CHEST

Intermittent Hypoxemia and OSA
Implications for Comorbidities

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OSA is a common chronic disorder that is associated with significant morbidity and mortality including cardiovascular, metabolic, and neurocognitive disease and increased cancer-related deaths. OSA is characterized by recurrent episodes of apneas and hypopneas associated with repetitive episodes of intermittent hypoxemia, intrathoracic pressure changes, and arousals. Intermittent hypoxemia (IH) is now being recognized as a potential major factor contributing to the pathogenesis of OSA-related comorbidities. OSA-related high-frequency IH is characterized by cycles of hypoxemia with reoxygenation that is distinctly different than sustained low-frequency hypoxia and contributes to ischemia-reperfusion injury. Data from both animal and human studies support mechanistic links between IH and its adverse impact at the tissue level. IH promotes oxidative stress by increased production of reactive oxygen species and angiogenesis, increased sympathetic activation with BP elevation, and systemic and vascular inflammation with endothelial dysfunction that contributes to diverse multiorgan chronic morbidity and mortality affecting cardiovascular disease, metabolic dysfunction, cognitive decline, and progression of cancer. Data from observational studies in large population groups also support the role for hypoxia in the pathogenesis of OSA comorbidity. Treatment with CPAP to reverse OSA-related symptoms and comorbidities has been shown to provide variable benefit in some but not all patient groups. Early treatment with CPAP makes intuitive sense to promote maximal functional recovery and minimize residual injury. More studies are needed to determine the interacting effects of IH and obesity, differential effects of both short-term and long-term hypoxemia, and the effect of CPAP treatment. CHEST 2015; 147(1):266-274

ABBREVIATIONS: AF = atrial fibrillation; AHI = apnea-hypopnea index; HIF = hypoxia-inducible factor; IH = intermittent hypoxemia; NADPH = reduced nicotinamide adenine dinucleotide phosphate; NO = nitric oxide; ROS = reactive oxygen species; Spo_2 = pulse oximetry blood oxygen saturation; VEGF = vascular endothelial growth factor

OSA is a common chronic disorder with an estimated prevalence of moderate to severe sleep apnea in 6% to 13% of the adult population affecting >20 million Americans.[1] It is also associated with significant morbidity and mortality that includes cardiovascular, metabolic, and neurocognitive impairment.[2] Emerging data also suggest an increased

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incidence of cancer-related deaths in patients with OSA.[3] Such diverse and extensive comorbidity related to OSA begs a simple question. Is there a common link that contributes to these comorbidities?

OSA is characterized by repetitive episodes of apneas and hypopneas associated with recurrent cycles of intermittent hypoxemia (IH) (cyclical desaturation-reoxygenation), repetitive reductions in intrathoracic pressure (from inspiration against an occluded airway), and arousals with sleep fragmentation. Although arousals and airway pressure changes contribute to sympathetic activation and comorbidity, IH is being suggested as the major factor responsible for morbidity and mortality and is the subject of this review.

Pathogenesis of IH and Its Impact at the Tissue Level

Two broad patterns of hypoxemia have been recognized.[4] Patients with OSA typically manifest short intermittent high-frequency hypoxemia (cyclical pattern of oxygen desaturation lasting 15-60 s followed by reoxygenation) that occurs for 8 to 9 h during sleep and lasts for weeks to months or longer. In contrast, sustained or low-frequency hypoxemia with oxygen saturation ranging between 80% and 85% that lasts from a few minutes to hours can be seen during rapid ascent and descent from altitude and in chronic lung disease during sleep. The major difference between the short intermittent high-frequency hypoxemia, as seen in OSA, and sustained prolonged low-frequency hypoxemia is the cycles of reoxygenation. These cyclical changes of hypoxemia with reoxygenation are, thus, similar to ischemia-reperfusion injury and contribute to increased production of reactive oxygen species (ROS) and oxidative stress.

Chronic continuous hypoxemia as seen at high altitude or in chronic lung disease can also promote both adaptive and maladaptive responses leading to an increase in erythropoiesis and pulmonary hypertension while IH generally leads to maladaptive responses by differential modulation of hypoxia-inducible factor (HIF) 1 and 2.[5] IH, as compared with sustained hypoxemia, also produces differential effects in certain tissues[6] and its effect is dependent upon the severity of chronic intermittent hypoxia[7] and is the subject for further discussion.

Both animal and human models of chronic IH appear to show a significant role for IH in the pathogenesis of OSA comorbidity.[2,8] Several pathways[9-16] are likely involved and are summarized in Figure 1. It is been increasingly recognized that IH promotes increased oxidative stress, systemic and vascular inflammation with endothelial dysfunction, increased sympathetic activation, and BP elevation thus contributing to multiorgan comorbidity. It has also been recognized that reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidases play a critical role in generating ROS and drugs that block their activity may represent potential therapeutic targets to reduce oxidative stress.[17]

Cardiovascular Dysfunction and Disease

While it is likely that apnea-related stressors such as negative intrathoracic pressure swings, sleep fragmentation, and arousal-related sympathetic activation during sleep contribute to OSA-related cardiovascular pathophysiology, the available evidence strongly implicates repetitive hypoxemia as a major mediator of cardiac and vascular disease and dysfunction.[18-22]

IH and Cardiovascular Disease Mechanisms

Hypoxemia elicits chemoreflex stimulation, with consequent sympathetic activation and vasoconstriction.[18] Sympathetic responses to hypoxemia are attenuated by stretch of thoracic afferents. Hence, apnea, and absence of chest inflation, potentiates the sympathetic vasoconstrictor effects of hypoxemia.[18,19] The key role of the chemoreflex in modulating hypoxemia-driven cardiovascular pathophysiology is evidenced by the following considerations. First, chemoreflex responses to hypoxemia are heightened in patients with OSA.[20] Second, hypertension is closely linked to OSA, and patients with borderline hypertension manifest markedly potentiated chemoreflex responses to hypoxemia.[21] Third, even during normoxic daytime wakefulness, patients with OSA have very high levels of sympathetic activation,[22] comparable to that seen in patients with heart failure. Administration of 100% oxygen lowers sympathetic drive, BP, and heart rate, arguing for tonic chemoreflex activation as a contributor to increased daytime sympathetic drive.[23] Fourth, apnea-induced nocturnal hypoxemia elicits even further increases in sympathetic activity, with consequent surges in BP to levels as high as 240/130 mm Hg,[22] with the patterns of sympathetic activation and inhibition during apnea and subsequent hyperventilation closely following those evident during administration of low inspiratory oxygen combined with voluntary apnea.[18,19] Last, the primary response to hypoxemia is bradycardia,[24,25] as is seen in the diving reflex.[25,26] Varying degrees of bradycardia and bradyarrhythmias are often seen in patients with OSA, and in some patients may manifest as Mobitz II, complete heart block, and sinus arrest. Treatment in these cases should

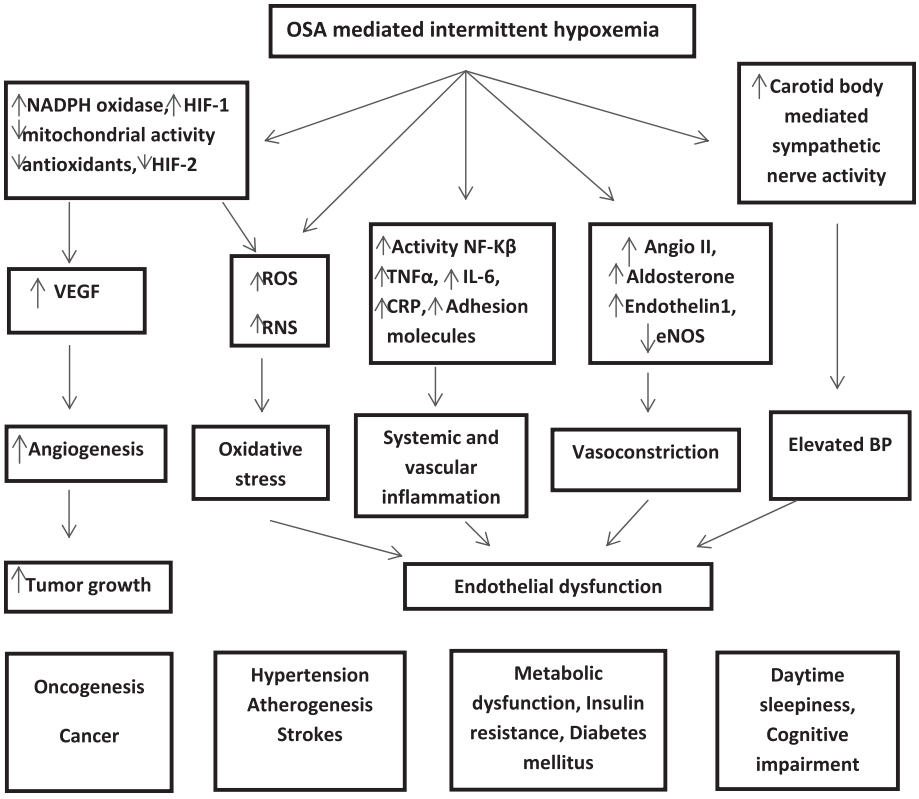

Figure 1 – *Pathway for intermittent hypoxemia (IH) and OSA comorbidities. OSA-associated IH promotes increased activity of NADPH oxidase via stimulation of HIF-1 with impaired mitochondrial function and reduction in antioxidant levels via HIF-2 to increase ROS and RNS contributing to oxidative stress. Increased activity of HIF-1 may also contribute to tumor growth by increased expression of VEGF and angiogenesis. IH also promotes increased carotid body-mediated sympathetic nerve activity with BP elevation, systemic and vascular inflammation by increased activity of NF-κB, with enhanced levels of cytokines such as TNF-α, IL-6, and CRP with increased expression of adhesion molecules on the endothelial surface. IH also causes activation of type 1 angiotensin II receptors with increased aldosterone levels, increased endothelin 1 levels, and decreased activity of eNOS to promote vasoconstriction and BP elevation. OSA thus leads to increased oxidative stress, systemic and vascular inflammation, vasoconstriction, and elevated BP to promote multiorgan comorbidity. Angio II = angiotensin II receptor; CRP = C-reactive protein; eNOS = endothelial nitric oxide synthetase; HIF = hypoxia-inducible factor; NADPH = reduced nicotinamide adenine dinucleotide phosphate; NF-KB = nuclear factor-κB; RNS = reactive nitrogen species; ROS = reactive oxygen species; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor. (Partly adapted with permission from Kohler and Stradling.[12])*

usually consist of treatment of apnea, rather than pacemaker placement.

Hypoxemia and reperfusion also have important effects on vascular function. These are mediated by several mechanisms, including systemic inflammation, endothelin release, and attenuated production of nitric oxide (NO). Patients with OSA have increased levels of C-reactive protein[27] and evidence of leukocyte activation.[28] Hypoxemia is an important trigger for endothelial cell endothelin production.[29,30] Endothelin is a highly potent vasoconstrictor, and acute untreated OSA results in elevations of both endothelin and BP[31] with attenuation of both after CPAP treatment. Conversely, patients with OSA have reduced levels of circulating NO, which increase after CPAP therapy.[32] These hypoxemia-driven effects on systemic inflammation, endothelin, and NO likely contribute to the endothelial dysfunction evident in patients with OSA.[33]

IH and Cardiovascular Disease

Studies in animals by Brooks et al[34] showed that while sleep fragmentation acutely increased nighttime BP, daytime BP was relatively unchanged. In contrast, nighttime BP increased during obstructive apneas, with persistence of elevated BP into the daytime, suggesting that nocturnal hypoxemia, and not arousals, are a key driver for elevated daytime BP, with clear implications for OSA-related hypertension.

Hypoxemia may also be an important trigger for OSA-induced atrial fibrillation (AF). In dog studies, Ghias et al[35] showed that apnea-induced hypoxemia, in the absence of arousals or inspiratory effort, significantly reduced atrial refractory periods, thus lowering the threshold for development of AF. In a cohort study of 3,542 adults, all of whom were free of any history of AF, Gami et al[36] reported that in those younger than 65 years of age, OSA was associated with an increased risk of

incident AF. The magnitude of decrease in nocturnal oxygen saturation, but not apnea-hypopnea index (AHI), was an independent predictor of risk of developing new-onset AF. In patients undergoing cardioversion for AF, observational data also suggest a role for nocturnal hypoxemia as a predictor of recurrence of AF. Patients with OSA who remain untreated after cardioversion have a markedly increased likelihood of AF recurrence as compared with those whose OSA is treated.[37] In the OSA-untreated group, those most likely to recur were those with the most marked nocturnal oxygen desaturation.[37]

Hypoxemia may also be a trigger for nocturnal cardiac ischemia[38] and perhaps myocardial infarction.[39] Increasing levels of nocturnal oxygen desaturation are associated with heightened likelihood of ST segment depression, an ECG marker of cardiac ischemia.[40]

The role of hypoxemia in arrhythmogenesis, including bradycardia, as well as hypoxemia potentiating cardiac ischemia, may be important in understanding mechanisms underlying sudden cardiac death related to OSA. Patients with OSA who experience sudden death are more likely to die at night as compared with those without OSA, who are more likely to die in the morning.[41] However, while OSA influences the timing of sudden death, it also increases the overall sudden death risk. In a follow-up of >10,000 individuals, those with OSA had a greater risk of sudden death.[42] In multivariate analysis, the degree of oxygen desaturation, but not AHI, emerged as an independent predictor of increased sudden death risk.

Analysis of data from the Sleep Heart Health Study has added further substance to the critical role of hypoxemia in OSA-related cardiovascular risk. Punjabi et al[43] evaluated the association between hypopneas and cardiovascular disease, finding that only those hypopneas associated with a desaturation of 4% or more were independently associated with cardiovascular disease, with no association evident for hypopneas accompanied by mild desaturations or arousals.

Mild to moderate pulmonary hypertension has also been reported to occur in up to 20% of patients with OSA in absence of other known cardiopulmonary disorders.[44] Elevated pulmonary artery pressure appears to correlate with severity of sleep apnea and resting daytime hypoxemia, and may sometimes improve with CPAP treatment.[45] However, whether OSA causes pulmonary hypertension remains unclear.

In summary, while the observational data are strongly suggestive of OSA being a risk factor for cardiovascular disease, and hypoxemia likely being a key trigger for OSA-related cardiovascular risk, definitive evidence for both of these awaits completion of randomized control trials, evaluating the effects of OSA treatment on cardiovascular outcomes.

IH and Metabolic Dysfunction: Mechanisms

Animal experiments in mice exposed to IH for 14 days showed marked changes in insulin resistance, impaired β-cell function, and increases in oxidative stress that improved only partially after cessation of hypoxic exposure.[46] Intermittent hypoxia as compared with room air also caused dyslipidemia in mice with elevation in serum total cholesterol and triglyceride levels that correlated with the degree of hypoxemia and was more marked in lean than obese mice.[7] Data also suggest differential metabolic effects of high-frequency IH compared with those of sustained low-frequency hypoxia and that the metabolic adaptation that occurs with acute exposure to hypoxia is improved to a greater extent with chronic sustained hypoxia than with chronic high-frequency IH.[47]

The effect of acute and intermittent hypoxia has also been studied in healthy volunteers. Glucose tolerance was significantly decreased in the acute hypoxic group (75% oxygen saturation for 30 min) as compared with the control group.[48] Glucose metabolism was also impaired as evidenced by decreased insulin sensitivity, glucose effectiveness, and insulin secretion in volunteers exposed to acute intermittent hypoxia sustained over 5 h.[49] In both studies, hypoxia was associated with an increase in heart rate and symptoms of anxiety, suggesting activation of the sympathetic system.

OSA, Glucose Intolerance, and Diabetes Risk

Cross-sectional studies in subjects with OSA have shown an association between severity of sleep apnea and glucose intolerance and the likely risk for developing diabetes.[50] The Sleep Heart Health Study that followed 2,665 subjects for 5 years showed an independent association between severity of sleep apnea as determined by AHI and nocturnal hypoxemia and an increased risk of developing glucose intolerance and potentially type 2 diabetes mellitus.[51] This effect was independent of BMI and waist circumference. However, not all studies have shown an independent association of sleep apnea severity and diabetes after adjustment of abdominal girth,[52] suggesting obesity is potentially an important confounding variable. A plausible explanation may be that since obesity is a shared risk factor for both OSA and cardiometabolic dysfunction, IH associated with OSA likely exacerbates the cardiometabolic risk

attributed to obesity and the metabolic syndrome. Treatment of OSA may decrease the cardiometabolic risk associated with obesity.[53]

Glucose disposition and insulin sensitivity were also decreased in nondiabetic subjects with sleep apnea as compared with normal subjects and correlated with the severity of sleep apnea and average degree of nocturnal oxygen desaturation.[54] Nocturnal intermittent hypoxia was also associated with an increased risk for developing type 2 diabetes in a large community-based middle-aged Japanese group.[55] More recently, correlation was also noted between severity of hypoxemia (average pulse oximetry blood oxygen saturation [Spo_2] and percentage of sleep time with $Spo_2 < 90\%$) and HbA1C levels in nondiabetic subjects with OSA; treatment with CPAP over 3 to 5 months decreased HbA1C only in patients with severe sleep apnea.[56]

Studies of the effect of CPAP on glycemic control in patients with OSA have produced mixed results. Although initial small uncontrolled studies showed benefit with the use of CPAP over 3 months,[57] the results of randomized sham-controlled CPAP trials have shown conflicting results. The first study was done in 42 known diabetic patients with newly diagnosed OSA.[58] The use of therapeutic CPAP ($n = 20$) over 3 months did not show any benefit on insulin resistance and glycemic control as compared with sham CPAP ($n = 22$). The second study randomized 61 Chinese men with moderate to severe sleep apnea to therapeutic CPAP ($n = 31$) and sham CPAP ($n = 30$).[59] The use of therapeutic CPAP for 12 weeks showed improved insulin sensitivity as compared with sham CPAP and this benefit was seen in the group of 20 patients with a BMI > 25 kg/m^2. The third study was done in 50 moderately obese patients with moderate to severe OSA (AHI > 15) and impaired glucose tolerance.[60] Subjects were randomized to 8 weeks of CPAP or sham CPAP and crossed over after 4 weeks of a washout period. The use of CPAP overall did not normalize the insulin glucose tolerance as compared with sham CPAP; however, insulin sensitivity improved significantly in the subgroup of 25 patients with severe sleep apnea (AHI > 30) and correlated with hours of CPAP adherence.

In summary, these data suggest that sleep apnea increases the risk of developing insulin resistance and diabetes, independent of other risk factors, and that hypoxemia likely plays a significant role in promoting glucose intolerance. The use of CPAP treatment, although not beneficial in all patients, may provide benefit in moderately obese patients with severe sleep apnea and hypoxemia. It can also be speculated that insufficient sleep may be a contributing factor for glucose intolerance, and greater duration of nightly CPAP use and improved adherence to CPAP over 3 to 6 months is likely to be more beneficial.

IH and Cognitive Impairment: Mechanisms

Adults rats exposed to IH (12 h/d up to 14 days) showed impaired cognition that persisted at 14 days of recovery. A sevenfold to eightfold greater increase in apoptosis was also noted in the CA-1 hippocampus and cortical region after 1 to 2 days of IH.[61] Experiments in a rat model showed differential effects of intermittent hypoxia and OSA on the brain.[62] Brain tissue oxygen levels were higher in rats subjected to obstructive apneas compared with those subjected to intermittent hypoxia, and this may be attributed to hypercapnia. Long-term IH can enhance the production of angiotensin II, and upregulate NADPH oxidase activity, which promotes oxidative tissue injury in the hippocampal catecholamine neurons. This selective loss of the catecholaminergic wake-active neurons may contribute to impaired wakefulness.[63]

Neuroimaging studies of the brain in patients with OSA have demonstrated structural, morphologic, and functional changes in the brain suggesting a plausible mechanism for cognitive impairment.[64] These changes were noted in some but not all studies, and were attributed to different methodologies.[65] Morphologic changes manifesting reduction in gray matter volume have also been correlated with neurocognitive changes and the degree of hypoxemia that may improve with CPAP treatment.[66] Further studies are needed to assess brain morphologic and functional changes in patients with OSA and neurocognitive impairment.

IH, OSA, and Cognitive Impairment

Cognitive impairment in OSA includes daytime sleepiness and other cognitive and behavioral deficits that extend well beyond daytime sleepiness. Mild cognitive impairment similar to aging is also noted in patients with severe OSA. Cognitive impairment and dementia were seen more commonly in elderly women who had OSA as compared with no OSA and correlated with the severity of sleep apnea and hypoxia.[67] Mild cognitive impairment as noted in the Apnea Positive Pressure Long-term Efficacy Study (APPLES),[68] also correlated best with the severity of hypoxemia. An earlier onset of cognitive impairment was noted in elderly subjects who had OSA as compared with no OSA.[69] These data suggest that although aging is linked to mild cognitive impairment and dementia, the presence of comorbid OSA with attendant hypoxia may accelerate this decline.

The improvement of cognitive function in patients with OSA with CPAP treatment is variable. Daytime sleepiness generally responds well to CPAP treatment but residual sleepiness may persist[70] and not all patients revert to normal. In a study of 174 patients with moderate to severe OSA (AHI > 30), the use of CPAP for 3 months reverted daytime sleepiness to normal in only 50% of the patients with little impact on reaction times and executive errors.[71] In a large randomized sham-controlled trial in 1,098 study participants with OSA (APPLES), the use of CPAP over 6 months improved both subjective and objective sleepiness specially in individuals with severe OSA (AHI > 30), but only showed mild transient improvement in executive and frontal lobe function, thus suggesting complex interactions between OSA and neurocognitive dysfunction.[72] In another small study of 17 patients with severe OSA (AHI, 55.8) and 15 age-matched control subjects, brain MRI studies showed focal reductions in gray matter volume in the hippocampus and frontoparietal region that correlated with neurocognitive functional deficits.[66] Cognitive function improved after 3 months of CPAP treatment in most domains with parallel improvements in gray matter volume in the hippocampal and frontal structures. Both structural changes and functional cognitive deficits correlated with the degree of hypoxemia and its improvement with CPAP, thus highlighting the need for early diagnosis and effective treatment of severe sleep apnea.

In summary, the presence of selective neuronal damage as shown in animal studies in conjunction with MRI changes and neurocognitive deficits that do not completely reverse with CPAP therapy would raise the question of irreversible injury from OSA. Further studies are needed to define a comprehensive phenotype of brain dysfunction and injury in OSA.[73]

OSA, Oncogenesis, and Cancer Risk

In vitro studies have demonstrated the pro-oncogenic properties of hypoxia.[74] This is mediated mainly by the enhanced posttranslational effect of HIF, which in turn results in increased expression of vascular endothelial growth factor (VEGF), formation of new capillaries, tumor growth, and metastasis.[15,16,74] Laboratory studies have also demonstrated that low-frequency intermittent hypoxia has similar proangiogenic and tumor growth promoting effects.[14,75,76]

Based on this evidence, a melanoma mouse model was designed to specifically test whether intermittent hypoxia that mimics the periodicity and intensity of sleep apnea in human patients is associated with tumor growth.[77] The results of this study demonstrated that the growth of melanoma tumor in the mice exposed to intermittent hypoxia was about twice as large (in both size and weight) as that in the control mice and this may be attributed to alterations in host immunity.[78] Consistent with the evidence from in vitro studies, this effect appeared to be mediated by an increased production of VEGF and tumor vascularization. In a follow-up study using the same melanoma mouse model, the effect of intermittent hypoxia on both increased VEGF and cancer growth was stronger in lean than in obese mice.[79] Furthermore, intermittent hypoxia also increased lung metastasis in both a spontaneous metastasis model (subcutaneous injection of melanoma cells) and in an induced metastasis model (IV injection of melanoma cells) in mice.[80]

Inspired by these laboratory studies and animal models, datasets from existing longitudinal epidemiologic studies have recently been interrogated to assess whether sleep apnea is associated with cancer risk in human populations. A 22-year follow-up study among participants in the Wisconsin Sleep Cohort Study showed that presence and severity of sleep apnea (as indicated by the AHI) is associated with an increased risk of total cancer mortality in a dose-response fashion (Fig 2).[3] When the hypoxemia index (percentage of sleep time with $Spo_2 < 90\%$) was used to characterize sleep apnea severity, the association was even stronger, with participants with severe sleep apnea being about eight times more likely to die of cancer than those without sleep apnea, even after controlling for obesity, smoking, and other potential confounding factors. Two additional studies, one in an Australian cohort followed for about 20 years and another in a large clinical cohort in Spain, also found a statistically significant elevated risk of cancer mortality associated with high hypoxemia index.[81,82]

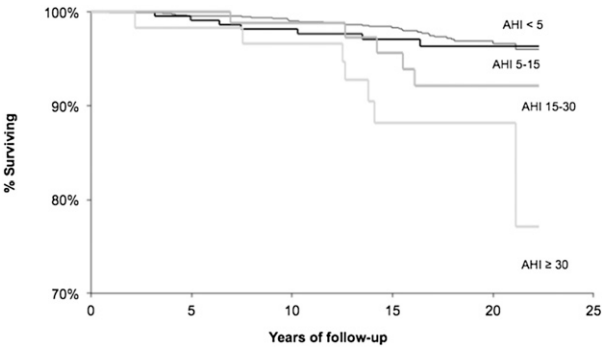

Figure 2 – *Survival free of cancer mortality according to categories of sleep-disordered breathing, Wisconsin Sleep Cohort, 1989-2011; Kaplan-Meier estimates. AHI = apnea-hypopnea index. (Reproduced with permission from Nieto et al.[3])*

These studies, however, looked at overall mortality and thus it is not clear whether the increased risk can be attributed to increased incidence or to decreased survival after cancer initiation. Two studies have explored whether sleep apnea is associated with cancer incidence in the same Spanish clinical cohort[83] and in a population-based study in Denmark.[84] The results of these studies have not been entirely conclusive and reinforce the notion that additional epidemiologic studies are needed.[85,86]

If the hypothesis that sleep apnea affects cancer risk or cancer prognosis is confirmed, this could have profound implications for cancer prevention and/or cancer clinical management. Thus, further research is needed that clearly elucidates whether sleep apnea affects cancer incidence or survival (or both), whether this effect is present only in certain types of cancer, and, ultimately, whether proper management of sleep apnea (eg, treatment with CPAP) can improve cancer prognosis.

Conclusions

In summary, data from both animal and human studies suggests a dominant role for OSA-associated IH as a major contributor to multiorgan comorbidity and mortality. More studies are needed to address the interacting effects of IH and obesity, the differential effects of both short-term and long-term hypoxia, and the effect of CPAP treatment.

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