HOKKAIDO UNIVERSITY

Title	Sleep duration and risk of breast cancer : The JACC Study
Author(s)	Cao, Jinhong; Eshak, Ehab S.; Liu, Keyang; Muraki, Isao; Cui, Renzhe; Iso, Hiroyasu; Tamakoshi, Akiko; Mori, Mitsuru; Kaneko, Yoshihiro; Tsuji, Ichiro; Nakamura, Yosikazu; Yamagishi, Kazumasa; Mikami, Haruo; Kurosawa, Michiko; Hoshiyama, Yoshiharu; Tanabe, Naohito; Tamakoshi, Koji; Wakai, Kenji; Tokudome, Shinkan; Suzuki, Koji; Hashimoto, Shuji; Yatsuya, Hiroshi; Kikuchi, Shogo; Wada, Yasuhiko; Kawamura, Takashi; Watanabe, Yoshiyuki; Ozasa, Kotaro; Mikami, Kazuya; Date, Chigusa; Sakata, Kiyomi; Kurozawa, Yoichi; Yoshimura, Takesumi; Fujino, Yoshihisa; Shibata, Akira; Okamoto, Naoyuki; Shio, Hideo
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	http://hdl.handle.net/2115/76650
Rights	The final publication is available at link.springer.com
Type	article (author version)
File Information	final1 breast cancer research and treatment R1.pdf

1 **Sleep Duration and Risk of Breast Cancer：The JACC Study**

2 Jinhong Cao[1], Ehab S Eshak [1,2], Keyang Liu[1], Isao Muraki[1], Renzhe Cui[1],

3 Hiroyasu Iso[*,1], Akiko Tamakoshi[3] and JACC Study Group*

4 [1] Public Health, Department of Social Medicine, Osaka University

5 Graduate School of Medicine, Osaka, Japan.

6 [2]Department of Public Health, Community and Preventive Medicine,

7 Faculty of Medicine, Minia University, Minia, Egypt.

8 [3]Department of Public Health, Faculty of Medicine, Hokkaido University,

9 Sapporo, Japan.

10

11 **Correspondence**: Hiroyasu Iso, MD, Ph.D, MPH, Professor of Public

12 Health, Department of Social Medicine, Osaka University Graduate

13 School of Medicine, 2-2 Yamadaoka, Suita-shi, Osaka 565-0871, Japan.

14 Phone: +81-6-6879-3911

15 Fax: +81-6-6879-3919

16 E–mail: iso@pbhel.med.osaka-u.ac.jp

17

18

19

20

21

22

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 $\leq$ 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.

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 ($\geq$ 9h/d) [8-10], while some other studies indicated that longer sleep duration ($\geq$ 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

4

89 endogenous estrogen [23]. Furthermore, short sleep duration, especially

90 among postmenopausal women, was associated with high risk of breast

91 cancer in several cohort studies [8-10, 24]. Abundant previous findings

92 have also shown parity as an indicator for breast cancer risk [25-27].

93 Meanwhile, multiparous women have reported longer sleep duration than

94 nulliparous women [28].

95   Thus, we thought to examine the associations between sleep duration

96 and risk of breast cancer among premenopausal and postmenopausal

97 women, and among low and high parous women in a large

98 population-based Japanese study, the Japan Collaborative Cohort study

99 (JACC).

100

101 **Materials and methods**

102 **Study population and ascertainment of breast cancer**

103 Details of the study design and subjects have been described elsewhere

104 [29]. Briefly, the baseline data of the JACC Study were collected from

105 1988 to 1990, and 110 585 individuals (46 395 men and 64 190 women)

106 aged 40 to 79 years in 45 study areas throughout Japan participated in the

107 study. The follow-up survey for cancer incidence was conducted from the

108 baseline, and finalized at the end of the 2009. In 24 areas out of the 45

109 study areas, data on cancer incidence such as date of diagnosis and

110 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

133   We obtained information about the average sleep duration on weekdays

134   during the preceding year. The average sleep duration per day was

135   classified into 3 categories: ≤ 6, 7 and ≥ 8 hours. Fractions hours were

136   rounded off (e g, 7 hours represented responses from 7.0 to 7.9 hours).

137   **Statistical analysis**

138   Mean values (standard deviations) and proportions of baseline risk

139   characteristics were calculated, and the linear trends in those variables

140   according to sleep duration were tested by the linear regression analysis

141   for continuous variables and the logistic regression analysis for

142   proportional variables. Person-years of follow-up were calculated from

143   the responding date to the baseline questionnaire until the obtainment of

144   one out of four possible endpoints as follows: 1) incidence of breast

145   cancer event, 2) relocation from the study area, 3) the end of the study on

146   31 December 2009, or 4) death. Because some study areas discontinued

147   the follow-up survey regarding cancer before 2009 (1994 in one study

148   area, 1997 in two areas, 1999 in one area, 2000 in one area, 2002 in one

149   area, 2003 in one area, 2006 in two areas, and 2008 in two areas).

150   Cox proportional hazard regression age- and multivariable-adjusted

151   models were used to estimate the hazard ratios (HRs) with 95%

152   confidence intervals (CIs) for breast cancer incidence according to sleep

153   duration (≤ 6h, 7h and ≥ 8 h/d) as the reference to ≥ 8 h/d, and in relation

154   to 1-SD decrement (1.07 h/d) of sleep duration. The confounding factors

155　included age (continuous), age of menarche (< 14, 14-15 and >15 y), age

156　of menopause (< 45, 45-50 and >50 y), age at first child birth (< 25 and ≥

157　25 y), type of menopause (nature or operation), body mass index

158　(continuous), sport time per week (never, <1, 1-2, 3-4 and ≥5 h/wk),

159　walking time per day (never, < 30, 30-60 and ≥60 minutes/d), currently

160　married (yes or no), smoking status (never, ex-smoker and current

161　smoker), alcohol intake (never, ex-drinker and current drinker of 0.1-22.9,

162　23.0-45.9, and ≥ 46.0 g ethanol/d), parity (0, 1, 2 and ≥3), use of sex

163　hormone (yes or no), family history of breast cancer (yes or no), and

164　history of diabetes (yes or no). The stratification analyses were performed

165　by potential effect modifiers such as menopausal status and number of

166　children. Values for P-interaction were calculated for cross-product terms

167　of menopausal status (dichotomous) or number of children (continuous)

168　with sleep duration categories (1 to 3 corresponding to ≤ 6, 7 and ≥ 8 h/d

169　of sleep duration) for the categorical analysis and sleep duration (h/d) for

170　the continuous analysis. We used SAS Version 9.4 software (SAS

171　Institute Inc, Cary, NC) for statistical analysis. All statistical tests were

172　2-tailed and values of P <0.05 were regarded as significant.

173

174　**Results**

175　Table 1 shows the baseline characteristics of women according to sleep

176　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 ($P_{interaction}$ = 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, $P_{interaction}$ = 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

221 (0.56–3.93, P for trend = 0.27) (P for interaction = 0.70) [10]. Among 33

222 528 women participated in the Singapore Chinese Health Study, Wu et al

223 reported inverse trends in breast cancer risk across sleep duration

224 categories among postmenopausal women, but not among total or

225 premenopausal women. In reference to sleep duration for ≤ 6 h/d, the

226 multivariable HRs (95%CIs) among postmenopausal women in the

227 categories 7, 8 and ≥ 9 h/d were 0.94 (0.70-1.20), 0.81 (0.60-1.10) and

228 0.67 (0.40-1.10) (P for trend = 0.047) [9]. Previous studies have shown

229 high risk of breast cancer in nulliparous or women with low parity than

230 that in multiparous women [25]. Again, the inverse association between

231 sleep duration and risk of breast cancer was observed among women with

232 < 3 children including nulliparous women more than that among those

233 with ≥ 3 children.

234   Shorter sleep duration was associated with lower levels of urinary

235 melatonin; 42% lower in Chinese women reported ≤ 6 h of sleep duration

236 than levels in women reported ≥ 9 h of sleep duration in the Singapore

237 Chinese Health Study [9]. Because sleep stimulates the release of

238 melatonin [9], melatonin is suggested a biological mediator for the

239 sleep/breast cancer association. Higher levels of melatonin may associate

240 with reduced risk of breast cancer by the following mechanisms; (a)

241 melatonin interacts with estrogen receptors (ER) on the epithelial

242 mammary cells, leading to direct inhibition of mammary cell proliferation

11

243 and invasiveness [23]; (b) melatonin interacts with the neuroendocrine

244 reproductive axis and the hypothalamic-pituitary reproductive axis,

245 leading to a down-regulation of some hormones which promote tumor

246 growth, especially gonadal estrogens and prolactin [30]; (c) melatonin

247 inhibits telomerase enzymes activity, responsible for estrogen synthesis in

248 tumor cells and adjacent peritumor fat tissues [31]; (d) melatonin has

249 antioxidant properties of melatonin can suppress oncogenesis [32].

250 Postmenopausal women are at higher risk of breast cancer than

251 premenopausal women because of higher levels of adiposity among

252 postmenopausal women [21-22] which serve as the primary source of

253 endogenous estrogen transformed from androgen by enhanced aromatase

254 expression and activity [22]. On the other hand, nulliparous and women

255 with low parity showed lower urinary excretion of melatonin [15] and

256 higher levels of estrogens and prolactin, but lower levels of sex

257 hormone-binding globulins [33-35]. These factors were associated with

258 increased risk of estrogen-receptor-positive carcinogenic tumors. Thus,

259 the sleep-induced melatonin secretion could, at least partially, explain the

260 inverse association of sleep duration with risk of breast cancer in high

261 risk group of postmenopausal women and women with low parity in our

262 study.

263 The strengths of our study were its prospective design, which avoided

264 recall bias and the availability of information on potential confounding

12

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

13

287   women with low parity < 3 children. Finally, we did not collect the data

288   on blood melatonin levels or urinary excretions; therefore, the exact

289   contribution of melatonin in the observed associations between sleep

290   duration and risk of incident breast cancer cannot be certified.

291   In summary, short sleep duration was associated with increased risk

292   of incident breast cancer, especially among postmenopausal women and

293   women with low parity. Health education to women about the need for

294   proper sleep duration is suggested and further research is needed to

295   confirm the observed associations.

296

297

298

299

300

301

302

303

304

305

306

307

308

15

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

363

364

365

366

367

368

369

370

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.

393   6. Qin Y, Zhou Y, Zhang X, Wei X, He J. Sleep duration and breast

394   cancer risk: A meta-analysis of observational studies. Int J Cancer.

395   2013; 134: 1166-1173.

396   7. Pinheiro SP, Schernhammer ES, Tworoger SS, Michels KB.

397   A prospective study on habitual duration of sleep and incidence of

398   breast cancer in a large cohort of women. Cancer Res. 2006; 66(10):

399   5521-5525.

400   8. Verkasalo PK, Lillberg K, Stevens RG, Hublin C, Partinen M, Koskenvuo

401   M, Kaprio J. Sleep Duration and Breast Cancer : A Prospective Cohort

402   Study. Cancer Res. 2005; 65(20): 9595-9601.

403   9. Wu AH, Wang R, Koh W, Stanczyk Z, Lee H, Yu MC. Sleep duration ,

404   melatonin and breast cancer among Chinese women in Singapore.

405   Carcinogenesis. 2008; 29: 1244-1248.

406   10.Kakizaki M, Kuriyama S, Sone T, Ohmori-Matsuda K, Hozawa A,

407   Nakaya N, Fukudo S, Tsuji I. Sleep duration and the risk of breast

408   cancer: the Ohsaki Cohort Study. Br J Cancer. 2008; 99: 1502-1505.

409   11.Mcelroy JA, Newcomb PA, Titus- L, Egan KM. Duration of sleep and

410   breast cancer risk in a large population- based case-control study. J

411   Sleep Res. 2006; 15(3): 241-249.

412   12.Hurley S, Goldberg D, Bernstein L, Reynolds P, Hurley S. Sleep duration

413   and cancer risk in women. Cancer Causes & Control. 2015; 26(7):

414   1037-1045.

415 13. Brzezinski A. Melatonin in humans. N Engl J Med. 1997; 336: 186-195.

416 14. Schernhammer ES, Schulmeister K. Melatonin and cancer risk: does

417   light at night compromise physiologic cancer protection by lowering

418   serum melatonin levels? Br J Cancer. 2004; 90: 941-943.

419 15. Schernhammer ES, Kroenke CH, Dowsett M, Folkerd E, Hankinson SE.

420   Urinary 6-sulfatoxymelatonin levels and their correlations with

421   lifestyle factors and steroid hormone levels. *J Pineal Res. 2006;* 40:

422   116-124.

423 16. Anisimov VN. The role of pineal gland in breast cancer development.

424   Crit Rev Oncol Hematol. 2003; 46: 221-34.

425 17. Cohen M, Lippman M, Chabner B. Role of the pineal gland in

426   theaetiology and treatment of breast cancer. Lancet. 1978; 2: 814-881.

427 18. Blask DE, Wilson ST, Zalatan F. Physiological melatonin inhibition of

428   human breast cancer cell growth in vitro: evidence for a

429   glutathione-mediated pathway. Cancer Res. 1997; 57: 1909-1914.

430 19. Cos S, Gonzalez A, Martinez-Campa C, Mediavilla

431   MD, Alonso-Gonzalez C, Sanchez-Barcelo EJ. Estrogen-signaling

432   pathway: a link between breast cancer and melatonin oncostatic

433   actions. Cancer Detect Prev. 2006; 30(2): 118-28.

434 20. Surakasula A, Nagarjunapu GC, Raghavaiah KV. A comparative

435   study of pre- and post-menopausal breast cancer: Risk factors,

436   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,

Hwang H, Khoury T, Jandorf L, Bovbjerg DH, Pawlish K, Bandera E. Parity and Breastfeeding among African-American Women: Differential Effects on Breast Cancer Risk by Estrogen Receptor Status in the Women's Circle of Health Study. Cancer Causes Control. 2014; 25(2): 259-265.

28. Signal TL, Gander PH, Sangalli MR, Travier N, Firestone RT, Tuohy JF. Sleep duration and quality in healthy nulliparous and multiparous women across pregnancy and post-partum.Aust N Z J Obstet Gynaecol. 2007; 47(1): 16-22.

29. Tamakoshi A, Ozasa K, Fujino Y, Suzuki K, Sakata K, Mori M, Kikuchi S , Iso H, the JACC Study Group. Cohort Profile of the Japan Collaborative Cohort Study. J Epidemiol. 2013; 23: 227-232.

30. Reiter RJ. The pineal and its hormones in the control of reproduction in mammals. Endocr Rev. 1980; 1: 109-131.

31. Leon-Blanco MM, Guerrero JM, Reiter RJ, Calvo JR, Pozo D. Melatonin inhibits telomerase activity in the MCF-7 tumor cell line both in vivo and in vitro. J Pineal Res. 2003; 35(3): 204-11.

32. Allegra M, Reiter RJ, Tan DX, Gentile C, Tesoriere L, Livrea MA. The chemistry of melatonin's interaction with reactive species. J Pineal Res. 2003; 34: 1-10.

33. Longcope C, Speizer FE. Reproductive factors and family history of breast cancer in relation to plasma estrogen and prolactin levels in

481   postmenopausal women in the Nurses' Health Study (United States).

482   Cancer Causes & Control. 1995; 6: 217-224.

483 34.Kwa HG, Cleton F, Bulbrook RD, Wang DY, Hayward JL. Plasma

484   prolactin levels and breast cancer: relation to parity, weight and

485   height, and age at first birth. Int J Cancer. 1981; 28: 31-4.

486 35.Bernstein L, Pike MC, Ross RK, Judd HL, Brown JB, Henderson BE.

487   Estrogen and sex hormone-binding globulin levels in nulliparous and

488   parous women. J Natl Cancer Inst. 1985; 74: 741-5.

489 36.Tamakoshi K, Yatsuya H, Wakai K, Suzuki S, Nishio K, Lin Y, Niwa

490   Y, Kondo T, Yamamoto A, Tokudome S, Toyoshima H, Tamakoshi

491   A, JACC Study Group. Impact of menstrual and reproductive factors

492   on breast cancer risk in Japan: results of the JACC study. Cancer Sci.

493   2005; 96(1): 57-62.

494 37.Ukawa S, Tamakoshi A, Mori M, Ikehara S, Shirakawa T, Yatsuya

495   H, Iso H, JACC study group. Association between average daily

496   television viewing time and the incidence of ovarian cancer: findings

497   from the Japan Collaborative Cohort Study. Cancer Causes Control.

498   2018; 29(2): 213-219.

499 38.Fang HF, Miao NF, Chen CD, Sithole T, Chung MH.

500   Risk of cancer in patients with insomnia, parasomnia, and obstructive

501   sleep apnea: a nationwide nested case-control study. J Cancer. 2015;

502   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 trend
	≤ 6 h	7 h	≥ 8 h	
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 | 1SD decrement（1.07 h/d）of sleep duration |
	≤ 6 h	7 h	≥ 8 h	trend	
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）
$P_{\text{interaction}}$				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.