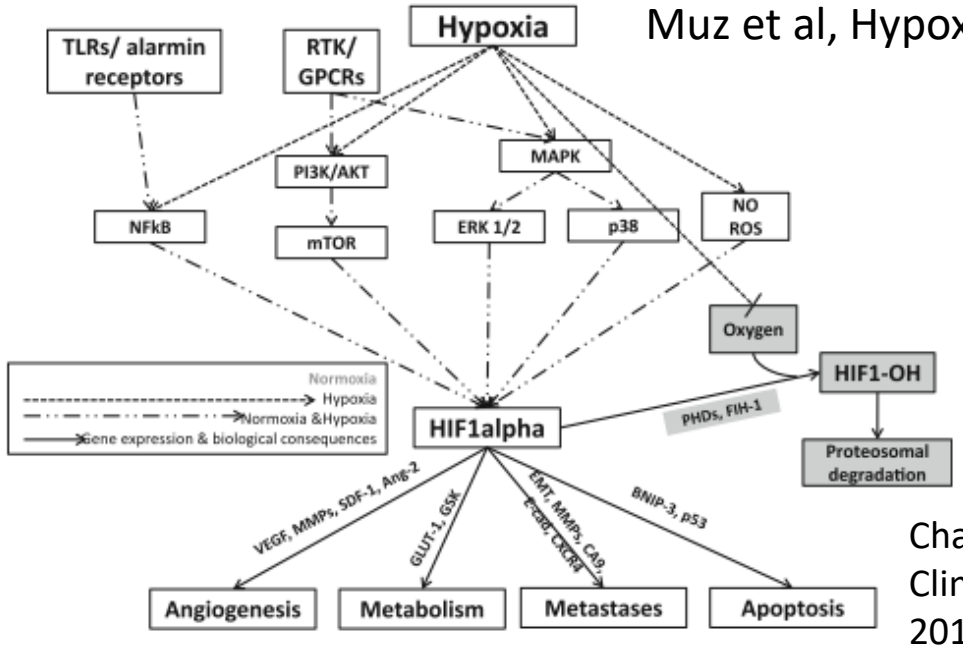
The link of OSA and lung cancer: HIF



Dewan et al, Chest 2015



Muz et al, Hypoxia 2015



Challapalli et al, Clin Transl Imaging 2017

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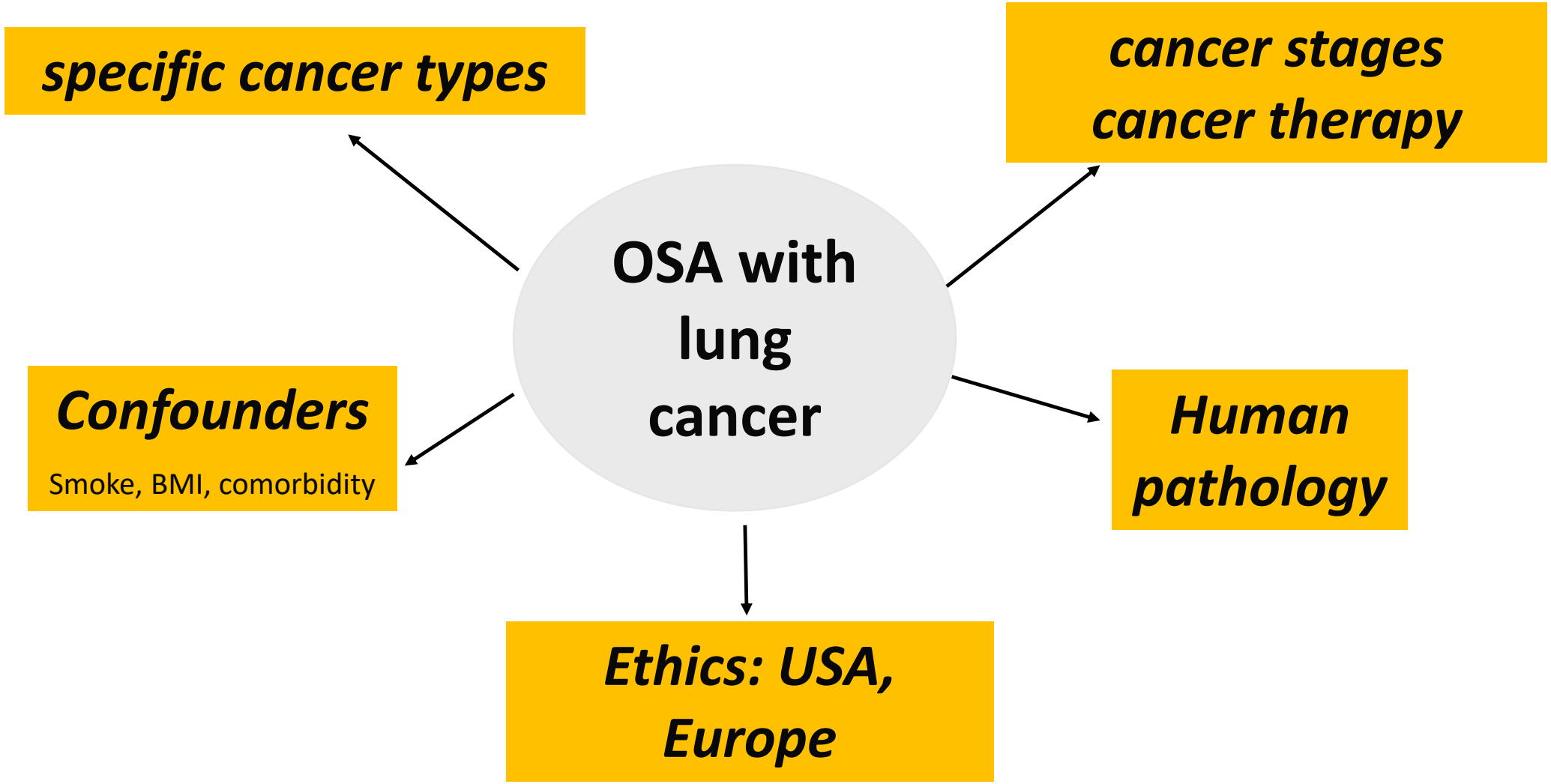
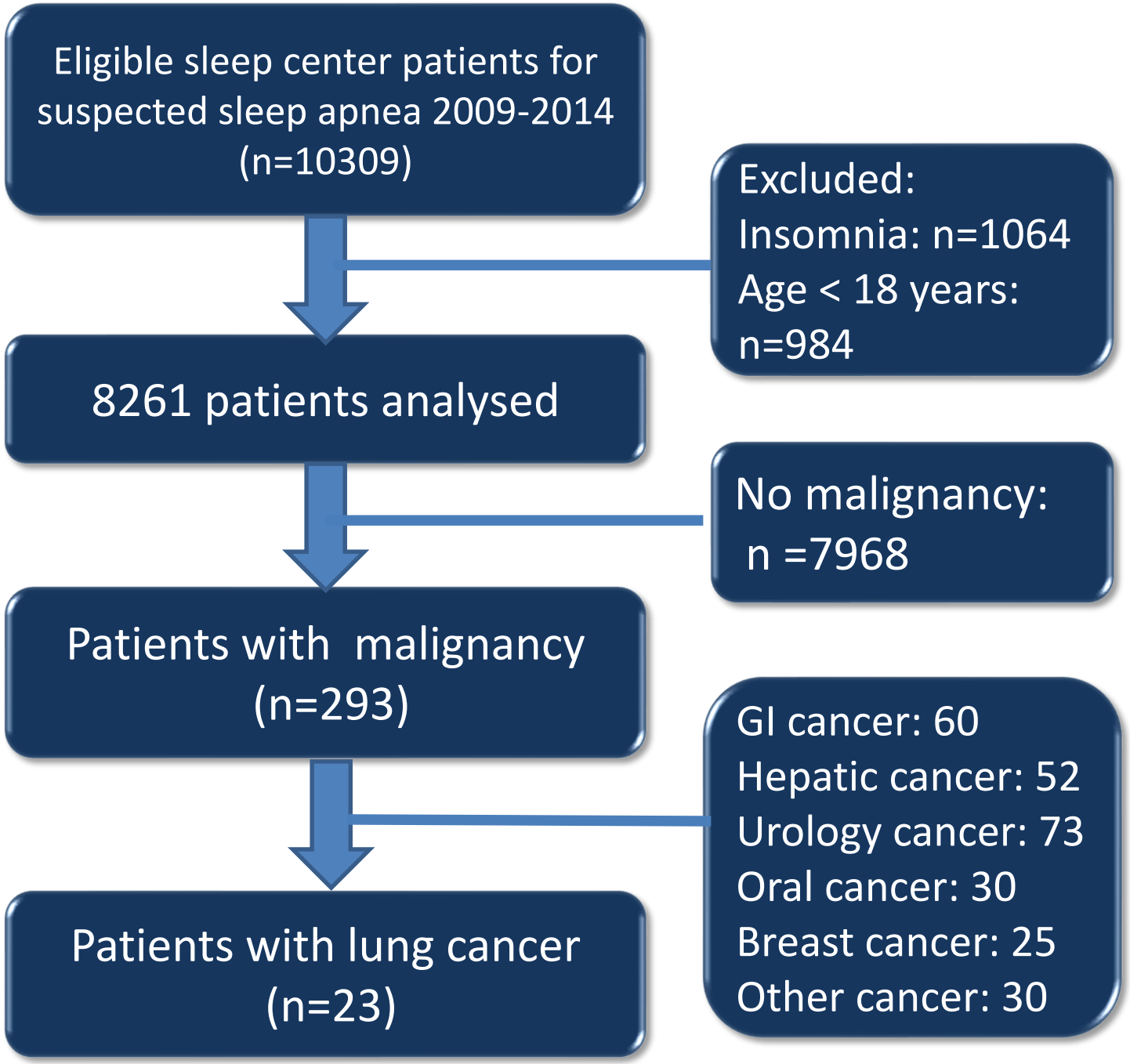
Introduction



Study flow


Eligible sleep center patients for suspected sleep apnea 2009-2014 (n=10309)
Excluded:
Insomnia: n=1064
Age < 18 years: n=984
8261 patients analysed
No malignancy: n =7968
Patients with malignancy (n=293)
GI cancer: 60
Hepatic cancer: 52
Urology cancer: 73
Oral cancer: 30
Breast cancer: 25
Other cancer: 30
Patients with lung cancer (n=23)

Method

- All patients underwent an overnight in-laboratory polysomnography from 2009~2014
- AHI, ODI and Tsat90% (Percentage of sleep time with oxygen saturation <90%) were recorded
- Adult OSA with diagnosis of lung cancer (AJCC 7th)
- Cancer mortality was the main end point and April 1, 2018 was the census date

Results

- Among 8261 suspected OSA patients, 23 were diagnosed with lung cancer
- The incidence of lung cancer was significantly higher in suspected OSA patients than the entire adult population in Taiwan (242.1 vs 51.5 per 10^5 persons, $p<0.001$)
- No CPAP treatment

Characteristics of sleep cohort with lung cancer

	Total (N= 23)	Stage I-II (N= 7)	Stage III-IV (N = 16)	P
Age, yrs	62.4±11.6	62.4±12.7	62.4±11.5	0.99
Gender, male	22	7	15	1.00
BMI	26.6±4.8	26.1±6.2	26.8±4.2	0.89
Smoke, PKY	37.4±37.2	24.3±26.4	43.1±40.5	0.34
ESS score	11.6±4.9	12.1±5.8	11.4±4.6	0.52
Polysomnography				
AHI	41.3±27.0	37.0±22.4	43.3±29.4	0.59
ODI	31.6±25.0	37.7±24.2	28.2±25.8	0.43
Lowest SpO_2	81.9±5.8	82.1±3.2	81.8±6.9	0.88
Tsat90%	17.1±26.7	13.2±26.2	19.1±27.1	0.43

Characteristics of sleep cohort with lung cancer

	Total (N= 23)	Stage I-II (N= 7)	Stage III-IV (N = 16)	P
OSA severity				0.59
Normal	2(9%)	0(0%)	2(13%)	
Mild	2(9%)	1(13%)	1(6%)	
Moderate	4(17%)	2(29%)	2(13%)	
Severe	15(65%)	4(58%)	11(68%)	
ECOG status	0.7±0.7	0±0	1±0.6	<0.01*
Pathology				1.00
Adenocarcinoma	14(61%)	4(57%)	10(66%)	
Squamous cell	6(26%)	3(43%)	3(18%)	
Other	3(13%)	0(0%)	3(18%)	
3 year mortality	65%	1(14%)	13(81%)	0.005*
5 year mortality	83%	1(14%)	15(94%)	<0.005*

Characteristics of stage III-IV lung cancer of the sleep cohort

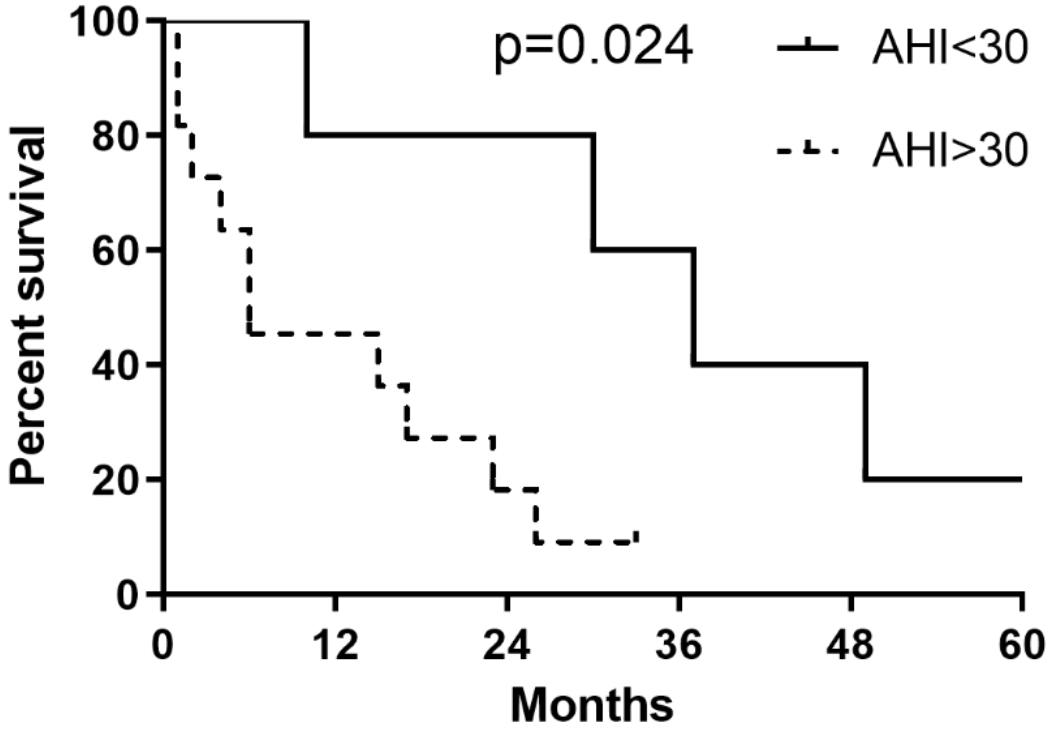
	Total (N= 16)	AHI<30 (N= 5)	AHI>=30 (N = 11)	p
Age, yrs	62.4±11.5	64.2±10.9	63.3±11.4	1.00
Gender, male	15	4	11	0.31
BMI	26.8±4.2	25.8±4.3	27.2±4.3	0.46
Smoke, PKY	43.1±40.5	20.0±15.8	53.6±44.3	0.09
ECOG status	1±0.6	0.8±0.4	1.1±0.7	0.43
Polysomnography				
AHI	43.3±29.4	10.8±8.9	59.5±20.8	<0.01*
ODI	28.2±25.8	7.8±4.0	41.0±25.5	<0.01*
Lowest SpO_2	81.8±6.9	84.0±5.3	80.7±7.5	0.50
$TSpO_2$90%	19.1±27.1	2.5±2.1	29.5±31.5	0.05
Pathology				0.59
Adenocarcinoma	10(66%)	4(80%)	6(55%)	
Squamous cell	3(18%)	1(20%)	2(18%)	
Other	3(18%)	0(0%)	3(27%)	

Characteristics of stage III-IV lung cancer of the sleep cohort

	Total (N= 16)	AHI<30 (N= 5)	AHI>=30 (N = 11)	p
Stage 4 (%)	12(75%)	3(60%)	9(82%)	0.55
3 year mortality	81.3%	40%	100%	0.08
5 year mortality	93.7%	80%	100%	0.31
EGFR mutation	7	3	4	0.38
No mutation	3	1	2	
First line cancer therapy				0.36
Target therapy	4	3	4	
CCRT	3	2	1	
Chemotherapy	4	0	4	
Radiotherapy	1	0	1	
Supportive care	1	0	1	

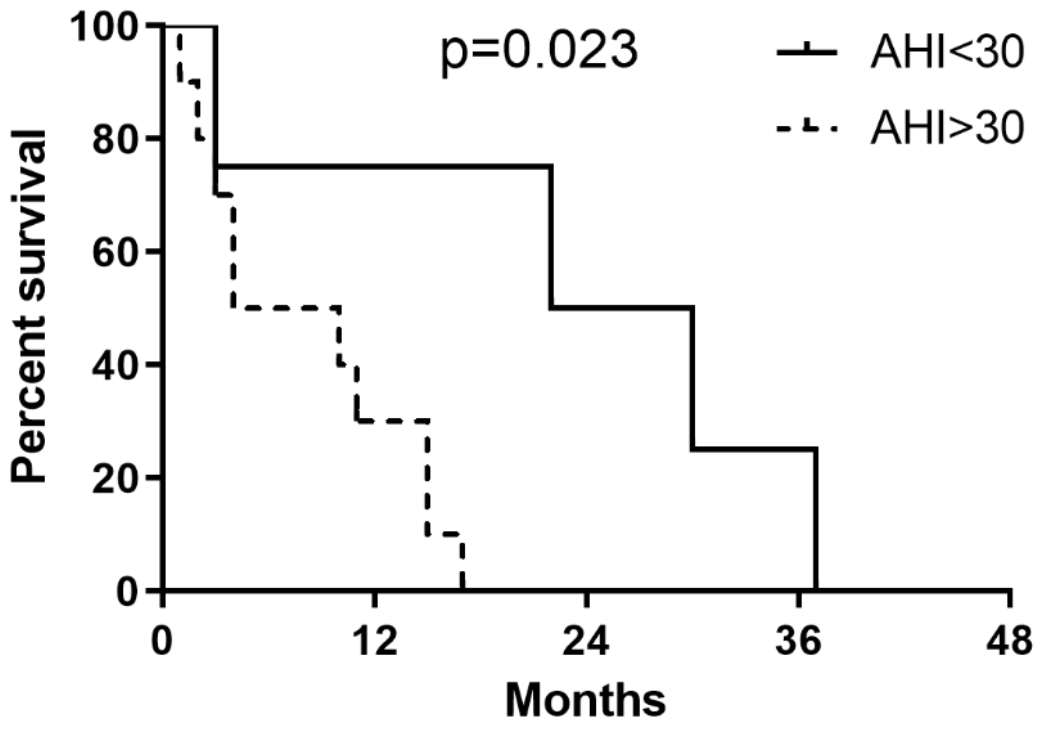
Stage III-IV lung cancer with severe OSA has worse survival

Overall survival



Median survival: 37 vs 6 months

Progression free survival

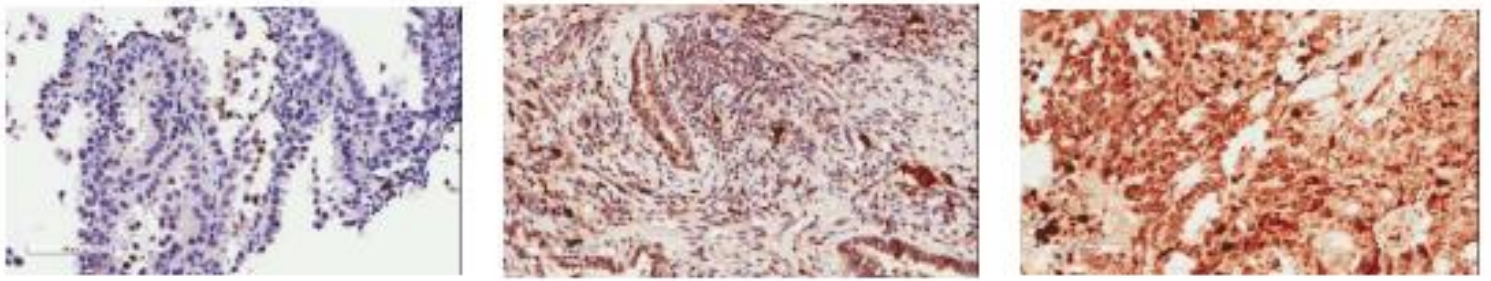


Median survival: 26 vs 7 months

Immunohistochemistry

HIF-1α expression

Low expression | Moderate expression | High expression



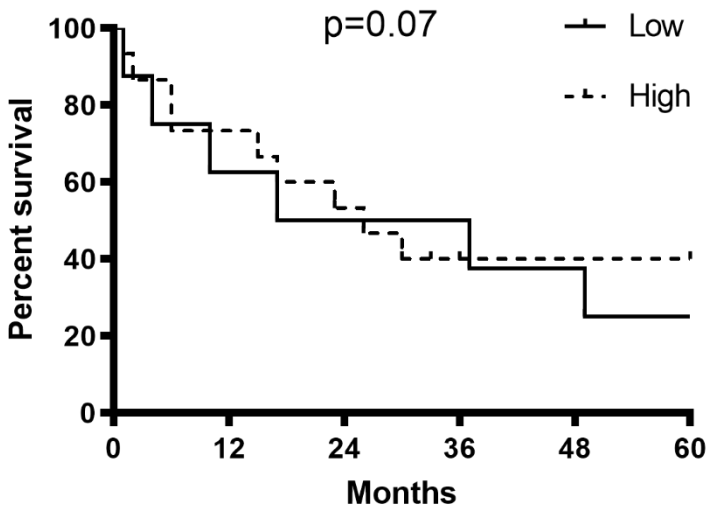
VEGF expression

Low expression | Moderate expression | High expression

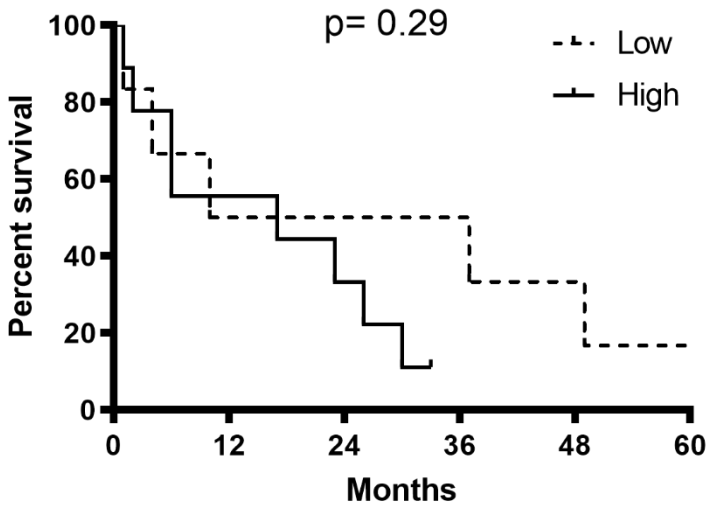
The expression of HIF-1α is positively associated with AHI

	HIF-1α high expression (N= 14)	HIF-1α low expression (N = 8)	Odds ratio	P
Age, yrs	62.3±10.8	62.3±14.2	1(0.93-1.08)	0.99
Gender, male	14	7		1.00
AHI	46.5±21.8	22.7±22.7	1.05(1.0-1.11)	0.04*
ODI	32.8±21.6	21.4±21.8	1.03(0.98-1.08)	0.28
Lowest SpO_2	82.3±5.6	82.7.±5.4	0.99(0.83-1.17)	0.88
Tsat90%	14.3±26.2	16.4±27.1	1.0(0.96-1.03)	0.86
Pathology				
Adenocarcinoma	8(57%)	5(63%)	1.00	
Squamous cell	4(29%)	2(25%)	1.25(0.16-9.54)	0.83
Other	2(14%)	1(12%)	1.25(0.09-17.6)	0.87

stage I-IV Overall survival



stage III-IV Overall survival



Limitation

- Retrospective study design
- Only include lung cancer diagnosis in CGMH
- Limited number of cancer patients in the cohort, unable to perform multivariate analysis

Conclusion

- Our sleep cohort had a higher incidence of lung cancer in sleep breathing disorder compared to the general population
- Severe obstructive sleep apnea associated with higher mortality in stage III-IV lung cancer
- The expression of HIF-1α is positively associated with AHI, but not significant in the mortality of lung cancer
- Future trials will be needed to confirm if severe OSA is a risk factor of lung cancer mortality and to evaluate the effect of CPAP on these patients.

Acknowledgments

- Sleep Center of Chang Gung Memorial Hospital
- Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Chang Gung Memorial Hospital
- Research Services Center for Health Information, Chang Gung University

Summary:

- Lung cancer was not significantly higher among OSA patients when while controlling for age, gender and comorbidity in US insurance cohort
- Severity of OSA is associated with overall cancer mortality
- Lung cancer is the leading cause of cancer mortality in OSA
- Sleep apnea and nocturnal hypoxemia are highly prevalent in patients with lung cancer
- HIF is the link of OSA and lung cancer; The tumor size, invasiveness,and extent of metastasis increase in intermittent hypoxia animal model.