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Joint effects of multiple sleep characteristics on breast cancer progression by menopausal status

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ABSTRACT

Objectives: Sleep has been closely linked to breast cancer risk. However, the association between sleep and breast cancer prognosis remains unclear. The aim of this study was to evaluate the separate and joint effects of multiple sleep characteristics on breast cancer prognosis among Chinese women.
Methods: A total of 1580 breast cancer patients were recruited between October 2008 and December 2014 and followed up until December 31, 2017 in Guangzhou. Multivariate Cox models were conducted to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) for breast cancer prognosis in association with sleep characteristics.
Results: Long sleep duration at night (>9 h) (HR = 2.33, 95%CI: 1.01–5.42), poor sleep quality (HR = 3.08, 95%CI: 1.74–5.47), and impaired daytime function (HR = 2.49, 95%CI: 1.65–3.79) after diagnosis were associated with an increased risk of breast cancer progression. Both short sleep duration (<6 h) (HR = 2.00, 95%CI: 1.06–3.77, $P_{interaction} = 0.011$) and long sleep duration (>9 h) (HR = 4.69, 95%CI: 1.31–16.78, $P_{interaction} = 0.187$) increased the progression risk only among patients with impaired but not normal daytime function. In addition, daytime napping significantly modified the effect of short sleep duration on the progression (HR = 3.55, 0.59, 95%CI: 1.55–7.97, 0.23–1.53 for patients without and with daytime napping, respectively, $P_{interaction} = 0.005$). Stratification results suggested that the associations were more evident among pre-menopausal patients, although no significant interaction was observed.
Conclusion: Our findings suggested that inadequate sleep duration to feel one's best and poor sleep quality after diagnosis were associated with an increased risk of breast cancer progression, particularly for pre-menopausal women.

1. Introduction

Breast cancer is the most common malignancy among women worldwide, accounting for 25% of all cancers [1]. Furthermore, it is the most commonly diagnosed cancer in Chinese women, and the incidence rate has increased rapidly over the past few decades [2]. The prognosis of breast cancer is relatively better than most other cancers, with estimated five year survival rates of 90.2% and 83.2% in US and China, respectively [3], resulting in a large amount of breast cancer survivors. Therefore, identification of potential lifestyle factors that may improve breast cancer prognosis is particularly significant to patients and their caregivers.

Sleep is one of the most important lifestyles related to multiple health outcomes. A growing body of evidence has suggested that sleep was closely linked to breast cancer risk [4–8]. A few studies have also examined the associations between sleep and breast cancer prognosis, which mostly focused on pre-diagnostic sleep characteristics [9–13]. Yet, many patients changed their sleep habits and experienced new sleep problems after diagnosis and treatment [14]. Therefore, post-diagnostic sleep characteristics might have more implications for breast cancer prognosis. Several

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studies have explored associations between post-diagnostic sleep characteristics and breast cancer prognosis. For example, Hahm BJ et al., and Palesh O et al., found that bedtime misalignment and sleep disruption were associated with poor prognosis among metastatic breast cancer patients [15,16]. Moreover, two other studies from Women's Healthy Eating and Living (WHEL) and Nurses' Health Study (NHS) indicated that long or increased sleep duration after diagnosis was associated with a higher risk of disease progression [17,18]. However, these studies ignored the multidimensional nature of sleep [19], and the joint effects of sleep characteristics on breast cancer prognosis have not been assessed. In addition, these previous studies did not differentiate menopausal status (few pre-menopausal patients), while pre- and post-menopausal breast cancers may be different diseases [20].

Thus, we conducted an analysis for the associations of several post-diagnostic sleep characteristics with progression-free survival of breast cancer patients stratified by menopausal status, using data from the Guangzhou Breast Cancer Study (GZBCS) in China [21].

2. Material and methods

2.1. Study population

The subjects were recruited between October 2008 and December 2014 in the GZBCS, as described previously [21]. Patients with pathological confirmed primary breast cancer were collected from the First and the Second Affiliated Hospitals and the Cancer Center of Sun Yat-sen University in Guangzhou, China. A total of 1861 patients who completed follow-up and reported post-diagnostic sleep characteristics were eligible for this study. Patients who reported disease progression before sleep assessment (N = 180) and carcinoma in situ (N = 101) were excluded, yielding an analytic sample of 1580 cases. The informed consents were obtained from all the participants. This study was approved by the Ethical Committee of the School of Public Health at Sun Yat-sen University.

2.2. Data collection

Baseline information was collected by face-to-face interview using the structural questionnaire as previously described [22]. The information included demographic characteristics, menstrual and reproductive history, family history of breast cancer, and preexisting disease at baseline. Height and weight were measured on admission to hospitals and used to calculate the body mass index (BMI). BMI was categorized into underweight (<18.5), normal (18.5–23.9), and overweight (≥24) according to the recommendations for Chinese [23]. The presence of preexisting diseases was based on self-reported doctor diagnosis. These diseases were assigned scores according to the calculation of Charlson Comorbidity Index [24]. Clinical characteristics were extracted from medical records. The status of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) was determined by pathologists using immunohistochemical tests. Detailed definitions of ER, PR, and HER2 status were previously described in detail [25].

All participants were followed up at least every three months during the first year, and every six months during the second and the third year. Thereafter, patients were followed up with once every year until either death or December 31, 2017. We collected the following information by means of phone call and outpatient department visits: updated contact information, health condition (eg, recurrence, metastasis, death or other newly diagnosed diseases), and treatment information (eg, radiotherapy, chemotherapy, and hormone therapy). We conducted a post-diagnostic sleep assessment from 2015 to 2017. The endpoint of this study was progression-free survival (PFS), defined as the time from diagnosis to disease progression (recurrence, metastasis or death from breast cancer). Survival status was censored at the date of the latest interview or December 31, 2017.

2.3. Sleep-related variables

We assessed multiple post-diagnostic sleep characteristics using the Pittsburgh Sleep Quality Index (PSQI) [26] and questions about daytime napping. Sleep duration was assessed by querying the participants about their total hours of actual sleep at night. We selected the sleep quality item of the PSQI to represent the quality domain. As described in our previous work [27], habitual daytime napping was defined as daytime napping at least three times per week. Sleep efficiency was calculated as the ratio of actual sleep duration at night to time in bed to present continuity of sleep [19]. Daytime function reflects the capacity maintaining wakefulness and functionality during the day. Measurement of daytime function was derived from the daytime dysfunction component of PSQI. Patients with impaired daytime function reported daytime dysfunction score greater than zero, while the patients with normal daytime function reported daytime dysfunction score equal to zero [28].

2.4. Statistical analysis

Cox proportional hazards models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95%CI) for breast cancer prognosis in association with sleep characteristics. We adjusted for following covariates in the models: age at diagnosis (continuous), clinical stage (I/II, III/IV), chemotherapy (Yes/No), hormone therapy (Yes/No), HER2 status (positive/negative), scores of Charlson Comorbidity Index (0/≥1), BMI (<18.5, 18.5–23.9, ≥24), menopausal status (pre-menopausal/post-menopausal), and educational level (below junior school, senior high school, college or above). To assess the linear trend, we calculated the *P*-value by entering the medians of each category as continuous parameters in the models; we calculated the *P*-value for the non-linear trend across categories of sleep characteristics, using the quadratic term for the sleep variables.

To assess the joint effects of different sleep characteristics associated with breast cancer prognosis, we cross-classified the patients by different sleep characteristics. Further stratification analyses were performed by menopausal status (pre-menopausal vs. post-menopausal) to assess the interactions between menopausal status and sleep characteristics on breast cancer progression. Tests for multiplicative interactions were conducted using −2 log likelihood ratio test statistics, which compared models with and without the interaction terms.

To strengthen the association between sleep and breast cancer prognosis, we performed sensitivity analyses excluding stage IV patients (N = 34) and patients who had disease progression one year following the sleep assessment (N = 20). We also conducted examinations stratified by clinical stage (I/II vs. III/IV) and scores of Charlson Comorbidity Index (0 vs. ≥1) to see if the associations were similar across the baseline healthy status. All analyses were conducted using R software version 3.4 with a two-sided *P*-value of 0.05.

3. Results

3.1. Baseline characteristics of breast cancer patients

The distribution of demographic and clinical characteristics and the associations with breast cancer progression were shown in

Table 1. At the time of diagnosis, the median age of patients was 46 years (Interquartile Range (IQR): 40–55 years) and almost two-thirds of them were pre-menopausal (64.43%). Nearly half of the participants had below junior school as their highest attained educational level (43.67%). Majority of the patients were diagnosed with early cancer (stage I/II: 75.89%) and nearly a quintile of them reported one or more comorbidities (19.56%). Most of the participants have received chemotherapy/hormone therapy (79.6% for patients received chemotherapy and 68.2% for patients received hormone therapy, respectively). Except for clinical stage and chemotherapy, these characteristics were not significantly associated with breast cancer progression.

3.2. Associations between sleep characteristics and breast cancer progression

Over the follow-up period (median 4.2 years, IQR 3.2–5.1 years), a total of 111 disease progressions occurred, including 11 breast cancer deaths and 100 breast cancer recurrence/metastasis. Table 2 displayed the associations between post-diagnostic sleep characteristics and breast cancer prognosis. Compared to patients who slept 6–9 h at night, those who reported long sleep duration at night (>9 h) had a higher risk of disease progression (HR = 2.33, 95%CI: 1.01–5.42), while short sleep duration at night (<6 h) was associated with a non-significant elevated risk of disease progression (HR = 1.45, 95%CI: 0.83–2.54), showing a U-shaped pattern.

Table 1
Characteristics at baseline and the associations with progression-free survival of 1580 breast cancer patients.

Characteristics	Total (%)	Events	HR	95%CI
Age at diagnosis				
Continuous (Median, IQR)	(46, 40–55)		0.99	0.97–1.01
≤39	365 (23.1)	32	1.00	Reference
40–49	595 (37.7)	39	0.75	0.47–1.20
50–59	401 (25.4)	27	0.78	0.47–1.30
≥60	219 (13.9)	13	0.66	0.35–1.26
Menopausal status				
Pre-menopausal	1018 (64.4)	74	1.00	Reference
Post-menopausal	537 (34.0)	35	0.88	0.59–1.32
Educational level				
Below junior school	690 (43.7)	50	1.00	Reference
Senior high school	446 (28.2)	36	1.14	0.74–1.75
College or above	391 (24.7)	22	0.78	0.47–1.29
BMI (kg/m^2)				
<18.5	85 (5.4)	7	1.20	0.55–2.62
18.5–23.9	903 (57.2)	61	1.00	Reference
≥24	529 (33.5)	39	1.10	0.74–1.65
Clinical stage				
I/II	1199 (75.9)	57	1.00	Reference
III/IV	272 (17.2)	47	**4.05**	**2.75–5.96**
Unknown	109 (6.9)	7	1.27	0.58–2.80
ER status				
Negative	330 (20.9)	26	1.00	Reference
Positive	1136 (71.9)	77	0.88	0.56–1.37
Unknown	114 (7.2)	8	0.84	0.38–1.87
HER2 status				
Negative	896 (56.7)	65	1.00	Reference
Positive/equivocal	548 (34.7)	34	0.98	0.65–1.48
Unknown	136 (8.6)	12	1.24	0.67–2.31
Chemotherapy				
No	231 (14.6)	6	1.00	Reference
Yes	1259 (79.7)	95	**2.92**	**1.28–6.68**
Hormone therapy				
No	327 (20.7)	20	1.00	Reference
Yes	1078 (68.2)	76	1.17	0.72–1.92
Charlson comorbidity index				
0	1201 (76.0)	85	1.00	Reference
≥1	309 (19.6)	24	1.08	0.69–1.70

IQR: interquartile range; BMI: body mass index.
Bold indicates statistically significant values.

Table 2
Association between post-diagnostic sleep characteristics and progression free survival.

Sleep characteristics	Total	Events	HR (95%CI)[a]	HR (95%CI)[b]
Daytime napping				
No	434	32	1.00 (reference)	1.00 (reference)
Yes	966	65	0.91 (0.60,1.39)	0.94 (0.61,1.44)
Sleep duration at night				
< 6 h	162	16	**1.80 (1.05,3.09)**	1.45 (0.83,2.54)
6–9 h	1224	76	1.00 (reference)	1.00 (reference)
>9 h	42	6	**2.33 (1.02,5.37)**	**2.33 (1.01,5.42)**
P for trend[c]			**0.018**	**0.001**
Sleep efficiency				
Continuous			**0.17 (0.04,0.77)**	**0.14 (0.03,0.75)**
≥85%	1201	75	1.00 (reference)	1.00 (reference)
< 85%	158	15	**1.74 (1.00,3.04)**	**1.65 (0.92, 2.92)**
Sleep quality				
Good	438	18	1.00 (reference)	1.00 (reference)
Somewhat good	714	48	1.58 (0.92,2.71)	1.86 (1.06,3.25)
Bad/very bad	374	42	**2.93 (1.68,5.09)**	**3.08 (1.74,5.47)**
P for trend[d]			**< 0.001**	**< 0.001**
Daytime function				
Normal	865	41	1.00 (reference)	1.00 (reference)
Impaired	600	61	**2.24 (1.51,3.33)**	**2.49 (1.65,3.79)**

Bold indicates statistically significant values.
[a] Adjusted for age at diagnosis (continuous).
[b] Adjusted for age at diagnosis (continuous), stage (I/II, III/IV), chemotherapy (Yes/No), hormone therapy (Yes/No), HER2 status (positive/negative), scores of Charlson Comorbidity Index (0/≥1), BMI (<18.5, 18.5–23.9 and ≥ 24), menopausal status (pre-menopausal/post-menopausal) and educational level (below junior school, senior high school, and college or above).
[c] P for non-linear trend.
[d] P for linear trend.

Accordingly, the *P*-value for the non-linear trend was statistically significant in the adjusted model ($P_{non\text{-}linear} = 0.001$). Women who reported poor sleep quality (HR = 3.08, 95%CI: 1.74–5.47, $P_{linear} < 0.001$) or impaired daytime function (HR = 2.49, 95%CI: 1.65–3.79) after diagnosis experienced a poorer outcome. There were no significant associations between other sleep characteristics and progression-free survival after adjusting for covariates.

3.3. Joint effects of sleep characteristics

Because of the limited number of outcome, only some post-diagnostic sleep characteristics were examined for the joint effects of each other. As shown in Table 3, we found a significant interaction between short sleep duration at night and daytime function ($P_{interaction} = 0.011$). Short sleep duration (HR = 2.00, 95% CI: 1.06–3.77) significantly increased the risk of disease progression among patients with impaired daytime function, whereas it was associated with a non-significant reduced risk (HR = 0.25, 95% CI: 0.03–1.88) among those who reported normal daytime function. Long sleep duration was also associated with the elevated risk of disease progression among patients with impaired daytime function (HR = 4.69, 95%CI: 1.31–16.78), while the association was not significant among the patients with normal daytime function (HR = 1.43, 95%CI: 0.34–6.08), although the significant interaction was not observed ($P_{interaction} = 0.187$). Furthermore, we found that daytime napping could modify the effect of short sleep duration on breast cancer progression ($P_{interaction} = 0.005$). Patients with short sleep duration had a marked higher risk of disease progression (HR = 3.55, 95%CI: 1.58–7.97) among patients without napping habit, whereas the risk was somewhat reduced (HR = 0.59, 95%CI: 0.23–1.53) among those with napping habit. Poor sleep quality was significantly associated with disease progression among the patients who reported impaired daytime function (HR = 1.83, 95%CI: 1.08–3.08) or those who did not take habitual daytime napping (HR = 2.53, 95%CI: 1.20–5.31), yet no significant interactions were

Table 3
Joint effects of post-diagnostic sleep characteristics on progression free survival.

Sleep characteristics		Total	Events	HR (95%CI)[a]
Daytime function	**Sleep duration at night**			
Normal	< 6 h	61	1	0.25 (0.03, 1.88)
	6–9 h	724	34	1.00 (reference)
	>9 h	30	2	1.43 (0.34,6.08)
Impaired	< 6 h	92	14	**2.00 (1.06, 3.77)**
	6–9 h	455	38	1.00 (reference)
	>9 h	11	3	**4.69 (1.31,16.78)**
P for interaction	**0.011**[b]/0.187[c]			
Daytime napping	**Sleep duration at night**			
No	<6 h	49	10	**3.55 (1.58,7.97)**
	6–9 h	350	21	1.00 (reference)
	>9 h	14	1	1.21 (0.18,9.26)
Yes	<6 h	105	5	0.59 (0.23,1.53)
	6–9 h	795	50	1.00 (reference)
	>9 h	40	6	**3.41 (1.34,8.72)**
P for interaction	**0.005**[b]/0.290[c]			
Daytime function	**Sleep quality**			
Normal	Good/somewhat good	744	34	1.00 (reference)
	Bad/very bad	108	6	1.05 (0.44,2.53)
Impaired	Good/somewhat good	345	27	1.00 (reference)
	Bad/very bad	244	33	**1.83 (1.08,3.08)**
P for interaction	0.264			
Daytime napping	**Sleep quality**			
No	Good/somewhat good	304	17	1.00 (reference)
	Bad/very bad	118	15	**2.53 (1.20,5.31)**
Yes	Good/somewhat good	711	44	1.00 (reference)
	Bad/very bad	224	20	1.35 (0.79,2.31)
P for interaction	0.282			
Daytime napping	**Daytime function**			
No	Normal	230	10	1.00 (reference)
	Impaired	187	21	**3.26 (1.45,7.37)**
Yes	Normal	552	28	1.00 (reference)
	Impaired	366	33	**1.89 (1.14,3.14)**
P for interaction	0.425			

Bold indicates statistically significant values.
[a] Adjusted for age at diagnosis (continuous), stage (I/II, III/IV), chemotherapy (Yes/No), hormone therapy (Yes/No), HER2 status (positive/negative) and scores of Charlson Comorbidity Index (0/≥1).
[b] Between daytime function/daytime napping and sleep duration at night (<6 h vs. 6–9 h)/sleep quality (somewhat good vs. good).
[c] Between daytime function/daytime napping and sleep duration at night (>9 h vs. 6–9 h)/sleep quality (bad/very bad vs. good).

observed ($P_{interaction}$ = 0.264 and 0.282, respectively). In addition, the interaction between napping and daytime function on the progression did not occur either ($P_{interaction}$ = 0.425).

3.4. Stratified associations between sleep characteristics and breast cancer progression by menopausal status

As shown in Table 4, both short sleep duration (HR = 1.97, 95%CI: 1.01–3.84) and long sleep duration (HR = 3.17, 95%CI: 1.32–7.60) increased the risk of disease progression among pre-menopausal breast cancer patients, whereas no significant associations were observed among post-menopausal breast cancer patients. Moreover, the interactions were marginally significant ($P_{interaction}$ = 0.086 and 0.083, respectively). In addition, the strength of associations between breast cancer progression and sleep efficiency (HR = 2.03, 95%CI: 1.00–4.10), sleep quality (HR = 3.64, 95% CI: 1.75–7.57), and daytime function (HR = 2.58, 95%CI: 1.55–4.30) were stronger among pre-menopausal breast cancer patients than post-menopausal counterparts, though the interactions were not significant (all $P_{interaction} > 0.05$).

3.5. Sensitivity analyses

After excluding the stage IV patients (N = 34) and patients who had disease progression one year following the sleep assessment (N = 20), the main results did not change fundamentally (Supplementary Table S1). When stratified by clinical stage (I/II vs. III/IV) and scores of Charlson Comorbidity Index (0 vs. ≥1) at baseline, we found that the associations between sleep characteristics and breast cancer prognosis were similar across every stratum (Supplementary Table S2–3).

4. Discussion

In the current study, we found that long and short sleep duration, poor sleep quality, and impaired daytime function after diagnosis were associated with an elevated risk of breast cancer progression. Both short and long sleep duration increased the risk of disease progression only among the patients with impaired daytime function, but not those with normal daytime function. The habitual daytime napping conferred some degree of protection against breast cancer progression among short sleepers. The strength of the associations between post-diagnostic sleep characteristics and breast cancer progression were stronger among the pre-menopausal patients than post-menopausal women.

Few studies have explored the associations between sleep duration and breast cancer prognosis, yielding inconsistent results [10,17,18]. Phipps et al., found that short sleep duration before diagnosis was associated with a poor breast cancer survival while long sleep duration was a potential protective factor for the survival [10]; Marinac et al., showed that long sleep duration after diagnosis increased the risk of breast cancer progression while short sleep duration decreased the risk [18]. Meanwhile, in the NHS, it was shown that both long and short sleep duration after diagnosis increased the risk of breast cancer progression compared with the normal sleep duration, which was consistent with our results [17]. In addition, many studies exploring the associations between sleep duration and breast cancer initiation suggested that both long and short sleep duration may increase the risk of breast cancer [4,8,27]; and we have identified a similar pattern associated with breast cancer prognosis in the current study. The mechanisms underlying these effects were complicated, possibly involving multiple biological processes and health behavioral changes. It was reported that short sleep duration altered melatonin release, immune function, oxidative stress, and inflammatory pathways, then consequently influencing breast cancer progression [5,7,8,29]. The association between long sleep duration and disease progression might be explained by the lack of physical activity and shortened photoperiod [30]. Meanwhile, it could not be excluded that long sleep duration after diagnosis might reflect the underlying poor health condition and long sleepers were susceptible to poor breast cancer prognosis. In the present study, however, the associations between sleep duration and breast cancer prognosis were similar across health status at baseline (clinical stage and comorbidity), and our main results remained unchanged after excluding the patients with severe health status (Supplementary Table S1–3), making the association more robust.

Our finding that both short and long sleep duration after diagnosis were associated with a poor prognosis only among women with impaired daytime function, suggested that impaired daytime function may play a more important role in carcinogenesis. Impaired daytime function acts as a marker of inadequate sleep to fulfill one's need. This finding supported the hypothesis that individuals were programmed to need different hours to sleep and tended to have different “biological night” [31,32]. The mismatch between sleep duration needed and actual sleep duration might lead to circadian disruption, which played an important role in breast cancer carcinogenesis [8]. A recent study showed that not getting enough sleep to feel one's best was associated with elevated breast cancer risk, whereas sleep duration was not associated with

Table 4
Association between post-diagnostic sleep characteristics and progression free survival stratified by menopausal status.

Sleep characteristics	Pre-menopausal			Post-menopausal			P for interaction
	Total	Events	HR (95%CI)[a]	Total	Events	HR (95%CI)[a]	
Daytime napping							0.122
No	287	26	1.00 (reference)	143	6	1.00 (reference)	
Yes	617	40	0.69 (0.42,1.13)	332	23	2.07 (0.82,5.22)	
Sleep duration at night							0.086[b]/0.083[c]
< 6 h	92	11	**1.97 (1.01,3.84)**	68	4	0.85 (0.28,2.60)	
6–9 h	814	53	1.00 (reference)	389	22	1.00 (reference)	
> 9 h	27	6	**3.17 (1.32,7.60)**	15	0	–	
Sleep efficiency							0.703
≥85%	795	53	1.00 (reference)	388	21	1.00 (reference)	
< 85%	94	10	**2.03 (1.00,4.10)**	60	4	1.52 (0.51,4.58)	
Sleep quality							0.234
Good	256	7	1.00 (reference)	123	7	1.00 (reference)	
Somewhat good	406	27	2.00 (0.98,4.08)	221	11	1.17 (0.47,2.87)	
Bad/very bad	204	23	**3.64 (1.75,7.57)**	124	10	1.46 (0.57,3.77)	
Daytime function							0.108
Normal	546	25	1.00 (reference)	305	16	1.00 (reference)	
Impaired	402	41	**2.58 (1.55,4.30)**	189	18	**2.14 (1.06,4.35)**	

Bold indicates statistically significant values.
[a] Adjusted for age at diagnosis (continuous), stage (I/II, III/IV), chemotherapy (Yes/No), hormone therapy (Yes/No), HER2 status (positive/negative) and scores of Charlson Comorbidity Index (0/≥1).
[b] P value for interaction between menopause status and sleep duration at night (<6 h vs. 6–9 h).
[c] P value for interaction between menopause status and sleep duration at night (>9 h vs. 6–9 h).

breast cancer risk [33]. Hahm et al., also found that bedtime misalignment (going to bed earlier or later than preferred bedtime) was associated with rapid progression among metastatic breast cancer patients [15]. Such findings indicated that what was characterized as “normal sleep duration” might vary across individuals and not getting appropriate sleep to fulfill the need might explain the association between post-diagnostic sleep duration and breast cancer prognosis.

Habitual daytime napping was not associated with the breast cancer prognosis, though it has been regarded as a protective factor of breast cancer risk in our previous study [27]. Further analyses in the current study showed that habitual daytime napping after diagnosis reduced the risk of disease progression among patients with short sleep duration at night, while it increased the risk among those with long sleep duration at night. Daytime napping might supplement sleep duration at night among short sleepers and improve their prognosis. Prior studies suggested that the biological mechanisms of napping included reducing estrogen levels [34], altering cortisol pattern [35], and regulating the immune system [36]. As for long sleepers, daytime napping might be associated with physical activity deficits and disrupt the sleep-wake pattern [37], which might continue to impact the breast cancer progression.

Sleep quality is another important sleep characteristic closely linked to breast cancer risk [33,38,39] and it was found to be associated with the elevated risk of breast cancer progression in the present study. Similar results were also shown in previous studies [11,17]. Poor sleep quality might influence breast cancer prognosis through the same mechanisms as short sleep duration [5,7,8,29]. Further analyses in the present study revealed that the associations between post-diagnostic sleep quality and breast cancer progression were similar across different statuses of daytime function and daytime napping; indicating that sleep quality was a better predictor of breast cancer progression beyond sleep duration (which had differentiated associations on daytime function and daytime napping). Such findings suggested that improving sleep quality would be more important for breast cancer survival than maintaining proper sleep duration, which was a basis for the cognitive behavioral treatment that trade sleep duration for sleep quality via sleep restriction [40].

Notably, the associations of post-diagnostic sleep characteristics and breast cancer prognosis were more evident among pre-menopausal patients, although no significant interaction effect was observed. Vaughn et al., also found that the pre-diagnostic sleep disturbance was associated with a higher risk of breast cancer mortality among pre-menopausal women [11]. Prior studies indicated that poor sleep suppressed melatonin secretion and indirectly, led to an increase in circulating estrogen levels and up-regulation of estrogen signaling pathways [29,41], facilitating the progression of breast cancer, particularly for pre-menopausal patients. In addition, a study conducted in Taiwan showed that habitual sleep-wake behaviors could alter diurnal cortisol patterns among young breast cancer women (<40 years old) [42], while cortisol aberration increased the risk of breast cancer progression [43,44], which further supported the present results. However, the exact reasons why sleep had greater effects on pre-menopausal breast cancer patients remained to be explored.

Our study had some limitations. First, our measures of sleep characteristics were self-reported, which inevitably caused measurement bias. Next, underlying disease progression or baseline health status might alter patients' sleep characteristics. However, the sensitivity analyses and stratified analyses by healthy status in this study helped lower the likelihood of this issue. It should be noted that the event frequencies were quite few in some strata, resulting in lack of statistical power and unstable results. Finally, some important confounders were not available in this study; particularly, we hypothesized that the deficit of physical activity might be the reason why long sleepers who had habitual daytime napping had worse breast cancer prognosis, hindering further explanation of the hypothesis. More confounders should be considered in future studies.

5. Conclusion

To our knowledge, this was the first study examining the associations between multiple sleep characteristics and breast cancer prognosis in China. Our findings did suggest that inadequate sleep duration to feel one's best and poor sleep quality were associated with an increased risk of breast cancer progression, particularly for pre-menopausal patients. Future studies should explore the

underlying mechanisms and clarify the effect of evidence-based sleep intervention on breast cancer prognosis.

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Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.10.025.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2018.10.025.

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