Sleep deficiency and breast cancer risk among postmenopausal women in the California teachers study (CTS)

S. Hurley1 · D. Goldberg1 · J. Von Behren1 · J. Clague DeHart2 · S. Wang3 · P. Reynolds1

Received: 9 December 2019 / Accepted: 16 September 2020 / Published online: 26 September 2020
© Springer Nature Switzerland AG 2020

Abstract
Purpose There is provocative, yet inconsistent, evidence that sleep deficiency may influence the development of breast cancer. The purpose of this study was to evaluate the risk of breast cancer associated with sleep deficiency among postmenopausal women in the California Teachers Study (CTS).
Methods We conducted a case–control study of 2,856 invasive breast cancer cases and 38,649 cancer-free controls, nested within the CTS. Self-administered questionnaires were used to ascertain several components of sleep deficiency, including quality, latency, duration, disturbance and use of sleep medications. Additionally, a Global Sleep Index (GSI) was created by summing the individual sleep components and categorizing into quartiles. Multivariable logistic regression analyses were used to estimate odds ratios and 95% confidence intervals (OR, 95% CI).
Results Increased breast cancer risks were associated with sleep deficiency. With the exception of duration, linear increases in risk were associated with all the other individual components of sleep deficiency (p-trend ≤ 0.002). The OR for the highest GSI quartile vs. lowest was 1.24, 95% CI 1.12–1.38; (p-trend < 0.001).
Conclusions Sleep deficiency may be a risk factor for breast cancer. Additional prospective studies and those aimed at elucidating underlying mechanism are warranted.

Keywords Sleep · Breast cancer · Etiology · Case–control

Introduction
The CDC has declared insufficient sleep to be a “public health epidemic,” noting that an estimated 50–70 million US adults have sleep or wakefulness disorders [1, 2]. Inadequate sleep has been linked to a number of chronic conditions including cardiovascular disease, obesity and diabetes, as well as to overall increases in mortality [2, 3]. Bolstered by the recognition of circadian disruption as a probable human carcinogen by the International Agency for Research on Cancer (IARC) in 2010 [4, 5], the role of sleep in the development of cancer has garnered increasing attention over the last decade [2, 6]. Beyond its integral role in helping to maintain circadian rhythms, sleep has been shown in laboratory studies to play a fundamental role in regulating key processes critical to carcinogenesis, including cellular replication and proliferation, inflammation, and immune surveillance [7, 8]. Sleep may be particularly germane to breast cancer risk as insufficient sleep has been shown to influence estrogen signaling pathways by melatonin suppression [9–12]. The degree to which such effects may translate to breast cancer risk in humans remains unclear [13–18].

There are many dimensions of sleep and the field of sleep research is filled with competing terminology. The predominant construct, however, is that of ‘sleep deficiency,’ defined as a “deficit in the quantity or quality of sleep obtained versus the amount needed for optimal health, performance,
and well-being.” [19] Sleep deficiencies can have multiple components, including: insufficient duration of sleep (sleep deprivation); poor sleep efficiency characterized by long latency (i.e., taking a long time to fall asleep) and disturbance (i.e., waking frequently and not falling back to sleep quickly/easily); inappropriate timing of sleep (out of sync with the body’s natural clock or circadian rhythm); and sleep disorders, such as apnea, that interfere with adequate duration and/or sleep quality.

Epidemiologic evidence for an etiologic link between sleep deficiency and cancer is sparse and inconsistent [13, 14, 16]. While a number of studies have provided provocative evidence for a link between sleep apnea and risk for a variety of cancers (including breast cancer), results have not been consistent, and have varied by cancer site [20–24]. Studies focused on breast cancer predominantly have evaluated sleep duration and have yielded inconsistent findings with some reporting elevated risks associated with short sleep duration [25–27], some with long sleep duration [28–30], and some reporting no effect [31–33]. Data from the few breast cancer studies that have evaluated other components of sleep have provided some suggestive, though very limited, evidence that other dimensions of sleep deficiency may play a role in breast cancer development [14, 34].

The objective of this study was to evaluate the risk of breast cancer associated with several dimensions of sleep deficiency in a population of postmenopausal California women.

Methods

Study population

This is a case–control study nested within the California Teachers Study (CTS). The CTS is a prospective cohort study of female California professional school employees, specifically designed to study breast cancer risk [35]. In 1995 and 1996 over 133,000 women aged 22 to 104 were enrolled in the CTS by responding to a survey that was mailed to all active and retired female members of the California State Teachers Retirement System. Upon entry into the study, all participants provided informed consent to use their data for research purposes such as this study. Subsequent to enrollment, two CTS participants requested to be withdrawn from the study and are not included in the present analysis. The CTS has been actively followed for cancer diagnosis, death and change of address from its inception, as described previously [35]. Upon entry into the cohort, CTS members completed a baseline survey that included questions on reproductive history, personal and family medical history, health behaviors and other lifestyle factors. Five subsequent mailed questionnaires were administered to update the baseline data and collect new information on exposures, risk factors, and health outcomes of emerging interest. Detailed questions about sleep were included on the fifth CTS Questionnaire (Q5), administered in 2012–2015. Overall, approximately 60% of CTS members who received the Q5 survey responded, 99% of whom answered at least one question regarding sleep. A full description of the CTS creation and its characteristics are described elsewhere [35].

Ascertainment of breast cancer cases and controls

Cases and controls for the current analysis were drawn from 44,480 postmenopausal CTS participants who provided sleep information on the CTS Q5, were under the age of 90 at the time they responded to the CTS Q5, had no history of breast cancer prior to CTS enrollment, and had resided in California continuously from baseline through Q5. Incident cases of primary invasive breast cancer (SEER site = 26,000) diagnosed from baseline through completion of the CTS Q5 were identified by annual linkages of the CTS to the California Cancer Registry (CCR). Case ascertainment for the CCR is estimated to be 99% complete [36]. Participants diagnosed with in situ cancer of the breast were excluded. Remaining CTS participants without a breast cancer diagnosis served as controls, excluding those with diagnoses of other invasive cancers (n = 2,975). This resulted in the identification of 2,856 cases of primary invasive breast cancer and 38,649 cancer-free women who served as controls for the current analysis.

Assessment of sleep characteristics

Sleep characteristics were derived from CTS Q5 responses (available online at: https://www.calteachersstudy.org/past-questionnaires). Questions were adapted from the Pittsburgh Sleep Quality Index (PSQI), a standardized and validated self-administered questionnaire developed for the assessment of subjective sleep quality and widely used in health studies [37–39]. The PSQI comprises 19 self-rated questions. The 19 questions are scored and combined to form seven components (quality, latency, duration, disturbance, efficiency, daytime dysfunction and medication use). The seven components are then summed to create the PSQI global score. Due to space constraints, we were not able to include all 19 of the PSQI questions on the CTS Q5. Specifically, we did not include questions that captured sleep efficiency or daytime dysfunction. To create a modified summary global sleep index (GSI) we adapted the PSQI approach, scoring each of the five components for which we had information (quality, latency, duration, disturbance, and medication use) from zero to three, with zero being best and three being the worst. We then summed the individual scored components to generate a continuous variable with discrete
whole number values ranging from zero to 15, which was then converted to an ordinal variable based on the quartile distribution, with the lowest quartile representing the best sleep. The GSI was not generated for approximately 3% of participants who were missing or had invalid responses for any of the five individual components.

To maintain consistency with the PSQI, the questions were asked about sleep during the prior month. Furthermore, participants were asked if the characteristics they reported for the prior month were typical of sleep during other periods during their life (including the prior year, 2–5 years prior, 6–10 years prior and 11 or more prior years).

**Assessment of covariates**

Information on breast cancer risk factors was ascertained by self-report on the CTS questionnaires. Factors included age, race, family history of breast cancer, parity, age at first full-term pregnancy, age at menopause, age at menarche, lactation history, hormone therapy use, alcohol consumption, smoking, household income, and neighborhood socioeconomic status. We also considered information from the CTS questionnaires on factors potentially related to sleep deficiency including body mass index (BMI), physical activity, marital status, and current medication use (including depression medications, prescription pain medications, and non-steroid anti-inflammatory drugs (NSAIDs)). Comorbidities were defined as having reported ever receiving a physician diagnosis of diabetes, chronic obstructive pulmonary disease (COPD), Parkinson’s disease, depression, chronic fatigue syndrome (CFS), Lupus, inflammatory bowel disease (IBD), Crohn’s Disease, and multiple sclerosis. From these data, we created a comorbidity index by summing the number of comorbid conditions and then categorizing as none, one, two, or three or more. Information on chronotype was collected on the CTS Q5 using an abbreviated version of the Horne-Ostberg Morningness-Eveningness Questionnaire (MEQ), a standardized and validated survey instrument used to characterize a person’s underlying circadian rhythm [40–43]. These questions were used to characterize participants into five chronotypes: definite morning, more morning than evening, neither morning nor evening, more evening than morning, definite evening. Details of the assignment of chronotype are described in an earlier analysis of chronotype and breast cancer in this study population [44].

**Statistical analysis**

The risk of breast cancer associated with sleep deficiency was evaluated through unconditional logistic regression analyses. Regression models were run using PROC LOGISTIC in the SAS/STAT software version 9.4 of the SAS system to estimate odds ratios (ORs) and 95% confidence intervals (CIs) separately for each of the individual components of sleep deficiency (quality, latency, disturbance, duration, and medication use) as well as for our global sleep index (GSI). A test for linear trend was performed with categories of each sleep variable modeled as an ordinal variable. Initial models were adjusted for only age and race. Fully adjusted multi-variable models were built via a two-step process. Starting with the full set of potential covariates, a backwards elimination approach was used, starting with a model that included all potential covariates and forced inclusion of the sleep variable, age and race. All factors for which the \( p \) value for the Wald Chi-square was < 0.10 were kept as covariates. We then further evaluated potential confounding by adding each of the excluded variables back into the model one at a time keeping those that changed the estimated odds ratio for the sleep variable by 10% or more. While we conducted this process separately for each sleep variable, it resulted in the same set of covariates for all sleep variables. The set of covariates included in our final multivariable models appear in the footnote of Table 4.

To evaluate potential effect modifiers, we conducted analyses stratified by BMI (\(< 25 \text{ kg/m}^2\), 25–29 kg/m\(^2\), \(\geq 30 \text{ kg/m}^2\)), age (40–64 years, 65–79 years, 80–89 years) and chronotype (morning type, evening type, neither type). Tests for statistical interactions were calculated based on the \( p \)-value of likelihood ratio tests comparing nested models with and without a multiplicative interaction term for each of these variables and the sleep variables. To evaluate whether risks differed between cases with hormonally responsive tumors (estrogen receptor positive (ER+) or progesterone receptor positive (PR+)) and non-responsive tumors (estrogen receptor negative (ER-) and progesterone negative tumors (PR–)) we conducted multivariable polytomous logistic regression.

Because information on sleep was ascertained post-diagnosis for cases, we conducted a number of sensitivity analyses to address the potential for reverse causality. We repeated our analyses, excluding the 178 and 363 breast cancer cases that were diagnosed within one and two years prior to completing Q5, respectively. We also repeated our analyses restricted to the subset of participants who indicated that their sleep habits had not change recently (i.e., that their reported sleep was typical of the past year) and restricted to those with long-term sleep stability (i.e., that their reported sleep was typical of at least the prior five years).

**Results**

The characteristics of the study population, overall and by case control status, are presented in Table 1. Participants ranged in age from 40 to 89 years of age, with the majority (68%) falling between the ages of 60 and 79. Similar to the
| Characteristic | Case–control status | All | Chi-square p value |
|---------------|---------------------|-----|--------------------|
|               | Non-case | Case | n | % | n | % | n | % |
| Full Study Population | 38,649 | 2856 | 41,505 | 100 | <0.001 |
| Age (years) | | | | | |
| 40–49 | 742 | 33 | 775 | 2 |
| 50–59 | 6699 | 295 | 6994 | 17 |
| 60–69 | 16,184 | 1018 | 17,202 | 41 |
| 70–79 | 10,076 | 1026 | 11,102 | 27 |
| 80–89 | 4948 | 484 | 5432 | 13 |
| Race/Ethnicity | | | | | 0.007 |
| White | 33,624 | 2535 | 36,159 | 87 |
| Non-White | 5025 | 321 | 5346 | 13 |
| Chronotype | | | | | 0.006 |
| Morning type | 14,406 | 978 | 15,384 | 37 |
| More morning than evening type | 7776 | 568 | 8344 | 20 |
| Neither morning/evening type | 5031 | 397 | 5428 | 13 |
| More evening than morning type | 5687 | 434 | 6121 | 15 |
| Evening type | 4762 | 406 | 5168 | 12 |
| Unknown | 987 | 73 | 1060 | 3 |
| Smoking status at baseline | | | | | <0.001 |
| Never | 25,939 | 1755 | 27,694 | 67 |
| Former | 11,102 | 949 | 12,051 | 29 |
| Current | 1444 | 136 | 1580 | 4 |
| Unknown | 164 | 16 | 180 | 0 |
| Smoking pack-years at baseline | | | | | <0.001 |
| ≤ 10 | 6771 | 521 | 7292 | 18 |
| 11–20 | 2252 | 201 | 2453 | 6 |
| 21–30 | 1190 | 106 | 1296 | 3 |
| ≥ 31 | 1267 | 160 | 1427 | 3 |
| Unknown | 1230 | 113 | 1343 | 3 |
| Never smokers | 25,939 | 1755 | 27,694 | 67 |
| Alcohol consumption (g/day) at baseline | | | | | <0.001 |
| None | 11,497 | 793 | 12,290 | 30 |
| < 20 | 22,723 | 1670 | 24,393 | 59 |
| ≥ 20 | 3055 | 289 | 3344 | 8 |
| Unknown | 1374 | 104 | 1478 | 4 |
| Age at menarche reported (years) at baseline | | | | | 0.464 |
| ≤ 11 | 8951 | 691 | 9642 | 23 |
| 12–13 | 21,929 | 1579 | 23,508 | 57 |
| ≥ 14 | 7331 | 551 | 7882 | 19 |
| Unknown/Never | 438 | 35 | 473 | 1 |
| Age at first full-term pregnancy(years) reported at baseline | | | | | 0.351 |
| No full-term pregnancy | 8760 | 660 | 9420 | 23 |
| ≤ 24 | 10,435 | 736 | 11,171 | 27 |
| 25–29 | 11,811 | 916 | 12,727 | 31 |
| ≥ 30 | 7101 | 506 | 7607 | 18 |
| Unknown | 542 | 38 | 580 | 1 |
| Breast feeding history(months) reported at baseline | | | | | 0.017 |
| Never pregnant | 6585 | 499 | 7084 | 17 |

Table 1: Characteristics of the study population (n = 41,505), and distribution by case–control status.
Table 1 (continued)

| Characteristic | Case–control status | All | Chi-square p value |
|----------------|---------------------|-----|-------------------|
|                | Non-case |        | Case  |         |        |        |        |
|                | n   | %   | n   | %   | n   | %   |        |        |
| Pregnancy, but no live birth | 2134 | 6  | 158 | 6  | 2292 | 6  |        |        |
| 0 months       | 5559 | 14 | 475 | 17 | 6034 | 15 |        |        |
| > 0 and < 6 months | 6437 | 17 | 488 | 17 | 6925 | 17 |        |        |
| 6–11           | 5670 | 15 | 387 | 14 | 6057 | 15 |        |        |
| ≥ 12           | 11,585 | 30 | 803 | 28 | 12,388 | 30 |        |        |
| Unknown        | 679  | 2  | 46  | 2  | 725  | 2  |        |        |
| BMI (kg/m²)    |        |     |     |     | 0.007 |     |        |        |
| 15.0–24.9      | 18,595 | 48 | 1293 | 45 | 19,888 | 48 |        |        |
| 25.0–29.9      | 11,068 | 29 | 889 | 31 | 11,957 | 29 |        |        |
| 30.0–54.8      | 7133  | 18 | 520 | 18 | 7653  | 18 |        |        |
| Unknown        | 1853  | 5  | 154 | 5  | 2007  | 5  |        |        |
| Physical activity (strenuous plus moderate, hours/week) | < 0.001 |     |     |     |        |     |        |        |
| 0 to < 2.38    | 12,485 | 32 | 1060 | 37 | 13,545 | 33 |        |        |
| 2.38 to < 5.88 | 12,927 | 33 | 932 | 33 | 13,859 | 33 |        |        |
| 5.88 to 24.00  | 13,112 | 34 | 856 | 30 | 13,968 | 34 |        |        |
| Unknown        | 125   | 0  | 8   | 0  | 133   | 0  |        |        |
| Family history of breast cancer reported at Q4 | < 0.001 |     |     |     |        |     |        |        |
| No             | 31,139 | 81 | 2104 | 74 | 33,243 | 80 |        |        |
| Yes            | 6438 | 17 | 667 | 23 | 7105 | 17 |        |        |
| Unknown        | 1072 | 3 | 85 | 3 | 1157 | 3 |        |        |
| Age at menopause (years) | 0.166 |     |     |     |        |     |        |        |
| 10–39          | 2890 | 7 | 196 | 7 | 3086 | 7 |        |        |
| 40–49          | 10,220 | 26 | 806 | 28 | 11,026 | 27 |        |        |
| 50–54          | 12,459 | 32 | 872 | 31 | 13,331 | 32 |        |        |
| 55–59          | 5065 | 13 | 370 | 13 | 5435 | 13 |        |        |
| 60–70          | 661 | 2 | 47 | 2 | 708 | 2 |        |        |
| Unknown        | 7354 | 19 | 565 | 20 | 7919 | 19 |        |        |
| Hormone Therapy Use | < 0.001 |     |     |     |        |     |        |        |
| Never          | 7551 | 20 | 493 | 17 | 8044 | 19 |        |        |
| Ever           | 26,856 | 69 | 2120 | 74 | 28,976 | 70 |        |        |
| Unknown        | 4242 | 11 | 243 | 9 | 4485 | 11 |        |        |
| Diabetes: Ever Diagnosed | 0.843 |     |     |     |        |     |        |        |
| No             | 35,048 | 91 | 2581 | 90 | 37,629 | 91 |        |        |
| Yes            | 3260 | 8 | 248 | 9 | 3508 | 8 |        |        |
| Unknown        | 341 | 1 | 27 | 1 | 368 | 1 |        |        |
| Chronic obstructive pulmonary disease (COPD): Ever Diagnosed | < 0.001 |     |     |     |        |     |        |        |
| No             | 36,085 | 93 | 2612 | 91 | 38,697 | 93 |        |        |
| Yes            | 1078 | 3 | 110 | 4 | 1188 | 3 |        |        |
| Unknown        | 1486 | 4 | 134 | 5 | 1620 | 4 |        |        |
| Parkinson's disease: Ever Diagnosed | 0.003 |     |     |     |        |     |        |        |
| No             | 37,032 | 96 | 2698 | 94 | 39,730 | 96 |        |        |
| Yes            | 197 | 1 | 18 | 1 | 215 | 1 |        |        |
| Unknown        | 1420 | 4 | 140 | 5 | 1560 | 4 |        |        |
| Depression: Ever Diagnosed | 0.001 |     |     |     |        |     |        |        |
| No             | 29,817 | 77 | 2171 | 76 | 31,988 | 77 |        |        |
| Yes            | 7262 | 19 | 529 | 19 | 7791 | 19 |        |        |
| Unknown        | 1570 | 4 | 156 | 5 | 1726 | 4 |        |        |
Table 1 (continued)

| Characteristic                  | Case–control status | All | Chi-square p value |
|--------------------------------|---------------------|-----|--------------------|
|                               | Non-case n | %   | Case n  | %   | n   | %   |                |
| Current use of depression medication |              |     |          |     |     |     | 0.009c         |
| No                             | 2994   | 8   | 183     | 6   | 3177 | 8   |                |
| Yes                            | 3264   | 8   | 270     | 9   | 3534 | 9   |                |
| Unknown medication use         | 1004   | 3   | 76      | 3   | 1080 | 3   |                |
| No/unknown depression          | 31,387 | 81  | 2327    | 81  | 33,714 | 81  |                |
| Chronic fatigue syndrome (CFS): Ever Diagnosed |          |     |          |     |     |     | 0.001          |
| No                             | 36,322 | 94  | 2640    | 92  | 38,962 | 94  |                |
| Yes                            | 820    | 2   | 64      | 2   | 884  | 2   |                |
| Unknown                        | 1507   | 4   | 152     | 5   | 1659 | 4   |                |
| Lupus: Ever Diagnosed         |          |     |          |     |     |     | 0.001          |
| No                             | 36,551 | 95  | 2658    | 93  | 39,209 | 94  |                |
| Yes                            | 313    | 1   | 22      | 1   | 335  | 1   |                |
| Unknown                        | 1785   | 5   | 176     | 6   | 1961 | 5   |                |
| Inflammatory bowel disease (IBD) or Crohn’s disease: Ever Diagnosed |          |     |          |     |     |     | 0.001          |
| No                             | 35,635 | 92  | 2606    | 91  | 38,241 | 92  |                |
| Yes                            | 1518   | 4   | 100     | 4   | 1618 | 4   |                |
| Unknown                        | 1496   | 4   | 150     | 5   | 1646 | 4   |                |
| Multiple Sclerosis: Ever Diagnosed |          |     |          |     |     |     | <0.001         |
| No                             | 37,056 | 96  | 2693    | 94  | 39,749 | 96  |                |
| Yes                            | 207    | 1   | 20      | 1   | 227  | 1   |                |
| Unknown                        | 1386   | 4   | 143     | 5   | 1529 | 4   |                |
| Comorbidities                 |          |     |          |     |     |     | 0.001          |
| None                           | 24,372 | 63  | 1756    | 61  | 26,128 | 63  |                |
| 1                              | 9862   | 26  | 703     | 25  | 10,565 | 25  |                |
| 2                              | 1853   | 5   | 151     | 5   | 2004 | 5   |                |
| ≥ 3                            | 331    | 1   | 32      | 1   | 363  | 1   |                |
| Unknown                        | 2231   | 6   | 214     | 7   | 2445 | 6   |                |
| Current Pain Medication Use (# tablets/week) |          |     |          |     |     |     | 0.065          |
| None or < 1/week               | 35,420 | 92  | 2586    | 91  | 38,006 | 92  |                |
| ≥ 1                            | 2083   | 5   | 183     | 6   | 2266 | 5   |                |
| Unknown                        | 1146   | 3   | 87      | 3   | 1233 | 3   |                |
| Current NSAID use (# tablets/week) |          |     |          |     |     |     | 0.466          |
| None or < 1/week               | 15,155 | 39  | 1105    | 39  | 16,260 | 39  |                |
| ≥ 1                            | 21,267 | 55  | 1599    | 56  | 22,866 | 55  |                |
| Unknown                        | 2227   | 6   | 152     | 5   | 2379 | 6   |                |
| Marital Status                 |          |     |          |     |     |     | <0.001         |
| Married                        | 24,537 | 63  | 1742    | 61  | 26,279 | 63  |                |
| Divorced/Separated             | 5641   | 15  | 391     | 14  | 6032 | 15  |                |
| Widowed                        | 5305   | 14  | 504     | 18  | 5809 | 14  |                |
| Never married                  | 2402   | 6   | 169     | 6   | 2571 | 6   |                |
| Unknown                        | 764    | 2   | 50      | 2   | 814  | 2   |                |
| Household income at Q4         |          |     |          |     |     |     | <0.001         |
| < $25,000–$49,999              | 4231   | 11  | 383     | 13  | 4614 | 11  |                |
| $50,000–$74,999                | 7656   | 20  | 639     | 22  | 8295 | 20  |                |
| $75,000–$99,999                | 7023   | 18  | 580     | 20  | 7603 | 18  |                |
| $100,000–$149,999              | 7169   | 19  | 452     | 16  | 7621 | 18  |                |
| $150,000–$200,000+             | 4620   | 12  | 309     | 11  | 4929 | 12  |                |
full CTS cohort, the study population was predominantly non-Hispanic White (87%). Overall, the reproductive and behavioral characteristics of the study population generally mirror those of the full CTS cohort. Given the large sample size, the distribution of a number of factors statistically differed between cases and controls \(p < 0.05\) but the magnitude of differences was generally quite small.

Reported sleep characteristics are summarized in Table 2. Overall the majority of participants reported very good (30%) or fairly good sleep (54%). Seven hours of sleep was the most common duration, reported by 42% of respondents. Consistent with national survey data \[45\], slightly more than a quarter reported insufficient sleep durations (i.e., < 7 h). Nearly half (47%) reported falling asleep within 15 min of going to bed while 4% reported that it took more than an hour. About a quarter of respondents (22%) reported no sleep disturbance in the last month, while a similar proportion (20%) reported experiencing sleep disturbance three or more times a week over the last month. Nearly a third of participants (31%) reported taking some kind of sleep medication in the last month. Other than for sleep quality, the distribution of all individual components of sleep deficiency, as well as of the GSI, differed between cases and controls \(p < 0.05\), with cases reporting worse sleep than the controls (Table 2). A majority of women indicated that their reported sleep characteristics over the past month were typical of the past year (88%) or past two to five years (72%). The distribution of sleep stability did not differ between cases and controls, other than a marginally higher proportion of controls reporting that their recent sleep was indicative of their sleep 11 or more years ago (43% vs. 41%, \(p = 0.02\)).

The correlation matrix for the sleep variables is presented in Table 3. Statistically significant positive correlations were observed between all sleep variables. Among the individual components of sleep deficiency, disturbance and quality were the most highly correlated \((r = 0.66)\). Sleep medication was the least correlated with the other individual sleep variables, with correlation coefficients all < 0.30. Correlations of the individual components with the GSI ranged from 0.55 for sleep medication to 0.79 for sleep disturbance.

The estimated risks of breast cancer associated with sleep deficiency are summarized in Table 4. Multivariable adjusted odds ratios \((OR_{adj})\) were generally similar to those generated from the age- and race-adjusted models. Risks of breast cancer were significantly associated with the GSI such that women with the worst GSI (highest quartile) had an approximately 25% greater risk of breast cancer compared to women in the lowest GSI quartile \((OR_{adj} = 1.24, 95\% CI 1.12–1.38, p\text{-trend} < 0.001)\). With the exception of sleep duration, increased risks of breast cancer were also observed for each of the individual components of sleep deficiency. Compared to those who reported very good sleep quality, respondents who reported fairly or very bad sleep quality had an approximate 20- to 30-percent increased risk of breast cancer \((p\text{-value for trend} \leq 0.002)\). Breast cancer risk also significantly increased with greater sleep latency and disturbance \((p\text{-trend} < 0.001)\). Women who reported taking sleep medications in the last month had greater risks of breast cancer compared to women who did not take any \((p\text{-trend} < 0.001)\).

Stratified analyses revealed no significant differences by categories of BMI or age \(\text{(data not shown)}\). Analyses stratified by chronotype suggested some differential risks associated for sleep disturbance \((p\text{-value for trend} = 0.032)\) and sleep medications \((p\text{-value for interaction} < 0.001)\) (Supplemental material, Table S1). Results from our polytomous regression analyses yielded generally similar risk estimates for hormonally responsive and non-responsive tumors; these analyses however were hindered by the small
Table 2 Distribution of sleep deficiency characteristics for entire study population (n = 41,505), and by case–control status

| Characteristic                        | Case–control status | All | Chi-square | p value |
|--------------------------------------|---------------------|-----|------------|---------|
|                                      | Non-case            | Case|            |         |
|                                      | n      | %     | n      | %     | n      | %     |
| Sleep quality                        |                    |     |          |        |
| Very good                            | 11,788  | 30    | 825    | 29    | 12,613  | 30    | 0.158   |
| Fairly good                          | 21,014  | 54    | 1562   | 55    | 22,576  | 54    |         |
| Fairly bad                           | 5175    | 13    | 407    | 14    | 5582    | 13    |         |
| Very bad                             | 488     | 1     | 45     | 2     | 533     | 1     |         |
| Unknown                              | 184     | 0     | 17     | 1     | 201     | 0     |         |
| Sleep duration (hours)               |                    |     |          |        |
| ≥ 9 h                                | 1762    | 5     | 162    | 6     | 1924    | 5     | 0.040   |
| 8 h                                  | 9982    | 26    | 715    | 25    | 10,697  | 26    |         |
| 7 h                                  | 16,120  | 42    | 1168   | 41    | 17,288  | 42    |         |
| 5–6 h                                | 9461    | 24    | 702    | 25    | 10,163  | 24    |         |
| < 5 h                                | 994     | 3     | 75     | 3     | 1069    | 3     |         |
| Unknown                              | 330     | 1     | 34     | 1     | 364     | 1     |         |
| Sleep latency                        |                    |     |          |        |
| < 15 min                             | 18,151  | 47    | 1188   | 42    | 19,339  | 47    | < 0.001 |
| 16–30 min                            | 13,876  | 36    | 1102   | 39    | 14,978  | 36    |         |
| 31–60 min                            | 4895    | 13    | 416    | 15    | 5311    | 13    |         |
| > 60 min                             | 1540    | 4     | 138    | 5     | 1678    | 4     |         |
| Unknown                              | 187     | 0     | 12     | 0     | 199     | 0     |         |
| Sleep disturbance                    |                    |     |          |        |
| Not during past month                | 8600    | 22    | 619    | 22    | 9219    | 22    | 0.003   |
| < 1 time/week in past month          | 12,579  | 33    | 868    | 30    | 13,447  | 32    |         |
| 1–2 times/week in past month         | 9575    | 25    | 701    | 25    | 10,276  | 25    |         |
| ≥ 3 times in past month              | 7752    | 20    | 658    | 23    | 8410    | 20    |         |
| Unknown                              | 143     | 0     | 10     | 0     | 153     | 0     |         |
| Sleep medication                     |                    |     |          |        |
| Not during past month                | 26,655  | 69    | 1841   | 64    | 28,496  | 69    | < 0.001 |
| < 1 time/week in past month          | 4201    | 11    | 347    | 12    | 4548    | 11    |         |
| 1–2 times/week in past month         | 2257    | 6     | 210    | 7     | 2467    | 6     |         |
| ≥ 3 times in past month              | 5200    | 13    | 427    | 15    | 5627    | 14    |         |
| Unknown                              | 336     | 1     | 31     | 1     | 367     | 1     |         |
| Global Sleep Index (GSI)             |                    |     |          |        |
| Lowest quartile (better sleep)       | 10,853  | 28    | 738    | 26    | 11,591  | 28    | < 0.001 |
| 2nd quartile                         | 9550    | 25    | 642    | 22    | 10,192  | 25    |         |
| 3rd quartile                         | 7540    | 20    | 587    | 21    | 8127    | 20    |         |
| Highest quartile (worse sleep)       | 9655    | 25    | 792    | 28    | 10,447  | 25    |         |
| Unknown                              | 1051    | 3     | 97     | 3     | 1148    | 3     |         |
| Sleep stability past year            |                    |     |          |        |
| No                                   | 2790    | 7     | 216    | 8     | 3006    | 7     | 0.060   |
| Yes                                  | 34,061  | 88    | 2481   | 87    | 36,542  | 88    |         |
| Unknown                              | 1798    | 5     | 159    | 6     | 1957    | 5     |         |
| Sleep stability past 2–5 years       |                    |     |          |        |
| No                                   | 8256    | 21    | 601    | 21    | 8857    | 21    | 0.161   |
| Yes                                  | 27,929  | 72    | 2047   | 72    | 29,976  | 72    |         |
| Unknown                              | 2464    | 6     | 208    | 7     | 2672    | 6     |         |
| Sleep stability past 6–10 years      |                    |     |          |        |
| No                                   | 16,408  | 42    | 1206   | 42    | 17,614  | 42    | 0.254   |
| Yes                                  | 19,372  | 50    | 1414   | 50    | 20,786  | 50    |         |
number of cases with ER-/PR- tumors (Supplemental material, Table S2).

On average, cases were diagnosed 8.2 years prior to reporting their sleep characteristics on the CTS Q5 (range = 1 day to 17.5 years). The median time interval from case diagnosis to CTS Q5 completion date did not significantly differ by reported sleep characteristics for any of the individual components of sleep (Wilcoxon Rank Sum test p-values > 0.05). Although cases with the worst GSI (highest quartile) were significantly more likely to be recently diagnosed than women in the lowest quartile (Wilcoxon Rank Sum test p-value = 0.015), the magnitude of case control differences were quite modest (median time interval from diagnosis to Q5 was 8.0 vs 9.1 years, respectively). Results of our sensitivity analyses are summarized in Table 5. When we repeated our regression analyses excluding cases who were diagnosed shortly before (one year and two years before) reporting their sleep characteristics on the CTS Q5, the estimates of risk for the GSI were essentially the same as those reported in the full study population. When we restricted our sample to the 36,542 women who reported no recent changes in sleep (i.e., reported sleep was typical of the past year), the estimated risks were similar to those reported in the full study population. Likewise, when we restricted our analyses to the 28,714 women with long-term sleep stability (i.e., reported sleep was typical of at least the past five years), risk estimates for the GSI were similar, albeit slightly attenuated. Sensitivity analyses focused on the individual sleep deficiency components produced similar results (data not shown).

Discussion

Our results suggest that sleep deficiency may increase the risk of postmenopausal breast cancer in women. With the exception of duration, linear increases in risk were associated with all individual components of sleep deficiency and with our global sleep index. Due to the high degree of correlation between the individual components of sleep, it is not possible to discern which component(s) of sleep deficiency are driving such risk. Our findings, however, indicate that deficiencies in sleep duration are not likely to be the primary driver of risk.

Most studies to date on this topic have focused on sleep duration. Our results add to this relatively small and somewhat mixed literature [25, 27–32, 34, 46–50]. Overall, the lack of an association between sleep duration and breast cancer risk in our study is consistent with the conclusions of several meta-analyses that found no significant association for either long or short sleep [13, 14, 16, 17]. However, there remains some uncertainty regarding the relationship of long sleep, as suggested by our own results and those from a recent meta-analysis conducted by Lu and colleagues [15]. The Lu meta-analysis used restricted cubic spline modeling to evaluate the shape of the dose–response relationship.
relationship and reported a pooled relative risk estimate of 1.11 (95% CI 1.03–1.19) for sleep durations of 10 or more hours [15]. This meta-analysis included results from a prior prospective analysis in the CTS that suggested increased breast cancer risks for very long sleepers based on broadly defined categories of sleep duration ascertained at the time of cohort entry (hazard ratio = 1.25, 95% CI 0.93–1.68 for 10+ h compared to 7–9 h) [32]. In our current analysis, we initially observed a statistically significant elevated OR for long sleep but it was diminished and lost statistical significance in our fully adjusted models. In their meta-analysis, Lu et al. reported that the pooled estimate of risk associated with long sleep duration was more pronounced in cases with ER + tumors. Consistent with this, although not statistically

| Sleep metric            | N cases\(^b\) (n=2856) | Adjusted for age and race OR (95% CI) | Fully adjusted\(^a\) OR (95% CI) |
|-------------------------|-------------------------|--------------------------------------|----------------------------------|
| Sleep quality           |                         |                                      |                                  |
| Very good               | 825                     | 1.00                                 | 1.00                             |
| Fairly good             | 1562                    | 1.11 (1.02, 1.21)                    | 1.10 (1.01, 1.20)                |
| Fairly bad              | 407                     | 1.20 (1.06, 1.36)                    | 1.18 (1.04, 1.33)                |
| Very bad                | 45                      | 1.35 (0.99, 1.85)                    | 1.32 (0.96, 1.82)                |
| p-value for trend       |                         | 0.001                                 | 0.002                            |
| Sleep latency           |                         |                                      |                                  |
| <15 min                 | 1188                    | 1.00                                 | 1.00                             |
| 16–30 min               | 1102                    | 1.19 (1.10, 1.30)                    | 1.19 (1.09, 1.30)                |
| 31–60 min               | 416                     | 1.31 (1.17, 1.48)                    | 1.30 (1.15, 1.46)                |
| >60 min                 | 138                     | 1.36 (1.13, 1.63)                    | 1.33 (1.11, 1.61)                |
| p-value for trend       |                         | <0.001                               | <0.001                           |
| Sleep disturbance       |                         |                                      |                                  |
| Not during past month   | 619                     | 1.00                                 | 1.00                             |
| <1 time/week in past month | 868                  | 1.00 (0.90, 1.11)                    | 1.00 (0.90, 1.12)                |
| 1–2 times/week in past month | 701                 | 1.07 (0.96, 1.20)                    | 1.08 (0.96, 1.21)                |
| ≥3 times in past month  | 658                     | 1.25 (1.11, 1.40)                    | 1.25 (1.11, 1.40)                |
| p-value for trend       |                         | <0.001                               | <0.001                           |
| Sleep duration          |                         |                                      |                                  |
| ≥9 h                    | 162                     | 1.22 (1.02, 1.46)                    | 1.17 (0.98, 1.41)                |
| 8 h                     | 715                     | 1.00                                 | 1.00                             |
| 7 h                     | 1168                    | 1.04 (0.94, 1.14)                    | 1.05 (0.95, 1.16)                |
| 5–6 h                   | 702                     | 1.06 (0.95, 1.19)                    | 1.07 (0.96, 1.20)                |
| <5 h                    | 75                      | 1.06 (0.83, 1.36)                    | 1.05 (0.82, 1.35)                |
| p-value for trend       |                         | 0.997                                 | 0.775                            |
| Sleep medication        |                         |                                      |                                  |
| Not during past month   | 1841                    | 1.00                                 | 1.00                             |
| <1 time/week            | 347                     | 1.23 (1.09, 1.38)                    | 1.24 (1.10, 1.40)                |
| 1–2 times/week          | 210                     | 1.36 (1.17, 1.58)                    | 1.36 (1.17, 1.58)                |
| ≥3 times/week           | 427                     | 1.17 (1.05, 1.30)                    | 1.15 (1.03, 1.29)                |
| p-value for trend       |                         | <0.001                               | <0.001                           |
| Global Sleep Index (GSI)|                         |                                      |                                  |
| Lowest quartile (better sleep) | 738             | 1.00                                 | 1.00                             |
| 2nd quartile            | 642                     | 1.03 (0.92, 1.15)                    | 1.02 (0.92, 1.14)                |
| 3rd quartile            | 587                     | 1.18 (1.06, 1.32)                    | 1.18 (1.05, 1.32)                |
| Highest quartile (worse sleep) | 792            | 1.25 (1.13, 1.39)                    | 1.24 (1.12, 1.38)                |
| p-value for trend       |                         | <0.001                               | <0.001                           |

\(^a\)Adjusted for age at Q5, race (white/non-white), total pack-years of smoking, age at first full-term pregnancy, BMI at Q5, physical activity at Q5, family history of breast cancer through Q4, age at menopause (calculated at Q5), medication use for depression at Q5, NSAID use at Q5, and marital status at Q5

\(^b\)Numbers do not sum to total due to missing/unknown values
significant, we observed higher risks associated with long sleep among cases whose tumors were ER+/PR+ than those with ER-/PR- (Supplemental Table 2). Our findings, however, were hampered by the small number of ER-/PR-cases with long durations of sleep (n = 15). While overall our findings on sleep duration do not provide evidence that insufficient sleep duration is related to breast cancer risk, the risks associated with long sleep duration may warrant further investigation.

Other than for sleep duration, our results provide evidence for increased breast cancer risks associated with other components of sleep deficiency, including quality, latency and disturbance. Our results add to a small body of inconsistent findings on this topic. They stand in contrast to findings from a handful of breast cancer studies that have examined these other components of sleep deficiency and reported null effects [27, 30, 31, 34]. Although we did not have data available to directly evaluate risks associated with sleep disorders, such as apnea, we did find an increased risk associated with sleep disturbance. As sleep disturbance is considered a hallmark of apnea, our findings are consistent with studies that have reported elevated risks of breast cancer associated with sleep apnea [21, 22, 24]. Our findings are also consistent with the prospective analyses from the NIEHS Sister Study that found some evidence of risk associated with sleep deficiency. Specifically, they reported that relative to women with no difficulty sleeping, those who reported difficulty more than four nights a week were at an approximate 30% increased risk for breast cancer—an effect that was more pronounced among postmenopausal women (HR = 1.51, 95% CI 1.24–1.85) [34].

Although a number of plausible mechanisms have been suggested, one of the prevailing hypotheses is that cancer risks associated with sleep deficiencies are driven by disruption in circadian rhythms mediated by reductions in melatonin due to light-at-night exposures [7, 13, 51]. In this context, sleep duration has been considered a proxy for light-at-night exposures. Although supported by strong laboratory evidence, the light-at-night hypothesis has not been confirmed in human populations [52]. Circadian disruption, however, is not solely driven by light-at-night exposures and improved measures in epidemiologic studies are needed. As noted in a recent review, [52] measurements of light exposures that incorporate the timing, intensity and spectral qualities of light throughout both the day and night would be highly valuable. Furthermore, integration of actigraphy data with information on light exposures could be used to characterize the synchronization of activity-rest cycles with light–dark exposures, allowing for a more meaningful measure of circadian disruption.

Overall, much remains to be learned about the pathophysiology of sleep and cancer [18, 53]. As noted in a recent review, the degree to which sleep directly impacts breast cancer risk, independent of disruptions in circadian rhythm, is difficult to discern because breast cancer studies typically have not simultaneously considered the impact of both sleep and circadian disruption and the possible interaction of the two [18]. In this review, Samuelsson and colleagues present a nice discussion of the bidirectional relationship between sleep patterns and the circadian system in which each affects the other and together contribute to circadian disruption. While we did not have information on circadian disruption for our study population, we did have information on chronotype. Chronotype (the behavioral manifestation of an individual’s underlying circadian rhythms), is primarily characterized by one’s propensity to sleep at a particular time during the 24-h cycle (e.g., morning larks and night owls). Research among night shift workers suggests that

### Table 5

Sensitivity analysis: estimated risk of breast cancer associated with global sleep index (GSI), estimated by multivariable logistic regression, applying various exclusions

| Study population | Adjusted odds ratios (95% CI)<sup>a</sup> |
|------------------|------------------------------------------|
|                  | Global sleep index (GSI)                 |
|                  | 1st Quartile (better sleep) | 2nd Quartile | 3rd Quartile | 4th Quartile (worse sleep) |
| Full study population (n = 41,505) | 1.00 | 1.02 (0.92, 1.14) | 1.18 (1.05, 1.32) | 1.24 (1.12, 1.38) |
| Excluding 363 cases diagnosed within two years of Q5 fill date | 1.00 | 0.98 (0.88, 1.11) | 1.13 (1.00, 1.27) | 1.20 (1.07, 1.34) |
| Excluding 178 cases diagnosed within one year of Q5 fill date | 1.00 | 1.00 (0.89, 1.12) | 1.15 (1.02, 1.29) | 1.20 (1.08, 1.34) |
| Restricted to those with no recent changes in sleep<sup>b</sup> (n = 36,542) | 1.00 | 1.02 (0.91, 1.14) | 1.17 (1.03, 1.31) | 1.16 (1.04, 1.30) |
| Restricted to those who report long-term sleep stability<sup>c</sup> (= 28,714) | 1.00 | 1.03 (0.91, 1.17) | 1.23 (1.08, 1.41) | 1.16 (1.02, 1.32) |

<sup>a</sup>Adjusted for age at Q5, race (white/non-white), total pack-years of smoking, age at first full-term pregnancy, BMI at Q5, physical activity at Q5, family history of breast cancer through Q4, age at menopause (calculated at Q5), medication use for depression at Q5, NSAID use at Q5, and marital status at Q5.

<sup>b</sup>Reported sleep habits were typical of the prior year.

<sup>c</sup>Reported sleep habits were typical of at least the prior five years.
chronotype may act as a susceptibility factor for circadian disruption [54–58]. Prior analyses in the CTS have shown a relationship between chronotype and breast cancer risk [44]. Building on these observations, we stratified our analyses to explore whether chronotype might modify the risks associated with sleep deficiency in our study. These analyses indicated that risks associated with some measures of sleep deficiency were significantly modified by chronotype (Supplemental Table S1). Interpretation of these findings, however, is difficult as there were no apparent and consistent patterns of risk. To our knowledge, only one other breast cancer study has evaluated the role of sleep deficiency in the context of chronotype [31]. While that study reported no evidence of differential risk by chronotype, there was some suggestion that risks may vary by the other characteristics of circadian rhythm (amplitude and stability)—data we did not collect.

With its large sample size, extensive information on covariates, and ascertainment of several metrics of sleep deficiency coupled with information on sleep stability and chronotype, our study offers a valuable contribution to the limited literature on this topic. There are, however, some limitations of our study worth noting. Sleep characteristics were ascertained by self-report and thus may not be accurate measures of sleep deficiency. Although validation studies have indicated moderate to good agreement between self-reported estimates of sleep duration with objectively measured assessments through polysomnography (PSG) or actigraphy, random error and systematic biases also have been noted [59–62].

As a case control study reliant on self-reported sleep data, we also cannot dismiss the potential for recall bias due to differential recall between cases and controls. A meta-analyses of sleep duration and breast cancer reported that on average, risk estimates have been approximately 16% higher in prospective cohort studies than in case–control studies [14]. This suggests that if our study was affected by recall bias, it is more likely to have resulted in underestimates than overestimates of risk—at least for sleep duration. The post-diagnostic recall of sleep characteristics among cases in our study introduces the potential for reverse causality, i.e., that the onset of breast cancer, or its treatment, caused changes in sleep rather than sleep causing the cancer. The results of our sensitivity analyses, however, provided little evidence of this. Among cases, we did not observe any differences in sleep characteristics among those who had been more recently diagnosed compared to those with more distant diagnoses. Likewise, exclusion of cases who completed the Q5 survey on sleep characteristics shortly after diagnosis (i.e., with one or two years), did not appreciably change the risk estimates for breast cancer. Furthermore, restriction of our analyses to participants who indicated that their reported sleep had not changed in the last year and was indicative of their sleep for at least five years or more did not alter the conclusions of our analyses. Although it is well-documented that sleep changes with aging, such changes predominantly occur earlier in life and tend to stabilize by about age 60 or 65 [63]. In our study, sleep stability was slightly greater among those aged 65 or older (data not shown) but no statistically significant differences in sleep-associated risks were observed for older (age 65+ years) compared to younger (<65 years) participants.

In summary, our findings provide evidence that sleep deficiency may increase the risk of postmenopausal breast cancer. While our study importantly captured dimensions of sleep latency and disturbance, our analyses did not capture all measures of sleep deficiency and could not directly assess circadian disruption. Furthermore, our analyses did not include an evaluation of sleep disorders, were limited to night-time sleep, and did not consider the timing of sleep in relation to circadian rhythms. Future epidemiologic studies should consider the use of existing actigraphy tools [64] to objectively measure elements of circadian disruption that capture multiple dimensions of sleep deficiency and would allow for an evaluation of the synchrony of sleep–wake activity patterns with detailed measures of light throughout the 24-h daily cycle. Additionally, the use of inflammatory, metabolic and immunologic biomarkers to detect upstream effects of sleep deficiency could help elucidate the etiologic underpinnings of breast carcinogenesis, as well as inform the development of potential interventions to improve sleep that ultimately could reduce the risk of this disease.

Acknowledgments The authors would like to thank the California Teachers Study Steering Committee that is responsible for the formation and maintenance of the Study within which this research was conducted. A full list of California Teachers Study team members is available at https://www.calteachersstudy.org/team. We also express our appreciation to all the participants in the California Teachers Study and to the phlebotomists, the researchers, analysts and staff who have contributed to the success of this research, including Nadia Chung, Christine Duffy, Kristen Savage, Emma Spieffogel, and Jane Sullivan-Halley.

Funding The California Teachers Study and the research reported in this publication were supported by the National Cancer Institute of the National Institutes of Health under award number U01-CA199277; P30-CA033572; P30-CA023100; UM1-CA164917; R01-CA077398; and R01 CA207020. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. The collection of cancer incidence data used in the California Teachers Study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention’s National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the National Cancer Institute’s Surveillance, Epidemiology and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN26120180001SI awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute. The opinions, findings, and
conclusions expressed herein are those of the author(s) and do not necessarily reflect the official views of the State of California, Department of Public Health, the National Cancer Institute, the National Institutes of Health, the Centers for Disease Control and Prevention or their Contractors and Subcontractors, or the Regents of the University of California, or any of its programs.

Data availability All of the data associated with this publication and in the California Teachers Study are available for research use. The California Teachers Study welcomes all such inquiries and encourages individuals to visit https://www.calteachersstudy.org/for-researchers.

Compliance with ethical standards

Conflict of interest None of the authors have any financial conflicts of interest.

References

1. Centers for Disease Control and Prevention (2011) Unhealthy sleep-related behaviors—12 States, 2009. MMWR Morb Mortal Wkly Rep 60:233–238
2. Institute of Medicine (2006) Sleep disorders and sleep deprivation: an unmet public health problem. The National Academies Press, Washington, DC
3. Liu Y, Wheaton AG, Chapman DP, Cunningham TJ, Lu H, Croft JB (2016) Prevalence of healthy sleep duration among adults—United States, 2014. MMWR Morb Mortal Wkly Rep 65:137–141
4. International Agency for Research on Cancer (2010) IARC monographs on the evaluation of carcinogenic risks to humans. Painting, fire-fighting, and shiftwork. International Agency for Research on Cancer, Lyon, pp 563–764
5. Straif K, Baan R, Grosse Y, Secretan B, El Ghissassi F, Bouvard V, Altieri A, Benbrahim-Tallaa L, Cogliano V, WHO International Agency For Research on Cancer Monograph Working Group (2007) Carcinogenicity of shift-work, painting, and fire-fighting. Lancet Oncol 8:1065–1066
6. FerriRE JE, Kumari M, Salo P, Singh-Manoux A, Kivimaki M (2011) Sleep epidemiology—a rapidly growing field. Int J Epide miol 40:1431–1437
7. Blask DE (2009) Melatonin, sleep disturbance and cancer risk. Sleep Med Rev 13:257–264
8. Irwin MR (2014) Why sleep is important for health: a psycho-neuroimmunology perspective. Annu Rev Psychol. https://doi.org/10.1146/annurev-psych-010213-115205
9. Alvarez-Garcia V, Gonzalez A, Martinez-Campa C, Alonso-Gonzalez C, Cos S (2013) Melatonin modulates aromatase activity and expression in endothelial cells. Oncol Rep 29:2058–2064
10. Cos S, Gonzalez A, Martinez-Campa C, Mediavilla MD, Alonso-Gonzalez C, Sanchez-Barcelo EJ (2008) Melatonin as a selective estrogen enzyme modulator. Curr Cancer Drug Targets 8:691–702
11. Hill SM, Belancio VP, Dauchy RT, Xiang S, Brimer S, Mao L, Hauch A, Lundberg PW, Summers W, Yuan L, Frasch T, Blask DE (2015) Melatonin: an inhibitor of breast cancer. Endocr Relat Cancer 22:R183–204
12. Hill SM, Blask DE, Xiang S, Yuan L, Mao L, Dauchy RT, Dauchy EM, Frasch T, Dupljes T (2011) Melatonin and associated signaling pathways that control normal breast epithelium and breast cancer. J Mammary Gland Biol Neoplasia 16:235–245
13. Chen Y, Tan F, Wei L, Li X, Lyu Z, Feng X, Wen Y, Guo L, He J, Dai M, Li N (2018) Sleep duration and the risk of cancer: a systematic review and meta-analysis including dose-response relationship. BMC Cancer 18:1149
14. Erren TC, Morfeld P, Foster RG, Reiter RJ, Gross JV, Westermann IK (2016) Sleep and cancer: synthesis of experimental data and meta-analyses of cancer incidence among some 1,500,000 study individuals in 13 countries. Chronobiol Int 33:325–350
15. Lu C, Sun H, Huang J, Yin S, Hou W, Zhang J, Wang Y, Xu X, Hu H (2017) Long-term sleep duration as a risk factor for breast cancer: evidence from a systematic review and dose-response meta-analysis. Biomed Res Int 2017:4845059
16. Lu Y, Tian N, Yin J, Shi Y, Huang Z (2013) Association between sleep duration and cancer risk: a meta-analysis of prospective cohort studies. PLoS ONE 8:e74723
17. Qin Y, Zhou Y, Zhang X, Wei X, He J (2014) Sleep duration and breast cancer risk: a meta-analysis of observational studies. Int J Cancer 134:1166–1173
18. Samuelsson LB, Bovbjerg DH, Roeckelein KA, Hall MH (2018) Sleep and circadian disruption and incident breast cancer risk: an evidence-based and theoretical review. Neurosci Biobehav Rev 84:35–48
19. National Institutes of Health (2011) 2011 National Institutes of Health Sleep Disorders Research Plan. Available at: https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2011-national-institutes-health-sleep-disorders. Accessed on 2019
20. Brenner R, Kidy s, Peker M, Reinhorn D, Keinan-Boker L, Silverman B, Liphitsiz I, Kolitz T, Levy C, Shlomi D, Pillar G, Peled N (2019) Increased risk for cancer in young patients with severe obstructive sleep apnea. Respiration 97:15–23
21. Choi JH, Lee JY, Han KD, Lim YC, Cho JH (2019) Association between obstructive sleep apnoea and breast cancer: the Korean National Health Insurance Service Data 2007–2014. Sci Rep 9:19044
22. Fang HF, Miao NF, Chen CD, Sithole T, Chung MH (2015) Risk of cancer in patients with insomnia, parasomnia, and obstructive sleep apnea: a nationwide nested case–control study. J Cancer 6:1140–1147
23. Gozal D, Ham SA, Mokhlesi B (2016) Sleep apnea and cancer: analysis of a nationwide population sample. Sleep 39:1493–1500
24. Sillah A, Watson NF, Gozal D, Phipps AI (2019) Obstructive sleep apnea severity and subsequent risk for cancer incidence. Prev Med Rep 15:100886
25. Kakizaki M, Kuriyama S, Sone T, Ohmori-Matsuda K, Hozawa A, Nakaya N, Fukushima S, Tsuji I (2008) Sleep duration and the risk of breast cancer: the Ohsaki Cohort Study. Br J Cancer 99:1502–1505
26. Khawaja A, Rao S, Li L, Thompson CL (2013) Sleep duration and breast cancer phenotype. J Cancer Epidemiol 2013:467927
27. Verkasalo PK, Lillberg K, Stevens RG, Hublin C, Partinen M, Koskenvuo M, Kaprio J (2005) Sleep duration and breast cancer: a prospective cohort study. Cancer Res 65:9595–9600
28. McElroy JA, Newcomb PA, Titus-Ernstoff L, Trentham-Dietz A, Hampton JM, Egan KM (2006) Duration of sleep and breast cancer risk in a large population-based case-control study. J Sleep Res 15:241–249
29. Pinheiro SP, Schernhammer ES, Tworoger SS, Michels KB (2006) A prospective study on habitual duration of sleep and incidence of breast cancer in a large cohort of women. Cancer Res 66:5521–5525
30. Vogtmann E, Levitan EB, Hale L, Shikany JM, Shah NA, Endeshaw Y, Lewis CE, Manson JE, Chlebowski RT (2013) Association between sleep and breast cancer incidence among postmenopausal women in the Women’s Health Initiative. Sleep 36:1437–1444
31. Girschik J, Heyworth J, Fritschi L (2013) Self-reported sleep duration, sleep quality, and breast cancer risk in a population-based case-control study. Am J Epidemiol 177:316–327
32. Hurley S, Goldberg D, Bernstein L, Reynolds P (2015) Sleep duration and cancer risk in women. Cancer Causes Control 26:1037–1045
33. Wu AH, Stanczyk FZ, Wang R, Koh WP, Yuan JM, Yu MC (2013) Sleep duration, spot urinary 6-sulfatoxymelatonin levels and risk of breast cancer among Chinese women in Singapore. Int J Cancer 132:891–896
34. White AJ, Weinberg CR, Park YM, D’Aloisio AA, Vogtmann E, Nichols HB, Sandler DP (2017) Sleep characteristics, light at night and breast cancer risk in a prospective cohort. Int J Cancer 141:2204–2214
35. Bernstein L, Allen M, Anton-Culver H, Deapen D, Horn-Ross PL, Peel D, Pinder R, Reynolds P, Sullivan-Halley J, West D, Wright W, Ziegas A, Ross RK (2002) High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). Cancer Causes Control 13:625–635
36. California Cancer Registry. Available at: https://www.ccrca l.org/abouthccr.html
37. Backhaus J, Junghans K, Broocks A, Riemann D, Hohagen F (2002) Test-retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. J Psychosom Res 53:737–740
38. Beck SL, Schwartz AL, Towsley G, Dudley W, Barsevick A, Brinton LA, Schairer C, Matthews CE (2015) Sleep duration, melatonin and breast cancer duration, spot urinary 6-sulfatoxymelatonin levels and risk of breast cancer among Chinese women in Singapore. Int J Cancer 132:891–896
39. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213
40. Adan A, Almirall H (1991) Horne and Ostberg morningness eveningness questionnaire—a reduced scale. Personality Individ Differ 12:241–253
41. Chelminski I, Petros TV, Plaud JJ, Ferraro R (2000) Psychometric properties of the reduced Horne and Ostberg questionnaires. Personality Individ Differ 29:469–478
42. Duffy JF, Rimmer DW, Czeisler CA (2001) Association of intrinsic circadian period with morningness-eveningness, usual wake time, and circadian phase. Behav Neurosci 115:895–899
43. Horne JA, Ostberg O (1976) A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol 4:97–110
44. Haus EL, Smolensky MH (2013) Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. Sleep Med Rev 17:273–284
45. Hunter CM, Figueiro MG (2017) Measuring light at night and melatonin levels in shift workers: a review of the literature. Biol Res Nurs 19:365–374
46. Li J, Vitiello MV, Gooneratne NS (2018) Sleep in normal aging. Sleep Med Clin 13:1–11
47. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ (2008) Individual differences in tolerance to shift work—a systematic review. Sleep Med Rev 15:221–235
48. Dement WC, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ (1989) The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 28:193–213
49. Hunter CM, Figueiro MG (2017) Measuring light at night and melatonin levels in shift workers: a review of the literature. Biol Res Nurs 19:365–374
50. Xiao Q, Signorello LB, Brinton LA, Cohen SS, Blot WJ, Matthews CE (2016) Sleep duration and breast cancer risk among black and white women. Sleep Med 20:25–29
51. Haus EL, Smolensky MH (2013) Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. Sleep Med Rev 17:273–284
52. Hunter CM, Figueiro MG (2017) Measuring light at night and melatonin levels in shift workers: a review of the literature. Biol Res Nurs 19:365–374