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Minireview

Cancer Prevention Research

Sleep and Breathing . . . and Cancer?

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Abstract

Sleep, like eating and breathing, is an essential part of the daily life cycle. Although the science is still emerging, sleep plays an important role in immune, cardiovascular, and neurocognitive function. Despite its great importance, nearly 40% of U.S. adults experience problems with sleep ranging from insufficient total sleep time, trouble initiating or maintaining sleep (Insomnia), circadian rhythm disorders, sleep-related movement disorders, and sleep-related breathing disorders such as obstructive sleep apnea (OSA). Herein, we discuss new evidence that suggests that sleep may also affect carcinogenesis. Specifically, we review recent epidemiologic data suggesting links between cancer and OSA. As OSA is a common, underdiagnosed, and undertreated condition, this has public health implications. Intriguing animal model data support a link between cancer and sleep/OSA, although mechanisms are not yet clear. Leaders in the fields of sleep medicine, pulmonology, and oncology recently met to review and discuss these data, as well as to outline future directions of study. We propose a multidisciplinary, three-pronged approach to studying the associations between cancer and sleep, utilizing mutually interactive epidemiologic studies, preclinical models, and early-phase clinical trials. *Cancer Prev Res; 9(11); 821–7. ©2016 AACR.*

Sleep and Breathing . . . and Cancer?

Many patients, and most clinicians, think that a "good night's sleep" is essential for maintaining health and for recovery from medical or psychiatric illness. Adequate sleep can promote attention, vigilance, and a sense of well-being. Conversely, sleep deprivation can lead to decreased cognitive performance and alertness, altered mood, and disorganized thinking. Although sleep is crucial for maintaining health in a variety of ways, sleep duration for many in the United States is suboptimal (1). Insufficient or irregular sleep is associated with insulin resistance (2), increased risk of myocardial infarction (3), and infection such as pneumonia (4). The relationships between sleep and cancer have not yet been adequately studied, but new evidence suggests that sleep also may be important for the development and progression of cancer.

Obstructive sleep apnea and cancer

Obstructive sleep apnea (OSA), a highly prevalent disorder in the general population, is increasingly recognized to have important neurocognitive, metabolic, and cardiovascular effects (5). OSA is characterized by repetitive collapse of the upper airway during sleep (Fig. 1). This collapse leads to cyclic hypoxemia and hypercapnia (5). The airway is opened again by an arousal from sleep which leads to surges in the sympathetic nervous system (with catecholamine release and subsequent hemodynamic effects) and sleep fragmentation along with these gas exchange abnormalities (Fig. 2). The recurrent disruption of sleep throughout the night results in daytime sleepiness among other neurocognitive outcomes.

OSA severity is typically characterized as the number of partial or complete obstructions in breathing per hour of sleep, termed the apnea-hypopnea index (AHI). In 1993, the population-based Wisconsin Sleep Cohort Study (WSCS) found a prevalence of sleep apnea syndrome (AHI > 5 events per hour with daytime symptoms) of 4% among men ages 30 to 60 years old, and 2% in women (6). Although a substantial minority of patients with OSA are not obese, obesity is by far the major modifiable risk factor for OSA. With an increasing prevalence of obesity over the last 20 years, it is likely that the prevalence of OSA has increased as well. The most recent estimate of OSA prevalence in the United States is that about 17% of middle-aged men, and 9% of women, have moderate (AHI > 15/hour) to severe (AHI > 30/hour) OSA (7). Although these numbers seem very high, a recent population-based study in Lausanne, Switzerland, of more than 2,000 randomly selected healthy participants found that nearly 50% of men had important sleep disease, as did 23% of women (8). Thus, the public health and economic impacts of OSA are enormous (9).

To address the consequences of OSA, the WSCS examined the relationship between OSA and all-cause mortality. Healthy participants were recruited, underwent polysomnography, and have been followed since 1988. This work confirmed that severe OSA was associated with increased risk of all-cause mortality by a factor of 4. As expected after 18 years of follow-up, death from cardiovascular disease was increased. Little noticed initially—even by the study's authors—was that the risk of death from cancer was also higher (1.9% in those with no OSA vs. 7.9% in those with

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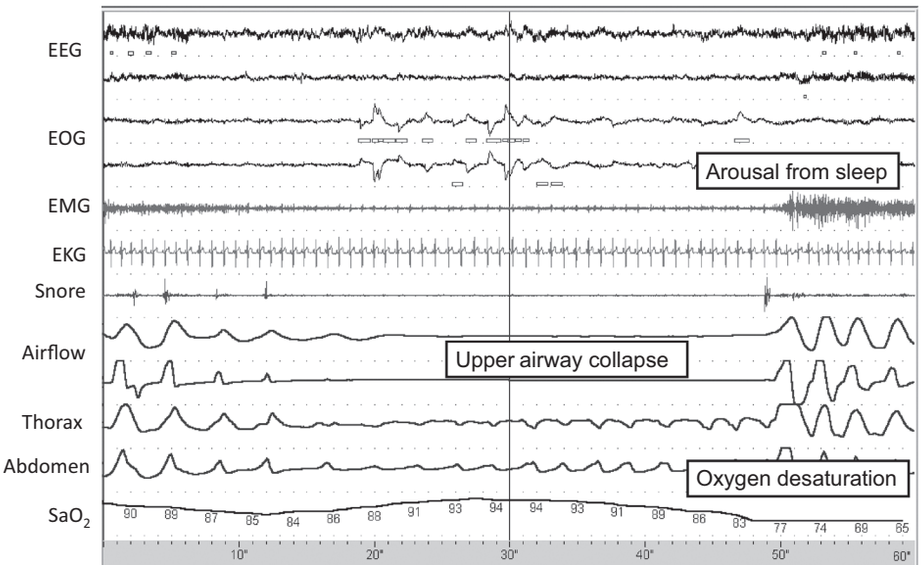

Figure 1.
A 60-second polysomnography recording from a patient with OSA. EEG, EOG, and EMG are used to determine sleep stage or wake. During sleep, there is upper airway collapse demonstrated by no airflow despite ongoing respiratory efforts (measured by movement of the thorax and abdomen). As a result, oxygen saturation falls. Eventually, there is an arousal from sleep that activates the upper airway muscles, opens the airway, and restores the flow of air. However, the cycle is likely to repeat once the subject falls back to sleep. EEG, Electroencephalogram; EOG, Electro-oculogram; EMG, Electromyogram.

severe OSA; Fig. 3; ref. 10). Intrigued by this unexpected finding, a Spanish group led by Ramon Farré examined the impact of intermittent hypoxia on tumor volume and weight in a mouse model of sleep apnea (Fig. 4; ref. 11) and found that intermittent hypoxia increased tumor growth, which spurred a number of subsequent epidemiologic and basic research studies.

Given the high prevalence and association with obesity of both OSA and cancer, as well as the existence of effective therapies for OSA, national leaders recently convened to consider the hypothesis that sleep and OSA are important for cancer development and progression. The meeting took place on January 5th and 6th, 2016, in La Jolla, CA, and included pulmonologists studying cancer and sleep, basic scientists studying sleep and hypoxia in cancer, and researchers with expertise spanning from epidemiology to clinical trials [The conference was funded by ResMed, Inc, but the agenda and scientific content were defined by the academic co-chairs (Scott Lippman, MD and Atul Malhotra, MD)]. The conference was designed to bring key opinion leaders together to review the existing literature, to synthesize scientific knowledge regarding sleep/hypoxia/cancer links, to build bridges between scientists of diverse backgrounds, and to define the path forward using a multidisciplinary scientific approach. This "white paper" has three goals in summarizing this recent session: (1) to educate researchers and clinicians about the potential link between OSA and cancer,(2) to highlight some of the available evidence to date, and (3) to identify gaps in knowledge and propose steps forward.

Epidemiologic studies of OSA and cancer

The WSCS described above is a prospectively identified group of 1,500 healthy participants who underwent baseline polysomnography. After other groups noted the uptick in cancer-related mortality, and animal studies suggested a link between intermittent hypoxia and malignancy, the cohort was re-analyzed in detail for cancer-related mortality. Cancer-related mortality was chosen as a straightforward and convenient outcome; the data have not yet been analyzed for cancer incidence or by specific cancer type. After 22 years of follow-up, cancer mortality in all participants was 1.92 per 1,000 person years. Severe OSA was associated with a relative hazard of cancer mortality of 4.8 compared with normal participants without sleep disordered breathing ($P < 0.01$; ref. 12). In a large Spanish cohort study consisting of 4,910 participants evaluated at an academic institution for suspected OSA, increasing levels of overnight hypoxia, an important feature of OSA, was associated with increased cancer incidence. For those patients who spent greater than 12% of the nighttime with an oxygen saturation less than 90%, the adjusted HR was 2.33 [$P < 0.0005$, 95% confidence interval (CI), 1.57–3.46]. In both of these studies, relatively small sample sizes precluded any meaningful analysis of whether specific cancer types are particularly correlated with OSA (13). Furthermore, these findings have been replicated by some groups (14, 15) but not all (16). A recent meta-analysis incorporating these studies and others did not find a significant relationship between OSA and cancer incidence and mortality, though trends were seen toward increasing risk of cancer with severe OSA (17). These first epidemiology studies of OSA and cancer outcomes were not "purpose-built" to investigate these associations and are thus limited in important ways including: (i) the use of highly selected (referred) sleep clinic populations (8, 11), (ii) "control" subjects that were not objectively evaluated to rule out

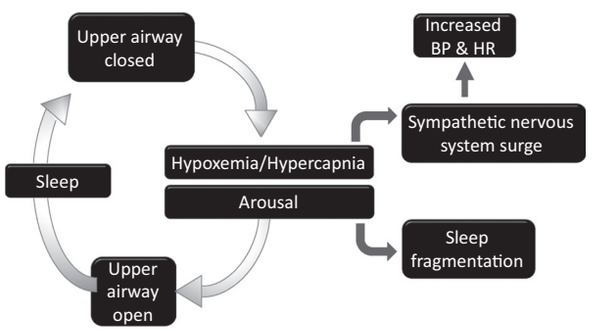

Figure 2.
The consequences of upper airway collapse during sleep. The airway is opened again by an arousal from sleep, which, along with gas exchange abnormalities, causes surges in the sympathetic nervous system (with catecholamine release and subsequent hemodynamic effects) and sleep fragmentation.

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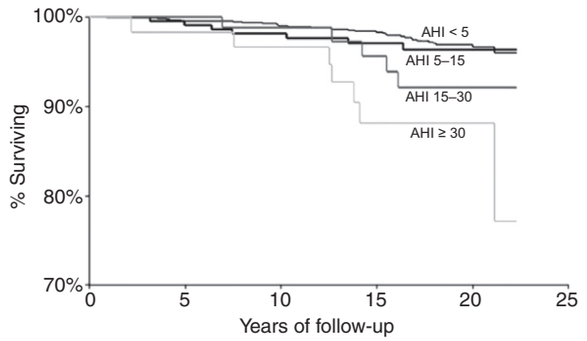

Figure 3.

Survival free of cancer mortality for participants of the Wisconsin Sleep Cohort according to categories of OSA. From Nieto et al, Am J Respir Crit Care Med 2012;186(2):190-194. Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. The American Journal of Respiratory and Critical Care Medicine is an official journal of the American Thoracic Society.

sleep apnea 9, (iii) small numbers of observed cancer events, (7,10) and (4) lack of information on other potential cancer risk factors (e.g., diet, exercise) and ascertainment of cancer outcomes. The strongest results for mortality (7) and incidence, (10) perhaps tellingly, emerge from studies that, despite relatively small numbers, had the theoretically most robust designs—that is, were longitudinal community-based cohorts that used objective assessment of OSA in all study subjects and carefully measured cancer risk factors that may confound OSA–cancer associations.

Experimental models of OSA and cancer

Animal models of OSA have been developed that have proved useful to examine the causal role of OSA in various pathologies such as hypertension, metabolic dysfunction, and atherosclerosis. As recently reviewed (18), very few mammals develop OSA spontaneously, and the OSA tends to be relatively mild. Therefore, most experimental models simulate OSA by exposing animals to deconstructed features of OSA such as either intermittent hypoxia (IH) or sleep fragmentation (SF) alone. In IH models, animals are subjected to oscillating flows of room air and hypoxia, where the timing, rate of decline in partial pressure of oxygen, and depth of hypoxia are important variables. In SF models, animals are frequently awakened, usually by a mechanical stimulus. IH is the most commonly used experimental model of OSA and has been applied both *in vivo* and *in vitro*. Some studies demonstrated substantial differences between continuous and intermittent hypoxic stimuli (19, 20), whereas others have shown similar acute metabolic consequences (21). It is also important to note that intermittent hypoxia *in vivo* may lead to varying degrees of hypoxia in various tissues (22).

IH mouse models have been used to study cancer progression. In a mouse model of melanoma, mice exposed to intermittent hypoxia developed significantly larger tumors compared with those mice exposed to constant room air and were more likely to develop metastatic disease (11, 23). Tumor-associated macrophages were also increased in the IH-exposed mice, suggesting that hypoxia can alter the immune response to tumor cells. Tumor-associated macrophages from IH-exposed mice demonstrated a decrease in M1 polarity and a shift toward the protumoral M2 phenotype. The mechanisms by which IH led to these changes remain unclear. Some candidate pathways include macrophage polarization arising from hypoxic adipose tissues (24), sympathetic activation and/or metabolic substrate changes by induced IH (25), and activation of hypoxia-inducible factor (26). How well IH models recapitulate human disease has been questioned due to the severity of the hypoxia induced as well as the lack of other features of OSA (18). Going forward, it will be important to develop more clinically relevant IH models to understand better the OSA–cancer link. In addition, animal experiments to date have been limited to only two types of cancer (melanoma and lung), and the effect of IH on distant metastasis has not been elucidated.

Another surprising finding is that SF without any hypoxia also promotes tumor growth (27). In this study, sleep fragmentation led to accelerated tumor growth and invasiveness through macrophage recruitment in a TLR4-dependent manner, as well as altered reactive oxygen species (ROS) signaling (28). It is tempting to correlate these findings with the observation that OSA with insomnia symptoms was a risk factor for central nervous system tumors (14). These results are consistent with the idea that SF may affect immune system response. Indeed, changes of hormone levels during sleep (29–32) promote a shift in the immune system regulation (33) and a change in functional polarization of different cell types, including macrophages (34). In addition, the contribution of obesity in general, and adipose tissues surrounding tumors in particular, has only now received some initial attention in the context of OSA (24).

Caveats

The epidemiologic studies described above are hypothesis generating but cannot be considered comprehensive for several reasons. Epidemiologic studies are generally unable to consider other aspects of sleep, such as sleep architecture or sleep fragmentation, which are difficult to measure unobtrusively. Or consider, for example, obesity. Obesity is the most important risk factor for OSA, but it is also a risk factor for depth of

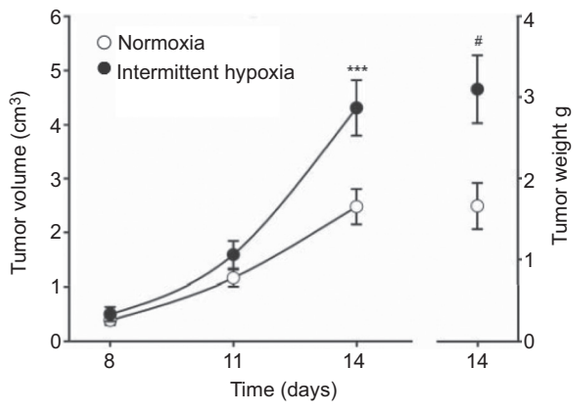

Figure 4.

Tumor size in mice subjected to intermittent hypoxia versus those as room air. This material has not been reviewed by European Respiratory Society prior to release; therefore, the European Respiratory Society may not be responsible for any errors, omissions, or inaccuracies, or for any consequences arising there from, in the content. Reproduced with permission of the European Respiratory Society ©: European Respiratory Journal Jan 2012, 39 (1) 215–217; DOI: 10.1183/09031936.00185110

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hypoxemia (a marker of OSA severity) with upper airway obstruction (35), and it is also clearly linked to higher rates of cancer mortality (36). Each of these epidemiologic studies has controlled for obesity using body mass index (BMI); however, BMI is an imperfect measure of the effects of obesity. Different body types may have the same BMI, but may have different OSA risk (for example, waist to hip ratio is a better predictor than BMI; ref. 37) and cancer risk, which might be more directly linked to visceral fat than BMI *per se* (38). In addition, BMI does not account for other important factors such as physical inactivity and nutrition which are difficult to quantify and capture for study purposes. Finally, many epidemiologic studies enrolled only patients referred for sleep studies or relied on self-reported symptoms—these methods are likely to underestimate severely the true prevalence of OSA, as many patients who have evidence of OSA on polysomnography do not report symptoms and are not referred for sleep studies in routine clinical practice (39). However, it is important to note that under-diagnosis would tend to diminish the observed association between OSA and cancer, i.e., bias toward null hypothesis. On the other hand, clinical-based populations may differ systematically from community-based cohorts, leading to uncertainty about the generalizability of some prior work.

The animal models reported to date have only examined the relationship between IH or SF and cancer progression (i.e., growth, local and metastatic invasion), not on *de novo* tumorigenesis or on the possibility of diminished response to treatment. Some of these animal and *in vitro* studies are based on severe hypoxemia, which may not be truly representative of the human disease.

Unanswered questions

Does OSA increase tumorigenesis or cancer progression (or both)? Studies have suggested an increased risk of cancer mortality in patients with sleep apnea; however, this relationship may not be straightforward. It is not clear whether OSA might affect carcinogenesis, cancer progression/metastasis, response to treatment, or all of these.(Fig. 5) These questions have major implications for cancer prevention or therapy. For example, tumor hypoxia is associated with resistance to various therapies, and OSA might hinder the therapeutic efficacy of preventive agents, chemotherapy, and/or radiotherapy.

What aspect(s) of OSA affect cancer development or progression? As above, the pathobiology of OSA is complex. In addition to recurrent, intermittent hypoxemia, patients with OSA also have intermittent hypercapnia, sleep fragmentation, and both excessive tonic sympathetic activity and cyclic sympathetic surges. All of these factors too may be important for cancer pathogenesis. Different cancer types have different biology, and it is not yet clear from epidemiologic studies which types of cancer may be preferentially affected by sleep apnea. To give one example of how OSA could affect a particular type of cancer: repetitive vibration injury from snoring and sleep apnea might predispose to cancers of the head and neck, much as snoring has been thought to promote carotid artery atherosclerosis (40, 41).

There are a substantial number of biologic pathways that have been identified as playing a role in cancer biology. Many such pathways are potentially modified or affected by OSA, and therefore, OSA might lead to more rapid development or progression of cancer. Although beyond the scope of this review, Fig. 6 illustrates the number and complexity of these pathways. OSA can affect inflammatory pathways, and there are known associations between

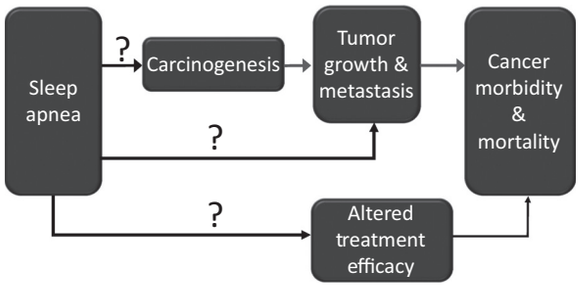

Figure 5.
Possible relationships between sleep apnea and cancer. Whether sleep apnea impacts carcinogenesis, tumor growth, or affects response to treatment, or all of these, will be important when considering epidemiologic data and studies necessary to explore these links.

inflammation and malignancy (42). Similarly, OSA is recognized to stimulate the sympathetic nervous system which in turn can modulate gene expression, inflammation, and angiogenesis; and hypoxia-inducible factors are involved in cancer progression (43). Studies are needed to delineate these relationships further.

Will treatment of OSA improve cancer outcomes? This is a critically important question to the field. If treatment of OSA can either reduce cancer risk or slow cancer growth or metastasis, identification and proper treatment of OSA becomes clinically relevant. A related question, however, is whether untreated OSA blunts the efficacy of treatments for cancer, such as chemotherapy or radiotherapy (44). If proper treatment of OSA could reduce cancer risk and/or increase tumor sensitivity to therapy, then sleep studies may become part of our routine work-up for obese patients and those with newly diagnosed malignancy.

Are other aspects of sleep important? We have deliberately focused on links between OSA and cancer. However, we acknowledge that other aspects of sleep such as total duration and the timing of sleep relative to the endogenous circadian rhythm are likely to be important. For example, some epidemiologic studies have found increased risk of breast cancer in women exposed to shift work and sleep deprivation (45). Misaligned sleep, where preferred sleep times are not aligned with actual sleep times, has also been associated with more rapid cancer progression in women with breast cancer (46). Animal studies have shown more rapid tumor progression in mice exposed to chronic "jet lag" (47). Clearly, research in this area will be important as well.

Future directions

From the aforementioned insights, it is apparent that much research will be required to understand these observations. We suggest the following:

Epidemiologic work Previous epidemiologic studies have evident weaknesses such as the inclusion of highly selected populations (i.e., those referred for sleep studies; ref. 13) and failure to ensure that the control subjects have been rigorously evaluated for OSA (14). Future epidemiologic studies should ascertain that selection methods for subjects are as unbiased as possible and that all subjects are appropriately evaluated for the presence or absence of OSA. Ideal studies should account for multiple potential confounders, such as obesity, tobacco, and alcohol use, and should

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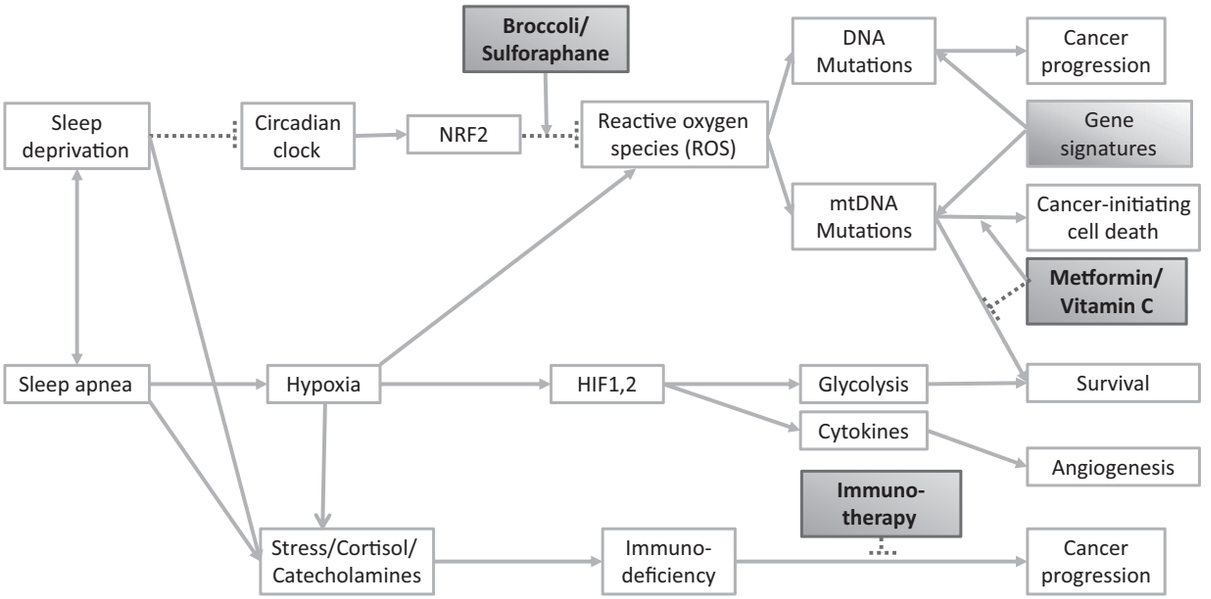

Figure 6.

Possible mechanisms linking sleep and OSA to carcinogenesis/cancer progression. Genetic insults such as environmental toxins can lead to creation of ROS, leading to mutations in DNA and mitochondrial DNA, which can lead to carcinogenesis and cancer progression. Sleep deprivation can exacerbate these effects—alterations of the circadian rhythm lead to decreased activity of NRF2, thereby decreasing protection against oxidative stress and allowing additional mutations (56). Hypoxia resulting from OSA can lead to increased HIF1 and HIF2, thereby increasing glycolysis and cytokine production, leading to increased cancer cell survival and angiogenesis. OSA, sleep fragmentation, and sleep deprivation can also lead to a stress response, with cortisol and catecholamine release, which in turn can modulate gene expression, inflammation, and angiogenesis.

report on outcomes for specific cancers, rather than for cancer as a single, undifferentiated entity. It will be of considerable interest to compare the spectrum of cancers potentially attributable to OSA versus the solid and hematologic malignancies linked to obesity. This type of comparison may help to distinguish OSA from obesity as a risk factor for cancer. Finally, many studies have focused on cancer mortality; although this is an important consideration, cancer incidence should also be considered.

Preclinical studies Existing preclinical models have largely studied cancer progression, not incidence, using xenograft models. It would be useful to study whether IH or SF accelerate cancer development in genetically engineered mice predisposed to cancer. Effects of IH or SF on cancer stem cells could also be investigated. For example, in the mouse lung, type II cells appear to be the initiating cells for certain types of lung adenocarcinoma (48). These cells could be isolated and studied *in vitro* after exposure to IH or SF. Effects of IH and SF on other common types of cancer, for instance breast cancer, and distant metastasis have to be evaluated. In addition, development of more realistic murine models showing upper airway obstruction during sleep, similar to human sleep apnea, would greatly contribute to the field. Also, mechanistic studies should be performed, to delineate better how OSA exactly affects cancer.

Clinical studies A large clinical trial solely focused on the links between sleep and cancer would be a major undertaking, and one unlikely to be justified based on the current state of the evidence. Therefore, we suggest multiple early-phase approaches to advancing the science in clinical studies. First, formal sleep evaluation should be incorporated into existing trials, both those looking at cancer development and progression/response to treatment. Large, ongoing trials are following patients at very high risk for lung cancer with imaging and bronchoscopy (e.g., DECAMP: Detection of Early Lung Cancer Among Military Personnel, NCT01785342)—adding sleep studies into these trials would give useful information with only a very modest incremental increase in cost and complexity. Home sleep testing equipment is relatively inexpensive, is generally well tolerated by subjects, and shows good agreement compared with gold-standard in-laboratory testing, particularly in subjects of greatest interest when considering links to cancer—those with moderate to severe disease (49–51). Oximetry data are highly accurate, although sleep fragmentation or sleep architecture cannot be assessed by most home systems. Similarly, sleep studies could also be incorporated into existing therapeutic trials, and potentially those with newly diagnosed OSA could undergo treatment with CPAP.

A second approach that might be possible in the future would be to look at the impact of sleep on indirect *biomarkers* of cancer activity, which could substantially shorten study length and complexity. The development of cancer biomarkers is rapidly progressing, and although not inclusive, we list several recent advances as examples of their power and diversity. In addition to serum proteins (e.g., prostate-specific antigen, PSA, or carcinoembryonic antigen, CEA), there have been major advances in liquid-biopsy technology detecting circulating tumor (ct) DNA in early-stage cancer and even premalignant lung lesions (52). For example, there is evidence in mouse models of lung cancer that exposure to intermittent hypoxia may increase levels of ctDNA (53); this relationship would be interesting to study in patients with both OSA and cancer, and in response to treatment of OSA in patients diagnosed with cancer (although change in a biomarker

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does not always correlate with disease response). Exosomes might be another potential biomarker of tumor activity. Breast cancer cells exposed to hypoxia release exosomes which can increase aggressiveness in cells at room air (54), and mice exposed to SF release exosomes that increase tumor cell proliferation and migration (55). If there is a link between OSA and carcinogenesis, surrogate endpoints might be important, as prevention trials with cancer incidence endpoints are expensive and require large populations and long follow-up.

Conclusions

Epidemiologic and preclinical studies suggest that OSA may be related to an increased risk of cancer incidence and mortality. Obesity is a well-established and major cause of both OSA and cancer. Further study is warranted to determine whether OSA contributes to the procarcinogenic effects of obesity, or constitutes an independent risk factor. As OSA is a common, underdiagnosed, and undertreated condition, this has public health implications. We propose a multidisciplinary, three-pronged approach to studying this association, utilizing mutually interactive epidemiologic studies, preclinical models, and early-phase clinical trials.

Disclosure of Potential Conflicts of Interest

Dr. R.L. Owens has received travel fees from ResMed (<$5,000). K. Gold has honoraria from the speakers bureau of Roche/Genentech and is a consultant/advisory board member for Clovis and Pfizer. The symposium was funded by ResMed, Inc., but the agenda and scientific content were defined by the academic co-chairs (S.M. Lippman, MD; and A. Malhotra, MD). This article was prepared by the members of the writing group without input or review by ResMed. No potential conflicts of interest were disclosed by the other authors.

The Editor-in-Chief (Scott M. Lippman) is an author on this article. In keeping with the AACR's editorial policy, the peer review of this submission was managed by a senior member of *Cancer Prevention Research*'s editorial team; a member of the AACR Publications Committee rendered the final decision concerning acceptability.

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Correction: Sleep and Breathing . . . and Cancer?

In this article (Cancer Prev Res 2016;9:821–7), which appeared in the November 2016 issue of *Cancer Prevention Research* (1), the sixth author, Andrew J. Dannenberg, was not included in the author byline. The authors and publisher regret the error.

The author byline should read, "Robert L. Owens, Kathryn A. Gold, David Gozal, Paul E. Peppard, Jonathan C. Jun, Andrew J. Dannenberg, Scott M. Lippman, and Atul Malhotra, and on behalf of the UCSD Sleep and Cancer Symposium Group."

Reference

1. Owens RL, Gold KA, Gozal D, Peppard PE, Jun JC, Dannenberg AJ, et al. Sleep and breathing . . . and cancer? Cancer Prev Res 2016;9:821–7.

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