Systematic Review and Meta-Analysis

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Cancer and obstructive sleep apnea

An updated meta-analysis

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Abstract

Objective: The relationship between cancers and obstructive sleep apnea (OSA) has been discussed for decades. However, the previous meta-analysis led to opposite conclusions. To further investigate this controversial issue, we performed this systematic review and meta-analysis update.

Methods: PubMed, Embase, and the Cochrane Library were systematically searched and studies on "cancer and OSA" were all included. Two reviewers independently searched articles, extracted data, and assessed the quality of included studies. Moreover, the overall incidence of cancer and OSA in corresponding populations was calculated.

Results: Of the 1434 titles identified, 22 articles involving more than 32.1 million patients were included in this meta-analysis. An overall incidence of OSA positive individuals in cancer was 46 (95%CI, 27–67)%, and the prevalence of cancers in OSA patients reached 1.53 (95%CI, 1.01–2.31) times higher than non-OSA individuals.

Conclusion: This meta-analysis indicated that there was a high prevalence of OSA in cancer patients, and individuals with OSA were more likely to develop tumors, and the incidence was related to the severity of OSA.

Abbreviations: AHI = apnea hypopnea index, BCAC = Breast Cancer Association Consortium, GWAS = genome-wide association study, HIF-1 = hypoxia-inducible factor-1, OSA = obstructive sleep apnea, ROS = reactive oxygen species, $Tsat_{90}$ = percent nighttime with oxygen saturation < 90%, VEGF = vascular endothelial growth factor.

Keywords: cancer, meta-analysis, obstructive sleep apnea, tumor

1. Introduction

Obstructive sleep apnea (OSA) is a medical disorder characterized by recurrent upper airway collapse caused by the partial or complete collapse of upper airway and cessation of airflow during sleep.[1] It is widespread in the general population. The overall prevalence of symptomatic OSA was 20% to 30% in men, and 10% to 15% in women, and the rates were still increasing.[2] OSA is currently recognized as a systemic disease, and is often associated with multiple comorbidities, including hypertension, myocardial infarction, stroke, mellitus diabetes, pulmonary hypertension, and depression.

Up to now, the pathophysiological mechanism of OSA is considered as intermittent hypoxia caused by apnea,[3] and this intermittent hypoxia may be related to the occurrence of tumors in OSA patients. Some scholars argued that intermittent hypoxia was similar to tissue ischemia-reperfusion.[4–6] Through repeated hypoxia and reoxygenation processes, a large number of transcriptional mediators of the hypoxic and inflammatory responses are generated, which increase oxidative stress, inflammation, and DNA damage, then, followed by tumorigenesis.[5]

Previous meta-analyses also discussed the relationship between cancers and OSA, however, it reached highly conflicting outcomes.[7,8] Recently epidemiological investigations have found that OSA is closely related to the occurrence and development of tumors.[9–11] With the release of some new data, we conducted this meta-analysis to assess the incidence of cancers and OSA in their respective populations, thus, re-evaluate the associating between cancers and OSA.

2. Method

2.1. Literature-search strategy

This literature search performed on March 20, 2020 without any restrictions in region, publication type, journal or language. The

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databases of PubMed (Medline), Embase (Excerpta Medica Database), Web of Science (Science Citation Index and Social Sciences Citation Index), and the Cochrane Library were thoroughly searched with the following strategy: ("cancer" or "tumor" or "carcinoma" or "neoplasm") and ("OSA" or "OSAH" or "sleep apnea" or "obstructive sleep apnea" or "obstructive sleep apnea-hypopnea syndrome").

The inclusion criteria were the following:

1. articles were published as original research,
2. written only in English,
3. tumor located in pharynx, larynx, oral cancer, etc, which may contribute to OSA anatomically.

The exclusion criteria were the following:

1. obstructive sleep apnea diagnosed after surgeon,
2. review article, case report, letter, editorial, commentary, and conference abstract,
3. study with unavailable data,
4. data from duplicate articles in previous studies.

2.2. Data extraction and quality assessment

Two reviewers (YC and PN) independently inspected all candidate articles independently. The following information was extracted from the included studies: author, year of publication, study country, region, sample size, study design, age, gender, BMI, apnea hypopnea index (AHI), diagnostic methods of OSA, follow-up period, and tumor location.

The quality of the included studies was evaluated according to the Newcastle-Ottawa Scale (NOS), and scores ≥6 were defined as high-quality. Two authors independently performed the analyses, and consensuses were reached on all decisions. Discrepancies were resolved by discussion with a senior author (QL).

2.3. Statistical analysis and data synthesis

All data were entered into STATA statistical software 13.0 (Stata Corp LP, College Station, TX) for meta-analysis. Data were presented as mean ± SD to evaluate the relationships between cancer and OSA. The heterogeneity of the studies was measured using the I^2 statistic, with the level of significance set at $P < .05$.

If I^2 value > 50%, we considered that substantial heterogeneity among studies and the random-effects model was used to calculate the pooled RR and 95%CI; otherwise, the fixed-effects model was applied. Likewise, subgroup analysis was conducted to compare observed effects between OSA and non-OSA, with $P < .05$ denoting statistical significance. Publication bias was assessed by Begg test and Egger test.

The conduct of this meta-analysis was consistent with the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Regarding the quality of studies, studies scored ≥6 stars in NOS which suggested high quality.

2.4. Ethics and dissemination

This study will not need to provide ethical approval, because this study based on the published data. We are expected to publish this study on peer-reviewed journals.

3. Results

3.1. Study characteristics

The characteristics of the included studies are shown in Table 1. There were 22 clinical studies that included more than 32.1 million individuals and met the criteria for meta-analysis.[9–29] The literature selection procedure is presented in Figure S1, Supplemental Digital Content, http://links.lww.com/MD2/A917. The included articles were published between 2011 and 2020, among which, 15 articles based on cancers in OSA patients (3 articles covered cancers in terms of OSA severity), and the rest 7 articles reported OSA in cancer patients. Regarding the quality of studies, all studies reached high-quality levels.

Seven articles reporting data from a total of 2269 cancer patients, and among whom 774 individuals were also suffered OSA. An overall incidence of 46 (95%CI, 27–67)% of OSA positivity in cancer patients was calculated in this meta-analysis, see Figure 1. Meanwhile, the meta-analysis showed the pooled prevalence of cancers in OSA patients reached 1.53 (95%CI, 1.01–2.31) times higher when compared to non-OSA individuals, see Figure 2.

3.2. Subgroup analysis

Based on the region of each study, the prevalence of cancers in OSA patients was 1.23 ($I^2 = 99.9\%$, $P < .0001$) times higher than the control group in developed countries. However, no statistical significance found in developing countries (Fig. S2, Supplemental Digital Content, http://links.lww.com/MD2/A918). And the cancer prevalence was still high in OSA when the patients were divided to three continents ($P < .0001$), Asia: RR 1.36 (95%CI, 1.22–1.51), America: RR 1.23, (95%CI, 1.22–1.24), and only one article in Oceania with 1.02 (95%CI, 0.27–1.44), see Figure S3, Supplemental Digital Content, http://links.lww.com/MD2/A919. In addition, subgroup analysis for cancer incidence according to the severity of OSA is displayed in Figure 3, and cancer incidence for mild OSA was 0.68 (95%CI, 0.52–0.84), 1.68 (95%CI, 1.07–2.30) for moderate to severe OSA, 0.44 (95%CI, 0.40–0.48) for moderate OSA. Severe OSA group has an incidence of 0.49 (95%CI, 0.44–0.54) for cancer.

3.3. Publication bias and sensitivity analysis

Egger test and funnel plot were used to assess the publication bias. Funnel plots of the studies appeared to be symmetrical by visual examination. The data suggested that there was no evidence of publication bias ($P > .05$; Fig. S5, Supplemental Digital Content, http://links.lww.com/MD2/A921 and Fig. S6, Supplemental Digital Content, http://links.lww.com/MD2/A922). Through omission of each of the included literature studies on prevalence of OSA positivity in cancer patients, results were less changed following sensitivity analysis (Fig. S7A, Supplemental Digital Content, http://links.lww.com/MD2/A923). However, sensitivity analysis on studies of cancers' prevalence in OSA patients demonstrated that prevalence changed to 0.82 (95%CI, 0.81–0.83) and 2.18 (95% CI, 2.15–2.21) by omission the study of Jara et al and Gozal et al, respectively[10,30] (Fig. S7B, Supplemental Digital Content, http://links.lww.com/MD2/A923).

4. Discussion

In recent years, there has been reported that OSA played a negative role in cancer incidence. And the high prevalence of OSA

Table 1

Characteristics of the included studies.

Author	Year	Country	Development	Population	Study design	Age	Gender	BMI	AHI	Diagnostic methods of OSA	Follow-up	Cancer	NOS
Gao	2020	China	Developing	2400	Mendelian randomization study	–	All women	OSA: case 23.97±3.21, control 23.88±3.17; breast cancer: case 23.96±3.20, control 23.90±3.24	–	PSG	–	Breast cancer	7
Chen	2019	China	Developing	20,900	Cohort study	OSA: 45.97 yr, control: 45.64 yrs	OSA: men 2970, women 1210, control: men 11,880, women 4840	–	–	ICD-9	14 yr	Colorectal cancer	7
Choi	2019	Korea	Developed	274,201	Retrospective cohort study	OSA: 48.7±14.2; control: 48.7±14.2	All women	–	–	ICD-10	3.7±2.3 yr	Breast cancer	6
Jara	2019	United States	Developed	1,377,285	Retrospective matched cohort	55.2±13.0	Men 1,294,648, women 82,637	–	–	ICD-9	8.1±4.3 yr	Cancers	7
Liu	2019	China	Developing	45	Case-control study	–	–	–	–	PSG	1 yr	Lung cancer	6
Polonis	2019	United States	Developed	161	Cohort study	Non-OSA: 35.6±11.0, OSA: 47.3±11.9	Non-OSA: men 59, women 29; OSA: men 64, women 9	Non-OSA: 26.9±5.1; OSA: 33.0±	Non-OSA: 1.0±1.3; OSA: 33.9±27.3	PSG	12.7 yr	Cancers	6
Sillah	2019	United States	Developed	1446	Case-cohort study	Case group: 57.2±10.8; subcohort: 50.4±12.9	Case group: men 173, women 131; subcohort: men 665, women 497	–	Case group: 47.0±31.1; subcohort: 41.3±34.7	PSG	1851 (IQR: 1002–2835) d	Cancers	8
Brenner	2018	Israel	Developed	5243	Retrospective cohort study	51±13.1	Men 3905, women 1338	29.7 (26.4–33.9)	18 (10–34)	PSG	5.9 yr	Cancers	7
Cabezas	2018	Spain	Developed	60	Cross-sectional study	67.8±11	Men 35, women 25	–	15.2 (6.9–29.4)	PSG	12 mo	Lung cancer	6
Campos-Rodriguez	2018	United States	Developed	83	Cross-sectional study	48.8±8.8	All women	27.4±5.4	5.1 (2–9.4)	PSG	–	Breast cancer	6
Dreher	2018	Germany	Developed	100	Cross-sectional study	68.1±8.6	Men 67, women 33	26.0±4.6	4.9 (2.0,10.4)	PSG	–	Lung cancer	6
Du	2018	China	Developing	10,388	Cross-sectional study	46.6±0.4	Men 5034, women 5354	-	–	Self-reported	–	Cancers	6
Martinez-Garcia	2018	Spain	Developed	443	Cross-sectional study	55.98±15.3	Men 224, women 219	27.3±4.5	8.6 (2.8–20.2)	PSG	–	Melanoma	6
Gozal	2016	United States	Developed	30.3 million	Cohort study	>30 yr	–	–	–	ICD-9	3 yr	Cancers	6
Lee	2016	Korea	Developed	163	Case-control study	OSA: 63.0±10.9, non-OSA: 54.9±14.5	OSA: men 32, women 79; non-OSA: men 32, women 20	OSA: 25.4±3.3, non-OSA: 24.5±3.3	–	PSG	–	Colorectal neoplasia	6
Chang	2014	China	Developing	5076	Matched case-controlled study	–	All women	–	–	ICD-9	5 yr	Breast cancer	6
Chen	2014	China	Developing	92,220	Cohort study	OSA: 37.6±8.2, control: 37.6±8.2	OSA: men 15,401, women 7654; control: men 46,202, women 22,963	–	–	PSG	10 yr	Primary central nervous system cancers	7
Kendzerska	2014	Canada	Developed	10,149	Cohort study	48 (39–58)	Men 6284, women 3865	28.9 (25.3–33.4)	–	PSG	7.8 yr	Cancers	7
Marshall	2014	Australia	Developed	393	Prospective cohort study	Non-OSA: 52.8±7.6, mild OSA: 54.7±7.3, moderate-severe OSA: 55.1±8.2	Men 290, women 103	Non-OSA: 26.2±3.7, mild OSA: 28.0±4.0, moderate-severe OSA: 34.3±7.3	–	4-channel portable home-monitoring device	20 yr	Cancers	8
Martinez-Garcia	2014	Spain	Developed	5427	Retrospective cohort study	53.9±13.1 median (IQR)	–	–	30 (14–52)	PSG	4.5 yr	Cancers	6
Campos-Rodriguez	2013	Spain	Developed	4910	Retrospective cohort study	–	–	–	–	PSG or validated respiratory polygraphy (RP)	4.5 (interquartile range, 3.4–5.2) yr	Cancers	7
Thompson	2011	United States	Developed	1240	Case-control study	Case group: 57.3±8.0; control: 54.7±8.8	Case group: men 154, women 184; control: men 293, women 605	Case group: 29.9±7.2; control: 29.2±6.8	–	PSQI	–	Colorectal adenoma	6

ICD = International classification of diseases, OSA = obstructive sleep apnea, PSG = polysomnography, PSQI = Pittsburgh sleep quality index.

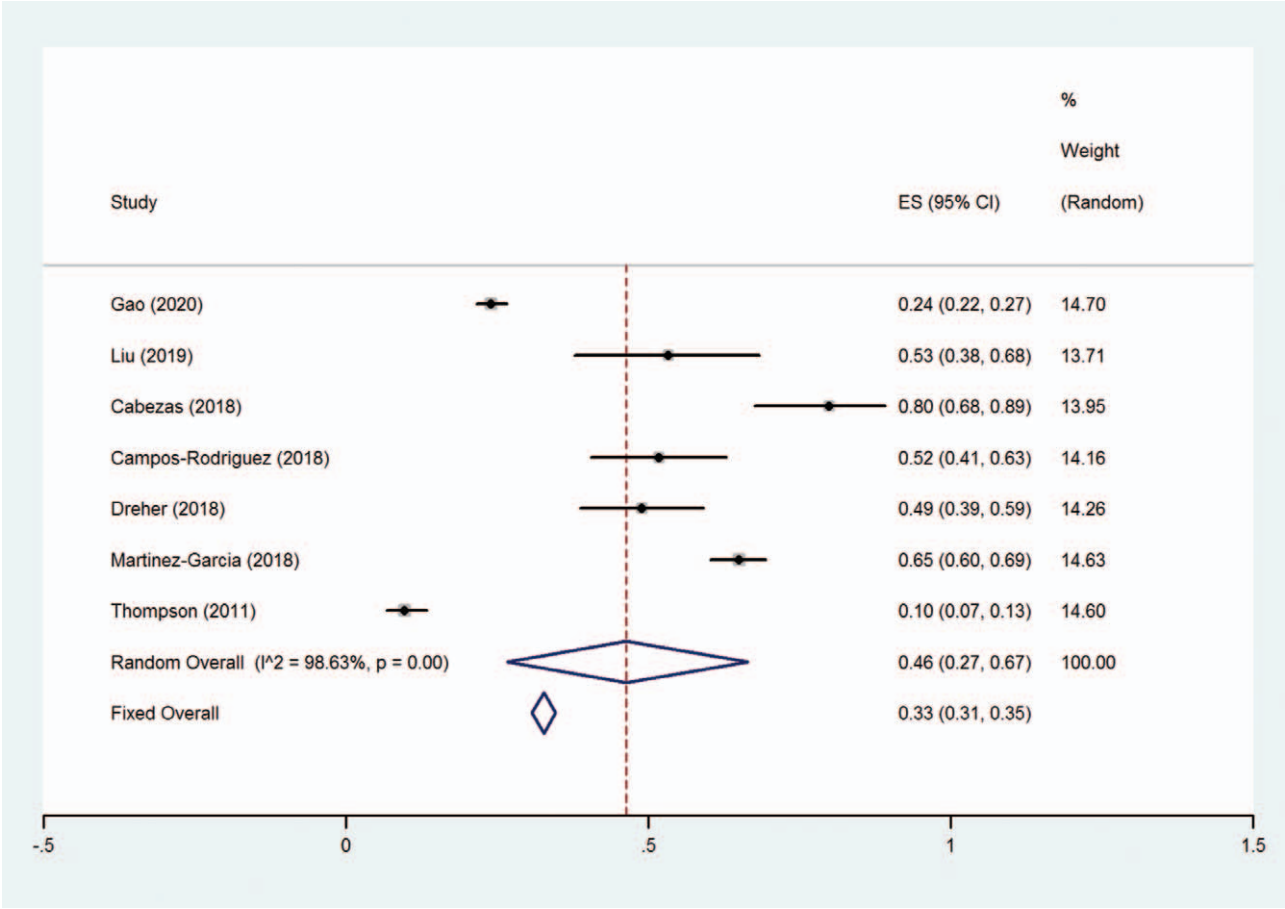

Figure 1. The overall prevalence of OSA positivity in cancer patients. OSA = obstructive sleep apnea.

epidemiologically linked to the increasing of cancer worldwide. Herein, we performed this study to further explore the overall incidence of cancer and OSA in the corresponding population, and provide some evidence on the association between the two entities. In this up-to-date meta-analysis, we found that more than half of the cancer patients also developed OSA. Additionally, OSA patients are 1.53 times more likely to suffer from cancer when compared to non-OSA patients.

Intermittent hypoxia and sleep fragmentation are highly prevalent conditions and hallmarks of sleep apnea, which have been proposed as the main causes of most of the commodities associated with OSA.[31] It has been demonstrated that intermittent hypoxia can stimulate the production of reactive oxygen species (ROS), which led to oxidative stress and systemic inflammation.[32] Increased activity of the hypoxia-inducible factor-1 (HIF-1) and reduction in antioxidant promoted by intermittent hypoxia could accelerate ROS production, thus contributing to oxidative stress.[6] Increased activity of HIF-1 also contributed to tumor growth by increasing expression of vascular endothelial growth factor (VEGF) and angiogenesis. In the meanwhile, Hakim and colleagues illustrated that sleep fragmentation can accelerate tumor growth and progression through tumor-associated macrophages recruitment and proinflammatory TLR4 signaling pathways in animal models.[33] From the perspective of tumor biology, hypoxia is a frequent phenomenon in solid tumor, and it enhanced the malignant properties in proliferation, invasion, metastasis and angiogenesis of cancer, however, the mechanisms varies from different tumors.[34] Hence, we inferred that OSA could not only increase the incidence of cancer in population, but also enhanced malignancy of cancer. Katarzyna et al investigated the association between telomere length (TL) and risk of cancer in OSA patients. In this study, the authors digged a considerable effect size of TL on the risk of cancer. Moderate-to-severe OSA individuals, who had longer telomeres on average, showed a higher risk of cancer than non-OSA individuals. On the other hand, longer telomeres kept a sustained capacity of cell proliferation to increase the possibility of attaining a critical number of genetic mutations. It speculated that the combination of OSA-mediated telomere elongation and a higher rate of genetic mutation accumulation may represent a survival advantage of precancerous cells, and thus predispose OSA patients to a higher risk of cancer.

Clinical studies did not achieve a unified consensus on the relationship between OSA and the incidence of tumors from earlier literatures.[35] The first clinical cohort investigation on OSA and cancer incidence was performed in Spanish by Campos-Rodriguez et al.[15] A total of 4910 patients from seven teaching hospitals were included and followed up for an average of 4.5 years. Percent nighttime with oxygen saturation $< 90\%$ ($Tsat_{90}$) and AHI were used to evaluate the severity of OSA. The result showed the cancer incidence in $Tsat_{90} > 12\%$ was 2.33 times higher than $Tsat_{90} < 1.2\%$ category. In stratified analyses, together with $Tsat_{90}$, AHI was associated with cancer incidence in patients younger than 65 years. In the same year, a prospective

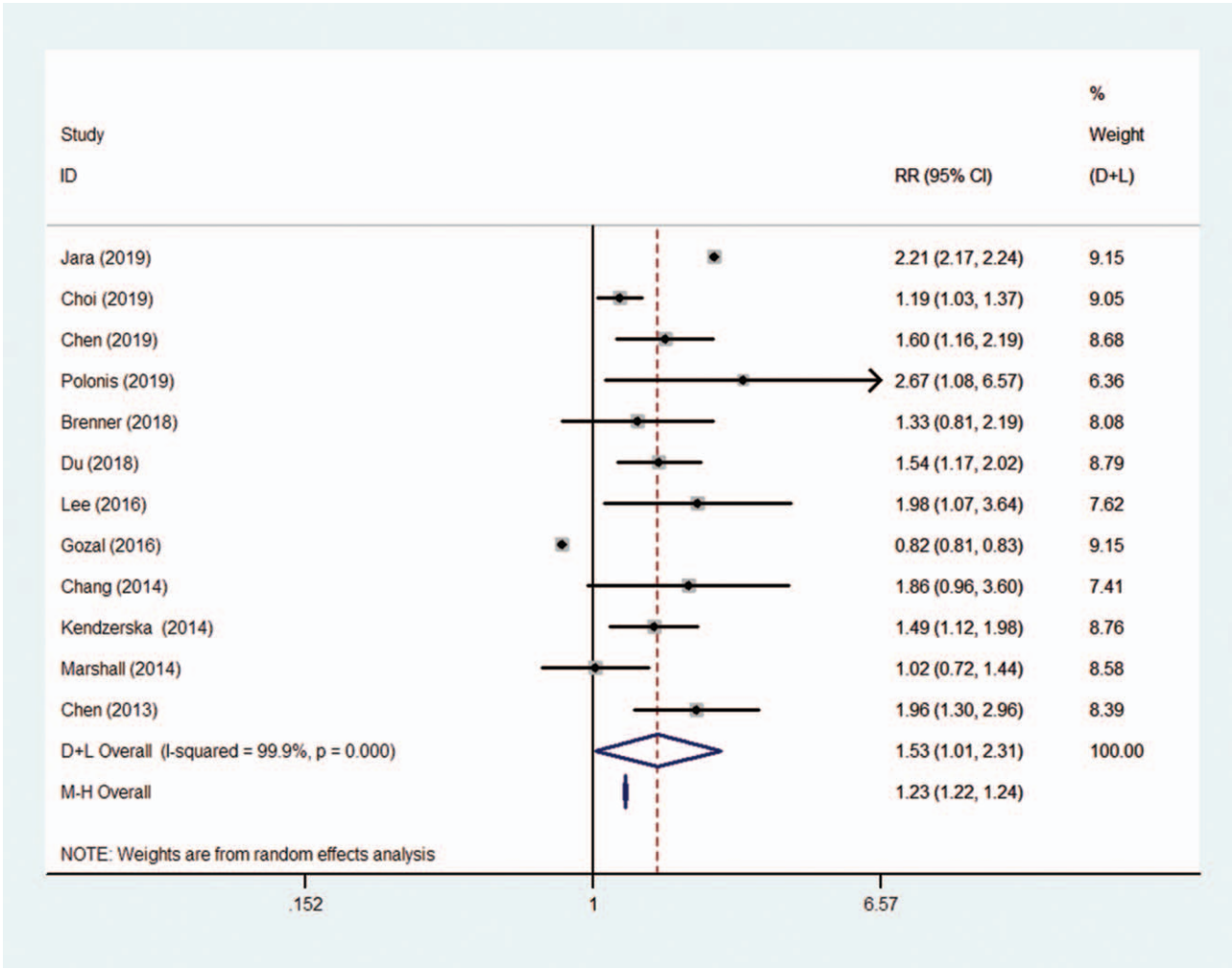

Figure 2. The overall prevalence of cancers in OSA patients vs non-OSA patients. OSA = obstructive sleep apnea.

study from Copenhagen was published by Christensen et al, however, no clear association was observed between the incidence of cancer and the presence of symptoms related to sleep-disordered breathing.[36] This negative result may be attributed to the inclusion of patients who were not diagnosed by polysomnography, but by questionnaires, which led to some non-OSA patients being calculated in this study. For further examine the higher prevalence of OSA among patients with solid tumors, a longitudinal nationwide-based cohort study base on more than 5.6 million individuals was reported. Sleep apnea appeared to increase the risk for only certain types of solid malignancies, including pancreatic and kidney cancer and melanoma, nevertheless, it did not increase the risk of colorectal, breast, and prostate cancers.[30] There was also evidence that the severity of OSA was linked to the aggressiveness of breast cancer and melanoma.[14,27] Because different tumor types have different biological behaviors, heterogeneity still existed in the current published data.

In this study, we found OSA is significantly related to the rising incidence of tumors, and subgroup analysis for severity of OSA disclosed that the incidence of cancers did not linearly increase according to the severity of OSA defined by AHI, from a group to group aspect, moderate to severe group presented a higher incidence than mild group, and severe group was higher than moderate group. Nevertheless, if we only analyzed the studies grouped by mild, moderate, and severe, mild OSA group has the lowest risk rate of 38 (95%CI, 36–41)% for cancer, moderate for 44 (95%CI, 40–48)%, severe for 49 (95%CI, 44–54)% (see Fig. S6, Supplemental Digital Content, http://links.lww.com/MD2/A922). This inconsistent may be caused by the different grouping comparison methods of the original literature. However, the high-risk cancer in OSA still not proved OSA directly participant the carcinogenesis, even growing evidences had demonstrated the pathophysiological of OSA related to immune response and biological pathways of cancers. To explore the causality of cancer and OSA, a genome-wide association study (GWAS) was reported in breast cancer to determine the causal effect of risk of OSA on breast cancer.[20] The authors conducted a two-sample study, one from real-world research, another from the Breast Cancer Association Consortium (BCAC), and provided the evidence that rs11588454 and rs11897825 were associated with increased risk of breast cancer. Then, the Mendelian randomization analyses found evidence of a detrimental causal effect of OSA on breast cancer risk was similar to the results of the real-world study. In lung cancer, OSA has also been confirmed to have a higher incidence than healthy control. In addition, the stage of

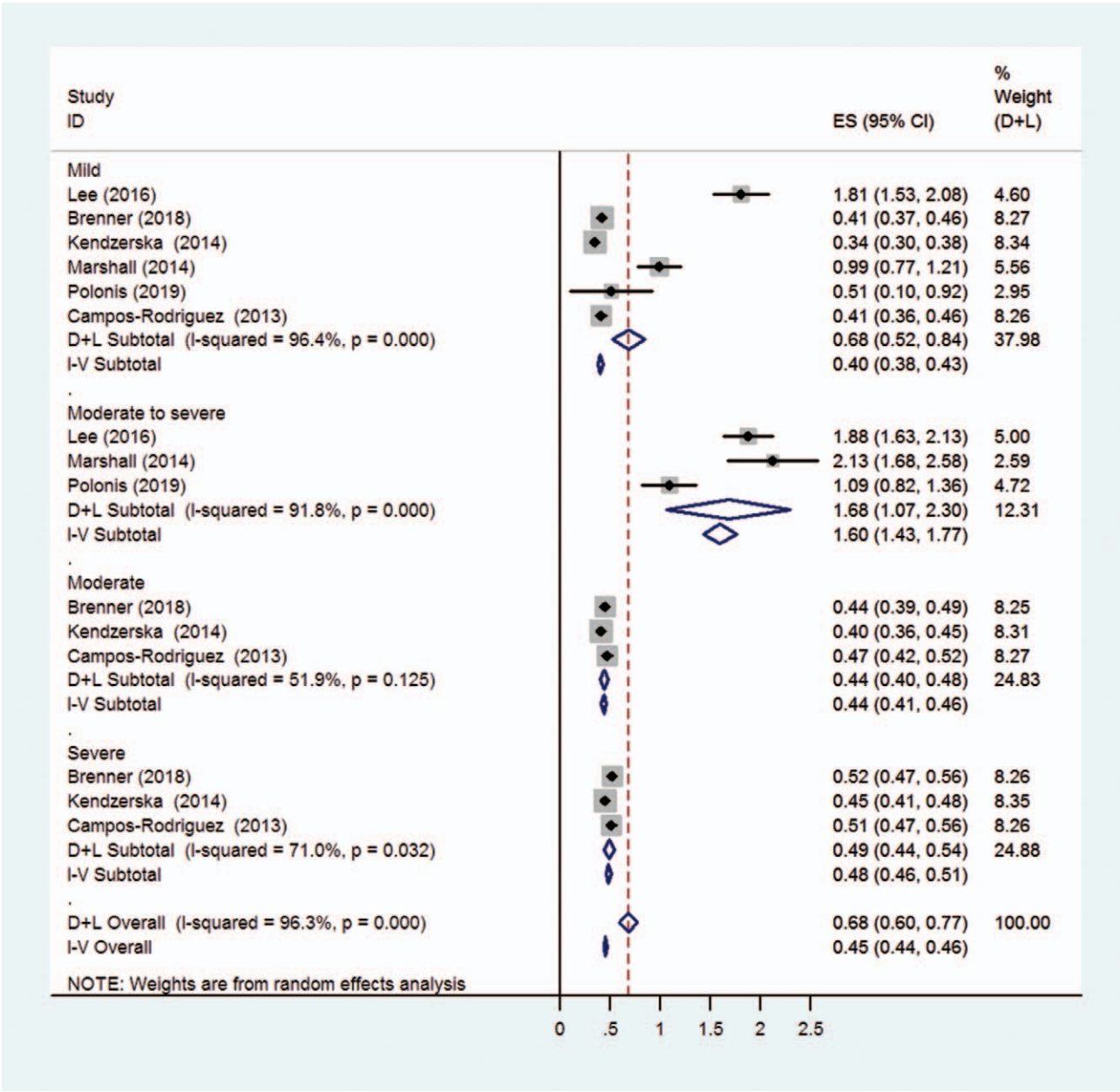

Figure 3. The cancer incidence in OSA patients subgroup by severity of OSA. OSA = obstructive sleep apnea.

lung cancer in OSA was more advanced, and the mortality, recurrence rate, and metastasis rate increased compared to healthy control in a 1-year follow-up.[24] Besides tumors located in the chest region, OSA also linked to the aggressiveness of cutaneous malignancy. By screening 443 patients who diagnosed with melanoma, 65% of OSA patients were sorted out by respiratory polygraphy, and results found intermittent nighttime oxyhemoglobin desaturation (DI4%) and AHI were independently associated with greater aggressiveness of cutaneous melanoma by detecting some clinical markers.[27]

In sensitivity analysis, we found that the two included studies had some influence on the prevalence of cancer in OSA individuals. Jara et al's study was a retrospective matched cohort study on all veterans diagnosed with OSA from October 1992 to September 2013. The result showed a nearly 2-fold higher hazard of developing any tumor in OSA compared to non-OSA individuals.[10] Such high ratio might related to certain reasons: the subjects included in the study are veterans, rather than the regular community population. As it mentioned in the original text, "the diagnosis of OSA could get disability benefits since 2004, which provided veterans with a financial incentive to receive an OSA diagnosis."[10] This may be the cause of OSA overdiagnosis in this study. A nationwide population survey based health insurance database conducted by Gozal et al identified that OSA only increased the risk of a very selective number of cancers.[21] Individuals with OSA only increased the risk of pancreatic and kidney cancer and melanoma by adjusted data. The prevalence of cancers in OSA patients reached 1.37 (95%CI, 0.91–20.7) times higher than non-OSA individuals. However, the national insurance data used in this epidemiologi-

cal survey ignored the uninsured people, who happen to be low-income and relatively poor people. These people lack primary health services and are at higher risk of cancerous diseases. Therefore, the prevalence of tumors with OSA obtained in this study was slightly lower (Supplemental Figure 4, http://links.lww.com/MD2/A920).

Some limitations still existed in this meta-analysis. Firstly, in this meta-analysis, there were still two studies diagnosed OSA by questionnaires, which will overdiagnose some healthy individuals, thus, strengthen the association between OSA and cancer. Secondly, in the studies of colorectal cancer, only Chen et al's study included malignant neoplasm. And in Lee et al's study, carcinoma in situ and intramucosal carcinoma were included for incidence statistics of colorectal neoplasia, meanwhile, Thompson et al's study screened colorectal adenoma by colonoscopy. These abnormal growths of glandular tissue in the gastrointestinal tract mentioned above could all attributed to precancerous lesions and included the two studies that might increase the incidence of cancer in this meta-analysis. Thirdly, besides some large epidemiologic studies, a part of the published studies included in our study has a small sample size, which may skew the results. Fourth, not all the studies included for calculating cancer incidence in OSA when compared to the control group were adjusted by age, gender, obesity, smoking, or alcohol intake. This inter-study heterogeneity might have some influence on our results. Lastly, publication bias existed in our study, because only published literatures in English were included.

5. Conclusion

In this study, despite these limitations, we deliberately focused on relationships between cancer and OSA, and currently available data suggested individuals with OSA were more likely to develop tumors, and the incidence was related to the severity of OSA. In the meantime, there was a high prevalence of OSA in cancer patients. Whether OSA potentially promoted the tumor malignancy, and how did it increase tumorigenesis or progression, need further studies to delineate.

Author contributions

Conceptualization: Yuan Cao, Pu Ning, Shuang Wu.
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Validation: Yuan Cao.
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Writing – original draft: Yuan Cao, Pu Ning, Qiao Li.
Writing – review & editing: Yuan Cao, Pu Ning, Qiao Li, Shuang Wu.

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