Sleep Disordered Breathing and Sleep Duration and the Risk of Psoriasis and Melanoma in the United States

Abstract

Sleep disordered breathing (snoring and obstructive sleep apnea (OSA)) has been associated with negative health outcomes including diabetes mellitus, cardiovascular disease, and reduced quality of life, presumably due to systemic inflammation. Long and short sleep duration have been associated with morbidity, all-cause mortality, and cancer-specific mortality. No large prospective studies exist to explore the relationship between sleep disordered breathing and sleep duration and psoriasis and melanoma risk.

This study prospectively evaluated the association between OSA and snoring and incident psoriasis in the Nurses' Health Study (NHS; 1997-2008) and the association between sleep duration and melanoma risk in the NHS (1986-2012), NHS II (2001-2009), and Health Professionals Follow-Up Study (HPFS; 2000-2012). Cox proportional hazards were used to calculate age-adjusted and multivariate risk ratios.

Over the follow-up period, there were 524 cases of psoriasis among the women who were assessed for sleep apnea. Women with OSA were more likely to have a higher BMI, be hypertensive, work night shifts, and have type 2 diabetes mellitus. The age-adjusted relative risk (RR) of psoriasis among women with OSA was 2.19 (95% CI, 1.39-3.45). The multivariate RR adjusting for night shift work and hypertension, cardiovascular disease, and type 2 diabetes mellitus was 1.91 (95% CI, 1.20-3.05). There was no effect modification by BMI (p=0.52), hypertension (p=0.34), or snoring (p=0.91). Sleep apnea was not associated with an increased risk of psoriatic arthritis. Although women with sleep apnea were more likely to be snorers, we did not find a statistically significant relationship between snoring and psoriasis risk.

In the three cohorts, there was no relationship between sleep duration and melanoma risk. The multivariate RRs were 0.90 (95% CI, 0.67-1.20) for ≤6 hours, 1.30 (95% CI, 1.08-1.56) for

8 hours, and 0.76 (95% CI, 0.51-1.12) for ≥9 hours (p trend=0.09) in the NHS and NHS II and 1.08 (95% CI, 0.77-1.51) for ≤6 hours, 0.95 (95% CI, 0.69-1.30) for 8 hours, and 1.06 (95% CI, 0.68-1.67) for ≥9 hours (p trend=0.71) in the HPFS. In the NHS, there was no association between OSA and melanoma risk (RR 1.04 (95% CI, 0.42-2.55)) and there was also no association between snoring status and melanoma risk in the three cohorts.

In this prospective study, we found that OSA was associated with an approximately two-fold increased risk of psoriasis among US women and we found no association between sleep duration, sleep apnea, or snoring and melanoma risk among US women and men.

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Glossary of Abbreviations

SDB: Sleep Disordered Breathing

OSA: Obstructive Sleep Apnea

OSAHS: Obstructive Sleep Apnea-Hypopnea Syndrome

BMI: Body Mass Index

TNF-α: Tumor Necrosis Factor-Alpha

IL- Interleukin

VEGF- Vascular Endothelial Growth Factor

AHI: Apnea-Hypopnea Index

NF-κB: Nuclear Factor-Kappa B

HIF-1α: Hypoxia Inducible Factor-One Alpha

Th- T Helper

NKT: Natural Killer T

IFN: Interferon

PASI: Psoriasis Area And Severity Index

NHS: Nurses' Health Study

HPFS: Health Professionals Follow-Up Study

PsA: Psoriatic Arthritis

RR: Risk Ratio

CI: Confidence Interval

UV: Ultraviolet

CPAP: Continuous Positive Airway Pressure

NIH: National Institutes of Health

Introduction

Sleep Disordered Breathing

Sleep disordered breathing (SDB) is a spectrum of disease comprised of snoring and obstructive sleep apnea (OSA) (also termed obstructive sleep apnea-hypopnea syndrome; OSAHS) (1). On the SDB spectrum, OSA characterizes the more severe end. SDB is a relatively common problem in the United States and approximately 50% of adults in the United States snore regularly, 20% have mild-moderate OSA, and 6-7% have severe OSA (2-5). The prevalence of OSA increases with age, and the prevalence is 2-3 fold higher in individuals over 65 years of age than in those between 30 and 64 years of age. OSA, however, tends to be less severe in older individuals than in middle-aged individuals. The burden of SDB in the United States has significant health and quality of life consequences (2, 3).

OSA is characterized by episodic reduction or cessation of air flow through the respiratory tract during sleep (2, 4). OSA can lead to adverse health outcomes, daytime sleepiness, psychosocial problems, decreased cognitive function, and decreased quality of life (2). OSA has also been found to increase the risk of cardiovascular disease, cerebrovascular disease, diabetes, metabolic syndrome, and cancer (3, 6, 7).

The most important risk factor for OSA is obesity, and a graded increase in risk as body mass index (BMI), neck circumference, and waist-to-hip ratio increase has been observed (4). However, many individuals with OSA are not obese and the condition may be under-diagnosed in individuals who are not obese (4). Craniofacial and upper airway anatomic abnormalities represent another important risk factor for OSA (4). Cigarette smoking, likely due to upper

airway inflammation, is also a risk factor for OSA (4). Additionally, OSA is more common among males than females; sex hormones likely play a role in mediating the difference in OSA prevalence between men and women, and postmenopausal women may have a higher risk of OSA than premenopausal women (4).

SDB is considered to be a systemic inflammatory disorder (1-3, 6). Systemic levels of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), C-reactive protein, and pro-inflammatory reactive oxygen species are increased in individuals with SDB (1-3, 6, 8). One study of 230 women who reported snoring and 170 women who did not report snoring who underwent polysomnography and blood tests for inflammatory markers showed that levels of TNF-α, IL-6, and lysozyme were higher in individuals with higher apnea-hypopnea indices (AHI). Moreover, the elevation in these biomarkers correlated with the AHI. Multiple regression analysis controlling for age, waist circumference, and smoking showed independent correlations between oxygen desaturation indices and elevations in IL-6 and TNF-α. This relationship was not seen with AHI. This finding suggests that intermittent hypoxia is related to systemic inflammation in SDB (1). The etiology of the elevations in pro-inflammatory cytokines is likely related to greater expression of transcription factors such as nuclear factor-kappa B (NF-κB) and hypoxia inducible factor-1 alpha (HIF-1α) as a result of fluctuating oxygen saturation levels (2, 3, 6). The systemic inflammatory milieu created by SDB contributes to the adverse health effects associated with the condition (1-3, 6).

Sleep Duration

Recently, several studies have explored the impact of sleep duration on the risk of adverse heath outcomes including diabetes, coronary heart disease, colorectal cancer, and mortality (9-15). One study using the Nurses' Health Study (NHS) cohort demonstrated an increased risk of all-cause mortality among women sleeping an average of 9 or more hours per 24 hour period after adjusting for pre-existing chronic diseases such as cancer and cardiovascular disease, age, BMI, smoking status, alcohol consumption, physical activity, depression, history of snoring, and history of shift work. Additional analyses revealed that sleep duration of greater than 9 hours per 24 hour period was associated with increased risks of death from cancer and cardiovascular disease (11). In addition to diabetes and cardiovascular disease risk, the risk of colorectal cancer has been associated with both long and short sleep duration (15).

Long sleep duration may reflect high exposure to somnogenic cytokines, like IL-1 and TNF-α, which have carcinogenic effects (11). Serum melatonin levels may be decreased in SDB, another potentially important factor in the increased cancer incidence in this population (16, 17). Other factors that may contribute to the association between sleep duration and cancer include the inverse relationship between physical activity and time spent outdoors and sleep duration (11).

Psoriasis

Psoriasis is a systemic inflammatory disorder, and it has been posited that systemic inflammation can play a role in the development of the disease (18). Therefore, the elevation of inflammatory cytokines and VEGF in OSA may predispose individuals to develop psoriasis by acting at various points in the cycle of interaction between the innate and adaptive immune responses and

keratinocytes (18). Specifically, cytokines such as TNF-α and IL-6 activate myeloid dendritic cells. Activated myeloid dendritic cells produce IL-12 and IL-23, which activate Th1 and Th17 cells, causing activation of keratinocytes, which leads to keratinocyte proliferation and more inflammatory cytokine production. This generates an inflammatory cycle by activating macrophages, plasmacytoid dendritic cells, and NKT cells. Additionally, VEGF is thought to play an important role in the vascular changes associated with psoriasis, including tortuous and leaky blood vessels, which promote the extravasation of inflammatory cells. Ultimately, the inflammatory activation and the changes to the microvasculature caused by OSA may promote the pathogenesis of psoriasis (18).

Studies have correlated the severity of psoriatic disease with the level of inflammatory cytokines (19). One study of 30 psoriasis patients and 23 age and sex matched controls measured the serum levels of TNF-a, IFN-γ, IL-6, IL-8, IL-12, and IL-8 and correlated levels to disease severity as measured by the psoriasis area and severity index (PASI) (19). Levels of these cytokines were higher in those with psoriasis than controls. Additionally, levels of IFN-γ, IL-12, and IL-8 were associated with disease severity as measured by the PASI (19). This suggests that inflammatory cytokines are an important factor in the pathophysiology of psoriasis. Moreover, the elevation of inflammatory cytokines and VEGF in SDB may predispose individuals to develop psoriasis by acting at various points in the cycle of interaction between the innate and adaptive immune responses and keratinocytes (18).

There has been some research into the impact of sleep on dermatologic disease and the impact of psoriasis on sleep, and one study investigating the relationship between OSA and psoriasis (20-

25). The study on OSA and psoriasis risk followed individuals for a three year period and found that individuals with OSA were more likely than those without OSA to be diagnosed with psoriasis (20). However, this study had a relatively small sample size comprised only of Taiwanese individuals and did not control for several important covariates.

Given the current burden of SDB in the United States and its associated negative health effects, a better understanding of the association between SDB and psoriasis among individuals from the US is important from a public health perspective as well as for optimal management of both conditions. Therefore, we sought to determine the relationship between SDB and the risk of psoriasis in a population of US women. We hypothesized that OSA would be associated with an increased risk of psoriasis.

Melanoma

Melanoma is one of the leading causes of cancer incidence and mortality and the incidence and death rates of melanoma have been increasing over the last several decades (26-28). The reasons for these trends are incompletely understood. The burden of melanoma incidence and mortality is an important public health concern, and a more complete understanding of the risk factors for this disease may contribute to more effective prevention and surveillance (29).

Melatonin, an indolamine regulator of circadian rhythms, has anticancer effects and has been demonstrated to have antitumor effects in melanoma cell lines (30, 31). Skin and malignant melanoma cells possess melatonin receptors on their surfaces, further suggesting that melatonin may play an important role in the physiology of normal skin and malignant melanoma (32). In

normal skin, melatonin has antioxidant properties against ultraviolet and x-ray radiation (31). In malignant melanoma, melatonin has been demonstrated to have oncostatic effects and to potentiate the oncostatic effects of interleukin-2 (31). It remains unknown if sleep duration or SDB is related to the risk of melanoma, so we evaluated the association between sleep duration, snoring, and OSA and the risk of incident melanoma in three prospective cohorts of US women (Nurses' Health Study (NHS) and NHS II) and men (Health Professionals Follow-Up Study (HPFS)).

Methods:

Introduction To The Cohorts:

The Nurses' Health Study (NHS) is a prospective cohort study that began in 1976 with 121,700 female registered nurses aged 30-55 years from the 11 most populous states in the United States (California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania, and Texas). Participants completed baseline questionnaires in 1976 and have subsequently completed questionnaires every two years. The NHS II is a similar prospective study of younger women between 25-46 years of age from 14 states in the United States (California, Connecticut, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Missouri, New York, North Carolina, Ohio, Pennsylvania, South Carolina, and Texas) that began in 1989 (12). The HPFS is a similar prospective cohort study of male health professionals (dentists, pharmacists, optometrists, osteopath physicians, podiatrists, and veterinarians) between 41-79 years of age that started in 1986 (33). The information collected pertains to lifestyle factors, medical history, and diet. The follow-up rate is approximately 90% for each two-year period. Questionnaires from all three studies are available online (NHS: http://www.channing.harvard.edu/nhs/?page_id=246; NHS II: http://www.channing.harvard.edu/nhs/?page_id=246; HPFS: http://www.hsph.harvard.edu/hpfs/hpfs_qx.htm).

Assessment of Sleep Apnea, Snoring, and Sleep Duration in the NHS, NHS II, and HPFS:

In 2008, NHS participants were asked if they had ever been diagnosed with sleep apnea by a physician. They were also asked when their diagnosis had been made if they indicated a diagnosis of sleep apnea (1997 and before, 1998-2001, 2002-2005, 2006-2007, 2008 and later).

Participants in the NHS, NHS II, and HPFS were asked if they snored multiple times. The answer choices provided were: every night, most nights, a few nights a week, occasionally, almost never, and don't know.

Participants were asked "On average, over a 24 hour period, do you sleep" or "How many total hours of actual sleep do you get in a 24-hr period?" The answer choices are ≥5, 6, 7, 8, 9, and 10+ hours, and in some years 11+ hours was included. Average sleep duration in a 24 hour period was asked in the NHS in 1986, 2000, 2002, and 2008, in NHS II in 2001 and 2009, and in HPFS in 1987, 2000, 2008, and 2012. This question has been validated in the NHS II using a sleep diary and reported sleep data closely matched that in a one week sleep diary (11). The reference group for the analyses was seven hours because previous studies have demonstrated the lowest all-cause and disease specific morbidity and mortality in the range of 6-7 hours of sleep per night (9-15).

Follow up in the NHS began in 1986 for snoring, 1997 for sleep apnea, and 1986 for average sleep duration, the first years in which corresponding information on each of these variables was available. Follow up for sleep duration and snoring in the NHS II began in 2001. Follow up began in 2000 for sleep duration and snoring in the HPFS.

Identification of Psoriasis Cases in NHS:

Participants in the NHS were asked if they had ever been diagnosed with psoriasis in 2008. They were also asked when their diagnosis had been made and were given the following answer choices: 1997 and before, 1998-2001, 2002-2005, 2006-2007, 2008 and later. Follow-up for

psoriasis began in 1996. Self-reported psoriasis diagnosis was validated using a mailed validated questionnaire (34, 35). Psoriatic arthritis (PsA) was asked in the same fashion as psoriasis, and the risk of self-reported psoriatic arthritis was also analyzed (34, 35).

Identification of Melanoma Cases in the NHS, NHS II, and HPFS:

Physician diagnosed melanoma has been documented biennially in all three cohorts.

This work has been approved by the Partners HealthCare Human Research Committee (NHS) and the Institutional Review Board of the Harvard School of Public Health (NHS II and HPFS) and informed consent was previously obtained from all study participants when they agreed to participate.

Statistical Analysis:

SDB and the Risk of Psoriasis (NHS):

Individuals who responded to the sleep apnea or snoring questions and had not reported a pre-existing diagnosis of psoriasis or PsA were included in this study. We excluded individuals who had a diagnosis of psoriasis prior to their diagnosis of sleep apnea or report of snoring. Individuals who were diagnosed with psoriasis within two years of their onset of snoring or sleep apnea diagnosis were also excluded to ensure that we only studied individuals who had a diagnosis of OSA prior to a diagnosis of psoriasis. Finally, we excluded individuals with missing snoring, psoriasis, weight, or height data.

The primary exposure was diagnosis of sleep apnea and the secondary exposures were snoring and average sleep duration. The participants contributed person-time from the point of return of their follow-up questionnaires indicating a diagnosis of sleep apnea, snoring, or average sleep duration. Accumulation of time stopped at report of diagnosis with psoriasis or the end of study follow up (whichever came first). Cox proportional hazards models were used to calculate risk ratios (RRs) and 95% confidence intervals (CIs). Multivariate models were simultaneously adjusted for age (continuous by year), BMI (continuous), current smoking status (yes or no), hypertension (yes or no), cardiovascular disease (defined as history of myocardial infarction, angina pectoris, congestive heart failure, and peripheral artery disease), type 2 diabetes (yes or no), and history of night shift work (yes or no). We conducted pre-specified analyses of interaction by BMI, hypertension, and snoring (when not the main exposure). We also analyzed the risk of self-reported psoriatic arthritis in the same manner. Self-reported cases were used because of the low number of confirmed cases of psoriatic arthritis in the cohort. Proportionality testing was done to ensure that the proportional hazards assumption was not violated.

Sleep Duration and SDB and the Risk of Melanoma (NHS, NHS II, HPFS):

Individuals who answered the question about average sleep duration in a 24 hour period who did not indicate a prior diagnosis of melanoma in the three cohorts were included in the analysis. We excluded individuals without data on snoring or sleep apnea (NHS) or those who had a diagnosis of melanoma before indicating snoring or sleep apnea for the SDB and melanoma risk analysis.

The primary exposure was average sleep duration in a 24 hour period and the secondary exposures were snoring and sleep apnea (SDB). Average sleep duration was divided into four categories: ≤6 hours, 7 hours (reference), 8 hours, and ≥9 hours. The answer choices provided for the snoring question in the NHS questionnaire were: every night, most nights, a few nights a week, occasionally, almost never, and don't know. For sleep duration and snoring, we pooled the NHS and NHS II data together. Data on OSA was only available in NHS. We analyzed the HPFS data separately, as there is evidence to suggest that estrogen plays a role in melanoma pathogenesis (36). RRs and 95% CIs of incident melanoma were estimated by using Cox proportional hazards models. Multivariate models were adjusted for age (continuous by year), gender (male or female), hair color (categorical), number of moles (continuous), reaction to the sun, tanning (categorical), UV flux (continuous), snoring (yes or no), and history of night shift work (yes or no).

All statistical analyses were performed using SAS (SAS Institute, Cary, North Carolina).

Results:

SDB and the Risk of Psoriasis (NHS):

Study Population Characteristics

In this study, a total of 71,598 women were included. For sleep apnea, there was a combined 844,733 person-years of follow up, for snoring there was a combined 515,883 person-years of follow up, and for sleep duration there was a combined 771,028 person-years of follow up. The median follow up time was 10 years. Individuals with sleep apnea were more likely to be snorers ($p<0.001$), have a higher BMI ($p<0.001$), be hypertensive ($p<0.001$), have cardiovascular disease ($p<0.001$), and have type 2 diabetes mellitus ($p<0.001$) (Table 1.1).

Obstructive Sleep Apnea and Psoriasis Risk

Of the 524 women who responded to the sleep apnea question and developed psoriasis, 504 indicated that they did not have sleep apnea and 20 of the women indicated that they had been diagnosed with sleep apnea. Compared to individuals without sleep apnea, those with sleep apnea had a higher age-adjusted and multivariate risk of developing psoriasis (Table 1.2). The age-adjusted RR for developing psoriasis in women with sleep apnea was 2.19 (95% CI, 1.39-3.45), the multivariate RR was 1.93 (95% CI, 1.21-3.08), and the multivariate RR that further adjusted for night shift work, hypertension, cardiovascular disease, and type 2 diabetes mellitus was 1.91 (95% CI, 1.20-3.05). Interaction analysis revealed no effect modification by BMI ($p=0.52$), hypertension ($p=0.34$), or snoring ($p=0.91$) on the relationship between OSA and psoriasis risk.

Snoring and Psoriasis Risk

In total, 353 women assessed for snoring developed psoriasis during the study period. Compared to non-snorers, individuals snoring a few nights per week, most nights, and every night had an increased age-adjusted risk of developing psoriasis, but no relationship between snoring and psoriasis was seen with multivariate analysis (Table 1.2). There was no material difference between the two multivariate models. For occasional snorers, the age-adjusted RR for developing psoriasis was 1.11 (95% CI, 0.85-1.43) and the multivariate RR that took night shift work and selected comorbid diseases into account was 1.04 (95% CI, 0.80-1.35). For those who snored a few nights per week, the age-adjusted RR for developing psoriasis was 1.37 (95% CI, 0.91-2.06) and multivariate RR (simultaneously adjusting for night shift work and selected comorbid diseases) was 1.25 (95% CI, 0.83-1.88). For individuals snoring most nights, the age-adjusted RR for developing psoriasis was 1.43 (95% CI, 1.02-2.01) and the multivariate RR that took night shift work and selected comorbid diseases into account was 1.24 (95% CI, 0.88-1.75). For every night snorers, the age-adjusted RR for developing psoriasis was 1.32 (95% CI, 0.86-2.05) and the multivariate RR was 1.10 (95% CI, 0.71-1.73). Interaction analysis revealed no effect modification by BMI (p=0.92) or hypertension (p=0.99) on the association between snoring and psoriasis.

Obstructive Sleep Apnea and Snoring and Psoriatic Arthritis Risk

Six women assessed for OSA developed psoriatic arthritis. We found an increased age-adjusted risk (RR 2.49 (1.07-5.79)) of developing psoriatic arthritis among individuals with OSA, but there was no significant difference after adjusting for age, BMI, smoking status, exercise, hypertension, cardiovascular disease, type 2 diabetes, and history of night shift work (RR 1.85 (0.78-4.38) (Table 1.4). Twenty-three women who were assessed for snoring developed

psoriatic arthritis. We found that snoring was not associated with risk of psoriatic arthritis (Table 1.4).

Sleep Duration and SDB and the Risk of Melanoma (NHS, NHS II, HPFS):

Study Population Characteristics

During 2,301,445 person-years of follow-up in the three cohorts, we documented 880 incident melanoma cases. In the NHS, shift workers were more likely to sleep ≤6 hours per night and in the NHS and NHS II there were more snorers in the ≥9 hours of sleep category than the ≤6, 7, or 8 hour category (11.70% vs. 10.19%, 8.72%, and 9.85% respectively in NHS and 28.0% vs. 25.7%, 23.2%, and 22.7% respectively in NHS II). Otherwise, there were no notable trends among different sleep duration categories in the three cohorts (Table 2.1).

Sleep Duration and the Risk of Melanoma

In the three cohorts, there was no apparent clear relationship between sleep duration and risk of melanoma (Table 2.2). In the NHS and NHS II, the multivariate RRs for incident melanoma were 0.90 (0.67-1.20) for women sleeping ≤6 hours, 1.30 (1.08-1.56) for 8 hours, and 0.76 (0.51-1.12) for ≥9 hours (p trend=0.09). In the HPFS, the corresponding multivariate RRs were 1.08 (0.77-1.51) for men sleeping ≤6 hours, 0.95 (0.69-1.30) for 8 hours, and 1.06 (0.68-1.67) for ≥9 hours (p trend=0.71).

Sleep Disordered Breathing and the Risk of Melanoma

In the NHS, there was no association between OSA and the risk of melanoma (Table 2.2); the multivariate RR for incident melanoma was 1.23 (0.54-2.79) for women with OSA. There was also no association between snoring status and risk of melanoma in the three cohorts (Table 2.3).

Discussion, Conclusions, and Suggestions for Future Work

Sleep Disordered Breathing and the Risk of Psoriasis:

This study demonstrates an association between OSA and psoriasis risk. This relationship persisted in two multivariate models that considered other known risk factors for psoriasis and SDB, demonstrating an association between these two entities. Although women with sleep apnea were more likely to be snorers, we found no association between snoring and psoriasis.

A recent study suggested a relationship between OSA and psoriasis (20). The study included a group of 2,250 Japanese individuals with OSA, but without psoriasis, and 11,255 matched controls with neither OSA nor psoriasis. The individuals were followed for three years to assess for a diagnosis of psoriasis. After adjusting for monthly income, urbanization level, geographic location, and obesity, the study authors found a hazard ratio of developing psoriasis of 2.30 (95% CI, 1.13-4.69; p=0.022) times greater for if individuals had OSA (20). This study had a relatively short duration given that both OSA and psoriasis are chronic conditions that are thought to develop over years. Additionally, the authors of this study did not address other important potential confounders such as cigarette smoking. Our study follows individuals for a longer period of time and uses two multivariate models that both simultaneously adjust for important risk factors for OSA and psoriasis. Although we cannot account for all unmeasured confounding, we included all known risk factors for both conditions into our models.

SDB has been associated with multiple comorbidities—including diabetes and cardiovascular disease—through a proposed mechanism of systemic inflammation (1, 3, 6, 37, 38). Individuals with OSA have been found to have higher levels of inflammatory cytokines such as TNF-α, IL-1,

and IL-6 (1-3, 6). These cytokines have also been demonstrated to be elevated in individuals with psoriasis (18, 19). We propose that the elevation in inflammatory cytokines may contribute to the manifestation of a psoriasis phenotype in an individual who is predisposed to developing psoriasis.

Together, snoring and OSA comprise a spectrum of SDB (1). Since OSA is on the more severe end of the continuum of SDB, individuals with OSA may have the greatest elevations in inflammatory cytokines (1). This may help to explain why we observed an increased risk of psoriasis in women with OSA, but did not see the same relationship in women who snored.

There are several strengths and limitations to this study. To our knowledge, this is the largest prospective assessment of SDB and psoriasis. The diagnoses of OSA and psoriasis were self-reported, however psoriasis diagnoses have been validated and their accuracy has been demonstrated, making the likelihood of misclassification low (34, 35). The fact that our study is restricted to female registered nurses represents both a strength and a weakness. Since these individuals are well educated, there is less socioeconomic variability in our cohort and there is a high rate of response. However, our results may not necessarily represent the female population in the United States. Our study is limited by the low PsA case number, which hampers our statistical power to assess the association between SDB and PsA. Furthermore, we are not able to infer a relationship between SDB and psoriasis in men based on this study. Finally, the age of individuals in our cohort more closely reflects the second peak of the bimodal pattern of psoriasis incidence, so these results may be most applicable to psoriasis that onsets later in life.

This prospective study demonstrates that women with OSA are at an approximately 2-fold increased risk of developing psoriasis. Physicians should be aware of the association between OSA and psoriasis. Our results suggest that managing SDB, and in particular OSA, may be a potential target for preventing and managing psoriasis, although our study did not examine this question directly. Future work may explore the effect of treatment of OSA with continuous positive airway pressure (CPAP) on psoriasis risk and severity.

Sleep Duration and Sleep Disordered Breathing and the Risk of Melanoma:

This study also showed no association between sleep duration or SDB and risk of incident melanoma. Recent studies have demonstrated a relationship between long and short sleep duration and all-cause and cause-specific morbidity and mortality (9-15). While it is evident that sleep is an integral part of health, the ideal amount of sleep remains unknown. Recent trends indicate that Americans are sleeping less, making questions about sleep and health more important and timely (11).

The mechanisms behind the associations between sleep duration and SDB and adverse health outcomes are poorly understood. Long sleep duration may indicate increased exposure to somnogenic cytokines (such as IL-1 and TNF-α), which are carcinogenic (11). In SDB, one potential contributor may be systemic inflammation. Several inflammatory cytokines—including TNF-α, IL-6, and VEGF—are increased in SDB (1-3, 6). Moreover, hypoxia has been associated with melanoma metastatic potential and in a mouse model, OSA has been shown to increase melanoma metastases (39, 40). Hypoxia accompanies OSA and has been proposed as an important factor in the increased risk of cancer in individuals with OSA (7). Melatonin is an indolamine molecule that functions as a regulator of circadian rhythms (30, 31). Melatonin receptors have been identified on normal skin and malignant melanoma cell surfaces (32). In normal skin, melatonin has antioxidant properties; in malignant melanoma, melatonin is oncostatic and potentiates the anticancer effects of interleukin-2 (31). Serum melatonin levels may be decreased in SDB, which may result in an increased risk of cancer among individuals with SDB (16, 17). Additionally, individuals with long sleep duration have been shown to be less physically active and spend less time outdoors, which may also play a role in the association

between long sleep duration and cancer risk (11). We adjusted for each of these factors and did not find any material difference in our result.

To our knowledge, this is the first prospective study to examine the relationship between sleep duration and SDB and melanoma risk. Limitations of our study include the possibility of misclassification of sleep duration and snoring because the information was self-reported. However, previous studies using the same information found some association with other disease endpoints including colorectal cancer, diabetes mellitus, and cardiovascular disease (33, 41, 42). Our study is also limited by the fact that most participants in the study are Caucasian and melanoma risk factors may vary by race (43, 44). This study was also limited by the relatively low number of melanoma cases in our cohorts.

We did not find any association between sleep duration and SDB and melanoma. This suggests that the inflammatory cytokines, dysregulation of melatonin levels, and hypoxia associated with long and short sleep duration and SDB either have no effect on melanoma risk or have an effect on melanoma risk that we were not able to detect in our study, possibly due to the relatively low number of cases of melanoma. Future work in this area may explore an association between sleep duration and severity of melanoma in terms of depth of invasion or risk of metastatic disease.

Summary

This study, using a large prospective cohort study of US women, demonstrates that OSA is associated with an increased risk of psoriasis. In the evaluation of three large prospective studies that prospectively assessed the association between sleep duration and SDB and risk of incident melanoma, we found no relationship between sleep duration and SDB and melanoma risk.

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Tables

Table 1.1: Baseline (1997) characteristics of Nurses' Health Study Participants

	No Sleep Apnea (N=71,108)	Sleep Apnea (N=490)
Age, mean (SD), years	61.0 (6.8)	61.2 (6.8)
Regular Snorer (%)	8.5	38.6
Average Sleep Duration, mean (SD), hours	6.99 (0.9)	6.90 (1.1)
Shift Worker (%)	3.54	4.86
BMI, mean (SD)	26.55 (5.1)	31.85 (7.1)
Physical Activity, Metabolic Equivalent Hour/Wk, mean (SD)	18.53 (22.6)	14.24 (21.0)
Alcohol Intake, gm/day, mean (SD)	4.99 (8.9)	2.84 (6.9)
Current Smoker (%)	10.83	9.25

Previous Smoker (%)	43.13	47.08
Hypertension (%)	38.01	60.12
Diabetes (%)	5.42	17.28
Cardiovascular Disease (%)	3.46	8.39

[a]Baseline characteristics between groups were compared using t test for continuous variables and chi-square test for categorical variables.

Table 1.2: Obstructive Sleep Apnea and Snoring and Psoriasis Risk

Obstructive Sleep Apnea	Cases	Person-years	Age-Adjusted RR (95% CI)	MV[a] RR (95% CI)	MV[b] RR (95% CI)
No	504	832,260	1	1	1
Yes	20	12,465	2.19 (1.39-3.45)	1.93 (1.21-3.08)	1.91 (1.20-3.05)
Snoring*					
Never	98	160,751	1	1	1
Occasionally	145	221,212	1.11 (0.85-1.43)	1.04 (0.80-1.35)	1.04 (0.80-1.35)
Few Nights/Week	31	39,619	1.37 (0.91-2.06)	1.24 (0.82-1.87)	1.25 (0.83-1.88)
Most Nights	53	61,583	1.43 (1.02-2.01)	1.24 (0.88-1.75)	1.24 (0.88-1.75)
Every night	26	32,719	1.32 (0.86-2.05)	1.11 (0.71-1.74)	1.10 (0.71-1.73)
P For Trend			0.02	0.2	0.2

[a]Multivariate: Age (continuous by year), BMI (continuous), Smoking Status (yes/no), Physical Activity and Alcohol Consumption.

[b]Multivariate: Age (continuous by year), BMI (continuous), Smoking Status (yes/no), Physical Activity, Alcohol Consumption, Hypertension (yes/no), Cardiovascular Disease (yes/no), Type 2 Diabetes (yes/no), History of Night Shift Work (yes/no).

*BMI treated as a dichotomous variable (<30, ≥30)

Table 1.3: Average Sleep Duration (Hours) and Psoriasis Risk

	Cases	Person-years	Age-Adjusted RR (95% CI)	MV[a] RR (95% CI)	MV[b] RR (95% CI)
≤6	129	209,733	0.98 (0.78-1.23)	0.96 (0.77-1.21)	0.96 (0.77-1.21)
7	187	301,056	1	1	1
≥8	186	260,240	1.10(0.89,1.35)	1.07(0.87,1.31)	1.07(0.87,1.31)
P trend			0.30	0.36	0.36

[a]Multivariate: Age (continuous by year), BMI*, Smoking Status (yes/no), Physical Activity and Alcohol Consumption.

[b]Multivariate: Age (continuous by year), BMI*, Smoking Status (yes/no), Physical Activity, Alcohol Consumption, Hypertension (yes/no), Cardiovascular Disease (yes/no), Type 2 Diabetes (yes/no), History of Night Shift Work (yes/no).

*BMI treated as a dichotomous variable (<30, ≥30)

Table 1.4: Obstructive Sleep Apnea and Snoring and Psoriatic Arthritis Risk

Obstructive Sleep Apnea	Cases	Person-years	Age-Adjusted RR (95% CI)	MV[a] RR (95% CI)	MV[b] RR (95% CI)
No	143	836,320	1	1	1
Yes	6	12,554	2.49 (1.07-5.79)	1.85 (0.79-4.37)	1.85 (0.78-4.38)
Snoring*					
Never	8	184,659	1	1	1
Occasionally	14	425,725	0.89 (0.35-2.25)	0.72 (0.27-1.86)	0.71 (0.27-1.87)
Regularly	1	58,134	0.39 (0.05-3.21)	0.19 (0.02-1.80)	0.19 (0.02-1.80)
P For Trend			0.4	0.1	0.1

[a]Multivariate: Age (continuous by year), BMI (continuous), Smoking Status (yes/no), Physical Activity and Alcohol Consumption.

[b]Multivariate: Age (continuous by year), BMI (continuous), Smoking Status (yes/no), Physical Activity, Alcohol Consumption, Hypertension (yes/no), Cardiovascular Disease (yes/no), Type 2 Diabetes (yes/no), History of Night Shift Work (yes/no).

*BMI treated as a dichotomous variable (<30, ≥ 30)

Table 2.1: Age-Standardized characteristics of individuals by average hours of sleep per 24 hour period in Nurses' Health Study (NHS) in 2000, Nurses' Health Study II (NHS II) in 2001, and Health Professionals Follow-Up Study (HPFS) in 2000

	Average Hours of Sleep Per 24 Hour Period			
	≤6	7	8	≥9
NHS	(N=19,873)	(N=28,228)	(N=19,249)	(N=3,178)
Age, mean (SD), years	52.4 (7.0)	51.9 (7.1)	52.5 (7.3)	52.8 (7.4)
Regular Snorer (%)	10.19	8.72	9.85	11.70
Shift Worker (%)	4.6	2.7	2.3	2.9
History of Sun Burn (%)	37.0	36.6	35.6	38.2
≥6 Moles (%)	4.7	4.5	4.5	5.0
Red or Blond Hair (%)	15.2	15.5	15.9	14.2
Painful Reaction to Sun (%)	37.2	35.8	36.3	36.4
Tan When in the Sun (%)	24.7	23.1	23.1	22.9
Family History of Melanoma (%)	10.4	10.5	10.3	10.7
NHS II	(N=22,243)	(N=32,140)	(N=17,753)	(N=4,040)
Age, mean (SD), years	46.4 (4.6)	46.1 (4.7)	45.9 (4.7)	46.0 (4.7)
Regular Snorer (%)	25.7	23.2	22.7	28.0
Shift Worker (%)	14.7	9.2	8.3	9.4
Ultraviolet B Flux, mean (SD)	124.0 (24.3)	124.9 (24.6)	126.3 (25.1)	127.5 (25.7)
History of Sun Burn (%)	67.6	66.1	65.7	67.5
≥5 Moles (%)	20.0	21.7	21.4	21.4
Red or Blond Hair (%)	19.8	20.2	20.4	21.7

Painful Reaction to the Sun (%)	49.1	47.5	46.6	49.7
Family History of Melanoma (%)	12.5	11.9	11.9	13.4
HPFS	(N=6,826)	(N=12,922)	(N=9,106)	(N=3,075)
Age, mean (SD), years	65.3 (9.1)	65.0 (8.8)	68.1 (9.1)	71.7 (8.9)
Regular Snorer (%)	45.3	46.4	46.9	46.4
Ultraviolet B Flux, mean (SD)	131.4 (28.2)	131.5 (28.1)	131.9 (28.3)	133.32 (28.25)
History of Sun Burn (%)	84.3	84.0	84.1	85.5
≥6 Moles	5.7	5.2	5.1	6.1
Red or Blond Hair (%)	13.2	13.2	14.2	16.7
Painful Reaction to the Sun (%)	71.0	70.6	70.2	70.6
Family History of Melanoma (%)	4.8	5.0	4.9	4.9

Table 2.2: Average Sleep Duration (Hours) and Melanoma Risk in the Nurses' Health Study, Nurses' Health Study II, and Health Professionals' Follow-Up Study

	No of Cases	Person-years	Age-Adjusted RR (95% CI)	MV RR (95% CI)
NHS (1986-2012) and NHS II (2001-2009)				
≤6	162	577,857	0.87 (0.62-1.21)	0.90 (0.67-1.20)
7	253	821,794	1	1
8	199	499,318	1.29 (1.07-1.55)	1.30 (1.08-1.56)
≥9	28	120,130	0.76 (0.51-1.12)	0.76 (0.51-1.12)
P for Trend			0.08	0.09
HPFS (2000-2012)				
≤6	54	61,125	1.08 (0.77-1.15)	1.08 (0.77-1.51)
7	94	115,257	1	1
8	65	79,876	0.94 (0.68-1.29)	0.95 (0.69-1.30)
≥9	25	26,088	1.06 (0.68-1.67)	1.06 (0.68-1.67)
P For Trend			0.69	0.71

Multivariate: Age (continuous), Number of Sun Burns (none,1-2,3-5,6+), Number of Moles (none,1-2,3-5,6+), Hair Color (red, blonde, light brown, dark brown, black), Family History of Melanoma (yes/no), Reaction to the Sun (no reaction, tan, burn), Tanning (only in NHS, none, light, average and deep tan), Caucasian Ethnicity (European/Mediterranean, Scandinavian, Native American, other Caucasian), UV Flux (quintiles), Snoring (never, occasionally, few nights, most nights, every night).

Table 2.3: Snoring and Melanoma Risk in the Nurses' Health Study, Nurses' Health Study II, and Health Professionals Follow-Up Study

	No of Cases	Person-years	Age-Adjusted RR (95% CI)	MV RR (95% CI)
NHS (2000-2012) and NHS II (2001-2009)				
Almost Never	123	162,161	1	1
Occasionally	148	222,178	0.84 (0.41-1.71)	0.85 (0.46-1.59)
Few Nights/Week	25	39,536	0.90 (0.60-1.36)	0.89 (0.59-1.34)
Most Nights	37	62,808	1.05 (0.72-1.55)	1.01 (0.69-1.49)
Every night	18	33,835	0.99 (0.72-1.37)	0.97 (0.71-1.34)
P For Trend			0.28	0.21
HPFS (2000-2012)				
Almost Never	39	54,789	1	1
Occasionally	80	92,828	1.20 (0.81-1.76)	1.17 (0.79-1.72)
Few Nights/Week	36	36,871	1.40 (0.88-2.23)	1.33 (0.84-2.12)
Most Nights	54	56,902	1.39 (0.91-2.11)	1.33 (0.87-2.02)

Every Night	31	39,476	1.21 (0.75-1.94)	1.14 (0.71-1.84)
P For Trend			0.24	0.37

Multivariate: Age (continuous), Number of Sun Burns (none,1-2,3-5,6+), Number of Moles (none,1-2,3-5,6+), Hair Color (red, blonde, light brown, dark brown, black), Family History of Melanoma (yes/no), Reaction to the Sun (no reaction, tan, burn), Tanning (only in NHS, none, light, average and deep tan), Caucasian Ethnicity (European/Mediterranean, Scandinavian, Native American and other Caucasian), UV Flux (quintiles).

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