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REVIEW PAPER

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Does insomnia predict a high risk of cancer? A systematic review and meta-analysis of cohort studies

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Abstract

Recently, emerging studies on the relationship between insomnia, the most common sleep disorder, and cancer have been published, but with inconsistent results. With the development of society and the accelerated pace of life, more and more people experience insomnia. Therefore, it is important to clarify the association. Relevant literature was obtained through a search of seven databases and supplementary searches. After a strict screening, eight cohort studies (seven prospective and one retrospective) involving 578,809 participants and 7,451 cancer events were incorporated into our analysis. The results demonstrate a modest 24% overall increased risk of cancer for individuals with insomnia in comparison to those without insomnia. The sensitivity analysis shows that the correlation between the two is stable. Subgroup analyses show that the risk of developing cancer was significantly higher in studies conducted in women (HR = 1.24; 95% CI, 1.01–1.53), but not in men (HR = 1.28; 95% CI, 0.90–1.80). Similarly, in terms of specific cancer types, the pooled HR was only significantly higher in thyroid cancer (HR = 1.36; 95% CI, 1.12–1.65) and not in other types of cancer ($p > 0.05$). Our findings suggest that insomnia may serve as an early warning sign of the onset of cancer and provide an opportunity for early detection and early intervention. Our findings should be treated with caution because of the limited number of included studies and potential bias. More additional studies are warranted to provide more information on the carcinogenic effect of insomnia.

KEYWORDS

incidence of cancer, longitudinal study, quantitative analysis, sleep deprivation

1 | INTRODUCTION

The latest report issued by the World Health Organization (WHO) shows that cancer is one of the most common causes of death, with nearly 7 million deaths each year worldwide. Right now, 24.6 million people are living with cancer, and by 2020 it is projected that there will be 16 million new cancer cases and 10 million cancer deaths every year (https://www.who.int/nmh/a5816/en/). All of the above indicate that identifying cancer-related risk factors is of great significance. To date, studies have found many causes of or triggers for cancer, including hormone levels, immune factors, genetic susceptibility, environmental carcinogenic factors and lifestyle habits (Bhatelia, Singh, & Singh, 2014; Mcnamara, Moore, Hickey, Sasano, & Tilley, 2014).

Insomnia is the most common sleep disorder, characterized by a feeling of difficulty initiating sleep or maintaining sleep or having a feeling of nonrestorative sleep (Morin & Benca, 2012). Similar to cancer, insomnia is a major public health concern, affecting 10%–30% of the general population (Ayoub, Attia, El Kady, & Ashour, 2014; Morin & Benca, 2012), and has been closely related to numerous adverse health outcomes such as diabetes, obesity and heart disease (Suls, Green, & Davidson, 2016).

Insomnia not only affects the patient's physical health, normal ability to work and quality of life, but also leads to psychological and mental health problems (Zhao, Tian, & Zhang, 2011). Many previous studies have looked at insomnia after a diagnosis of cancer (Fiorentino, Rissling, Liu, & Ancoli-Israel, 2011; Garland et al., 2014; Götze, Köhler, Taubenheim, Lordick, & Mehnert, 2018; Tell, Mathews, & Janusek, 2014); however, emerging evidence suggests that insomnia prior to cancer is independently associated with the risk of cancer among initially cancer-free individuals (Chiu, Huang, Fan, & Tsai, 2018; Fang, Miao, Chen, Sithole, & Chung, 2015; Gapstur et al., 2014; Lin, Liu, Wang, Chung, & Chien, 2019; Luo, Sands, Wactawski-Wende, Song, & Margolis, 2013; Luojus, Lehto, Tolmunen, Erkkilä, & Kauhanen, 2014; Sen et al., 2017; Sigurdardottir et al., 2012; Sturgeon, Luisi, Balasubramanian, & Reeves, 2012), although contrasting results also exist (Titus-Ernstoff, Perez, Cramer, & Harlow, 2001; Vogtmann et al., 2013).

Although the mechanism of the effect of insomnia on the risk of cancer is not well understood, studies to date have shown that melatonin plays an irreplaceable role in the carcinogenic effects of insomnia (Haus & Smolensky, 2013; Jung-Hynes et al., 2011; Viswanathan & Schernhammer, 2009). In addition, the oestrogen signalling pathway (Cos et al., 2006), obesity (Marshall, Glozier, & Grunstein, 2008; Salaün, Thariat, Vignot, Merrouche, & Vignot, 2017), the dysregulation of a number of genes involved in tumour suppression (Fu & Lee, 2003), circadian rhythm disruptions, which consist of a loss of rhythmicity in neuroendocrine and immune parameters (Mazzoccoli, Tarquini, Durfort, & Francois, 2011), and disturbed daily sleep-activity cycles (Du-Quiton et al., 2010; Grutsch et al., 2011; Miaskowski et al., 2012) have all been put forward as explanations for how insomnia might influence the risk of developing cancer.

With the development of society and the accelerated pace of life, more and more people are suffering from insomnia. Examination of the association between insomnia and the development of cancer is thought provoking and the public health implications could be significant given the projected increase in the number of people suffering from insomnia and cancers in the coming years. Shift work, short sleep duration, exposure to light at night and insomnia, all potential causes of circadian disruption, have been inconsistently associated with the risk of cancer. The impact of the combined and independent effects of exposure to different sources of circadian disruption (including shift work) has been proven by previous meta-analyses (Du, Bin, Liu, & Yang, 2017; He, Anand, Ebell, Vena, & Robb, 2015; Yuan et al., 2019). However, there is no meta-analysis to prove the impact of insomnia on the risk of cancer. Accordingly, this meta-analysis was conducted, aiming to explore the association, to quantify the size of the effects and to identify vulnerable populations in order to target prevention strategies, and also to provide clues for further study.

2 | MATERIALS AND METHODS

2.1 | Identification of studies

We performed a systematic literature search of PubMed, the Cochrane Library, the Web of Science, CBM (Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), the VIP (Chinese) Database and Wanfang (Chinese) through to January 18, 2019. A systematic search string was developed as follows: (insomnia OR sleep disorder* OR SD) and (cancer OR tumor OR tumour OR neoplasm OR carcinoma). Bibliographies of retrieved articles were also screened for relevant studies that were not captured in the initial online search. We have also searched unpublished data, including conference materials, abstracts, theses and dissertations, using the Google search engine. The search was limited to studies on humans, published in both English and Chinese. The study screening process is shown in Figure 1.

2.2 | Inclusion and exclusion criteria

A study was identified as eligible and incorporated into our analyses if it met the following criteria: (a) it focused on the association between insomnia and susceptibility to cancer; (b) it was an observational study (a cohort study or a case–control study); (c) it was in the English or Chinese language; and (d) hazard ratio (HR) and corresponding 95% confidence intervals (CIs) could be extracted directly (or allow recalculation). Studies were excluded if they only examined broader sleep disorders, sleep duration or sleep quality but did not specifically consider insomnia, were reviews or commentaries, were animal based, or were intervention studies.

Two investigators independently processed the data from each eligible study prior to conducting the meta-analysis.

2.3 | Data extraction and quality assessment

Data extraction was performed according to a predesigned data extraction form. Information was collected on: the first author and year of publication; the region where the study was performed; the study design; the follow-up period; the sample and the number of cancers; cancer types; age of the participants; diagnostic criteria of insomnia/cancer; controlling factors; adjusted point estimates with 95% CIs; and information required for quality assessment (Table 1). Quality evaluation was performed by using the appropriated Newcastle–Ottawa Scale (NOS). Scores of 0–3, 4–6 and 7–9 were rated as low, moderate and high quality, respectively.

The extraction of the data and quality assessment were carried out independently by two reviewers (TS and MM), and were judged by the third reviewer (ML) when there were discrepancies.

2.4 | Statistical analysis

For studies presenting data on the same cohort with a different follow-up, only the longer one was incorporated. When reporting both the crude and the adjusted HR values, only the adjusted values with corresponding 95% CI were included. When original studies presented multiple adjusted estimates for the same outcome, the estimates that had been adjusted for the largest number of confounders was used. Heterogeneity among included studies was

investigated using the I^2 statistics and Q test, and low statistical heterogeneity was defined as $I^2 \leq 50\%$ and $p > 0.1$, respectively. The existence of significant heterogeneity necessitated the use of a random-effects model when the test performance was summarized; otherwise, a fixed-effects model was used (Higgins, Thompson, Deeks, & Altman, 2003). We pooled the HRs to summarize associations between insomnia and incidence of cancer. To explore the sources of heterogeneity, subgroup analyses were performed according to sex, national income level, study region, study design (prospective or retrospective), NOS scores, sample size, follow-up years and cancer type. We identified the national income levels by using the World Bank classification of low-, middle- and high-national income levels (World Bank, 2017). We tested the stability of our results by examining the effect of excluding each study. Funnel plot asymmetry and Egger regression tests were all used to explore the publication bias. All statistical analyses were performed using Stata version 14.0 (Stata, version 14; Stata Corp, College Station, TX, USA). The difference was considered statistically significant when $p < 0.05$.

3 | RESULTS

3.1 | Study selection and characteristics of eligible studies

The search was performed until January 2019. After an initial systematic search and supplementary search, a total of 52,408 individual publications were identified. After the removal of duplication and screening of titles, abstracts and full text, 11 (eight cohort studies and three case–control studies) of the publications remained (Figure 1). Characteristics of eligible studies on the association between insomnia and cancer risks were summarized in Table 1. However, considering the bidirectional relationship between insomnia and cancer, and that a case–control study is considered to be a retrospective study, it is possible that the cancer itself or treatment may adversely impact sleep status. Data from cancer populations report that 25%–69% have difficulty sleeping, with 18%–29% reporting insomnia disorder (Garland et al., 2014; Palesh et al., 2010). About 30% of long-term survivors report continued insomnia after cancer treatment (Miller et al., 2016). Therefore, case–control studies on this topic are not as

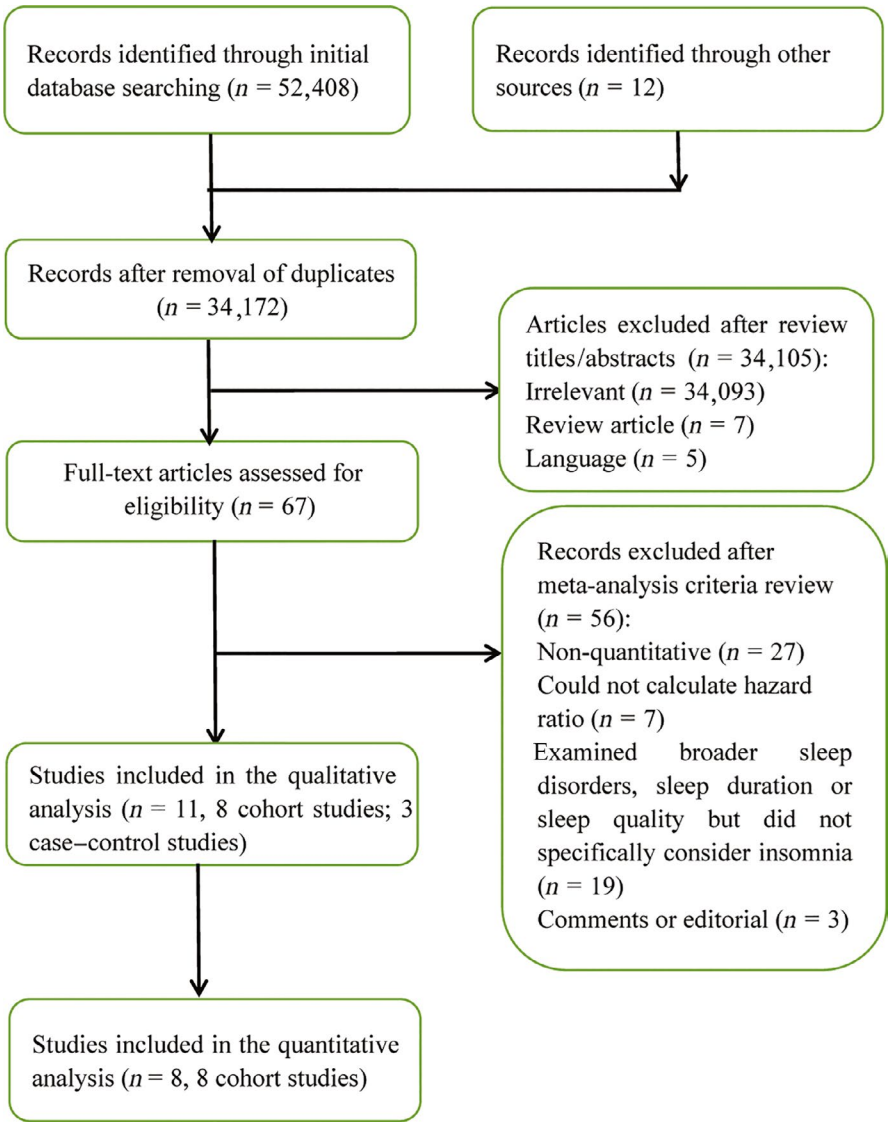

FIGURE 1 Flow diagram of the study search and selection process

TABLE 1 Characteristics of eligible studies included in this meta-analysis on insomnia and cancer risk

References	Region	Design	Follow-up (years)	Sample (*N*/cases)	Cancer type	Age (years)	Sex
Sturgeon et al. (2012)	USA	Pros.cohort	7.5	48,725/452	Endom-etrial cancer	50–79	F
Vogtmann et al. (2013)	USA	Pros.cohort	10.8	110,011/5,149	Breast cancer	50–79	F
Luojus et al. (2014)	Finland	Pros.cohort	23	2,586/81	Lung cancer	42–60	M
Luo et al. (2013)	USA	Pros.cohort	11	142,933/295	Thyroid cancer	50–79	F
Chiu et al. (2018)	Taiwan of China	Retros.cohort	13	33,063/NA	Breast cancer	≧20	F
Sen et al. (2017)	Sweden	Pros.cohort	14.7	33,332/862	Breast cancer	≧20	F
Gapstur et al. (2014)	USA	Pros.cohort	23	305,057/4,774	Fatal prostate cancer	53	M
Sigurdardottir et al. (2012)	USA	Pros.cohort	9	2,102/135	Prostate cancer	NA	M
Fang et al. (2015)	Taiwan of China	Case-control	/	205,266/68,422	All cancers	All	Both
Titus-Ernstoff et al. (2001)	Lebanon	Case-control	/	1,086/120	Ovarian cancer	All	F
Lin et al. (2019)	Taiwan of China	Case-control	/	36,775/7,355	Colorectal cancer	All	Both

Abbreviations: (*N*/cases), sample size of cohort and the number of cancers; Pros.cohort, prospective cohort study; Retros.cohort, retrospective study; NA, not available; BMI, body mass index; ICD, International Classification of Diseases; WHI, the Women's Health Initiative; NSAID, non-steroidal anti-inflammatory drugs; F, females; M, males; Both, both females and males.

good as cohort studies due to potential reverse causality. We think it would be a cleaner analysis if the three case–control studies were removed from our final meta-analysis. A detailed flow diagram of literature retrieval and selection is shown in Figure 1.

Finally, eight individual cohort studies (seven prospective studies and one retrospective study) published from 2012 to 2018 were included. From these, a total of 578,809 participants and 7,451 cancer events were investigated. Among the eight included studies, one prospective cohort study was published in the abstract form, but it provided most of the information we wanted. Based on the principle of a comprehensive search, we included it in this meta-analysis. Among the included studies, five were conducted in the USA and one each in Finland, Taiwan of China and Sweden. Five were conducted in women and three were conducted in men. The follow-up duration ranged from 7.5 to 23 years (two with a follow-up period of <10 years and six with a follow-up period of ≧10 years). Focused outcomes included breast cancer (*n* = 3), prostate cancer (*n* = 2), endometrial cancer (*n* = 1), lung cancer (*n* = 1) and thyroid cancer (*n* = 1). All included studies were classified either as moderate (*n* = 2) or as high quality (*n* = 6). The details are listed in Table 1.

3.2 | Results of the meta-analysis

3.2.1 | Overall estimates and sensitivity analysis

The overall pooled results are presented in Figure 2. The meta-analysis result from the random-effect model indicated a 24% (HR = 1.24; 95% CI, 1.06–1.45) increase in the risk of cancer in people suffering from insomnia compared to those who did not. There was no substantial change in the sensitivity analysis results, which proved that

Diagnostic criteria for insomnia	Diagnostic criteria for cancer	Controlling factors	NOS scores
Self-reported insomnia symptoms	Questionnaire, confirmed by local physician using pathology reports and additional medical records	Age, race, BMI, smoking, number of live births, physical activity, unopposed oestrogen use, oral contraceptive use, family history of endometrial cancer	7
The WHI insomnia rating scale	Confirmed by trained physician	Age, clinical trial arm assignment, number of live births, age at menarche, age at menopause, BMI, energy expenditure, education, income, race/ethnicity, marital status, age at first birth, previous use of hormone replacement therapy, history of benign breast disease, family history of breast cancer, alcohol consumption, smoking status	8
Self-administered questionnaires	ICD: 8, 9, 10	Age, examination years, cumulative smoking history, family cancer history, Human Population Laboratory Depression Scale scores, asthma and chronic bronchitis	6
Self-administered questionnaires	Questionnaire, confirmed by medical record review	Adjusted for age at enrolment, ethnicity, educational level, smoking, BMI, recreational physical activity, alcohol intake, family history of cancer, previous thyroid disease, history of hormone therapy use, depression score and different treatment assignments for Women's Health Initiative clinical trials	8
ICD-9-CM	ICD-9-CM	Age, DM, polycystic ovaries, thyroid cancer, autoimmune diseases, hormone replacement therapy, aspirin use, NSAID use and angiotensin-converting enzyme inhibitor use	7
Self-administered questionnaires, confirmed by clinical examination	ICD-7: code170	Age, physical activity, education, smoking, BMI, alcohol intake, parity, age at first birth, depression and anxiety scores	7
Self-administered questionnaire	Self-administered questionnaire	Age, race, education, BMI, smoking status, family history of prostate cancer and painful/frequent urination	8
Self-administered questionnaire	Confirmed by medical record review	NA	5
ICD-9-CM:codes 307.40, 307.42, 307.4307.49, 780.52	ICD-9-CM: codes 140–208	Age, gender, income, region, area and Charlson Comorbidity Index	7
In-person interviews	In-person interviews, pathologist	Age, state and parity	7
ICD-9-CM: 780.52	ICD-9-CM: 153–154	Age, gender, T2DM, hypertension, depression, stroke, dementia, CKD, urbanization level	8

the correlation between insomnia and cancer was relatively stable. The results are shown in Table 2. Excluding either one of the two studies with the longest follow-up period, did not lead to any substantial changes in the overall results (HR = 1.29; 95% CI, 1.06–1.57; HR = 1.25; 95% CI, 1.05–1.48); a similar observation was noted upon excluding the shortest follow-up (HR = 1.27; 95% CI, 1.06–1.53). The summary estimates were 1.20 (95% CI, 1.02–1.42) after omission of the study with the largest sample size, which was also the only retrospective cohort study included. A similar result was also derived after exclusion of the study with the smallest sample size (HR = 1.19; 95% CI, 1.02–1.38). Removal of the study conducted in Sweden also did not substantially change the results (HR = 1.20; 95% CI, 1.03–1.40). Removal of the study performed by Vogtmann et al. also did not substantially change the results (HR = 1.30; 95% CI, 1.11–1.51) and the association remained positive.

3.2.2 | Subgroup analyses

A number of prespecified subgroup analyses were performed, including the region where the study was conducted, the study design, NOS scores, follow-up years, sample size and cancer types (Table 3). However, because all included studies were conducted in high-income regions, the corresponding analysis was not achieved. Subgroup analysis showed that the HR for cancer incidence was 1.20 (95% CI, 1.02–1.42) for prospective studies and 1.43 (95% CI, 1.11–1.85) for retrospective studies. The HR for cancers was statistically significant higher in the studies conducted in women (HR = 1.24; 95% CI, 1.01–1.53), but was not statistically significant in men (HR = 1.28; 95% CI, 0.90–1.80). In terms of follow-up duration, six studies that followed study participants for ≧10 years indicated a significant impact of insomnia on the risk of developing

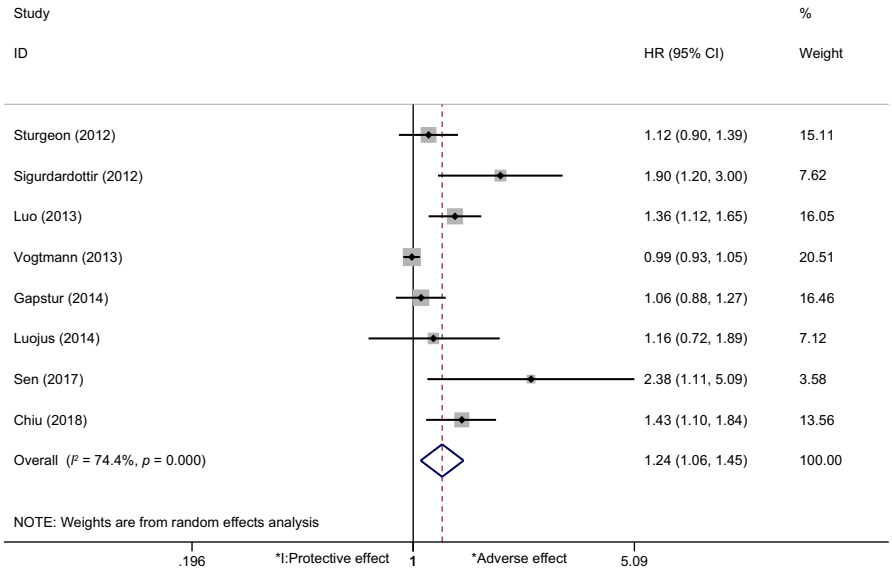

FIGURE 2 Meta-analysis of insomnia and incidence of cancer. HR. hazard ratio

TABLE 2 Results of sensitivity analyses

	Heterogeneity		Meta-analysis		
Study omitted	I^2 (%)	*p*	**HR**	**95% CI**	*p*
Sturgeon et al. (2012)	77.8	0.000	1.272	1.056–1.534	0.012
Vogtmann et al. (2013)	49.6	0.064	1.295	1.110–1.510	0.001
Luojus et al. (2014)	77.9	0.000	1.248	1.054–1.477	0.010
Luo et al. (2013)	70.4	0.002	1.210	1.024–1.431	0.025
Chiu et al. (2018)	72.4	0.001	1.204	1.023–1.418	0.026
Sen et al. (2017)	73.9	0.001	1.203	1.033–1.400	0.017
Gapstur et al. (2014)	78.1	0.000	1.294	1.064–1.573	0.010
Sigurdardottir et al. (2012)	71.3	0.002	1.186	1.186–1.377	0.026

Abbreviation: HR, hazard ratio.

cancer (HR = 1.21; 95% CI, 1.01–1.45); in the two studies with follow-up periods of <10 years, the association of insomnia and incidence of cancer was not statistically significant (HR = 1.40; 95% CI, 0.84–2.34). The impact of sample size on the final results was investigated by stratifying analyses according to sample size <10,000 and sample size ≧10,000, and statistically significant higher risk only limited in larger sample size (sample size ≧10,000: HR = 1.19; 95% CI, 1.02–1.40; sample size <10,000: HR = 1.49; 95% CI, 0.92–2.42). Based on NOS scores, the results were different when confined to different subgroups (moderate quality: HR = 1.49; 95% CI, 0.92–2.42; high quality: HR = 1.19; 95% CI, 1.02–1.40). These results suggested that the study design, follow-up period, sample size and study quality might have an effect on study outcomes. Based on study region, the association was not statistically significant in USA studies (HR = 1.17; 95% CI, 0.99–1.38), whereas in other regions it remained significant (HR = 1.44; 95% CI, 1.10–1.88). Subgroup analysis based on specific cancer type showed that the association only remain significant in thyroid cancer (HR = 1.36; 95% CI, 1.12–1.65).

3.2.3 | Publication bias

Publication bias was suspected by visual inspection of the funnel plot and Egger's test (p = 0.005). However, no publication bias was suspected when three case–control studies were included in the meta-analysis (the pooled estimates: HR = 1.27; 95% CI, 1.05–1.55; Egger's test: p = 0.361).

4 | DISCUSSION

Regarding the relationship between insomnia and cancer, the currently available epidemiological studies have not yet reached a consistent conclusion. Four of the eight included studies (Gapstur et al., 2014; Luojus et al., 2014; Sturgeon et al., 2012; Vogtmann et al., 2013) detected no relationship between insomnia and the risk of cancer. In contrast, Sigurdardottir et al. (2012), Luo et al. (2013), Sen et al. (2017) and Chiu et al. (2018) observed a higher risk of cancer among study participants who suffered from insomnia. The results of

TABLE 3 Results of subgroup analyses

Subgroups	N	RR (95% CI)	Z	p	Heterogeneity	
					I^2 (%)	P
Study population						
USA	5	1.168 (0.989–1.449)	1.83	0.067	76.5	0.002
Other country	3	1.437 (1.099–1.878)	2.65	0.008	18.1	0.295
Combined	8	1.237 (1.056–1.449)	2.64	0.008	74.4	0.000
Sex						
Female	5	1.243 (1.009–1.531)	2.05	0.040	80.7	0.000
Male	3	1.275 (0.901–1.802)	1.37	0.170	62.8	0.068
Combined	8	1.237 (1.056–1.449)	2.64	0.008	74.4	0.000
Study design						
Prospective	7	1.204 (1.023–1.418)	2.23	0.026	72.4	0.001
Retrospective	1	1.430 (1.106–1.849)	2.73	0.006	NA	NA
Combined	8	1.237 (1.056–1.449)	2.64	0.008	74.4	0.000
Follow–up duration						
<10 years	2	1.401 (0.840–2.338)	1.29	0.196	76.0	0.041
≧10 years	6	1.209 (1.011–1.447)	2.08	0.038	75.7	0.001
Combined	8	1.237 (1.056–1.449)	2.64	0.008	74.4	0.000
NOS scores						
Moderate	2	1.494 (0.921–2.422)	1.63	0.104	52.7	0.146
High	6	1.191 (1.015–1.399)	2.14	0.033	75.9	0.001
Combined	8	1.237 (1.056–1.449)	2.64	0.008	74.4	0.000
Sample size						
<10,000	2	1.494 (0.921–2.422)	1.63	0.104	52.7	0.146
≧10,000	6	1.191 (1.015–1.399)	2.14	0.033	75.9	0.001
Combined	8	1.237 (1.056–1.449)	2.64	0.008	74.4	0.000
Cancer type						
Endometrial cancer	1	1.120 (0.901–1.392)	1.02	0.307	NA	NA
Breast cancer	3	1.316 (0.895–1.933)	1.40	0.163	83.7	0.002
Lung cancer	1	1.160 (0.716–1.879)	0.60	0.547	NA	NA
Thyroid cancer	1	1.360 (1.120–1.651)	3.11	0.002	NA	NA
Prostate cancer	2	1.364 (0.774–2.405)	1.07	0.282	81.4	0.020
Combined	8	1.237 (1.056–1.449)	2.64	0.008	74.4	0.000

Abbreviations: *N*, the number of studies; NA, not available; RR, risk ratio.

the three case–control studies retrieved were also inconsistent. Two studies showed a positive correlation between insomnia and cancer (Fang et al., 2015; Lin et al., 2019), whereas the other one indicated a negative correlation (Titus-Ernstoff et al., 2001). Therefore, it is necessary to conduct a meta-analysis on this topic to clarify the association and to quantify the size of these effects as well. To the best of our knowledge, this article is the first systematic review and meta-analysis to summarize the relationship between insomnia and cancer. Our analyses of available epidemiological evidence indicated a 1.24-fold increase in the risk of cancer. Sensitivity analyses proved the stability of our study. Results of subgroup analyses suggested that the sex, study design, follow-up period, sample size and study quality might have an effect on study outcomes. In addition, the results of subgroup analysis also showed that there was a difference among different study populations and different cancer types. It should be underlined that six of the eight cohort studies (Chiu et al., 2018; Gapstur et al., 2014; Luo et al., 2013; Luojus et al., 2014; Sen et al., 2017; Vogtmann et al., 2013) followed study participants for >10 years and indicated a significant impact of insomnia on the risk of developing cancer (HR = 1.21; 95% CI, 1.01–1.45), whereas in the two studies (Sigurdardottir et al., 2012; Sturgeon et al., 2012) with a follow-up period of <10 years, the association was not statistically significant (HR = 1.40; 95% CI, 0.84–2.34). This is indicative of a temporal relation between insomnia and cancer because of Hill's criteria (Hill, 1965). We speculate that the reason may be that most cancers have a latent period of a few years or even decades (Friberg

& Mattson, 1997; Spratt, Meyer, & Spratt, 1996). Cancer itself or treatment can adversely impact sleep status (Garland et al., 2014; Miller et al., 2016; Palesh et al., 2010). Therefore, the short follow-up duration may not be sufficient and lead to reverse causation.

Several biologically plausible pathways have been put forward to explain how insomnia might influence the risk of developing cancer. First, studies have shown that melatonin plays an irreplaceable role in the carcinogenic effects of insomnia. Melatonin is produced by the pineal gland in a circadian pattern. Some studies have pointed out (Viswanathan & Schernhammer, 2009) that melatonin has the potential to reduce the risk of cancer through antimitotic, apoptotic, immune, antiangiogenic and anti-cell proliferation (Jung-Hynes et al., 2011) mechanisms. Evidence indicated that melatonin also appears to have anti-oestrogenic properties and the ability to suppress local oestrogen production by modulating aromatase activity (Viswanathan & Schernhammer, 2009). Our subgroup analysis also shows that women with insomnia were more vulnerable to cancers. Second, recent evidence has indicated that nocturnal awakenings coupled with exposure to artificial light at night (ALAN) may result in circadian clock gene dysregulation, which can alter cancer biology and lead to the development of cancer. For example, clock gene defects in the epithelium may trigger incorrect cell division, increase susceptibility to cancer and lead to more aggressive tumours (Blakeman, Williams, Meng, & Streuli, 2016; Savvidis & Koutsilieris, 2012). Third, studies also have shown that insomnia can lead to alterations in levels of appetite-regulating hormones, such as leptin and ghrelin, that lead to increased appetite and subsequently obesity, which is a risk factor for several cancers (Kitahara et al., 2011). In addition, several other common biological mechanisms also have been used to explain how insomnia can influence the development of cancer in general, including impaired immune function (Bovbjerg, 2003) and inflammation (Guarino, Castellone, Avilla, & Melillo, 2010). Specific cancer types may also have specific biological mechanisms. For example, insomnia may increase the risk of thyroid cancer by increasing thyroid-stimulating hormone levels (Gary et al., 1996).

Many effective treatment methods have been proposed for insomnia. At present, the commonly used treatment is oral benzodiazepines. There is a mounting body of evidence advocating the use of cognitive behavioural therapy (CBT-I) as a first-line treatment for insomnia (Qaseem, Kansagara, Forciea, Cooke, & Denberg, 2016; Riemann et al., 2017); it has been proved that this can not only significantly improve the quality of sleep but also help patients with chronic insomnia reduce the use of hypnotics (Wei et al., 2017). In addition, the clinical effect of acupuncture on insomnia is significant and deserves further clinical research and application (Chen, 2018; Garland et al., 2018). Previous studies also found that exercise can improve subjective sleep quality in patients with insomnia disorders and symptoms of insomnia (Lowe et al., 2019). From the perspective of the mechanism of the association of insomnia with cancer, melatonin suppression (Marshall, Glozier, & Grunstein, 2008; Zhong et al., 2019) and the oestrogen-signalling pathway (Cos et al., 2006) may also identify opportunities for chemo-prevention of some types of cancer. From the public health point of view, effective implementation of such measures has critical public health implications and should capture public health workers' attention. There may be specific biological mechanisms for specific cancer types. For example, insomnia may lead to thyroid cancer via an elevated thyroid-stimulating hormone level (Haymart et al., 2008; Meinhold et al., 2010).

There are several limitations that should be mentioned. First, our findings should be treated with caution because of the limited number of included studies and potential bias. Second, the studies we included were not specific to a particular type of cancer, which could lead to bias and higher heterogeneity. Third, insomnia assessment methods were heterogeneous in previous large epidemiological studies, and most studies identify insomnia through self-reported data or self-administrated questionnaire. Therefore, participants may have been misclassified on the primary exposure of interest and thus the risk of cancer associated with insomnia underestimated, which may add to the multiple conceptual problems concerned with the definition of insomnia, which could increase the heterogeneity in our meta-analysis. Fourth, the controlling factors are varied across the included studies. Although a majority of studies adjusted for some major confounding factors (e.g., age, sex, BMI, race, family history of cancer and smoking status), a limited number of studies adjusted for alcohol status, hormone replacement therapy, the use of hypnotics and socioeconomic status. These factors all have been shown to increase the risk of cancer in individuals and are substantial confounders and caution should be exercised when exploring a relationship between insomnia and cancer. However, among eight included studies, only three have been adjusted for alcohol intake status, one was conducted in premenopausal women (Chiu et al., 2018) and three were in postmenopausal women (Luo et al., 2013; Sturgeon et al., 2012; Vogtmann et al., 2013), and only one study considered the impact of hypnotic use on the association between insomnia and cancer (Chiu et al., 2018). Because of the lack of raw data, corresponding subgroup analyses cannot be achieved, but all these provide clues for further study on this association. Furthermore, socioeconomic status is also an important potential confounding factor; studies show that the prevalence of cancer is higher in low- and moderate-income regions (O'Connor, Sedghi, Dhodapkar, Kane, & Gross, 2018), but only one of the included studies adjusted for income. Our pooled HR may underestimate the true risk because all the studies included in this meta-analysis were carried out in high-income countries. This provides us with the idea of controlling potential confounding factors in our future research. Last but not least, moderate heterogeneity was observed in our study.

Despite the above-mentioned limitations, there are also some strengths of our study. First, all included studies were cohort studies (seven prospective and one retrospective), which minimized the selection and recall bias. Six of them followed the participants for more than 10 years. A sufficiently long follow-up is necessary because most cancers have a latent period of a few years or even decades (Friberg & Mattson, 1997; Spratt et al., 1996). Second, the included studies were of either moderate or high quality, which could make our research results more authentic. Third, all included studies were

conducted in patients aged <80 years, which could reduce confounding due to the effects of ageing (Zhong et al., 2019).

5 | CONCLUSION

In summary, our pooled results of currently available cohort studies demonstrated that insomnia is prospectively associated with a modest increase in the risk of developing cancer. From the public health perspective, if confirmed in future studies, the association between insomnia and cancer may open new avenues for prevention. Of course, we should admit that our study only indicates the possibility of a link between insomnia and cancer; the findings should also be treated with caution because of the limited number of included studies and potential bias. Additional well-designed large-scale longitudinal studies targeting heterogeneous cancer sites and people with different pathophysiological characteristics are warranted to better assess the association between insomnia and cancer.

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CONFLICTS OF INTEREST

All the authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

TS was responsible for the conception and design, analysis of the data, and writing the manuscript. TS and MM conducted the primary literature searches, quality assessment and data extraction for meta-analysis. All the authors took part in the interpretation of data and language modification.

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