HOKKAIDO UNIVERSITY

Title	Sleep duration and risk of breast cancer : The JACC Study
Author(s)	Cao, Jinhong; Eshak, Ehab S.; Liu, Keyang et al.
Citation	Breast cancer research and treatment, 174(1), 219-225 https://doi.org/10.1007/s10549-018-4995-4
Issue Date	2019-02
Doc URL	https://hdl.handle.net/2115/76650
Rights	The final publication is available at link.springer.com
Type	journal article
File Information	inal1 breast cancer research and treatment R1.pdf



Hokkaido University Collection of Scholarly and Academic Papers : HUSCAP

Sleep Duration and Risk of Breast Cancer：The JACC Study

Jinhong Cao[1], Ehab S Eshak [1,2], Keyang Liu[1], Isao Muraki[1], Renzhe Cui[1], Hiroyasu Iso[*,1], Akiko Tamakoshi[3] and JACC Study Group*

[1] Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, Osaka, Japan.

[2]Department of Public Health, Community and Preventive Medicine, Faculty of Medicine, Minia University, Minia, Egypt.

[3]Department of Public Health, Faculty of Medicine, Hokkaido University, Sapporo, Japan.

Correspondence: Hiroyasu Iso, MD, Ph.D, MPH, Professor of Public Health, Department of Social Medicine, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita-shi, Osaka 565-0871, Japan.

Phone: +81-6-6879-3911

Fax: +81-6-6879-3919

E–mail: iso@pbhel.med.osaka-u.ac.jp

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.

Acknowledgements

The authors thank all staff members involved in this study for their valuable help in conducting the baseline survey and follow-up.

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.

Funding: This work was supported by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT) (Monbusho); Grants-in-Aid for Scientific Research on Priority Areas of Cancer; and Grants-in-Aid for Scientific Research on Priority Areas of Cancer Epidemiology from MEXT (MonbuKagaku-sho) (Nos. 61010076, 62010074, 63010074, 1010068, 2151065, 3151064, 4151063, 5151069, 6279102, 11181101, 17015022, 18014011, 20014026, 20390156, and 26293138), Comprehensive

Research on Cardiovascular and Life-Style Related Diseases (H26-Junkankitou [Seisaku]-Ippan-001and H29–Junkankitou [Seishuu]–Ippan–003), JSPS KAKENHI Grant Number JP 16H06277, and Grants-in-Aid for China Scholarship Council (CSC file No. 201608050113).

Study investigators

Members of the JACC Study Group: Dr. Akiko Tamakoshi (present chairperson of the study group), Hokkaido University Graduate School of Medicine, Dr. Mitsuru Mori, Sapporo Medical University School of Medicine, Dr. Yoshihiro Kaneko, Akita University Graduate School of Medicine, Dr. Ichiro Tsuji, Tohoku University Graduate School of Medicine, Dr. Yosikazu Nakamura, Jichi Medical School, Dr. Hiroyasu Iso, Osaka University School of Medicine, Dr, Kazumasa Yamagishi, Faculty of Medicine, University of Tsukuba, Dr. Haruo Mikami, Chiba Cancer Center, Dr. Michiko Kurosawa, Juntendo University School of Medicine Dr. Yoshiharu Hoshiyama, Yokohama Soei University, Dr. Naohito Tanabe, University of Niigata Prefecture, Dr. Koji Tamakoshi, Nagoya University Graduate School of Health Science, Dr. Kenji Wakai, Nagoya University Graduate School of Medicine, Dr. Shinkan Tokudome, National Institute of Health and Nutrition, Dr. Koji Suzuki, Fujita Health University School of Health Sciences, Drs. Shuji Hashimoto and Hiroshi

Yatsuya, Fujita Health University School of Medicine, Dr. Shogo Kikuchi, Aichi Medical University School of Medicine, Dr. Yasuhiko Wada, Faculty of Nutrition, University of Kochi, Dr. Takashi Kawamura, Kyoto University Health Service, Dr. Yoshiyuki Watanabe, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Dr. Kotaro Ozasa, Radiation Effects Research Foundation, Dr. Kazuya Mikami, Kyoto Prefectural University of Medicine Graduate School of Medical Science, Dr. Chigusa Date, School of Human Science and Environment, University of Hyogo, Dr. Kiyomi Sakata, Iwate Medical University, Dr. Yoichi Kurozawa, Tottori University Faculty of Medicine, Drs. Takesumi Yoshimura and Yoshihisa Fujino, University of Occupational and Environmental Health, Dr. Akira Shibata, Kurume University, Dr. Naoyuki Okamoto, Kanagawa Cancer Center, and Dr. Hideo Shio, Long-Term Care Health Facility Caretown Minamikusatsu, Shiga.

References

1. Matsuda A, Matsuda T, Shibata A, Katanoda K, Sobue T, Nishimoto H, Japan Cancer Surveillance Research Group. Cancer incidence and incidence rates in Japan in 2008: A Study of 25 population-based cancer registries for the Monitoring of Cancer Incidence in Japan (MCIJ) Project. Jpn J Clin Oncol. 2013; 44: 388-96.
2. Qian X, Brinton LA, Schairer C, Matthews CE. Sleep duration and breast cancer risk in the Breast Cancer Detection Demonstration Project follow-up cohort. British Journal of Cancer. 2015; 112: 567-571.
3. Vogtmann E, Levitan EB, Hale L, Shikany JM, Shah NA, Endeshaw Y, Lewis CE, Manson JE, Chlebowski RT. Association between sleep and breast cancer incidence among postmenopausal women in the women's health initiative. Sleep. 2013; 36: 1437-1444.
4. Girschik J, Heyworth J, Fritschi L. Self-reported Sleep Duration , Sleep Quality , and Breast Cancer Risk in a Population-based Case-Control Study. American Journal of Epidemiology. 2013; 177: 316-327.
5. Wu AH, Stanczyk FZ, Wang R, Koh WP, Yuan JM, Yu MC. Sleep duration, spot urinary 6-sulfatoxymelatonin levels and risk of breast cancer among Chinese women in Singapore. Int J Cancer. 2013; 132: 891-896.

6. Qin Y, Zhou Y, Zhang X, Wei X, He J. Sleep duration and breast cancer risk: A meta-analysis of observational studies. Int J Cancer. 2013; 134: 1166-1173.
7. Pinheiro SP, Schernhammer ES, Tworoger SS, Michels KB. A prospective study on habitual duration of sleep and incidence of breast cancer in a large cohort of women. Cancer Res. 2006; 66(10): 5521-5525.
8. Verkasalo PK, Lillberg K, Stevens RG, Hublin C, Partinen M, Koskenvuo M, Kaprio J. Sleep Duration and Breast Cancer : A Prospective Cohort Study. Cancer Res. 2005; 65(20): 9595-9601.
9. Wu AH, Wang R, Koh W, Stanczyk Z, Lee H, Yu MC. Sleep duration , melatonin and breast cancer among Chinese women in Singapore. Carcinogenesis. 2008; 29: 1244-1248.
10. Kakizaki M, Kuriyama S, Sone T, Ohmori-Matsuda K, Hozawa A, Nakaya N, Fukudo S, Tsuji I. Sleep duration and the risk of breast cancer: the Ohsaki Cohort Study. Br J Cancer. 2008; 99: 1502-1505.
11. Mcelroy JA, Newcomb PA, Titus- L, Egan KM. Duration of sleep and breast cancer risk in a large population- based case-control study. J Sleep Res. 2006; 15(3): 241-249.
12. Hurley S, Goldberg D, Bernstein L, Reynolds P, Hurley S. Sleep duration and cancer risk in women. Cancer Causes & Control. 2015; 26(7): 1037-1045.

13. Brzezinski A. Melatonin in humans. N Engl J Med. 1997; 336: 186-195.
14. Schernhammer ES, Schulmeister K. Melatonin and cancer risk: does light at night compromise physiologic cancer protection by lowering serum melatonin levels? Br J Cancer. 2004; 90: 941-943.
15. Schernhammer ES, Kroenke CH, Dowsett M, Folkerd E, Hankinson SE. Urinary 6-sulfatoxymelatonin levels and their correlations with lifestyle factors and steroid hormone levels. *J Pineal Res. 2006;* 40: 116-124.
16. Anisimov VN. The role of pineal gland in breast cancer development. Crit Rev Oncol Hematol. 2003; 46: 221-34.
17. Cohen M, Lippman M, Chabner B. Role of the pineal gland in theaetiology and treatment of breast cancer. Lancet. 1978; 2: 814-881.
18. Blask DE, Wilson ST, Zalatan F. Physiological melatonin inhibition of human breast cancer cell growth in vitro: evidence for a glutathione-mediated pathway. Cancer Res. 1997; 57: 1909-1914.
19. Cos S, Gonzalez A, Martinez-Campa C, Mediavilla MD, Alonso-Gonzalez C, Sanchez-Barcelo EJ. Estrogen-signaling pathway: a link between breast cancer and melatonin oncostatic actions. Cancer Detect Prev. 2006; 30(2): 118-28.
20. Surakasula A, Nagarjunapu GC, Raghavaiah KV. A comparative study of pre- and post-menopausal breast cancer: Risk factors, presentation, characteristics and management. J Res Pharm Pract. 2014;

437 3(1): 12-18.
438 21.Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased
439 visceral fat and decreased energy expenditure during the menopausal
440 transition. Int J Obes. 2008; 32(6): 949-958.
441 22.Cleary MP, Grossmann ME. Obesity and breast cancer: the
442 estrogen connection. Endocrinology. 2009; 150(6): 2537-2542.
443 23.Molis TM, Spriggs LL, Hill SM. Modulation of estrogen receptor
444 mRNA expression by melatonin in MCF-7 human breast cancer cells.
445 Mol Endocrinol. 1994; 8: 1681-1690.
446 24.Xiao Q, Signorello LB, Brinton LA, Cohen SS, Blot WJ, Matthews
447 CE. Sleep duration and breast cancer risk among black and white
448 women. Sleep Med. 2016; 20: 25-9.
449 25.Lambe M, Hsieh CC, Chan HW, Ekbom A, Trichopoulos D, Adami
450 HO. Parity, age at first and last birth, and risk of breast cancer: a
451 population-based study in Sweden. Breast Cancer Res Treat. 1996;
452 38(3): 305-11.
453 26.Palmer JR, Boggs DA, Wise LA, Ambrosone CB, Adams-Campbell
454 LL, Rosenberg L. Parity and lactation in relation to estrogen receptor
455 negative breast cancer in African American women. Cancer
456 Epidemiology Biomarkers and Prevention. 2011; 20: 1883-1891.
457 27.Ambrosone CB, Zirpoli G, Ruszczyk M, Shankar J,
458 Hong CC, McIlwain D, Roberts M, Yao S, McCann SE, Ciupak G,

459 Hwang H, Khoury T, Jandorf L, Bovbjerg DH, Pawlish K, Bandera E.
460 Parity and Breastfeeding among African-American Women:
461 Differential Effects on Breast Cancer Risk by Estrogen Receptor
462 Status in the Women's Circle of Health Study. Cancer Causes Control.
463 2014; 25(2): 259-265.
464 28.Signal TL, Gander PH, Sangalli MR, Travier N, Firestone RT, Tuohy
465 JF. Sleep duration and quality in healthy nulliparous and
466 multiparous women across pregnancy and post-partum.Aust N Z J
467 Obstet Gynaecol. 2007; 47(1): 16-22.
468 29.Tamakoshi A, Ozasa K, Fujino Y, Suzuki K, Sakata K, Mori M,
469 Kikuchi S , Iso H, the JACC Study Group. Cohort Profile of the Japan
470 Collaborative Cohort Study. J Epidemiol. 2013; 23: 227-232.
471 30.Reiter RJ. The pineal and its hormones in the control of reproduction
472 in mammals. Endocr Rev. 1980; 1: 109-131.
473 31. Leon-Blanco MM, Guerrero JM, Reiter RJ, Calvo JR, Pozo D.
474 Melatonin inhibits telomerase activity in the MCF-7 tumor cell line
475 both in vivo and in vitro. J Pineal Res. 2003; 35(3): 204-11.
476 32. Allegra M, Reiter RJ, Tan DX, Gentile C, Tesoriere L, Livrea MA.
477 The chemistry of melatonin's interaction with reactive species. J
478 Pineal Res. 2003; 34: 1-10.
479 33.Longcope C, Speizer FE. Reproductive factors and family history of
480 breast cancer in relation to plasma estrogen and prolactin levels in

postmenopausal women in the Nurses' Health Study (United States). Cancer Causes & Control. 1995; 6: 217-224.

34. Kwa HG, Cleton F, Bulbrook RD, Wang DY, Hayward JL. Plasma prolactin levels and breast cancer: relation to parity, weight and height, and age at first birth. Int J Cancer. 1981; 28: 31-4.

35. Bernstein L, Pike MC, Ross RK, Judd HL, Brown JB, Henderson BE. Estrogen and sex hormone-binding globulin levels in nulliparous and parous women. J Natl Cancer Inst. 1985; 74: 741-5.

36. Tamakoshi K, Yatsuya H, Wakai K, Suzuki S, Nishio K, Lin Y, Niwa Y, Kondo T, Yamamoto A, Tokudome S, Toyoshima H, Tamakoshi A, JACC Study Group. Impact of menstrual and reproductive factors on breast cancer risk in Japan: results of the JACC study. Cancer Sci. 2005; 96(1): 57-62.

37. Ukawa S, Tamakoshi A, Mori M, Ikehara S, Shirakawa T, Yatsuya H, Iso H, JACC study group. Association between average daily television viewing time and the incidence of ovarian cancer: findings from the Japan Collaborative Cohort Study. Cancer Causes Control. 2018; 29(2): 213-219.

38. Fang HF, Miao NF, Chen CD, Sithole T, Chung MH. Risk of cancer in patients with insomnia, parasomnia, and obstructive sleep apnea: a nationwide nested case-control study. J Cancer. 2015; 6(11): 1140-7.

503 39.Lockley SW, Skene DJ, Arendt J. Comparison between subjective and
504 actigraphic measurement of sleep and sleep rhythms. Journal of Sleep
505 Research. 1999; 8: 175-183.
506
507

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.