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