Light exposure at night, sleep duration, melatonin, and breast cancer: a dose–response analysis of observational studies

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Evidence from observational studies on light at night (LAN) exposure, sleep duration, endogenous melatonin levels, and risk for breast cancer in women is conflicting. This led us to conduct a dose–response analysis of published observational data. Pertinent studies were identified by searching Medline, Web of Science, and EMBASE through April 2013. The dose–response relationship between sleep duration, urinary 6-sulphatoxymelatonin levels, and breast cancer was assessed using the restricted cubic spline model and by multivariate random-effects metaregression. A separate meta-analysis was also carried out to calculate the relative risks (RRs) with 95% confidence intervals (CIs) for breast cancer for the comparable categories or highest levels of exposure versus the lowest levels. Twelve case–control and four cohort studies were included in the analysis. High artificial LAN exposure is associated with an increased risk for breast cancer (RR = 1.17, 95% CI: 1.11–1.23), but not ambient LAN exposure (RR = 0.91, 95% CI: 0.78–1.07). The summary RR for breast cancer is 1.00 (95% CI: 0.995–1.01) for an increment of 1 h of sleep per night. No significant dose–response relationship between sleep duration and breast cancer was found either for the linearity test ($P_{trend} = 0.725$) or for the nonlinearity ($P_{trend} = 0.091$) test. An increasein of 15 ng/mg creatinine in urinary 6-sulphatoxymelatonin is associated with a 14% reduced risk for breast cancer (RR = 0.86, 95% CI: 0.78–0.95), with a linear dose–response trend ($P_{trend} = 0.003$). There was no evidence of substantial heterogeneity or publication bias in the analysis. Our study adds to the evidence of LAN breast cancer theory. Further research in this area is warranted. ***European Journal of Cancer Prevention*** **23:269–276 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Breast cancer is now the most frequently diagnosed cancer, as well as the leading cause of cancer-related death among women worldwide (Jemal *et al.*, 2011). Of late, with increasing economic and social demands, more and more people are part of a 24-h society with an increased exposure to artificial light at night (LAN) both at their homes and at their workplace in particular (Rajaratnam and Arendt, 2001). It has been hypothesized that LAN may be associated with an increased risk for incident breast cancer (Stevens, 1987) by decreasing the production of melatonin by the pineal gland (Stevens and Davis, 1996). Pertinent experimental studies have also shown that melatonin could inhibit breast carcinogenesis in rodents and suppress estrogen-induced proliferation of human mammary cancer cells *in vitro* (Blask *et al.*, 2011). The hypothesis was further supported by animal in-vivo studies (Blask *et al.*, 2005, 2009) suggesting breast tumorigenesis after exposure to constant light.

However, human observational studies on the relationship between melatonin levels and female breast cancer risk have yielded conflicting results (Travis *et al.*, 2004; Schernhammer and Hankinson, 2005, 2009; Schernhammer *et al.*, 2008, 2010; Wu *et al.*, 2008, 2013). In addition, epidemiological evidence for the association between LAN, sleep duration as a potential proxy for exposure to darkness, and risk for breast cancer is also controversial, varying from inverse (Verkasalo *et al.*, 2005; Kakizaki *et al.*, 2008), to positive (O'Leary *et al.*, 2006; Kloog *et al.*, 2008, 2010, 2011; Bauer *et al.*, 2013) to null (Davis *et al.*, 2001; McElroy *et al.*, 2006; Pinheiro *et al.*, 2006; Wu *et al.*, 2008, 2013; Li *et al.*, 2010; Girschik *et al.*, 2013). Although such discrepancy could be due to many factors including differing exposure measures and study designs and the lack of adjustments for important covariates such as estrogen-related conditions, sleep medications, and smoking, limited sample size and a consequence of insufficient statistical power or chance among results may at least in part interpret this and do not allow firm conclusions.

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Therefore, we conducted a dose–response analysis of published observational data to investigate the associations among LAN, sleep duration, melatonin levels, and risk for breast cancer. Given a recent meta-analysis of night-shift work and breast cancer published in 2013 (Kamdar *et al.*, 2013), we did not evaluate the risk for breast cancer associated with circadian disruption.

Methods

Data sources and searches

We comprehensively identified studies through searching Medline (PubMed), EMBASE, and Web of Science through April 2013 for both case–control and cohort studies that assessed the association among light exposure at night, sleep duration, melatonin, and breast cancer risk. No language restriction was applied. The search strategy included terms for outcome (mammary cancer and breast cancer), exposure (electric light, artificial light, ambient light; sleep, sleeping habits, sleep duration, sleep quality, sleep hours; melatonin, 6-sulphatoxymelatonin, and pineal gland), and study design (case–control study, case–referent study, cohort study, prospective study, and longitudinal study). The reference lists of retrieved articles were also scanned to locate additional relevant studies.

Study selection criteria

Published studies were included in the analysis if they (i) had a case–control or cohort design, (ii) evaluated the association among light exposure at night, sleep duration, endogenous melatonin levels, and risk for incident breast cancer, and (iii) presented odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) and their 95% confidence intervals (CIs) or SE. The studies were considered for inclusion in a dose–response meta-analysis if the authors additionally provided adjusted RRs or HRs and 95% CIs for three or more categories of sleep hours and 6-sulfatoxymelatonin (aMT6s) levels, together with the corresponding number of cases and person-years or subjects for each category. If publications were duplicates or articles from the same study population, the most recent publication was included. Ecological study of population levels for LAN exposure and breast cancer risk was not included in this analysis. Artificial LAN in our study was defined as an electric or man-made light in the bedroom while sleeping; ambient LAN in a bedroom was defined as a general illumination that comes from all directions into a bedroom that has no visible source, which is in contrast to directional artificial light in a bedroom.

Data extraction and quality assessment

Two authors independently evaluated study eligibility and conducted data extraction and quality assessment using a unified data form; discrepancies were settled by consensus or by involving a third reviewer for adjudication. Relevant variables included in the data form are as follows: study name, study region, study design, number of cases and controls (if case–control design), cohort size (if cohort design), follow-up years (if cohort design), ORs or RRs with 95% CIs, which reflected the greatest degree of control for potential confounders, and variables matched on or adjusted for in the design or data analysis.

To assess the study quality, a nine-point scoring system on the basis of the Newcastle–Ottawa Scale was used, in which each study was judged on three broad perspectives: selection of the study groups, comparability of the groups, and ascertainment of either the exposure or the outcome of interest for case–control and cohort studies, respectively. A high-quality study in the present analysis was defined as a study with 7 points or higher.

Statistical methods

To study the dose–response relationships between sleep duration, urinary aMT6s, and breast cancer, a two-stage procedure (Orsini *et al.*, 2012) was adopted. In the first stage, restricted cubic spline models (Durrleman and Simon, 1989) were used to derive the dose–response slope in each study separately, with a unified increment while accounting for the correlation within each set of published risk estimates (Orsini *et al.*, 2006). The mean sleep hours and urinary aMT6s levels for each category were assigned to each corresponding RR for every study. In the second stage, the study-specific slopes were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis (Jackson *et al.*, 2010). *P*-values for testing linearity and nonlinearity (U-shaped) were calculated using the method suggested by Greenland and Longnecker (1992).

Heterogeneity across studies was detected using Cochran's Q and I^2 statistics. The null hypothesis that the studies are homogeneous was rejected if the *P*-value for heterogeneity was less than 0.10 or if I^2 was less than 50% (Higgins *et al.*, 2003). Begg's rank correlation method was used to evaluate the potential publication bias (Begg and Mazumdar, 1994).

We also carried out a random-effects meta-analysis (DerSimonian and Laird, 1986) to calculate the summary RRs with 95% CIs for breast cancer for comparable categories or the highest category of exposure as compared with the lowest category in each study. In this approach, we pooled the categories of sleep duration into five groups: less than 6 h, 6–7 h, 7–8 h (reference), 8–9 h, and 9 h or more; the summary RRs for the highest levels of LAN, sleep duration, and urinary aMT6s versus the lowest levels were also calculated.

A subgroup analysis was carried out by study design (case–control vs. prospective studies), study population (Asians vs. non-Asians), menopausal status (premenopause vs. postmenopause), and breast cancer type (invasive vs. in-situ breast cancer) if two or more studies were included in each stratum.

All data analyses were carried out using R 2.15.3 (R Development Core Team) and SAS 9.2 (SAS Institute, Cary, North Carolina, USA) software, and a two-sided *P*-value of 0.05 was considered statistically significant if not specified.

Results

Literature search and study characteristics

A total of 16 articles, comprising 12 case–control and four cohort studies, were included in the final analysis after the literature search. A flow diagram that shows how we identified relevant studies is presented in Fig. 1. Descriptive data for the included studies are summarized in Table 1. All of the studies were published between 2001 and 2013 and were conducted in Asia ($n=4$), Europe ($n=6$), and the USA ($n=6$). Most studies were matched or adjusted for a wide range of potential confounders, including menopausal status, BMI, smoking, alcohol drinking, and physical activity. As shown in Supplemental digital content 1 and Table 1, all of the studies except one (Bauer *et al.*, 2013) were defined as high-quality studies (quality ≥ 7) according to the nine-point scoring system. The range of quality scores was from 2 to 9; the median scores for all, case–control, and cohort studies were 8, 7.5, and 8, respectively.

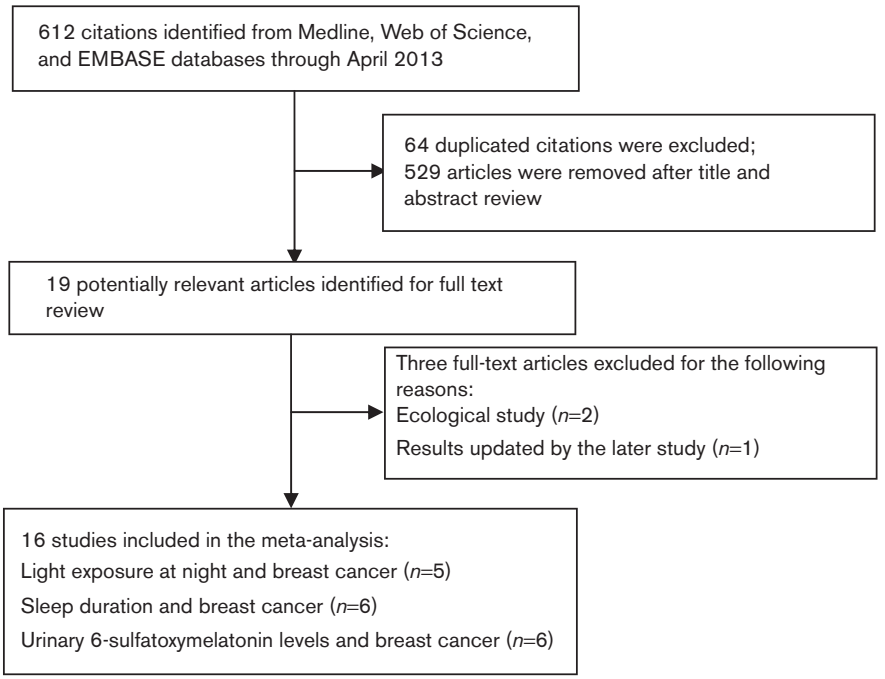
Exposure to light at night and breast cancer

Five publications on LAN and breast cancer (Davis *et al.*, 2001; O'Leary *et al.*, 2006; Li *et al.*, 2010; Kloog *et al.*, 2011; Bauer *et al.*, 2013) were included in the meta-analysis with 36 599 cases among 53 676 participants. The definitions of high and low LAN exposures in each individual study are summarized in Supplemental digital content 2. As shown in Table 2 and Fig. 2, a high exposure to artificial LAN can significantly increase the risk for breast cancer (RR = 1.17, 95% CI: 1.11–1.23). Findings were slightly different when analyses were restricted to four high-quality studies (quality scores ≥ 7; RR = 1.23, 95% CI: 1.14–1.33). Results from the analysis after excluding the study with the largest statistical weight (Bauer *et al.*, 2013; RR = 1.23, 95% CI: 1.14–1.33) did not appreciably alter the overall summary risk estimate. When the four studies on ambient LAN exposure were combined, the summary RR for breast cancer for the highest versus lowest categories was 0.91 (95% CI: 0.78–1.07). No significant heterogeneity ($Q=5.09$, $P=0.405$, $I^2=1.9\%$) and publication bias ($P=0.573$) were observed.

Sleep duration and breast cancer

Two population-based case–control studies (McElroy *et al.*, 2006; Girschik *et al.*, 2013) and four cohort studies (Verkasalo *et al.*, 2005; McElroy *et al.*, 2006; Kakizaki *et al.*, 2008; Wu *et al.*, 2013), including 10 676 cases among 160 004 participants, were combined in the dose–response meta-analysis of sleep duration and breast cancer. As shown in Table 2 and Fig. 3, the summary RR for breast cancer is 1.00 (95% CI: 0.995–1.01) for an

Fig. 1



Literature search for the meta-analysis.

Table 1 Characteristics of epidemiologic studies of light exposure at night, sleep hours, melatonin, and breast cancer

References	Region	Design	No. of cases	No. of controls/ cohort size	Exposure	Study quality	Matched or adjusted variables
Sleep duration and breast cancer							
Girschik *et al.* (2013)	Australia	PCC	1205	1789	Self-reported sleep hours	7	A E H M P O
Wu *et al.* (2013)	Singapore	CS	820	34 028	Self-reported sleep hours	9	A B M O
Kakizaki *et al.* (2008)	Japan	CS	143	23 995	Self-reported sleep hours	7	A B E M S P O
McElroy *et al.* (2006)	USA	PCC	4033	5314	Self-reported sleep hours	8	A B E M O
Pinheiro *et al.* (2006)	USA	CS	4233	77 418	Self-reported sleep hours	7	A B E M S P O
Verkasalo *et al.* (2005)	Finland	CS	242	12 222	Self-reported sleep hours	8	A B E S P
LAN and breast cancer							
Davis *et al.* (2001)	USA	PCC	813	793	Ambient and artificial LAN in bedroom	8	A E H O
O'Leary *et al.* (2006)	Long Island	PCC	576	585	Artificial LAN in bedroom	7	A O
Li *et al.* (2010)	USA	PCC	363	356	Ambient and artificial LAN in bedroom	8	A B E S O
Kloog *et al.* (2011)	Israel	PCC	794	885	Ambient and artificial LAN in bedroom	7	A E O
Bauer *et al.* (2013)	Georgia	CC[a]	34 053	14 458	Artificial LAN in bedroom	2	A S O
Melatonin and breast cancer							
Wu *et al.* (2013)	Singapore	NCC	248	743	24-h spot urinary aMT6s	9	A B M O
Travis *et al.* (2004)	British Isles	NCC	127	353	24-h urinary aMT6s	8	A B M O
Schernhammer and Hankinson (2005)	USA	NCC	147	291	First spot morning urinary aMT6s	8	B E M O
Schernhammer *et al.* (2008)	Italy	NCC	178	710	12-h overnight urinary aMT6s	9	A B E M O
Schernhammer and Hankinson (2009)	USA	NCC	357	533	First spot morning urinary aMT6s	8	B E M O
Schernhammer *et al.* (2010)	Italy	NCC	180	683	12-h overnight urinary aMT6s	9	A B E M S O

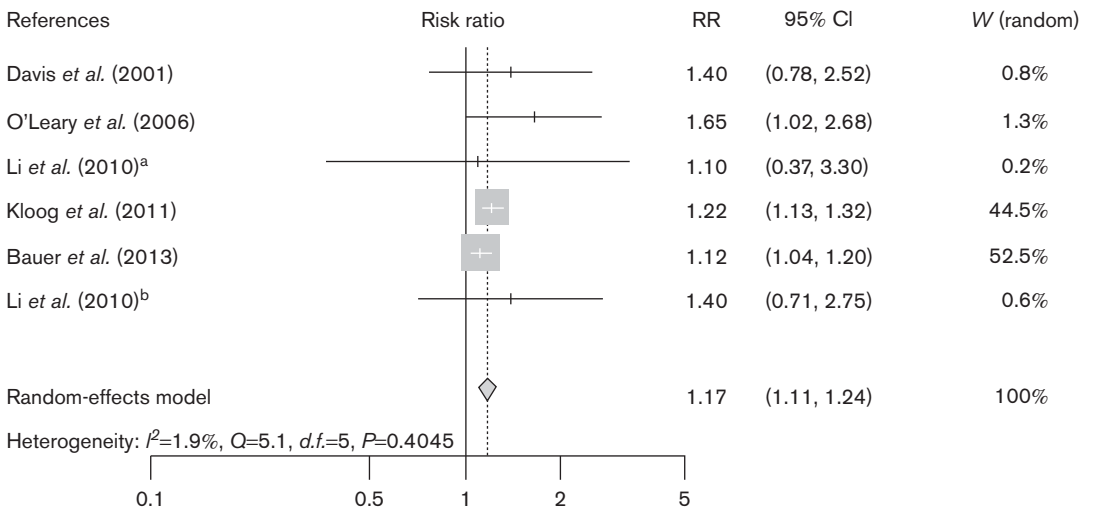
A, age; B, BMI; CC, case–control study; CS, cohort study; E, ethanol-related conditions; H, hormone replacement therapy; LAN, light at night; M, menopausal status; NCC, nested case–control studies; O, others; P, physical activity; PCC, population-based case–control study; S, smoking.
[a]The controls in this study were lung cancer patients.

Table 2 Summary relative risks and 95% confidence intervals of breast cancer associated with light exposure at night, sleep duration, and melatonin

	No. of studies	Summary RR (95% CI)	*Q*-statistic	*P*-value for heterogeneity	I^2 (%)
Sleep duration					
1 h per night increase	6	1.00 (0.995–1.01)	2.66	0.752	0
Highest vs. lowest levels in each study	6	0.96 (0.77–1.19)	10.99	0.052	54.5
Study design					
Case–control study	2	1.00 (0.99–1.01)	0.14	0.711	0
Cohort study	4	1.00 (0.99–1.01)	2.52	0.472	0
Sleep hours					
< 6 h	5	1.07 (0.92–1.24)	3.61	0.307	16.8
6–7 h	3	0.96 (0.90–1.05)	2.61	0.271	23.5
7–8 h	5	1 (referent)	–	–	–
8–9 h	4	1.09 (0.97–1.23)	5.21	0.157	42.5
> 9 h	4	0.85 (0.57–1.25)	9.89	0.020	69.7
Menopausal status					
Yes	4	1.03 (0.92–1.16)	3.03	0.387	1.0
No	4	1.07 (0.80–1.42)	2.28	0.516	0
Study region					
Asia	3	1.00 (0.99–1.01)	0.22	0.896	0
Europe plus USA	3	1.00 (0.99–1.01)	2.35	0.309	14.9
Urinary 6-sulfatoxymelatonin levels					
15 ng/mg creatinine increase	5	0.86 (0.78–0.95)	7.47	0.113	46.4
Highest vs. lowest levels in each study	6	0.71 (0.61–0.83)	6.87	0.231	27.2
Menopausal status					
Yes	2	0.81 (0.70–0.92)	0.53	0.768	0
No	2	1.20 (0.91–1.59)	0.64	0.424	0
Cancer type					
Invasive breast cancer	3	0.84 (0.74–0.94)	1.12	0.571	0
In-situ breast cancer	1	0.54 (0.37–0.78)	NA	NA	NA
Light exposure at night[a]					
Artificial light in bedroom	5	1.17 (1.11–1.23)	5.09	0.405	1.9
Ambient light in bedroom	3	0.91 (0.78–1.07)	2.26	0.520	0

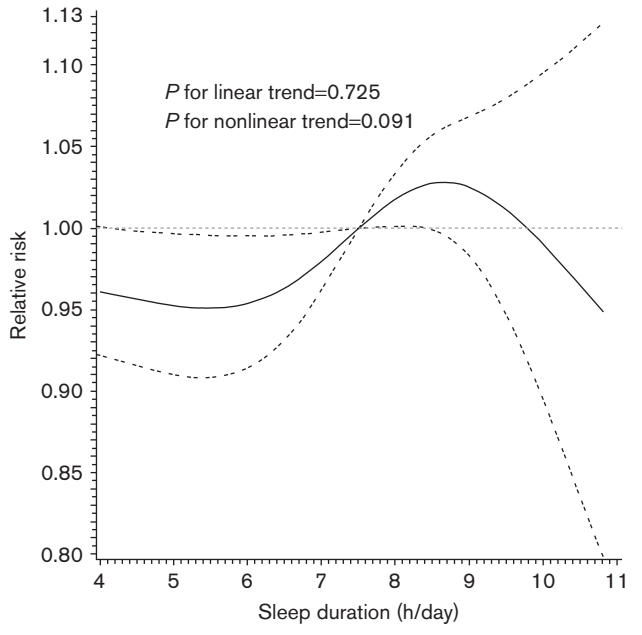
CI, confidence interval; RR, relative risk.
[a]Artificial light in bedroom was defined as an electric or man-made light exposure in the bedroom while sleeping; ambient light in bedroom was defined as a general illumination that comes from all directions into a bedroom that has no visible source, which is in contrast to directional artificial light in bedroom.

Fig. 2



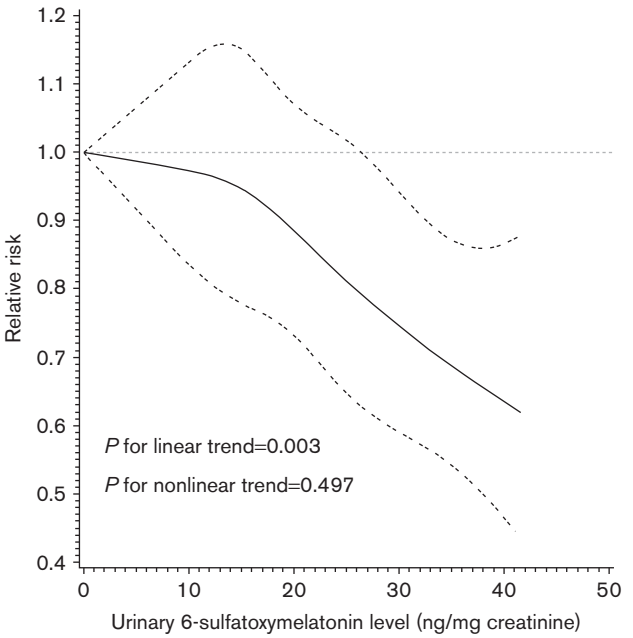
Risk estimates [95% confidence intervals (95% CIs)] of artificial light exposure at night and breast cancer risk among women. Squares represent study-specific estimates; horizontal lines represent 95% CIs, and diamonds represent summary estimates with corresponding 95% CIs. [a]Premenopausal women; [b]postmenopausal women.

Fig. 3



Dose–response analysis between sleep duration and risk for breast cancer, with restricted cubic splines in a random-effects model. The solid line and the long dashed line represent the estimated relative risks and their 95% confidence intervals. Eight hours of sleep per day was used as the reference. *P*-values for testing for linearity and nonlinearity were calculated using the method proposed by Greenland and Longnecker (1992).

Fig. 4



Dose–response analysis between urinary aMT6s levels and risk for breast cancer with restricted cubic splines in a random-effects model. The solid line and the long dashed line represent the estimated relative risks and their 95% confidence intervals. *P*-values for testing for linearity and nonlinearity were calculated using the method proposed by Greenland and Longnecker (1992).

increment of 1 h of sleep per night. No significant dose–response relationship between sleep hours at night and breast cancer was found either for the linearity test ($P_{trend} = 0.725$) or for the nonlinearity test ($P_{trend} = 0.091$). This null association remained when the highest levels of sleep duration were compared with the lowest levels of

sleep duration (RR = 0.96, 95% CI: 0.77–1.19) in all six studies. The summary RRs for breast cancer with very short (< 6 h, five studies; Verkasalo *et al.*, 2005; McElroy *et al.*, 2006; Pinheiro *et al.*, 2006; Kakizaki *et al.*, 2008; Girschik *et al.*, 2013), short (6–7 h, three studies; McElroy *et al.*, 2006; Pinheiro *et al.*, 2006; Girschik *et al.*, 2013), average (7–8 h; five studies; Verkasalo *et al.*, 2005; McElroy *et al.*, 2006; Pinheiro *et al.*, 2006; Kakizaki *et al.*, 2008; Girschik *et al.*, 2013), long (8–9 h, four studies; McElroy *et al.*, 2006; Pinheiro *et al.*, 2006; Kakizaki *et al.*, 2008; Girschik *et al.*, 2013), and very long (>9 h, four studies; Verkasalo *et al.*, 2005; McElroy *et al.*, 2006; Pinheiro *et al.*, 2006; Kakizaki *et al.*, 2008) sleep durations were 1.07 (95% CI: 0.92–1.24), 0.96 (95% CI: 0.90–1.05), 1 (referent), 1.09 (95% CI: 0.97–1.23), and 0.85 (95% CI: 0.57–1.25), respectively. Subgroup analysis by study design, study region, and menopausal status yielded consistent results with overall analysis. No significant heterogeneity ($Q = 2.66$, $P = 0.752$, $I^2 = 0$) or publication bias ($P = 0.189$) was found.

Urinary 6-sulfatoxymelatonin levels and breast cancer

Six prospective nested case–control studies (Travis *et al.*, 2004; Schernhammer and Hankinson, 2005, 2009; Schernhammer *et al.*, 2008, 2010; Wu *et al.*, 2013) with 1237 cases and 3313 controls were included in the meta-analysis of urinary aMT6s levels and breast cancer, of which five studies (Travis *et al.*, 2004; Schernhammer and Hankinson, 2005, 2009; Schernhammer *et al.*, 2008, 2010) were included in a dose–response meta-analysis. As shown in Fig. 4, an increase in urinary aMT6s of 15 ng/mg creatinine is associated with a 14% reduced risk for breast cancer (RR = 0.86, 95% CI: 0.78–0.95), with a linear dose–response trend ($P_{\text{trend}} = 0.003$). This inverse association was unchanged in subgroup analysis by breast cancer type or in the analysis that compared the highest with the lowest level of aMT6s in all six included studies. However, when stratified by menopausal status, the inverse association appeared to be confined to post-menopausal women (RR = 0.81, 95% CI: 0.70–0.92; Table 2). No significant heterogeneity ($Q = 7.47$, $P = 0.113$, $I^2 = 46.4$) or publication bias ($P = 0.189$) was found in the meta-analysis.

The exclusion of studies (Travis *et al.*, 2004; Wu *et al.*, 2013) that used a randomly timed spot or 24-h urine samples to determine aMT6s levels and one study with the largest weight (Schernhammer and Hankinson, 2009) in the analysis yielded similar results, with summary RRs of 0.66 (95% CI: 0.58–0.75) and 0.73 (95% CI: 0.63–0.85), respectively.

Discussion

No meta-analysis, to our knowledge, has evaluated the dose–response relationship between sleep duration, urinary aMT6s levels, and the risk for human breast cancer to date. In this dose–response meta-analysis, we found that sleep duration could be not associated with the development of breast cancer among women, whereas prediagnosed urinary aMT6s level, as a proxy for endogenous melatonin, is linearly associated with the reduced risk for breast cancer. Compared with those with low exposure to artificial LAN, women with a high LAN exposure have a 17% increased risk for incident breast cancer. These findings somewhat add to the evidence of the LAN breast cancer theory.

Two plausible biological mechanisms may explain the scientific rationale behind the LAN theory of breast cancer causation. The synthesis and secretion of melatonin is stimulated by darkness and inhibited by light through photic information from the retina (Brzezinski, 1997). In addition to a direct antiproliferative effect, melatonin could also exhibit an indirect effect of breast cancer prevention by neuroendocrine suppression of circulating estrogen levels, enhancement of immune activity, and free-radical scavenging (Brzezinski, 1997). Increased exposure to light could lower the production of melatonin by the pineal gland and may thereby increase the risk for breast cancer. Another possible mechanism is that light might cause the disruption of circadian rhythm through alteration of clock gene functioning and desynchronization of the master clock in the suprachiasmatic nuclei from the peripheral clocks in tissue, leading to a number of pathological conditions including untoward effects on cell cycle regulation in mammary tissue (Stevens, 2009). A recent meta-analysis revealed that women with ever night-shift work have a 21% (95% CI: 1.00–1.47) elevated risk for breast cancer (Kamdar *et al.*, 2013), indicating that circadian disruption may be correlated with breast cancer among women.

We found a null association between sleep duration and breast cancer risk regardless of study design, study region, study quality, and menopausal status. This finding appeared to somewhat contradict the positive associations of breast cancer with night-shift work (Kamdar *et al.*, 2013), LAN exposure, and urinary aMT6s levels. There are many factors that could interpret these controversies, including methodological issues in measuring sleep duration, as well as sleep quality, different study designs, and the lack of adjustment for important confounding factors such as estrogen-related conditions, sleep medications, night-time lighting conditions, and alcohol use among individual studies. In addition, given that a recent meta-analysis by Kamdar *et al.* (2013) has pooled several extreme work schedules (overnight or long-term night/shift work), differences in the results of our study compared with their meta-analysis are understandable.

In contrast, whether the sleep duration is a useful indicator or proxy for exposure to darkness is unclear. Although melatonin release depends on a stable 24-h light/dark cycle, sleep is not necessarily required for

synchronization of the endogenous circadian rhythm (Blask, 2009). In addition to sleep duration *per se*, other sleep patterns including habitual timing of sleep, waking up frequency, night-time lighting conditions, and sleep quality may also influence melatonin release. However, only a few included studies considered waking up times (O'Leary *et al.*, 2006), two studies considered habitual sleep starting time (Davis *et al.*, 2001; O'Leary *et al.*, 2006), and two studies (Verkasalo *et al.*, 2005; Girschik *et al.*, 2013) evaluated sleep quality. For the above, our analysis underscores the need for future studies on breast cancer that simultaneously take into account the sleep duration, sleep starting time, waking up frequency, and sleep quality to fully characterize the sleep–breast cancer association. Moreover, the proportion of short (<6 h) and long sleepers (≥9 h) varied substantially among each individual study, which may reflect different sleeping patterns in different study populations. By comparison, there were ~30 and 5%, and ~34 and ~7% short and long sleepers in the Nurses' Health Study (Pinheiro *et al.*, 2006) in the USA and a Singapore cohort (Wu *et al.*, 2008), respectively; in a Finnish cohort, a Japanese cohort, and an Australian case–control study (Verkasalo *et al.*, 2005; Kakizaki *et al.*, 2008; Girschik *et al.*, 2013), the proportions of short and long sleepers were about 10–19% and 14–16%, respectively, whereas McElroy *et al.* (2006) reported proportions of 4–5% for short and ~5.5% for long sleepers in a US population-based case–control study. These intrinsic differences in different populations may also partly explain the above controversies.

Strengths of our study include the use of study-specific RRs, which reflect the greatest degree of control for potential confounders, a lesser degree of influence by heterogeneity and publication bias, and a moderate to high quality of studies included in the meta-analysis. However, this study has limitations. First, information on sleep duration and LAN exposure was based on subjective self-reported data among almost all of the individual studies; thus, the misclassification bias cannot be ruled out. These could also partly explain the inconsistency among the existing epidemiological evidence on sleep duration, LAN, and breast cancer. Among studies on sleep duration, only one study (Girschik *et al.*, 2013) carefully considered the validity of self-reported sleep; however, it showed poor consistency with the wrist actigraphy results in a sample of participants. First, among the studies on LAN, one study (Bauer *et al.*, 2013) measured the individual levels of artificial LAN exposure using time series satellite imagery; however, as the author stated, it is a challenge to estimate indoor exposure ranges or to obtain reliable, consistent reports of individuals' nocturnal behavior when using satellite images. Thus, the difficulty of how best to measure sleep and LAN in observational studies needs to be solved urgently. Second, urine collection at different time points among individual studies may bias the results on the association of breast cancer with urinary aMT6s levels in the meta-analysis. Because the daytime rhythm in urinary aMT6s concentrations parallels the day–night cycle (Lynch *et al.*, 1975), the urine collecting time can strongly influence the urinary aMT6s levels. In our meta-analysis, the urinary aMT6s levels in the four studies were determined in 12-h overnight or first morning urine samples (Schernhammer and Hankinson, 2005, 2009; Schernhammer *et al.*, 2008, 2010), whereas in one study (Travis *et al.*, 2004) the levels were measured in a 24-h urine sample, and in one study levels in randomly timed spot urine samples were measured (Wu *et al.*, 2013). However, sensitivity analysis that excluded studies using 24-h or randomly timed spot urine samples (Travis *et al.*, 2004; Wu *et al.*, 2013) yielded a consistent result. Third, because of the inability to fully adjust for various confounders, the observed associations may be confounded by unadjusted risk factors. Nevertheless, most studies matched or adjusted for a wide range of potential confounders, including menopausal status ($n=10$), BMI ($n=11$), smoking ($n=5$), and alcohol drinking ($n=11$).

Conclusion

Our study adds to the evidence on the LAN breast cancer theory. Given emerging hypothesis that circadian rhythm may play a role in the etiology of breast cancer, as well as other cancers, the difficulty of how best to measure sleep and LAN in epidemiological studies needs to be solved urgently.

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Conflicts of interest

There are no conflicts of interest.

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