Sleep Medicine ■■ (2015) ■■–■■

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Association between sleep-disordered breathing, obstructive sleep apnea, and cancer incidence: a systematic review and meta-analysis

Ghanshyam Palamaner Subash Shantha [a], Anita Ashok Kumar [b], Lawrence J. Cheskin [c,d,e], Samir Bipin Pancholy [a,f,*]

[a] Department of Cardiovascular Medicine, The Wright Center for Graduate Medical Education, 501 Madison Avenue, Scranton, PA 18510, USA
[b] Department of Epidemiology, The Johns Hopkins Bloomberg School of Public Health, 550 N. Broadway Suite 1001, Baltimore, MD 21205, USA
[c] Johns Hopkins Weight Management Center, Johns Hopkins University, 550 N. Broadway Suite 1001, Baltimore, MD 21205, USA
[d] Department of International Health, Center for Human Nutrition, Johns Hopkins Bloomberg School of Public Health, 550 N. Broadway Suite 1001, Baltimore, MD 21205, USA
[e] Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, 550 N. Broadway Suite 1001, Baltimore, MD 21205, USA
[f] Department of Medicine, The Commonwealth Medical College, 501 Madison Avenue, Scranton, PA 18510, USA

ARTICLE INFO

Article history:
Received 7 January 2015
Received in revised form 24 March 2015
Accepted 9 April 2015
Available online

Keywords:
Sleep-disordered breathing
Obstructive sleep apnea
Cancer
Meta-analysis

ABSTRACT

Objective/background: Via this systematic review and meta-analysis, we assessed the associatio between sleep-disordered breathing (SDB)/obstructive sleep apnea (OSA) and cancer incidence.
Method: Medline, Embase, Cochrane Central, and electronic databases were searched for relevant studies in any language. Studies were included based on the following criteria: (1) those on patients with SDB/OSA, (2) those reporting cancer incidence rates specific to patients with SDB/OSA, and (3) those defining SDB/OSA using sleep-study-based objective measures. The quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOQA).
Results: Of the 8766 retrieved citations, five studies that defined SDB/OSA using the apnea-hypopnea index (AHI) or the respiratory disturbance index (RDI) totaling 34,848 patients with SDB and 77,380 patients without SDB were pooled into a meta-analysis. All five studies were of good quality (NOQA ≥ 6). A total of 574 (1.6%) and 290 (0.37%) incident cancers were reported in patients with and without SDB, respectively. In the unadjusted analysis, patients with SDB/OSA were at an increased risk of incident cancer (relative risk [RR]: 1.53, 95% confidence interval [CI]: 1.31–1.79, $P < 0.001$, I^2: 0, five included studies). When adjusted for traditional cancer risk factors, the association between SDB/OSA and cancer incidence, although attenuated (RR: 1.40, 95% CI: 1.01–1.95, $P = 0.04$, I^2: 60%, five included studies), remains significant.
Conclusions: SDB/OSA may increase the risk of incident cancer. Inferring an independent association is not possible from our analysis considering the retrospective cohort design of the included studies and high inter-study heterogeneity. An individual patient data meta-analysis would help validate our findings.

1. Introduction

Sleep-disordered breathing (SDB) is an important public health problem. Population prevalence estimates range between 5% and 20% [1,2], depending on the population studied and the definition used. Many individuals with this disorder remain undiagnosed in the general population [3]. With the global obesity epidemic, the prevalence of SDB is likely to increase severalfold [4,5]. Obstructive sleep apnea (OSA), the most common form of SDB, is known to be associated with adverse cardiovascular outcomes, including hypertension (HTN), coronary artery disease, and stroke [6,7], and it increases cardiovascular and all-cause mortality [6,7]. OSA also increases the risk of motor vehicle and other accidents [8,9], type 2 diabetes [10], and postoperative complications [11], and it adversely affects the health-related quality of life [12].

The association between sleep disorders and cancer remains unclear. Although two systematic reviews have supported an association between duration of sleep and risk of cancer [13,14], a review by Lu et al. refuted an overall association [15], not excluding the existence of a positive association in specific cancer subtypes. Although most studies that assessed the association between SDB and cancer supported a positive association [16–20], evidence contrary to this also exists [21]. A pooled analysis combining all available evidence that has assessed the association between SDB and cancer

* Corresponding author. The Wright Center for Graduate Medical Education, The Commonwealth Medical College, 501 Madison Avenue, Scranton, PA 18510, USA. Tel.: +001 570 587 7817; fax: +570 587 7815.
E-mail address: pancholys@gmail.com (S.B. Pancholy).

http://dx.doi.org/10.1016/j.sleep.2015.04.014
1389-9457/

incidence is lacking in the literature. Via this systematic review and meta-analysis, we aimed to assess the association between SDB and cancer incidence.

2. Methods

2.1. Data sources

The Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were followed for planning, data abstraction, and reporting [19]. We searched Medline, Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Ovid, the Cochrane Library database, Web of Science, and Google Scholar for studies assessing the association between SDB and cancer. No language or time restriction was imposed. The last search was performed on 28 December 2014. Search strategy and search terms are detailed in the eMethods.

2.2. Study selection

The inclusion criteria were as follows: (1) Studies that involved patients with SDB were included, especially those that defined SDB using sleep-study-based objective measures (eg, apnea–hypopnea index [AHI] and respiratory disturbance index [RDI]), but excluding studies that used subjective measures such as self-reported snoring, Epworth Sleepiness Scale score etc. (2) Studies that also reported cancer incidence rates in their patients were included. In this paper, the term "incident cancer" denotes a newly diagnosed cancer. We included conference abstracts that reported data relevant to our research question. We excluded case reports. Two reviewers independently assessed studies for eligibility. Discrepancy was resolved by consensus.

2.3. Data extraction

The following information was abstracted by two independent reviewers: last name of first author; publication year; country/region where the study was performed; study design; total participants in the study; number with/without SDB; total number of cancers in the study cohort; number of cancers in the SDB and non-SDB groups; demographics (age, gender, and body mass index (BMI)); AHI if reported; and the baseline prevalence of smoking, alcohol intake, and comorbid conditions (diagnoses of type 2 diabetes mellitus [DM], HTN, dyslipidemia, and history of heart disease) in the total cohort, SDB group, and non-SDB group. The quality of the included studies was assessed using the Newcastle-Ottawa Quality Assessment Scale for cohort studies [20].

2.4. Statistical analysis

Abstracted data from included studies were entered into the RevMan 5.1 (Nordic Cochrane Center, Copenhagen, Denmark) statistical software [22]. In the unadjusted meta-analysis, using raw numbers of cancer incidence rates in the SDB/OSA group and the group without SDB/OSA, we assessed the association between SDB (presence/absence) and cancer incidence. Data were combined using DerSimonian and Laird's random-effects model with inverse variance weighting [23]. Estimates were reported as risk ratios (RRs) with 95% confidence intervals (CIs). Of the five included studies [16,17,24–26], three studies [16,17,26] performed multivariate Cox proportional-hazards regression and reported adjusted hazard ratios of the association between SDB/OSA and incident cancer. On the other hand, the remaining two included studies [24,25] performed multivariate logistic regression analysis and reported adjusted odds ratios of the association between SDB/OSA and incident cancer. The odds ratios were converted to RRs using Revman statistical software [22], and the hazard ratios were interchangeably used as RRs. Thus, the five adjusted RRs obtained from the five included studies were pooled to arrive at the adjusted risk estimate of association between SDB/OSA and incident cancer. We performed a sensitivity analysis, a one-study-removed analysis, where one study was removed at a time from the pooled analysis, to assess the effect of each study on the combined effect. We planned a priori to perform a sensitivity analysis based on study quality. As all studies included in the meta-analysis were of a good quality (Newcastle-Ottawa Quality Assessment Scale ≥ 6), we could not perform this sensitivity analysis. In addition, we performed a meta-influence analysis to assess if one or more studies had a greater impact on the strength of association, and we evaluated the effect of removal of such studies on the pooled estimate.

Heterogeneity across studies was assessed with Cochran's Q statistic (χ^2), with $P < 0.10$ for significance, and with the I^2 test [27]. Considering the high statistical heterogeneity in the adjusted analysis, we performed meta-regression investigating the sources of heterogeneity in the included studies. Difference in age (years), difference in gender (%), difference in BMI, and difference in proportions of patients who were smokers (%) were the sources of heterogeneity assessed. These were the variables uniformly reported by the included studies.

Egger's linear regression test [28], visual inspection of funnel plots, and the Begg–Mazumdar test were used to assess publication bias. The trim-and-fill method was used to adjust for publication bias using STATA version 11 [29]. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Literature search

From a total of 8766 citations retrieved using the search strategy, five studies [16,17,24–26] that defined SDB/OSA using sleep-study-based objective measures and reported incident cancer were included in the meta-analysis. See Fig. 1 for study selection details.

3.1.1. Study characteristics and patient profile

The characteristics of included studies, assessment of study quality, and the patient profile of the included studies are detailed in Tables 1–3 and the supplemental file. In brief, between 2003 and 2007, using a large, multicentered, hospital-based cohort of seven Spanish teaching hospitals, Campos-Rodriguez, et al. [16] prospectively followed up study participants until cancer incidence, defined as the first occurrence of a malignant neoplasm at any time between the sleep study and the final follow-up date of 31 December 2010. Cancer diagnosis was verified using multiple concurrent sources of information including cancer and pathology registries, medical records, and computerized databases, and by contacting the primary care provider if needed. AHI and TSat90 (percentage of nighttime spent with $SO_2 < 90\%$) were the OSA severity indices used. AHI scores ≤5, 6 to < 18.7, 18.7–43, and > 43 indicated no, mild, moderate, and severe OSA, respectively. By the end of the follow-up period (median: 4.5 years), 261 patients developed cancer. Forty-three cases (16.5%) with colorectal cancers, 42 (16.1%) were prostate cancers, 24 (9.2%) were lung cancers, and 20 (7.7%) were breast cancers. Of these, 194 cases (6%) were reported in the SDB group and 67 (4.1%) in the non-S DB group. Hence, the authors conclude a positive association between SDB and cancer. Between 1981 and 1990, Marshall et al. [17] studied 400 community participants (mean follow-up: six years) from the Australian town of Busselton. The OSA severity was graded using RDI. RDI was defined as the sum of the total number of respiratory disturbances (oxygen desaturation ≥3% + heart rate increase of >10 beats/min) divided by the participants' hours of sleep during the sleep study to arrive at an events/h estimate. An RDI score <5

Please cite this article in press as: Ghanshyam Palamaner Subash Shantha, Anita Ashok Kumar, Lawrence J. Cheskin, Samir Bipin Pancholy, Association between sleep-disordered breathing, obstructive sleep apnea, and cancer incidence: a systematic review and meta-analysis, Sleep Medicine (2015), doi: 10.1016/j.sleep.2015.04.014

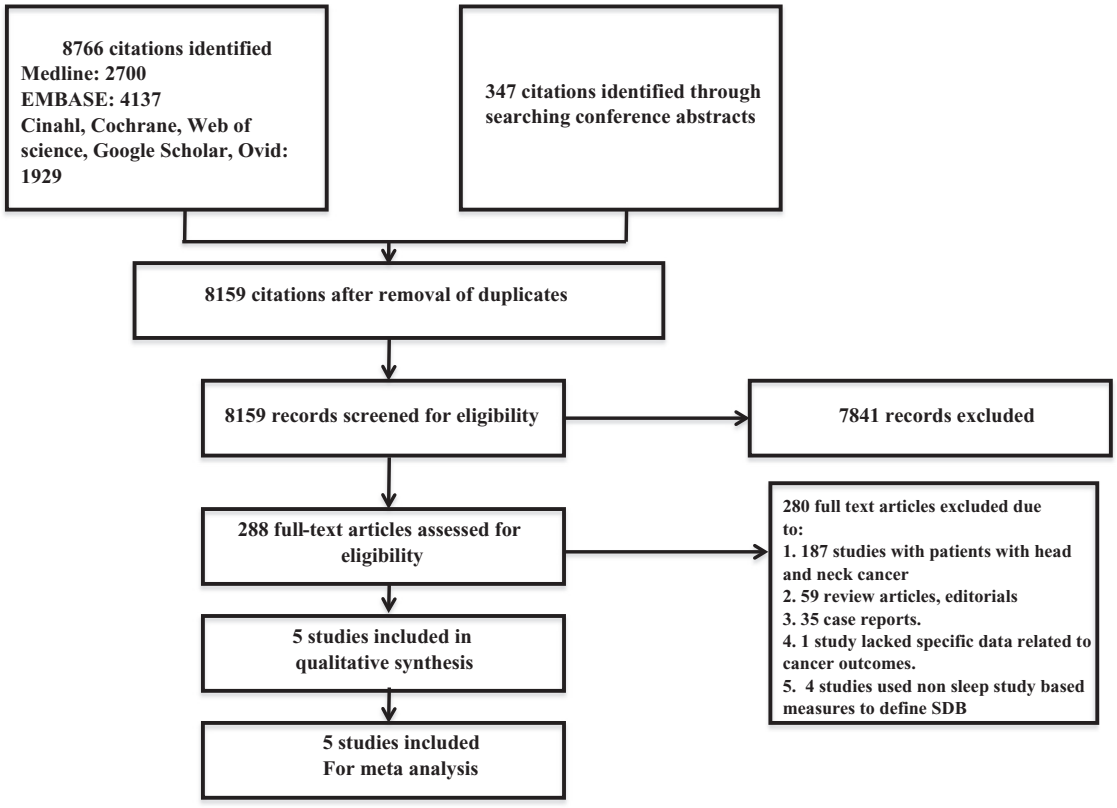

Fig. 1. Study selection flow diagram.
Caption: Flow diagram detailing study selection process.

indicated no SDB, whereas an RDI score of 5–15 and >15 indicated mild and moderate–severe SDB, respectively. Incident cancer was defined as new-onset cancer diagnosed during the study period. Cancer diagnosis was determined using the West Australian Cancer registry, the database that registers all diagnosed cancers in West Australia, and data were abstracted from this registry using International Classification of Disease (ICD)-9 codes. In total, 120 cancer cases (87 (30%) in the SDB group and 33 (33%) in the non-SDB group) were reported, but the cancer subtypes were not evaluated.

Kendzerska et al. [24] enrolled 10,149 patients at a single hospital in Canada from 1994 to 2010. OSA was defined as AHI ≥5 events/h. Hypopnea was defined as a decrease of >50% in the baseline amplitude of breathing and/or an associated 3% drop in oxygen saturation or an arousal. The median follow-up was 7.8 years. AHI and TSat90 were the OSA severity indices used. By the end of the follow-up period, 627 new cancer cases (reported as newly diagnosed cancer during the study period) were reported. Prostate ($n = 125$), breast ($n = 75$), colorectal ($n = 64$), and lung ($n = 61$) cancers were the most common cancers reported. Cancer diagnosis was obtained from Ontario Cancer Registry, which the authors report being a good-quality and complete registry based on published data. The cumulative 5-year cancer incidence in groups with AHI <5 (no OSA), AHI 5–15 (mild OSA), AHI 15–30 (moderate OSA), and AHI >30 (severe OSA) were, respectively, 2.6%, 2.9%, 4.0%, and 4.9%. Between 2000 and 2003, Chen et al. [25] studied 23,055 new cases of sleep apnea from 2000 to 2003 in the medical claims database of Taiwan's national health institute. AHI was the OSA severity index used, and an AHI score >5 was used to diagnose OSA. Severity gradients of OSA were not mentioned at follow-up (10 years); 38 (0.16%) primary central nervous system (CNS) cancers (brain, 32; spinal cord, six) were detected in the OSA group and 85 (0.12%) (brain, 65; spinal cord, 20) in the non-OSA group. Incident CNS cancer was defined as any CNS cancer diagnosed after two years of study initiation. Cancer diagnosis was obtained from the Taiwan national institute database.

Chang et al. [26] studied 846 women diagnosed with sleep apnea (SA) between 2003 and 2005, identified from the National Health Insurance Research Database (NHIRD), which is managed by the Taiwan National Health Research Institutes (NHRI). SA was defined

Table 1
Characteristics of included studies.

First author	Year	Nation	Design	Total cohort	Cancers (n)	[a]SDB		Non-SDB		[b]Study quality
						Total	Cancer	Total	Cancer	
Campos-Rodriguez [16]	2013	Spain	Retros. cohort	4910	261	3273	194	1637	67	7
Marshall [17]	2014	Australia	Retros. cohort	391	120	292	87	99	33	7
Kendzerska [24]	2014	Canada	Retros. cohort	9629	356	7575	297	2054	54	7
Chen [25]	2014	Taiwan	Retros. cohort	92,220	123	23,055	38	69,165	85	6
Chang [26]	2014	Taiwan	Retros. cohort	5076	44	846	12	4230	32	6

[a] SDB: sleep-disordered breathing.
[b] Newcastle-Ottawa Quality Assessment Scale for cohort studies.

Please cite this article in press as: Ghanshyam Palamaner Subash Shantha, Anita Ashok Kumar, Lawrence J. Cheskin, Samir Bipin Pancholy, Association between sleep-disordered breathing, obstructive sleep apnea, and cancer incidence: a systematic review and meta-analysis, Sleep Medicine (2015), doi: 10.1016/j.sleep.2015.04.014

Table 2
Baseline characteristics of study participants from included studies.

First author	Year	Age (years)		Males (%)		[b]BMI (kg/m^2)		[c]AHI		Smoking (%)		Alcohol (%)	
		[a]SDB	N-SDB	SDB	N-SDB	SDB	N-SDB	SDB	N-SDB	SDB	N-SDB	SDB	N-SDB
Campos-Rodriguez [16]	2013	56	51	71	57	32	30	47	9	26	22	NR	NR
Marshall [17]	2014	55	53	74	73	34	26	NR	NR	20	15	NR	NR
Kendzerska [24]	2014	52	42	77	46	32	26	49	2	17	19	NR	NR
Chen [25]	2014	38	38	67	67	NR	NR	NR	NR	NR	NR	NR	NR
Chang [26]	2014	NR[d]	NR	0	0	NR	NR	NR	NR	NR	NR	1.2	0.2

[a] SDB: sleep-disordered breathing.
[b] BMI: body mass index.
[c] AHI: apnea–hypopnea index.
[d] NR: not reported; data specific to SDB and N-SDB groups were not reported in the studies.

Table 3
Comorbid factors in the study participants.

First author	Year	[b]DM (%)		[c]HTN (%)		Dyslipidemia (%)		Heart disease (%)		Obesity (%)	
		SDB	N-SDB	SDB	N-SDB	SDB	N-SDB	[a]SDB	N-SDB	SDB	N-SDB
Campos-Rodriguez [16]	2013	[d]NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Marshall [17]	2014	11	2	NR	NR	NR	NR	6	3	NR	NR
Kendzerska [24]	2014	21	7	49	19	NR	NR	NR	NR	NR	NR
Chen [25]	2014	8	3	18	4	15	3	2	0.3	4.1	0.1
Chang [26]	2014	28	21	49	37	45	31	NR	NR	7	2

[a] SDB: sleep-disordered breathing.
[b] DM: diabetes mellitus.
[c] HTN: hypertension.
[d] NR: not reported; data specific to SDB and N-SDB groups were not reported in the studies.

based on polysomnography. However, the precise definition for SA or severity grading of SA used in the study was not mentioned. For each patient with SA, five age-matched controls were selected to form a comparison cohort ($n = 4230$). During 5-year follow-up, 44 incident breast cancers (SA cohort: 12 (1.4%), comparison cohort: 32 (0.75%)) were identified. The cancer diagnosis method was not mentioned in the study.

3.1.2. *Association between SDB/OSA and cancer incidence (meta-analysis)*

In the pooled analysis, five studies [16,17,24–26] totaling 34,848 patients with SDB and 77,380 patients without SDB were included. A total of 574 (1.6%) and 290 (0.37%) incident cancers were reported in the SDB group and the non-SDB group, respectively. In the unadjusted analysis (Fig. 2), patients with SDB/OSA were identified to have an increased risk of incident cancer (RR: 1.53, 95% CI: 1.31–1.79, $P < 0.001$, I^2: 0, five included studies). When adjusted RRs (adjusted for traditional cancer risk factors mentioned in eTable 1) were used, the association between SDB/OSA and cancer, although attenuated (RR: 1.40, 95% CI: 1.01–1.95, $P = 0.04$, I^2: 60%, five included studies) (Fig. 3), remained significant. The factors adjusted for to arrive at these adjusted RRs are mentioned in Supplemental Table S1. In general, all studies adjusted for age, whereas the majority adjusted for gender, obesity, smoking, and alcohol intake. In the meta-influence analysis, the study by Kendzerska et al. [24] exerted a higher impact on the effect estimate, and removal of this study increased the RR for incident cancer in the SDB group (RR: 1.6, 95% CI: 1.20–2.06) (eFig. S1). In the sensitivity analyses with one study removed at a time, the RR of association between OSA and incident cancer varied between 1.26 and 1.60, with 95% CI ranging between 0.92 and 2.33.

3.1.3. *Meta-regression analysis*

As revealed by meta-regression analyses, differences in age (β coefficient: –0.05, $P = 0.148$), gender proportions (–0.02, $P = 0.171$), BMI (0.11, $P = 0.534$), and smoking prevalence (0.08, $P = 0.567$) could not account as significant sources for heterogeneity (eFig. S2–S5).

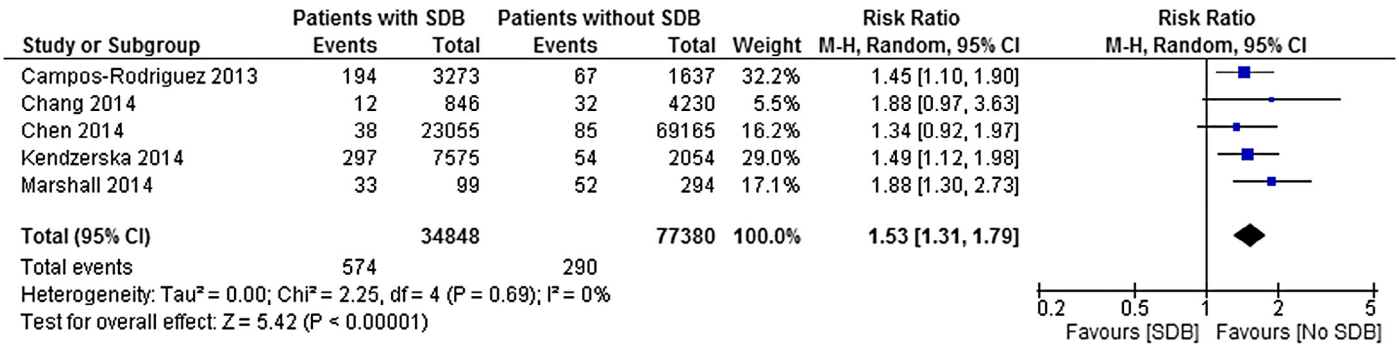

Fig. 2. unadjusted association between sleep-disordered breathing and incident cancer.
Caption: Forest plots showing the unadjusted risk ratios of association between sleep-disordered breathing and incident cancer.

Please cite this article in press as: Ghanshyam Palamaner Subash Shantha, Anita Ashok Kumar, Lawrence J. Cheskin, Samir Bipin Pancholy, Association between sleep-disordered breathing, obstructive sleep apnea, and cancer incidence: a systematic review and meta-analysis, Sleep Medicine (2015), doi: 10.1016/j.sleep.2015.04.014

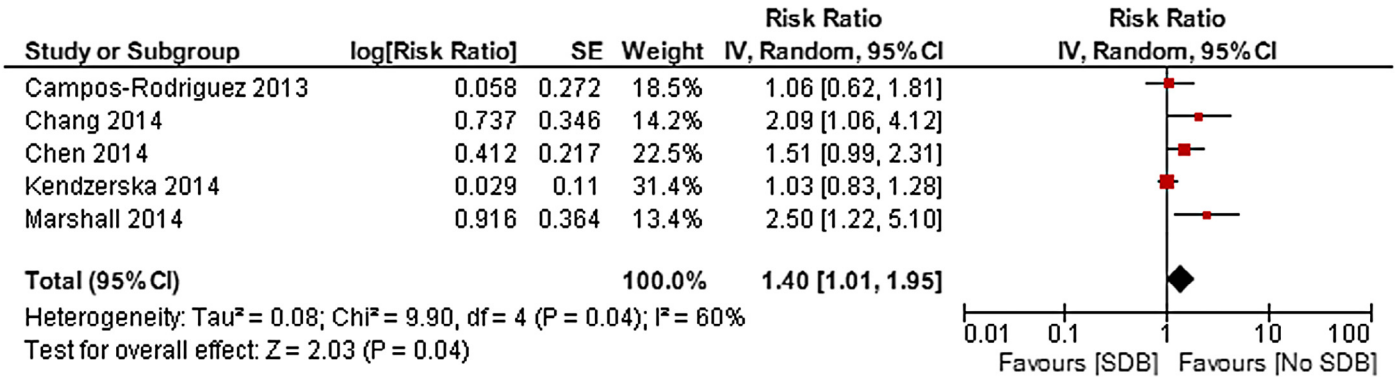

Fig. 3. adjusted association between obstructive sleep apnea and incident cancer.
Caption: Forest plots showing the adjusted association between obstructive sleep apnea and incident cancer.

3.1.4. Publication bias

Visual inspection of funnel plots revealed evidence for missing studies with small sample sizes and with weakly positive or null effect sizes (eFig. S6). Egger's test ($P = 0.069$) and Begg's test ($P = 0.086$) did not support this concept. The results of the "trim-and-fill" analysis suggested the possibility of two missing studies, and the addition of the two missing studies pushed the risk association between SDB and incident cancer to null (RR: 1.14, 95% CI: 0.8–1.6) (eFig. S7).

4. Discussion

Our meta-analysis, involving 34,848 participants with SDB and 77,380 participants without SDB from five studies, suggests that people with SDB have a nearly 50% greater overall cancer risk compared with people without SDB. However, in the adjusted analysis, we observed that the association between SDB and cancer incidence is significantly attenuated when adjusting for the traditional cancer risk factors such as age, gender, obesity, smoking, and alcohol use.

Molecular mechanisms support the biological plausibility of an association between SDB and cancer. A hallmark of severe OSA, intermittent hypoxia increases tumor growth, tumor necrosis, and predisposition to metastasis [30,31]. Furthermore, reactive oxygen species (ROS) generated during the reoxygenation phases of intermittent hypoxia affects processes such as gene transformations and transcription factor activations, which are key pathways in tumor genesis [31,32]. In addition, patients with sleep apnea have decreased antioxidant capacity [33], and hence multiple potential mechanisms are observed to suggest poor defense against carcinogenesis.

Our qualitative synthesis included good-quality studies with large sample sizes. The meta-analysis, by using objective sleep-study-based definitions for SDB, should have minimal exposure misclassification. However, in spite of these strengths, inferring an independent association between SDB and cancer is difficult. Our results need to be interpreted in the context of the following three validity issues: (1) confounding due to cancer risk factors, (2) clinical and statistical heterogeneity between the included studies, and (3) the possibility of publication bias. In the adjusted analysis, the association between SDB and cancer incidence is significantly attenuated when adjusting for traditional cancer risk factors (Fig. 3). This increases the possibility that the observed association between SDB and cancer may largely be due to confounding traditional cancer risk factors. Although our adjusted analysis maintained statistical significance, in spite of using adjusted RRs from included studies that were adjusted for fairly similar variables (Supplemental Table S1), the strength of association was weak, and residual confounding due to variables such as study center characteristics is still possible as some of our included studies were population based, where some were sleep clinic based. Adjusting for this variability via subgroup analysis based on the study center was not possible because of the small number of studies in our analysis. Further, variability in the baseline prevalence of SDB (range 6–60%), variability in cancer incidence (<1% to 30%), and variability in follow-up reported in the included studies (range 5 – 22 years) and some studies assessing specific types of cancers with some studies assessing all cancers are factors that contribute to clinical heterogeneity in our analysis, and could not be controlled for. In addition, the high statistical heterogeneity observed in our adjusted analysis (Fig. 3, I_2: 60%) could not be explained, as the variables assessed in the meta-regression analyses did not account as significant contributors to this heterogeneity (eFig. S2–S5). However, the possible reasons for high statistical heterogeneity in the adjusted analysis may be variability in the analysis methods used in the included studies with three of the five included studies [16,17,26] performing Cox proportional-hazards regression and reporting hazard ratios and the remaining two included studies [24,25] performing logistic regression analysis and reporting odds ratios of association. Further, our funnel plots and trim-and-fill analysis suggest the possibility of potential publication bias where small studies and those with weakly positive or null effect sizes may have been missed. As only five studies were pooled for the meta-analysis, caution should be exercised in drawing strong conclusions based on the meta-regression analyses and the analysis for publication bias.

The recent American College of Physicians (ACP) guidelines, although recommending sleep studies in patients at a high risk of OSA, grade their recommendation as "weak," [34] mainly because of the inability to establish a causal association between OSA and clinical outcomes. Confounding is a major bias that precludes causal associations in OSA outcomes research. Recent molecular evidence has identified the beneficial role of continuous positive airway pressure (CPAP) in favorably altering transcription in cancer-related pathways [35]. Hence, inclusion of cancer outcomes in randomized controlled trials (RCTs) evaluating treatment options for OSA may be a viable means of validating our findings, although the feasibility of conducting such an RCT is questionable. As our meta-analysis involved 34,848 participants with SDB and 77,380 participants without SDB, and reported a cancer incidence of 1.6% and 0.37% in the SDB and the non-SDB groups, respectively, an RCT powered to identify this small a difference in cancer incidence between groups may be impractical. Performing more population-based studies with robust strategies to control for confounders, or meta-analyses of individual patient data, may be more practical. Publication of all studies, including those with weak or null effect sizes, is needed in order to avoid publication bias.

Please cite this article in press as: Ghanshyam Palamaner Subash Shantha, Anita Ashok Kumar, Lawrence J. Cheskin, Samir Bipin Pancholy, Association between sleep-disordered breathing, obstructive sleep apnea, and cancer incidence: a systematic review and meta-analysis, Sleep Medicine (2015), doi: 10.1016/j.sleep.2015.04.014

5. Conclusion

Our systematic review and meta-analysis supports a prospective association between SDB/OSA and cancer incidence. However, confirming an independent association is not currently possible because of limitations of the available data. Validation of an independent association between SDB and cancer incidence would have major clinical implications for the evaluation and treatment of sleep disorders.

Funding sources

None.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.04.014.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2015.04.014.

References

[1] Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5(2):136–43.
[2] Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 2001;163(3 Pt 1):685–9.
[3] Diagnostic Classification Steering Committee of the American Sleep Disorders Association. The international classification of sleep disorders: diagnostic and coding manual. Rochester, MN: American Sleep Disorders Association; 1990.
[4] Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA 2012;307(5):491–7.
[5] Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. JAMA 2004;291(16):2013–16.
[6] Peppard PE, Young T, Palta M, Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342(19):1378–84.
[7] Loke YK, Brown JW, Kwok CS, Niruban A, Myint PK. Association of obstructive sleep apnea with risk of serious cardiovascular events: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2012;5(5):720–8.
[8] Howard ME, Desai AV, Grunstein RR, et al. Sleepiness, sleep-disordered breathing, and accident risk factors in commercial vehicle drivers. Am J Respir Crit Care Med 2004;170(9):1014–21.
[9] Terán-Santos J, Jiménez-Gómez A, Cordero-Guevara J. The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. N Engl J Med 1999;340(11):847–51.
[10] Babu AR, Herdegen J, Fogelfeld L, Shott S, Mazzone T. Type 2 diabetes, glycemic control, and continuous positive airway pressure in obstructive sleep apnea. Arch Intern Med 2005;165(4):447–52.
[11] Chung SA, Yuan H, Chung F. A systemic review of obstructive sleep apnea and its implications for anesthesiologists. Anesth Analg 2008;107(5):1543–63.
[12] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328(17):1230–5.
[13] Zhao H, Yin JY, Yang WS, et al. Sleep duration and cancer risk: a systematic review and meta-analysis of prospective studies. Asian Pac J Cancer Prev 2013;14(12):7509–15.
[14] Qin Y, Zhou Y, Zhang X, Wei X, He J. Sleep duration and breast cancer risk: a meta-analysis of observational studies. Int J Cancer 2014;134(5):1166–73.
[15] Lu Y, Tian N, Yin J, Shi Y, Huang Z. Association between sleep duration and cancer risk: a meta-analysis of prospective cohort studies. PLoS ONE 2013;8(9):e74723.
[16] Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, Spanish Sleep Network, et al. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. Am J Respir Crit Care Med 2013;187(1):99–105.
[17] Marshall NS, Wong KK, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the busselton health study cohort. J Clin Sleep Med 2014;10(4):355–62.
[18] Zhang X, Giovannucci EL, Wu K, et al. Associations of self-reported sleep duration and snoring with colorectal cancer risk in men and women. Sleep 2013;36(5):681–8.
[19] Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 2000;283(15):2008–12.
[20] Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603–5.
[21] Christensen AS, Clark A, Salo P, et al. Symptoms of sleep disordered breathing and risk of cancer: a prospective cohort study. Sleep 2013;36(10):1429–35.
[22] Deeks JJ, Higgins JPT, Altman DG. Analysing data and undertaking meta-analyses, Chapter 9. In: Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions. Chichester, UK: John Wiley & Sons; 2008 [Chapter 9].
[23] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177–88.
[24] Kendzerska T, Leung RS, Hawker G, Tomlinson G, Gershon AS. Obstructive sleep apnea and the prevalence and incidence of cancer. CMAJ 2014;186(13):985–92. pii: cmaj.140238.
[25] Chen JC, Hwang JH. Sleep apnea increased incidence of primary central nervous system cancers: a nationwide cohort study. Sleep Med 2014;15:749–54.
[26] Chang WP, Liu ME, Chang WC, et al. Sleep apnea and the subsequent risk of breast cancer in women: a nationwide population-based cohort study. Sleep Med 2014;15(9):1016–20.
[27] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60.
[28] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629–34.
[29] StataCorp. Stata statistical software: release 8.2. College Station, TX: StataCorp LP; 2004.
[30] Almendros I, Montserrat JM, Ramírez J, et al. Intermittent hypoxia enhances cancer progression in a mouse model of sleep apnoea. Eur Respir J 2012;39(1):215–17.
[31] Toffoli S, Michiels C. Intermittent hypoxia is a key regulator of cancer cell and endothelial cell interplay in tumours. FEBS J 2008;275(12):2991–3002.
[32] Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: how are they linked? Free Radic Biol Med 2010;49(11):1603–16.
[33] Barceló A, Barbé F, de la Peña M, et al. Antioxidant status in patients with sleep apnoea and impact of continuous positive airway pressure treatment. Eur Respir J 2006;27(4):756–60.
[34] Qaseem A, Dallas P, Owens DK, et al. Diagnosis of obstructive sleep apnea in adults: a clinical practice guideline from the American college of physicians. Ann Intern Med 2014;161(3):210–20.
[35] Gharib SA, Seiger AN, Hayes AL, Mehra R, Patel SR. Treatment of obstructive sleep apnea alters cancer-associated transcriptional signatures in circulating leukocytes. Sleep 2014;37(4):709–14.

Please cite this article in press as: Ghanshyam Palamaner Subash Shantha, Anita Ashok Kumar, Lawrence J. Cheskin, Samir Bipin Pancholy, Association between sleep-disordered breathing, obstructive sleep apnea, and cancer incidence: a systematic review and meta-analysis, Sleep Medicine (2015), doi: 10.1016/j.sleep.2015.04.014