Sleep Duration and Risk of Breast Cancer：The JACC Study

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Abstract

Purpose—The evidence on beneficial or adverse effects of sleep duration on risk of breast cancer remains controversial and limited, especially in Asia.

Methods—A prospective study of 34 350 women aged 40-79 years in whom sleep duration, menstrual and reproductive histories were determined by a self-administered questionnaire. The follow-up period was from 1988 to 2009, and hazard ratios (HRs) with 95% confidence intervals (CIs) of breast cancer incidence were calculated for shorter sleep duration in reference to sleep duration of ≥ 8 h/d by Cox proportional hazard models.

Results—During 19.2-year median follow-up (236 cases), we found a significant inverse association between sleep duration and risk of breast cancer, especially among postmenopausal women and women with low parity (nulliparous and women with < 3 children); the multivariable HRs (95% CIs) among postmenopausal women who reported 7h/d and ≤ 6h/d of sleep in reference to ≥ 8 h/d were 1.49 (0.81-2.76) and 1.98 (1.08-3.70) (P for trend = 0.028), and those values among women with low parity were 1.50 (0.96-2.35) and 1.76 (1.01-2.79) (P for trend = 0.018).

Conclusions—Short sleep duration was associated with increased risk of incident breast cancer, especially among postmenopausal women and women with low parity.

Keywords: sleep duration; breast cancer; incidence; cohort study; postmenopausal; parity; Japan

Introduction

Breast cancer is the most common cancer among Japanese women followed by colon and rectum cancer [1]. The associations between sleep duration and risk of breast cancer among women has a complex nature and remains controversial [2]. Previous case-control and cohort studies have reported no association between sleep duration and risk of breast cancer [2-7]. However, several other studies showed lower risk of breast cancer with longer sleep duration (≥ 9h/d) [8-10], while some other studies indicated that longer sleep duration (≥ 9h/d) was associated with increased risk of breast cancer [11-12].

Melatonin is suggested as an agent in the association between sleep duration and breast cancer [13-14]. Melatonin (5-methoxytryptamine) is synthesized and secreted by the pineal gland in the brain and controls the body's circadian rhythm [13]. Darkness during sleep stimulates the release of melatonin [7,9,15], and melatonin may inhibit breast tumorigenesis directly by inhibiting mammary cell proliferation and invasiveness, and indirectly by decreasing estrogen levels via a down-regulation of the hypothalamic-pituitary reproductive axis and regulating the activity of the aromatases, the enzymes responsible for the local estrogens synthesis [16-19].

Some studies showed menopausal status to be associated with risk of breast cancer because of ageing [20], higher levels of adiposity [21-22] or

endogenous estrogen [23]. Furthermore, short sleep duration, especially among postmenopausal women, was associated with high risk of breast cancer in several cohort studies [8-10, 24]. Abundant previous findings have also shown parity as an indicator for breast cancer risk [25-27]. Meanwhile, multiparous women have reported longer sleep duration than nulliparous women [28].

Thus, we thought to examine the associations between sleep duration and risk of breast cancer among premenopausal and postmenopausal women, and among low and high parous women in a large population-based Japanese study, the Japan Collaborative Cohort study (JACC).

Materials and methods

Study population and ascertainment of breast cancer

Details of the study design and subjects have been described elsewhere [29]. Briefly, the baseline data of the JACC Study were collected from 1988 to 1990, and 110 585 individuals (46 395 men and 64 190 women) aged 40 to 79 years in 45 study areas throughout Japan participated in the study. The follow-up survey for cancer incidence was conducted from the baseline, and finalized at the end of the 2009. In 24 areas out of the 45 study areas, data on cancer incidence such as date of diagnosis and primary site were collected simultaneously through population-based

cancer registries or by reviewing the records of local and major hospitals. After excluding male subjects, we confined the analysis to women from these 24 areas where cancer incidence information are available (n=36 266). Excluding data of women with previous diagnosis of breast cancer (n=11), and women with missing data on sleep duration (n =1 905) left a total of 34 350 (19 529 premenopausal, and 14 821 postmenopausal) women for the analysis. This study was sponsored by the Ministry of Education, Sports and Science. Informed consent was obtained from participants asking their will to participate to the JACC study in the baseline questionnaire. The ethics committees of Nagoya University School of Medicine and Osaka University approved the protocol of this study.

Exposure and other covariates assessment

Participants completed a self-administered questionnaire including sleep duration, information on age, family history of diseases, history of hypertension, diabetes mellitus, cardiovascular diseases, cancer, height, weight, education background, smoking status, alcohol drinking habit, physical activity, mental stress, dietary habits, reproductive and menstrual history, menopause and hormone use. Body mass index was calculated by dividing reported weight in kilograms by the square of reported height in meters.

Assessment of sleep duration

We obtained information about the average sleep duration on weekdays during the preceding year. The average sleep duration per day was classified into 3 categories: ≤ 6, 7 and ≥ 8 hours. Fractions hours were rounded off (e g, 7 hours represented responses from 7.0 to 7.9 hours).

Statistical analysis

Mean values (standard deviations) and proportions of baseline risk characteristics were calculated, and the linear trends in those variables according to sleep duration were tested by the linear regression analysis for continuous variables and the logistic regression analysis for proportional variables. Person-years of follow-up were calculated from the responding date to the baseline questionnaire until the obtainment of one out of four possible endpoints as follows: 1) incidence of breast cancer event, 2) relocation from the study area, 3) the end of the study on 31 December 2009, or 4) death. Because some study areas discontinued the follow-up survey regarding cancer before 2009 (1994 in one study area, 1997 in two areas, 1999 in one area, 2000 in one area, 2002 in one area, 2003 in one area, 2006 in two areas, and 2008 in two areas).

Cox proportional hazard regression age- and multivariable-adjusted models were used to estimate the hazard ratios (HRs) with 95% confidence intervals (CIs) for breast cancer incidence according to sleep duration (≤ 6h, 7h and ≥ 8 h/d) as the reference to ≥ 8 h/d, and in relation to 1-SD decrement (1.07 h/d) of sleep duration. The confounding factors

included age (continuous), age of menarche (< 14, 14-15 and >15 y), age of menopause (< 45, 45-50 and >50 y), age at first child birth (< 25 and ≥ 25 y), type of menopause (nature or operation), body mass index (continuous), sport time per week (never, <1, 1-2, 3-4 and ≥5 h/wk), walking time per day (never, < 30, 30-60 and ≥60 minutes/d), currently married (yes or no), smoking status (never, ex-smoker and current smoker), alcohol intake (never, ex-drinker and current drinker of 0.1-22.9, 23.0-45.9, and ≥ 46.0 g ethanol/d), parity (0, 1, 2 and ≥3), use of sex hormone (yes or no), family history of breast cancer (yes or no), and history of diabetes (yes or no). The stratification analyses were performed by potential effect modifiers such as menopausal status and number of children. Values for *P*-interaction were calculated for cross-product terms of menopausal status (dichotomous) or number of children (continuous) with sleep duration categories (1 to 3 corresponding to ≤ 6, 7 and ≥ 8 h/d of sleep duration) for the categorical analysis and sleep duration (h/d) for the continuous analysis. We used SAS Version 9.4 software (SAS Institute Inc, Cary, NC) for statistical analysis. All statistical tests were 2-tailed and values of P <0.05 were regarded as significant.

Results

Table 1 shows the baseline characteristics of women according to sleep duration. Women who reported ≤ 6 h/d of sleep were more likely to have

a family history of breast cancer and to have used sex hormones. On the other hand, women who reported ≥ 8 h/d of sleep were of older age at menarche, with higher BMI and were more likely to have natural menopause and ≥3 children.

With reference to women with sleep duration ≥ 8 h/d, there was higher risk of breast cancer among women with shorter sleep duration in total women (Table 2). The multivariable HRs (95% CIs) of breast cancer were 1.36 (0.98-1.90) for 7 h and 1.31 (0.92-1.86) for ≤ 6 h sleep per day.

Table 3 shows the stratification analyses by menopausal status and parity (number of children). The inverse associations between sleep duration and risk of breast cancer were confined to postmenopausal women, the multivariable HRs (95% CIs) of breast cancer were 1.49 (0.81-2.76) for 7 h and 1.98 (1.08-3.70) for ≤ 6 h sleep per day (P for trend = 0.028); however, the interaction by menopausal status was not statistically significant ($P_{\text{interaction}} = 0.264$). The inverse association was also evident among low parous women including nulliparous and women with < 3 children. The multivariable HRs (95% CIs) for breast cancer risk among low parous women who have reported 7 h and ≤ 6 h sleep per day compared with those repoted ≥ 8h/d were 1.50 (0.96-2.35) and 1.76 (1.01-2.79), respectively (P for trend = 0.018, $P_{\text{interaction}} = 0.002$).

Discussion

During 19.2-years median follow-up for 34 350 women aged ≥ 40 years, we observed that short sleep duration was associated with increased risk of incident breast cancer among Japanese women. This positive association was more evident for postmenopausal women and women with number of children < 3, although the interaction with parity but not menopausal status was statistically significant.

The high risk of incident breast cancer with short sleep duration found in our study is consistent with findings from previous prospective cohort studies [8, 24]. Among 42 840 women of the Southern Community Cohort Study, shorter sleep was associated with increased risk of breast cancer; odds ratios (95% CIs) were 2.13 (1.15- 3.93) for <6 h/day, 1.66 (0.92- 3.02) for 6 h/d and 2.22 (1.19-4.12) for 7 h/d compared with ≥ 8 h/d (P for trend = 0.04) [24]. Similar results were found among 7 396 Finnish women [8]. However, those studies did not examine the association by menopausal status or parity. In Japan, Kakizaki et al examined the association between sleep duration and risk of incident breast cancer among 23 995 women in the Ohsaki National Health Insurance (NHI) Cohort Study, and showed that women who reported ≥ 9 h/d sleep in reference to those with ≤ 6h/d had lower breast cancer risk: the multivariable HR (95%CI) was 0.29 (0.09–0.98, P for trend = 0.002). The reduced risk was observed among postmenopausal women; 0.74 (0.35–1.59, P for trend = 0.09) but not among premenopausal; 1.48

(0.56–3.93, P for trend = 0.27) (P for interaction = 0.70) [10]. Among 33 528 women participated in the Singapore Chinese Health Study, Wu et al reported inverse trends in breast cancer risk across sleep duration categories among postmenopausal women, but not among total or premenopausal women. In reference to sleep duration for ≤ 6 h/d, the multivariable HRs (95%CIs) among postmenopausal women in the categories 7, 8 and ≥ 9 h/d were 0.94 (0.70-1.20), 0.81 (0.60-1.10) and 0.67 (0.40-1.10) (P for trend = 0.047) [9]. Previous studies have shown high risk of breast cancer in nulliparous or women with low parity than that in multiparous women [25]. Again, the inverse association between sleep duration and risk of breast cancer was observed among women with < 3 children including nulliparous women more than that among those with ≥ 3 children.

Shorter sleep duration was associated with lower levels of urinary melatonin; 42% lower in Chinese women reported ≤ 6 h of sleep duration than levels in women reported ≥ 9 h of sleep duration in the Singapore Chinese Health Study [9]. Because sleep stimulates the release of melatonin [9], melatonin is suggested a biological mediator for the sleep/breast cancer association. Higher levels of melatonin may associate with reduced risk of breast cancer by the following mechanisms; (a) melatonin interacts with estrogen receptors (ER) on the epithelial mammary cells, leading to direct inhibition of mammary cell proliferation

and invasiveness [23]; (b) melatonin interacts with the neuroendocrine reproductive axis and the hypothalamic-pituitary reproductive axis, leading to a down-regulation of some hormones which promote tumor growth, especially gonadal estrogens and prolactin [30]; (c) melatonin inhibits telomerase enzymes activity, responsible for estrogen synthesis in tumor cells and adjacent peritumor fat tissues [31]; (d) melatonin has antioxidant properties of melatonin can suppress oncogenesis [32].

Postmenopausal women are at higher risk of breast cancer than premenopausal women because of higher levels of adiposity among postmenopausal women [21-22] which serve as the primary source of endogenous estrogen transformed from androgen by enhanced aromatase expression and activity [22]. On the other hand, nulliparous and women with low parity showed lower urinary excretion of melatonin [15] and higher levels of estrogens and prolactin, but lower levels of sex hormone-binding globulins [33-35]. These factors were associated with increased risk of estrogen-receptor-positive carcinogenic tumors. Thus, the sleep-induced melatonin secretion could, at least partially, explain the inverse association of sleep duration with risk of breast cancer in high risk group of postmenopausal women and women with low parity in our study.

The strengths of our study were its prospective design, which avoided recall bias and the availability of information on potential confounding

265 factors. Our subjects were recruited from the general population, the
266 sample was large and the response rate to the questionnaire was high
267 [29,36]. In addition, the cancer registry of the study had sufficient quality
268 to reduce the possibility of misclassification of outcomes [37].

269 There are several limitations in this study. First, we did not obtain
270 information about the quality of sleep, such as the presence or absence of
271 sleep apnea or other sleep disorders, which were associated with
272 increased risk of breast cancer via intermittent hypoxia and suppression
273 of the immune system [38]. Second, we used self-reported information on
274 sleep duration obtained only at baseline, we cannot rule out the possibility
275 of change in sleep duration during the long follow-up, and the self-report
276 may lead to some misclassification. However, self-reported sleep duration
277 was shown to yield valid results in comparison with quantitative sleep
278 assessment with actigraphy; r = 0.57 for nighttime sleep duration [39].
279 Third, we could not examine a potential adverse effect of long sleep
280 duration, because of the low proportion of participants and the few
281 number of cases in the long sleep duration of ≥ 9h/d category (5.6% of
282 participants and 6 breast cancer cases). Fourth, nulliparous women are at
283 high risk for breast cancer [25]. However, only 6.7% of our studied
284 women were nulliparous and there was no breast cancer case in the sleep
285 duration category of ≥ 8h/d. Therefore, we could not treat them as a
286 separate category in the stratification analysis; but, we added them to

women with low parity < 3 children. Finally, we did not collect the data on blood melatonin levels or urinary excretions; therefore, the exact contribution of melatonin in the observed associations between sleep duration and risk of incident breast cancer cannot be certified.

In summary, short sleep duration was associated with increased risk of incident breast cancer, especially among postmenopausal women and women with low parity. Health education to women about the need for proper sleep duration is suggested and further research is needed to confirm the observed associations.

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Compliance with Ethical Standards:

Conflict of Interest: All authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in this study were in accordance with the Helsinki declaration and was approved by Osaka and Nagoya Universities research ethics committees.

Informed consent: Informed consent was obtained from all participants included in the study at individual or community leader level.

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Table 1. Distributions of potential risk factors according to sleep duration in a cohort of 34,350 Japanese women.

Parameters	Sleep duration			P for
	⩽ 6 h	7 h	⩾ 8 h	trend
No. at risk	10064	12979	11307	
Age, y (SD)	60.7（7.7）	60.2（7.2）	62.6（7.6）	<0.001
Age at menarche, y (SD)	15.0（1.8）	15.0（1.7）	15.3（1.8）	<0.001
Age at menopause, y (SD)	48.6（4.6）	48.6（4.7）	48.7（4.5）	0.318
Natural menopause, %	86.6	87.2	88.1	0.005
Age at first child birth, y (SD)	24.7（3.3）	24.5（3.1）	24.2（3.0）	<0.001
Parity (number of children)				
0	3.0	3.4	3.2	<0.001
1	8.0	7.9	6.7	
2	34.5	35.8	28.7	
⩾ 3	54.5	52.9	61.3	
Family history of breast cancer, %	1.5	1.4	1.2	0.023
Body mass index, kg/m^2(SD)	22.9（3.2）	22.9（3.1）	23.1（3.3）	<0.001
Currently married, %	78.1	81.9	77.6	0.065
Sports ⩾3h/wk, %	10.9	10.9	11.5	0.500
Walking time ⩾60min/d, %	73.1	74.1	74.6	0.013
Current smoking, %	2.6	2.1	2.7	0.250
Alcohol intake, g ethanol/d (SD)	8.6（10.6）	8.4（10.6）	9.1（12.7）	0.838
Sex hormone use, %	5.1	4.6	3.7	<0.001
History of diabetes, %	5.7	4.1	6.1	0.403

Table 2. Age-adjusted and multivariable hazard ratios (95% confidence intervals) of incident breast cancer according to sleep duration for total women.

	Sleep duration			P for trend	[1]1SD decrement（1.07 h/d）of sleep duration
	⩽ 6 h	7 h	⩾ 8 h		
Total women					
Person-year	165359	221198	194205		
Breast cancer, n.	74	101	61		
Age-adjusted HR（95%CI）	1.31（0.93－1.85）	1.35（1.98－1.86）	1.00	0.133	1.11（0.97－1.27）
Multivariable HR（95%CI）[2]	1.31（0.92－1.86）	1.36（0.98－1.90）	1.00	0.149	1.13（0.98－1.29）

* [1] 1SD decrement in sleep duration = 1.07 h/d.

* [2] Adjusted for age, age at menarche, age at first child birth, body mass index, parity (number of children), family history of breast cancer, marital status, sport time, walking time, alcohol intake, smoking status, hormone use, history of diabetes, and age and type of menopause.

Table 3. Multivariable hazard ratios (95% confidence intervals) of incident breast cancer according to sleep duration, stratified by menopausal status and number of children.

	Sleep duration			P for	[1]1SD decrement（1.07 h/d）
	⩽ 6 h	7 h	⩾ 8 h	trend	of sleep duration
Menopausal status					
Premenopause					
Person-year	102201	138570	114858		
Breast cancer, n.	46	74	43		
Age-adjusted HR（95%CI）	1.10（0.72－1.69）	1.32（0.90－1.94）	1.00	0.689	1.05（0.89－1.24）
Multivariable HR（95%CI）[2]	1.11（0.72－1.71）	1.34（0.90－1.98）	1.00	0.687	1.07（0.90－1.27）
Postmenopause					
Person-year	63158	82628	79347		
Breast cancer, n.	28	27	18		
Age-adjusted HR（95%CI）	1.92（1.06－3.49）	1.43（0.78－2.60）	1.00	0.031	1.26（1.00－1.58）
Multivariable HR（95%CI）[3]	1.98（1.08－3.70）	1.49（0.81－2.76）	1.00	0.028	1.28（1.01－1.61）
$P_{interaction}$				0.264	0.400
Number of children					
0 to 2					
Person-year	89345	122823	94275		
Breast cancer, n.	52	60	32		
Age-adjusted HR（95%CI）	1.66（1.06－2.59）	1.40（0.91－2.16）	1.00	0.027	1.21（1.01－1.44）
Multivariable HR（95%CI）[4]	1.76（1.01－2.79）	1.50（0.96－2.35）	1.00	0.018	1.26（1.05－1.51）
⩾ 3					
Person-year	76014	98375	99929		

Breast cancer, n.	22	41	29		
Age-adjusted HR（95%CI）	0.88（0.50－1.55）	1.27（0.78－2.08）	1.00	0.692	0.98（0.80－1.21）
Multivariable HR（95%CI）[4]	0.83（0.46－1.48）	1.24（0.75－2.04）	1.00	0.562	0.96（0.77－1.20）
$P_{interaction}$				0.002	0.014

* [1] 1SD decrement in sleep duration = 1.07 h/d.

* [2] Adjusted for age, age at menarche, age at first child birth, body mass index, parity (number of children), family history of breast cancer, marital status, sport time, walking time, alcohol intake, smoking status, hormone use, history of diabetes.

* [3] Adjusted further for age and type of menopause.

*[4] Adjusted for age, age at menarche, age at first child birth, body mass index, family history of breast cancer, marital status, sport time, walking time, alcohol intake, smoking status, hormone use, history of diabetes, and age and type of menopause.