RESEARCH ARTICLE

Sleep Duration and Cancer Risk: a Systematic Review and Meta-analysis of Prospective Studies

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Abstract

To assess the risk of cancers associated with sleep duration using meta-analysis of published cohort studies, we performed a comprehensive search using PubMed, Embase and Web of Science through October 2013. We combined hazard ratios (HRs) from individual studies using meta-analysis approaches. A random effect dose-response analysis was used to evaluate the relationship between sleep duration and cancer risk. Subgroup analyses and sensitivity analyses were also performed. Publication bias was evaluated using Funnel plots and Begg's test. A total of 13 cohorts from 12 studies were included in this meta-analysis, which included 723, 337 participants with 15, 156 reported cancer outcomes during a follow-up period ranging from 7.5 to 22 years. The pooled adjusted HRs were 1.06 (95% CI: 0.92, 1.23; *P* for heterogeneity =0.003) for short sleep duration, 0.91 (95% CI: 0.78, 1.07; *P* for heterogeneity <0.0001) for long sleep duration. In subgroup analyses stratified by cancer type, long duration of sleep showed an inverse relation with hormone-related cancer (HR=0.79; 95% CI: 0.65, 0.97; *P* for heterogeneity =0.009) and a greater risk of colorectal cancer (HR=1.29; 95% CI: 1.09, 1.52; *P* for heterogeneity =0.346). Further meta-analysis on dose-response relationships showed that the relative risks of cancer were 1.00 (95% CI: 0.99, 1.01; *P* for linear trend=0.9151) for one hour of sleep increment per day, and 1.00 (95% CI: 0.98, 1.01; *P* for linear trend=0.7749) for one hour of sleep increment per night. No significant dose-response relationship between sleep duration and cancer was found on non-linearity testing (*P*=0.5053). Our meta-analysis suggests a positive association between long sleep duration and colorectal cancer, and an inverse association with incidence of hormone related cancers like those in the breast. Studies with larger sample size, longer follow-up times, more cancer types and detailed measure of sleep duration are warranted to confirm these results.

Keywords: Sleep duration - cancer risk - meta-analysis - hormone-related cancers

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Introduction

Interestingly, studies have shown that both short sleep duration, defined as sleeping ≤6 h per night, and long sleep duration, defined as sleeping ≥9 h, may be associated with many health outcomes, including total mortality (Gallicchio et al., 2009; Cappuccio et al., 2010b), cardiovascular disease (Ferrie et al., 2007; Meisinger et al., 2007; Ikehara et al., 2009; Stone et al., 2009), type 2 diabetes (Cappuccio et al., 2010a), hypertension (Guo et al., 2013), obesity (Cappuccio et al., 2008; Stranges et al., 2008a) and poor self-rated health (Steptoe et al., 2006), as well as cancers (Yang et al., 2013). Two studies reported a U-shaped association between sleep duration and cancer risk (Jiao et al., 2013; Zhang et al., 2013); whereas other studies did not reveal such an association (Kakizaki et al., 2008b; von Ruesten et al., 2012), or only found a null association (Verkasalo et al., 2005; McElroy et al., 2006; Pinheiro et al., 2006; Sturgeon et al., 2012; Luo et al., 2013). The mechanisms underlying the association between short or long sleep duration and cancer risk are not fully understood. Two potential biological mechanisms have been proposed to explain how short sleep duration directly influenced cancer incidence, including impaired immune function and metabolic pathways related to obesity (Knutson et al., 2007; Marshall et al., 2008). Moreover, the altered melatonin secretion has also been shown as a potential risk factor of cancer (Stevens et al., 2007; Benke et al., 2013). Melatonin is synthesized and secreted by the pineal gland, and could be regulated by the information of light/dark environment (Cutando et al., 2011), rather than by sleep per se. The concentration of

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melatonin is controlled by an endogenous circadian timing system and suppressed by light (Zeitzer et al., 2000). Usually, sleep has been viewed as a maker for "exposure to darkness", therefore may act as regulator of melatonin concentration, consequently, as a potential impact factor of cancer risk. To address this issue, we performed a meta-analysis to assess the relationship between short or long duration of sleep and cancers risk. The meta-analysis included prospective cohort studies with large sample size and long duration of follow-up, which ensured the higher statistical power compared to each individual study.

Materials and Methods

Literature Search

We developed a comprehensive search strategy to identify studies that reported the longitudinal association between duration of sleep and cancers risk. We searched the electronic databases PubMed, Embase and ISI Web of Science using the terms "sleep", "cancer", "tumor", "carcinoma", and "neoplasms". Furthermore, we reviewed reference lists of original and review articles to search for additional studies. Only those that were published as peer-reviewed study were considered. No language restriction was applied.

Inclusion and Exclusion Criteria

For inclusion, studies had to meet the following criteria: (1) original article, (2) prospective cohort design, (3) assessment of duration of sleep as baseline exposure, (4) cancer recorded prospectively as outcome, (5) follow-up of at least 3 years, (6) adult population, (7) based on the same cohort but reported different cancers. If publications were duplicated, we only included the one with the most detailed and latest information for both exposure and outcome. Studies were excluded if they: (1) had a case-control study or cross-sectional design, (2) were review articles or meeting abstracts, or (3) were not conducted in humans.

Data Extraction

The eligibility of each full-text article was assessed independently in a standardized manner by two investigators, and differences were resolved by discussion and consensus. Information extracted included first author's surname, publication year, country, recruitment year, study design, number of participants, number of cases, sample characteristics (e.g., gender, age), duration of follow up, method of sleep data collection, reference category of sleep, category for "short" and "long" sleep, cancer type, RRs or HRs that reflected the greatest degree of adjustment for potentially confounding variables by both short and long sleep duration, corresponding 95% CI, and covariates adjusted in the statistical analysis.

For every study, the median or mean sleep duration for each category was assigned to each corresponding relative risk. When the median or mean sleep duration per category was not reported in the article, we assigned the midpoint of the upper and lower boundaries in each category as the average duration. If the upper boundary for the highest was not provided, we assumed that the boundary had the same amplitude as the adjacent category. When the lowest category was open-ended, it was then assigned by 80% of the lowest boundary.

Definition of "Short" and "Long" Sleep Duration

In most of the studies, the reference category of sleep duration was 7-8 h or 7 h per night or 24 h except, while three studies defined as ≤6 h. Short sleep duration was defined as ≤5 h or ≤6 h; long sleep duration was defined as ≥9 h for either nighttime sleep or 24 h sleep in the majority of studies.

Statistical Analysis

The hazard ratios (HRs) or relative risks (RRs) were extracted from the selected publications and were used to measure the relationship between sleep duration and cancer risk. Their standard errors were calculated from the respective confidence intervals. The value from each study and the corresponding standard error were transformed into their natural logarithms to stabilize the variances and to normalize the distribution. The study-specified HRs or RRs were pooled using the fixed-effect model if no or low heterogeneity was detected, or the random-effects model otherwise. Forest plots were produced to visually assess the HRs and corresponding 95% confidence intervals across studies. In dose-response analysis, we used the method proposed by Greenland and Longnecker (Greenland et al., 1992) and Orsini (Orsini et al., 2006) to compute the trend from the correlated Log HR estimates across categories of sleep duration. We examined a potential nonlinear dose-response relationship between sleep durations and cancer risk by modeling sleep durations using restricted cubic splines with 3 knots at percentiles 25%, 50%, and 75% of the distribution (Harrell et al., 1988). Heterogeneity of HRs across studies was tested by Q-statistic ($P<0.05$ was considered indicative of statistically significant heterogeneity) and quantified by the I^2 statistic (values of 25%, 50%, and 75% were considered to represent low, medium, and high heterogeneity, respectively) (Higgins et al., 2003). P value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero. Funnel plot and Begg's test were used to detect the possibility of publication bias (Begg et al., 1994; Egger et al., 1997). We also conducted subgroup analyses by gender, sleep period, geographic location, occupational status, cancer type, menopause status, number of cases, and definition of short or long sleep duration and reference category. Moreover, sensitivity analyses were performed to evaluate the influences of included study and participant characteristics on study results. The dose-response analysis was conducted with SAS 9.2 (SAS Institute Inc., Cary, NC). Other statistical analyses were performed using STATA statistical software version 12.0 (StataCorp, College Station, Texas). P values were 2 sided with a significance level of 0.05.

Results

Search Results

Based on our selection criteria, 11547 citations were attained via the initial database search. After the first

Table 1. Description of the Studies Included in the Meta-analysis

Author (Year)	Country	Cohort	Year, Baseline	Gender	Sample size	Cases	Follow -up, y	Age, y (range)	Exposure assessment
Verkasalo(2005)	Finland	Finnish Twin Cohort	1975	female	12222	242	20	36.5	self-report
Pinheiro(2006)	USA	Nurses' Health Study	1986	female	77418	4223	16	(30-55)	self-report
Kakizaki(2008)	Japan	the Ohsaki Cohort Study	1994	male	22320	127	NA	(40-79)	self-report
Kakizaki(2008)	Japan	the Ohsaki Cohort Study	1994	female	23995	143	NA	(40-79)	self-report
Sturgeon(2012)	USA	Women's Health Initiative (WHI) Observational Study	1993	female	48725	452	7.5	(50-79)	self-report
von Ruesten(2012)	German	EPIC-Potsdam study	1994	male female	23620	846	7.8	(35–65)	self-report
Weiderpass(2012)	Japan	The Japan Public Health Center-based Prospective (JPHC) Study	1990-1994	female	45748	86	7.6	(40- 69)	self-report
Jiao(2013)	USA	Women's Health Initiative (WHI) Observational Study	1993-1998	female	75828	851	11.3	(50- 79)	self-report
Luo(2013)	USA	Women' s Health Initiative study	1993-1998	female	142933	295	11	(50-79)	self-report
Wu(2013)	Singapore	Singapore Chinese Health Study	1993-1998	female	34028	769	14	(45-74)	self-report
Zhang(2013)	USA	Nurses' Health Study	1986	female	76368	1264	22	(40-75)	self-report
		Health Professionals Follow-up Study	1988	male	30121	709	20	(30-55)	self-report
Vogtmann(2013)	USA	Women's Health Initiative	1993-1998	female	110011	5149	NA	(50-79)	Self-report

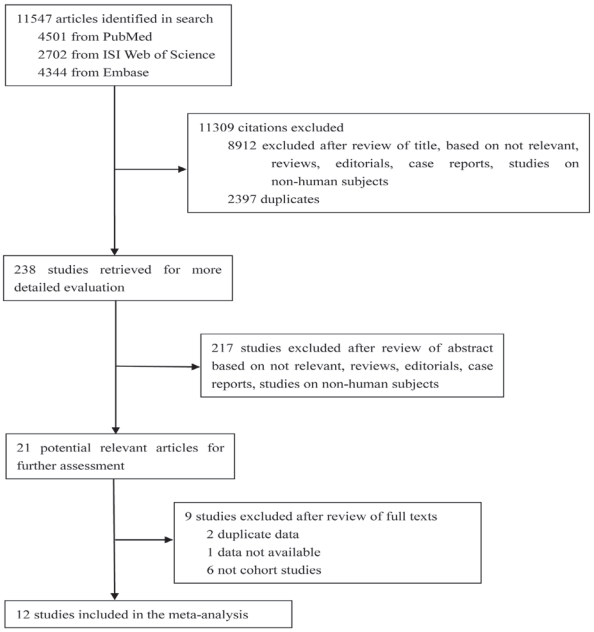

Figure 1. Flow Chart of the Study Selection Process

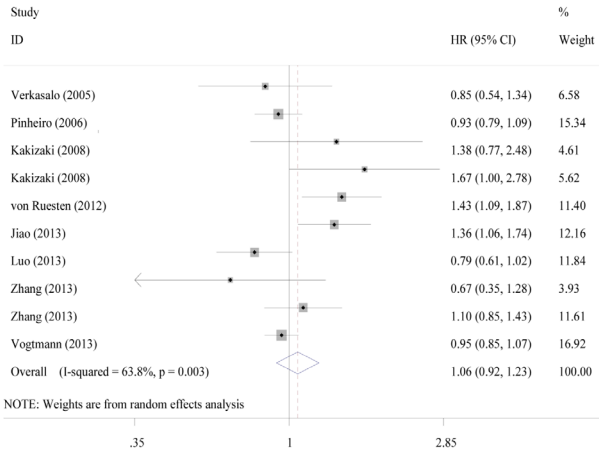

Figure 2. Forest Plot of the Association Between Short Sleep Duration and Cancer Risk. Results are expressed as hazard ratio(HR) and 95% confidence intervals(95% CI)

round of screening based on titles and abstracts, 21 articles needed for further assessment. After examining those articles in more detail, 9 papers were excluded for reasons shown in Figure 1. One cohort study which was published in two different journals reported the association between sleep duration and breast cancer in different time, the latest one was finally included (Wu et al., 2008; Wu et al., 2013). We were unable to include one study due to lack of data (Odegaard et al., 2013). Finally, 12 articles fulfilling the inclusion criteria were included in the meta-analysis.

Among these 12 articles, five studies reported breast cancer (Verkasalo et al., 2005; Pinheiro et al., 2006; Kakizaki et al., 2008b; Vogtmann et al., 2013; Wu et al., 2013), two studies on colorectal cancer (Jiao et al., 2013; Zhang et al., 2013), one each study on prostate cancer (Kakizaki et al., 2008a), endometrial cancer (Sturgeon et al., 2012), epithelial ovarian cancer (Weiderpass et al., 2012), thyroid cancer (Luo et al., 2013), and all type cancers (von Ruesten et al., 2012).

Study Characteristics

Characteristics of 12 selected studies including 13 cohorts are shown in Table 1. Overall, the total number of participants included was 723,337, with 15,156 reported cancer outcomes. Six studies were performed in USA, three in Japan (Kakizaki et al., 2008b; Weiderpass et al., 2012), and one each from German (von Ruesten et al., 2012), Finland (Verkasalo et al., 2005), and Singapore (Wu et al., 2008). The study samples ranged from 12, 222 to 142, 933, and the median of the follow-up durations is 11.3 years. Nine studies focused on the cancer of women, one only on men (Kakizaki et al., 2008a), one on men and women combined (von Ruesten et al., 2012), and one reporting men and women separately according to different cohorts (Zhang et al., 2013). Most of studies reported the sleep duration of 24 hours period, while four studies investigated typical night sleep duration (Sturgeon et al., 2012; Jiao et al., 2013; Luo et al., 2013; Vogtmann et al., 2013). In most of the studies, cancer was assessed by self-reported and confirmed by adjudicators via medical record review, four studies identified cancers through cancer registry data (Verkasalo et al., 2005; Kakizaki et al., 2008a; Kakizaki et al., 2008b; Wu et al.,

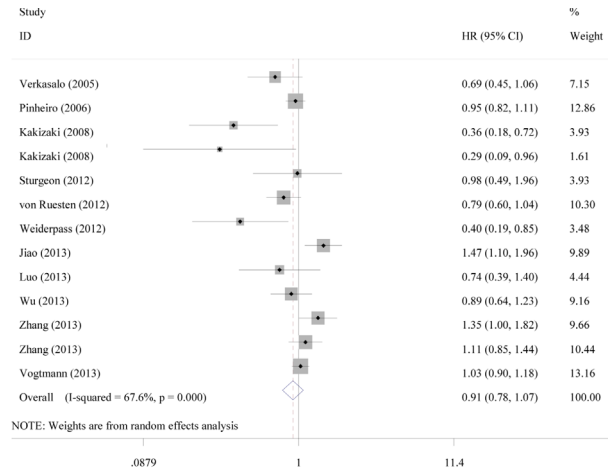

Figure 3. Forest Plot of the Association Between Long Sleep Duration and Cancer Risk. Results are expressed as hazard ratio(HR) and 95% confidence intervals(95% CI)

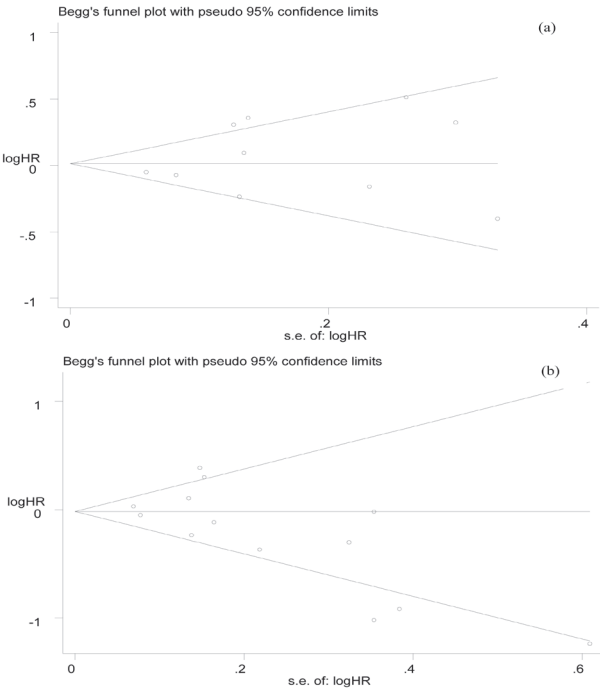

Figure 4. a. Funnel Plot for Meta-analyses of Short Duration of Sleep and Cancer Risk; b. Funnel Plot for Meta-analyses of Long Duration of Sleep and Cancer Risk

2013). Sleep duration was assessed by questionnaire in all studies. When results were reported for men and women separately, it was entered into meta-analysis as separate studies. Overall, there were 10 cohorts available for the relationship between short sleep duration and cancer risk and 13 cohorts available for the long sleep duration.

Quantitative Analyses

Figure 2 shows the forest plot of relationship between short sleep duration and risk of overall cancers. Short sleep duration was not significantly associated with all cancer risk (HR=1.06; 95% CI: 0.92-1.23), with no evidence of publication bias (Begg's test, *P*=0.531; Egger's test, *P*=0.373; Figure 4a). The heterogeneity was high (I^2=63.8%, *P*=0.003). The sensitivity analysis showed that omission of anyone of these studies did not change

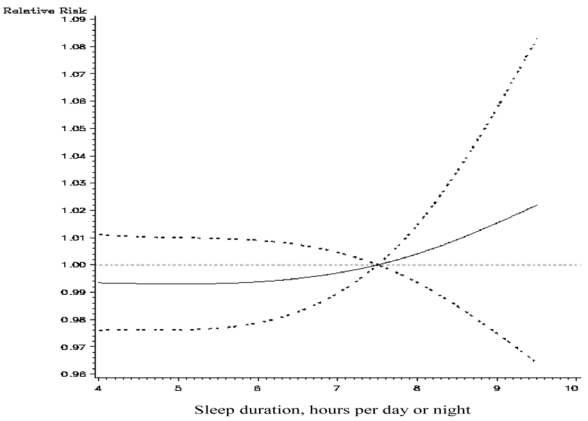

Figure 5. Dose-response Relations Between Sleep Duration and Cancers Risk (*P* for nonlinearity =0.5053). Data were modeled with random-effects restricted cubic spline models with 3 knots and using the Greenland and Longneckers method to estimate the covariances of multivariable-adjusted relative risks. 7.5 hours sleep per day or night used as reference. Solid line and the long dash line represent the estimated relative risks and their 95% confidence intervals

the quantitative relationship between short sleep duration and cancer risk (all *P*>0.05).

Figure 3 presents the pooled results of the relationship between long sleep duration and cancers risk. Long sleep duration was not significantly related to all cancer risk (HR=0.91; 95% CI: 0.78, 1.07), with no evidence of publication bias (Begg's test, *P*=0.050; Egger's test, *P*=0.072; Figure 4b) and high heterogeneity between studies (I^2=67.6%, *P*<0.001). Meanwhile, after omission each study one by one and recalculating the combined estimates on remaining studies., the results did not notably alter the main results (all *P*>0.05).

In dose-response analysis, we found no evidence on a nonlinear association between sleep duration and cancer risk (*P* for nonlinearity =0.5053) (Figure 5). Compared with 7.5 hours of sleep duration, the summary relative risk of cancer for per hour increase of sleep per day was 1.00 (95% CI: 0.99, 1.01; P for linear trend=0.9151), and one hour of sleep per night was 1.00 (95% CI: 0.98, 1.01; *P* for linear trend=0.7749).

Subgroup Analyses

As shown in Table 2, subgroup analyses showed that individuals with short sleep duration did not significantly change cancer risk either in men (HR=1.14, 95% CI: 0.90, 1.45) or women (HR=0.99, 95% CI: 0.84, 1.16). In terms of geographic location, it was not significant in Europe (HR=1.14, 95% CI: 0.69, 1.89) and USA (HR=0.98, 95% CI: 0.85, 1.13). No significant association between short sleep duration and cancer risk was observed in hormone-related cancers (breast cancer, prostate cancer, endometrial cancer, epithelial ovarian cancer, thyroid cancer, which were associated with hormone regulation (Henderson et al., 2000); HR=0.99, 95% CI: 0.79, 1.23) and colorectal cancer (HR=1.12, 95% CI: 0.84, 1.49).

As shown in Table 2, long sleep duration was found to be associated with cancer risk in Asian population (HR=0.49; 95% CI: 0.27, 0.90). In terms of cancer types, the associations were significant between long sleep

Table 2. Stratified Analyses of Hazard Ratio (HR) of Cancer Risk

Subgroup analyses	Short sleep duration				Long sleep duration			
for cancer risk	No. of Reports	HR(95% CI)	I^2 value	*P* value for Heterogeneity	NO. of	HR(95% CI)	I^2 value	*P* value for Heterogeneity
Gender								
Men	2	1.14(0.90-1.45)	0	0.488	2	0.66(0.22-1.99)	88.7	0.003
Women	7	0.99(0.84-1.16)	62.3	0.014	10	0.96(0.80-1.14)	64.5	0.003
Sleep period								
24 h	7	1.10(0.90-1.35)	57.2	0.03	9	0.82(0.66-1.02)	70.1	0.001
Night sleep	3	1.00(0.77-1.30)	79.4	0.008	4	1.10(0.85-1.42)	52.3	0.099
Geographic location								
Europe	2	1.14(0.69-1.89)	73.1	0.054	2	0.76(0.60-0.96)	0	0.6
USA	6	0.98(0.85-1.13)	58.7	0.033	7	1.09(0.96-1.25)	45.5	0.088
Asia	2	1.54(1.05-2.26)	0	0.63	4	0.49(0.27-0.90)	69.3	0.021
Occupational status								
General population	7	1.13(0.92-1.38)	72.2	0.001	10	0.80(0.63-1.01)	71.2	<0.0001
Health professional	3	0.96(0.82-1.13)	15.1	0.308	3	1.09(0.89-1.33)	55.8	0.104
Cancer type								
Hormone related cancer	6	0.96(0.83-1.10)	41.3	0.13	9	0.79(0.65-0.97)	60.8	0.009
Colorectal cancer	3	1.12(0.84-1.49)	55.2	0.107	3	1.29(1.09-1.52)	5.8	0.346
Menopause status								
Premenopausal	2	1.17(0.43-3.16)	68.1	0.078	1	0.92(0.57-1.48)	NA	NA
Postmenopausal	5	1.02(0.87-1.21)	66.4	0.165	6	1.01 (0.86-1.19)	48.7	0.083
No of cases								
>500	6	1.08(0.91-1.27)	68.5	0.007	7	1.05(0.92-1.20)	59.6	0.021
≤500	4	1.06(0.74-1.53)	64.6	0.037	6	0.58(0.42-0.81)	32.2	0.194
Definition of short or long sleep duration								
≤6 h[a] or ≥9 h[b]	5	1.14(0.83-1.58)	72.2	0.006	11	0.97(0.82-1.14)	65	0.001
≤5 h[a] or ≥10 h[b]	5	1.02(0.88-1.18)	57.4	0.052	1	0.79(0.60-1.04)	NA	NA
Definition of reference category								
7-8 h or 7 h	10	1.06(0.92-1.23)	63.8	0.003	10	0.94(0.79-1.12)	71	<0.001
≤6 h or <6 h	3	NA	NA	NA	3	0.75(0.47-1.20)	50	0.135

[a]represent the short sleep duration group; [b]represent the long sleep duration group

duration and hormone related cancer (HR=0.71; 95% CI: 0.55, 0.92) and colorectal cancer (HR=1.29; 95% CI: 1.09, 1.52). In addition, no significant associations were observed when stratified by gender or sleep period.

Discussion

Our studies provided a comprehensive review of the literature and quantitative estimates of longitudinal associations between short or long sleep duration and risk of cancers among cohort studies of adults around the world. Although, our results did not found short or long sleep duration associated with all cancer risk, long sleep duration among Asians presented a protect role in cancer initiation. Interestingly, in terms of cancer subtypes, long sleep duration was found to be associated with increased risk for colorectal cancer and decreased risk for hormone related cancer in the stratified analysis.

The protected effect of long sleep duration on hormone-related cancer was observed. Although, the mechanisms underlying are not fully understood, melatonin might exert its ant-cancer role via inducing tumor cells apoptosis and anti-proliferation and anti-angiogenesis (Di Bella et al., 2013). Melatonin has been described to be involved in inhibitory influences on sex hormone levels (Cohen et al., 1978), which have been reported to be associated with cancers of breast, endometrium, ovary, prostate, and thyroid (Henderson et al., 2000). In addition, Melatonin has shown dose-dependent anti-oxidative effect, providing protection against damage from carcinogenic substance, hence acting as a free radical scavenger (Reiter et al., 2008). Melatonin level was suggested to be positively related to sleep duration (Aeschbach et al., 2003). Therefore, longer sleepers may be possessed of higher melatonin concentration and subsequent protective effect in hormone-related cancers.

Conversely, a positive association between long sleep hours and colorectal cancer was observed. To our knowledge, the mechanism explained the effect of long sleep duration on cancer risk is still obscure. The association between long sleep duration and cancer may be explained by comorbidities (Knutson et al., 2006) and residual confounding. For instance, some other mental or physiologic disorder, low socioeconomic status, low level of physical activity, undiagnosed chronic comorbid conditions have been suggest to be correlated with long sleep duration and can confound the association with cancer incidence (Stranges et al., 2008b). The pooled results stratified by geographic location indicated that the effects for both short and long sleep duration were significant in studies performed in Asia, predominantly in Japan. The biologic difference between Asian and Caucasian study populations regarding melatonin suppression could be an explanation for some conflicting results (Girschik et al., 2010). Nonetheless, this subgroup finding of a positive association between sleep duration

and cancer risk was based on small number of studies and thus further studies should be warranted.

Several limitations of this meta-analysis should be considered. First, since the data were from observational studies, the confounding bias from included study per se cannot be excluded, though we made an attempt to include adjusted estimates from multivariate models from each contributing study. Second, all of the studies included in this meta-analysis assessed sleep duration using written questionnaires by self-reported which may not obtain actual information of sleep duration. Although correlations between subjective estimates of sleep duration and the more direct assessments have been found (Signal et al., 2005), this might still attenuate the effect of our study. Third, the studies included used different reference categories and definitions of short and long sleep duration, hence precluding our ability to provide sleep duration recommendations in public health practice. However, the pooled results in subgroup analyses did not changed significantly (as shown in Table 2). Fourth, sleep duration was assessed at one point in time in most of studies, and it might not accurately reflect the sustained effects of sleep duration over time when relating them to long-term development of cancer. Fifth, the cancer types reported in the majority of studies were restricted in breast, prostate, endometrial, thyroid,colorectal and epithelial ovarian cancers, except one study reported all types from German (von Ruesten et al., 2012). Therefore, it can only be representative of the cancer types that have been included and are unable to provide a representative inference of all cancer types.

In summary, our meta-analysis suggests a positive association between long sleep duration and colorectal cancer, and an inverse association between long sleep duration and incidence of hormone related cancer. Studies with larger sample size, longer follow-up times, more cancer types and detailed measure of sleep duration are warranted to confirm these results.

Acknowledgements

The author (s) declare that they have no competing interests.

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