Insomnia and the Risk of Breast Cancer: The HUNT Study

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ABSTRACT

Objective: The association of insomnia with subsequent breast cancer risk is largely unknown. Therefore, we assessed whether different symptoms of insomnia and their combination are associated with incident breast cancer in a large population-based study.

Methods: In a prospective cohort study, 33,332 women were followed to monitor the occurrence of their first invasive breast cancer identified by the Cancer Registry of Norway. Insomnia symptoms including (1) nonrestorative sleep and (2) difficulty initiating and (3) maintaining sleep were self-reported using a study specific measure reflecting the current *Diagnostic and Statistical Manual of Mental Disorders* criteria. Hazard ratios and 95% confidence intervals were calculated using multiadjusted Cox proportional hazards models.

Results: A total of 862 incident breast cancer cases occurred during a mean follow-up of 14.7 years. No consistent association was observed between the individual insomnia symptoms and breast cancer risk. However, compared to women reporting no insomnia complaints, those who reported having all three aspects of insomnia simultaneously were at increased risk (hazard ratio, 2.38; 95% confidence interval = 1.11–5.09).

Conclusion: Our results suggest that having only some aspects of insomnia may not predispose someone to breast cancer. In contrast, experiencing all insomnia symptoms simultaneously might confer considerable excess risk.

Key words: sleep, sleep disturbance, insomnia, prospective cohort study and breast cancer.

INTRODUCTION

Insomnia is the most common sleep disorder, characterized by a feeling of difficulty initiating sleep or maintaining sleep or having a feeling of nonrestorative sleep (1). It has been estimated that the prevalence of at least one insomnia symptom may vary from an average of 6% to 33% in the general population (2). Insomnia is a major public health concern and has been linked to numerous adverse health outcomes such as diabetes, obesity, and heart disease among others (3,4). Among breast cancer patients, insomnia complaints are very common, with a reported prevalence ranging from 20% to almost 70% (5). Many studies have looked at insomnia after diagnosis of breast cancer (5–8), but only a few have investigated whether insomnia is a risk factor for breast cancer among initially cancer-free women (9,10) and the bulk of such studies have examined shift workers (11,12). There are several biologically plausible pathways how insomnia might influence the risk of developing breast cancer such as obesity (13–15), internal desynchronization (16), the estrogen signalling pathway (17), melatonin suppression (18–20), or impaired immune function (21,22).

Therefore, we assessed the association between individual insomnia symptoms and their combinations, with subsequent risk of breast cancer in a large population-based cohort. In these analyses, we adjusted for reproductive factors that are known to influence risk and several demographic, anthropometric, and lifestyle factors.

METHODS

Study Population

The source population consisted of all female participants in the second wave of the population-based Nord-Trøndelag Health Study (HUNT study) conducted from August 1995 to June 1997. In total, 47,177 women 20 years

BMI = body mass index, **HR** = hazard ratio, **HUNT** = study Nord-Trøndelag health study

SDC Supplemental Content

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or older were invited to the study, and 34,650 (73.4%) of them attended, filled out a questionnaire, or had a clinical examination at baseline. The details of the study have been described elsewhere (23,24). All participants in the HUNT study have completed a written informed consent form, allowing linkage with register data using the unique 11-digit identification number of Norwegian citizens. We acquired information on date of first diagnosis of HUNT 2 participants from the Cancer Registry of Norway (www.krefregisteret.no). The study was approved by the Regional Committee for Ethics in Medical Research, the National Directorate of Health, and by the Norwegian Data Inspectorate.

Follow-Up

After participation, women were followed up; and exit time was date of first invasive cancer diagnosis, emigration, death, or censoring at the end of follow-up period, that is, December 31, 2012, whichever came first. Exit dates were available at the month level. Breast cancer was registered according to the *International Classification of Diseases, 7th Edition* (code 170). Of 34,650 women, we excluded 401 women who had prevalent breast cancer diagnosis and 885 women who had other prevalent cancers. Additional 32 women were excluded because they emigrated from the county or died in the same month as inclusion to the study. Thus, a total of 33,332 women were included and followed up in our present study.

Assessment of Insomnia

Three questions related to insomnia were asked. The first question was related to difficulty initiating sleep: "Have you had difficulties falling asleep in the last month?" with the following response options: "never/occasionally/often/almost every night." The second question was related to difficulty maintaining sleep: "During the last month, have you woken up too early and not been able to get back to sleep?" with the following response options: "never/occasionally/often/almost every night." The third question was related to having a feeling of nonrestorative sleep: "How often do you suffer from poor sleep?" with the following response options: "never or few times a year/1 to 2 times per month/about once a week/more than once a week." The last question was restricted to individuals 20 to 69 years of age due to space in the questionnaires and total work load (number of questions per questionnaire) for the participant who was expected to answer the given questionnaire. For individuals who were older than 70 years, questions related to "activities of daily living" questions were prioritized in the questionnaire. These self-reported questions on insomnia used in our current study have not been validated, but our operationalization reflects the current *Diagnostic and Statistical Manual of Mental Disorders* criteria for insomnia (1).

We assessed the influence of each insomnia symptom using the original four response categories. To assess the dose-dependent association between number of insomnia symptoms and risk for breast cancer, insomnia symptoms were also dichotomized; and the highest categories, that is, having difficulty initiating sleep almost every night, difficulty maintaining sleep almost every night, and having nonrestorative sleep more than once a week, were compared with the other categories. Thus, those in the highest categories were considered to have the respective insomnia symptoms in the analysis of the association between number of insomnia symptoms and breast cancer risk. We conducted an analysis of trend by assigning a value from zero to 3 of the response options for the three insomnia symptoms. The trend variable referred to the number of dichotomized insomnia symptoms. The number 0 indicates that a participant had not experienced any of the insomnia symptoms (i.e., have not had difficulties initiating sleep almost every night, difficulties maintaining sleep almost every night, nor nonrestorative sleep more than once a week). Values of 1 or 2 indicate that the participant had experienced one or two of the insomnia symptoms, respectively. Accordingly, a value of 3 indicated that the participant had experienced all three insomnia symptoms.

The response rate for women who responded to questions related to insomnia such as difficulty initiating asleep, difficulty maintaining sleep, or having feeling of nonrestorative sleep were 84.5%, 84.9%, and 81.2%, respectively.

Covariate Information

Information on age at first birth and parity, as well as level of physical activity, alcohol consumption, smoking status, level of education, and shift work, were self-reported at baseline. Height and weight were recorded with participants wearing light clothes without shoes; height was measured to the nearest 1 cm and weight to the nearest 0.5 kg. Body mass index (BMI) was calculated as weight (in kilograms) divided by the squared value of height (in meters). Shift work was defined as "Do you work shift at night or on call?" (response options: "yes" or "no"). The Hospital Anxiety and Depression Scale were used to assess core psychological symptoms of anxiety and depression during previous week. The questionnaire consisted of 14 four-point Likert-scaled items; seven anxiety questions reflect mostly symptoms of worry and tension, and seven depression questions reflect symptoms of anhedonia and loss of interest. Scores on both anxiety and depression subscales ranged from 0 point (no symptoms) to 21 points, and increasing scores indicated increased symptom load (25,26). Participants were also asked about their use of sleep medication/sedatives ("How often have you taken tranquilizers/sedatives or sleep medication in the last month?" with the following response options: daily/every week but not every day/less than once a week/never).

Statistical Analysis

Cox proportional hazard models were used to study the association between insomnia symptoms and invasive breast cancer incidence using age as the underlying time scale. We computed hazard ratios (HRs) with 95% confidence intervals (CIs).

The group of women with no insomnia complaints was used as the reference category in all statistical models. We assigned a numeric value of 0 to 3 to the insomnia symptoms, with 0 having no insomnia complaints and categories were treated as a continuous variable to test for linear trends. In alternative analyses, we also included a quadratic term to assess nonlinear trends. In a separate analysis, risk associated with increasing number of insomnia symptoms was calculated, using women without any symptoms as the reference group. Participants with missing data on any of the insomnia symptoms were excluded from these latter analyses. In addition, the assessment of having a feeling of nonrestorative sleep was restricted to participants 20 to 69 years of age, and the analysis on cumulative number of insomnia symptoms was therefore also restricted to this age group.

All multivariable models were adjusted for potential confounders, including age at first birth (nulliparous, <20, 20–24, 25–29, 30 years or older), parity (continuous), BMI (continuous in kg/m^2), alcohol consumption (abstainers, light drinkers as 0–1 drink per day, moderate drinkers as >1 but <2 drinks per day or heavy drinkers as ≥2 drinks per day), physical activity (<1 hour as light exercise, 1–3 hours of hard exercise or ≥3 hours of light activity per week as moderate exercise, ≥3 hours of hard physical activity per week as vigorous exercise), smoking (never, former, current), and education (<10, 10–12, or >12 years), anxiety and depression (respective Hospital Anxiety and Depression Scale score, <8, 8–11, ≥11) (27). Additional separate analyses were performed by further adjusting for shift work (yes or no) and use of menopausal hormone therapy (never, current, or former).

The inclusion of potential confounders to our models was based on previous knowledge concerning the covariates causal association with insomnia and breast cancer. This approach is strongly recommended in the modern epidemiologic literature (28,29).

We investigated potential effect modification by BMI (dichotomized at 25 kg/m^2), and by age (dichotomized at 50 years) to study the effect of insomnia symptoms on the risk of premenopausal and postmenopausal breast cancer. A sensitivity analysis was also conducted excluding the first 3 years of follow-up to account for the possibility of reversed causation. Moreover, in a separate analysis, we also excluded women who reported using sleep medications/sedatives on a daily basis.

The proportionality of hazards was tested using log-minus-log plots and formal tests of interaction with time or log time, and no evidence of violation was detected except for BMI ($p < .001$). Because of this violation,

TABLE 1. Baseline Characteristics of Participants According to Breast Cancer Occurrence During Follow-Up

		Incident Breast Cancer Cases During Follow-Up		No Breast Cancer During Follow-Up		
	N	*n*	(%)	*n*	(%)	*p*[a]
Total sample	33,332	862		32,470		
Difficulty initiating sleep						
Never	14,334	355	(41.2)	13,979	(43.1)	.15
Occasionally	10,850	308	(35.7)	10,542	(32.5)	
Often	1856	42	(4.9)	1814	(5.6)	
Almost every night	1141	36	(4.2)	1105	(3.4)	
Missing numbers	5151	121	(14.0)	5030	(15.5)	
Difficulty maintaining sleep						
Never	12,683	277	(32.1)	12,406	(38.2)	<.001
Occasionally	12,471	367	(42.6)	12,104	(37.3)	
Often	2312	70	(8.1)	2242	(6.9)	
Almost every night	817	28	(3.3)	789	(2.4)	
Missing numbers	5049	120	(13.9)	4929	(15.2)	
Feeling of nonrestorative sleep						
Never or a few times per year	15,342	381	(44.2)	14,961	(46.1)	.45
1–2 times per month	4100	107	(12.4)	3993	(12.3)	
Once a week	1892	45	(5.2)	1847	(5.7)	
More than once a week	2385	72	(8.4)	2313	(7.1)	
Missing numbers	9613	257	(29.8)	9356	(28.8)	
Smoking						
Never	21,427	544	(63.1)	20,883	(64.3)	.64
Ever	9773	257	(29.8)	9516	(29.3)	
Missing numbers	2243	61	(7.1)	2 071	(6.4)	
Alcohol						
Abstainer	15,565	393	(45.6)	15,172	(46.7)	.08
Light drinker	13,553	337	(39.1)	13,216	(40.7)	
Moderate drinker	1739	60	(7.0)	1679	(5.2)	
Heavy drinker	251	4	(0.5)	247	(0.8)	
Missing numbers	2224	68	(7.9)	2156	(6.6)	
Physical activity						
Inactive	12,814	360	(41.8)	12,454	(38.4)	.02
Moderately active	14,674	341	(39.6)	14,333	(44.1)	
Vigorous	1798	39	(4.5)	1759	(5.4)	
Missing numbers	4046	122	(14.2)	3924	(12.1)	
Shift work[b]	5245	139	(16.1)	5106	(15.7)	.75
Use of sleep medicine/sedatives	4599	132	(15.3)	4467	(14.1)	.23
Education, years						
≤9	12,517	346	(40.1)	12,171	(37.5)	.29
10–12	12,559	309	(35.9)	12,250	(37.7)	
>12	6382	161	(18.7)	6221	(19.2)	
Missing numbers	1874	46	(5.3)	1828	(5.6)	

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TABLE 1. *(Continued)*

		Incident Breast Cancer Cases During Follow-Up		No Breast Cancer During Follow-Up		
	N	*n*	(%)	*n*	(%)	p^a
Parity						
Nulliparus	4618	82	(9.5)	4536	(13.9)	.002
1 child	3882	100	(11.6)	3782	(11.7)	
2 children	10,468	288	(33.4)	10,180	(31.4)	
3 children	8199	239	(27.7)	7960	(24.5)	
≥4 children	5703	149	(17.3)	5554	(17.1)	
Missing numbers	462	4	(0.5)	458	(1.4)	
Age at first birth in years						
Nulliparous	4618	82	(9.5)	4536	(13.9)	<.001
<20	112	6	(0.7)	106	(0.3)	
20–25	3130	77	(8.9)	3053	(9.4)	
25–30	8278	201	(23.3)	8077	(24.9)	
≥ 30	12,942	395	(45.8)	12,547	(38.6)	
Missing numbers	4252	101	(11.7)	4151	(12.8)	
Use of menopausal hormone therapy						
Never	21,122	489	(56.7)	20,633	(63.5)	<.001
Current	2499	117	(13.6)	2382	(7.3)	
Former	1168	30	(3.5)	1138	(3.5)	
Missing numbers	8543	226	(26.2)	8317	(25.6)	
Depression score						
<8 (less depressed)	28,612	732	(84.9)	27,880	(85.9)	.47
8–11 (moderate depressed)	2380	69	(8)	2311	(7.1)	
>11 (severely depressed)	1020	30	(3.5)	990	(3.1)	
Missing numbers	1320	31	(3.6)	1289	(3.9)	
Anxiety score						
<8 (less anxious)	25,604	673	(78.1)	24,931	(76.8)	.44
8–11 (moderate anxious)	3654	95	(11.0)	3559	(11.0)	
>11 (severely anxious)	2036	44	(5.1)	1992	(6.1)	
Missing numbers	2038	50	(5.8)	1988	(6.1)	
		Mean	(SD)	Mean	(SD)	
Age	33,332	54.8	(14.1)	49.6	(17.5)	<.001
BMI, kg/m^2	32,896	26.9	(4.7)	26.2	(4.6)	<.001

BMI = body mass index; SD = standard deviation.

[a] *p* values were calculated via χ^2 test (categorized variables) and *t* test (for continuous variable).

[b] Those who answered yes to the question: Do you have shift work. night work or standing by duties?.

BMI was included as a time-dependent variable in all statistical models. All *p* values are two sided, and all analyses were conducted using STATA version 13 (Stata Corp, College Station, TX).

RESULTS

Table 1 presents the characteristics of the study population at baseline, by breast cancer status at follow-up. Among 33,332 women in the HUNT study, a total of 862 incident breast cancer cases were identified based on the information from the Cancer Registry of Norway, during a mean follow-up of 14.7 years (standard deviation, 3.2). Age-specific incidence of breast cancer in the present study largely corresponded to national data (30). Compared with women without breast cancer, those who had a diagnosis of breast cancer during the follow-up

TABLE 2. Hazard Ratios and 95% CIs for Breast Cancer According to the Individual Insomnia Symptoms

Variable	Events/ Person Years	Model 1 95% CI	Model 2 95% CI	Model 3 95% CI
Difficulty initiating sleep				
Never	355/216 742	Reference	Reference	Reference
Occasionally	308/159 497	1.02 (0.87–1.19)	1.12 (0.93–1.35)	1.12 (0.93–1.36)
Often	42/26 856	0.77 (0.56–1.06)	0.94 (0.64–1.37)	0.96 (0.65–1.44)
Almost every night	36/14 761	1.09 (0.77–1.54)	1.37 (0.89–2.13)	1.28 (0.79–2.06)
$p_{\text{linear-trend}}$		.71	.25	.42
Difficulty maintaining sleep				
Never	277/196 934	Reference	Reference	Reference
Occasionally	367/179 424	1.01 (0.86–1.19)	1.20 (0.98–1.46)	1.21 (0.99–1.48)
Often	70/32 301	0.99 (0.76–1.29)	1.27 (0.91–1.76)	1.37 (0.98–1.93)
Almost every night	28/10 512	1.14 (0.76–1.69)	1.42 (0.86–2.36)	1.49 (0.88–2.52)
$p_{\text{linear-trend}}$		.73	.03	.06
Feeling of nonrestorative sleep				
Never/Few times a year	381/241 635	Reference	Reference	Reference
1–2 times per month	107/63 587	0.91 (0.73–1.13)	1.02 (0.79–1.30)	1.02 (0.79–1.30)
Once a week	45/29 191	0.79 (0.58–1.07)	0.76 (0.52–1.12)	0.76 (0.51–1.13)
More than once a week	72/36 080	0.93 (0.72–1.20)	1.02 (0.75–1.39)	1.03 (0.74–1.43)
$p_{\text{linear-trend}}$		.24	.67	.66

Model 1. Adjusted for age.

Model 2. Model 1 plus adjusted for physical activity, education, smoking, BMI, alcohol intake, parity, age at first birth.

Model 3. Model 2 plus adjusted for depression and anxiety.

period had more difficulties initiating or maintaining sleep every night, had poor sleep quality, were physically less active, less educated, consumed more alcohol, had relatively higher BMI, and were more likely to be current or ever smokers.

Table 2 reports HRs and 95% CIs for the associations of insomnia symptoms with breast cancer risk. There were no consistent associations between each of the insomnia symptoms and breast cancer risk in age-adjusted models or in models with additional adjustment for age at first birth, parity, BMI, smoking, physical activity, alcohol consumption, and depression and anxiety scores. The point estimates remained unchanged after further adjustment for shift work or menopausal hormone therapy (data not shown). Because high body weight might be a

TABLE 3. HRs and 95% CIs for Breast Cancer According to Cumulative Number of Insomnia Symptoms

	Events/Person Years	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Number of Symptoms				
0	526/327,540	Reference	Reference	Reference
1	46/26,733	0.84 (0.62–1.14)	0.91 (0.63–1.31)	0.94 (0.65–1.38)
2	18/9352	0.93 (0.58–1.49)	0.97 (0.54–1.72)	0.92 (0.50–1.69)
3	9/2155	1.90 (0.98–3.68)	2.24 (1.06–4.76)	2.38 (1.11–5.09)
HR for each symptom increase		1.02 (0.87–1.19)	1.07 (0.89–1.29)	1.08 (0.89–1.32)
$p_{\text{linear trend}}$		.84	.45	.42

HR = hazard ratio; CI = confidence interval.

Model 1. Adjusted for age.

Model 2. Model 1 plus adjusted for physical activity, education, smoking, BMI, alcohol intake, parity, age at first birth.

Model 3. Model 2 plus adjusted for depression and anxiety scores.

potential mediator for the effect of insomnia on breast cancer risk, we repeated the multivariable analyses without adjustment for BMI, but the associations remained nearly identical.

No clear linear trend was observed between the cumulative number of insomnia symptoms and subsequent breast cancer risk (Table 3). The HR for each cumulative increase in symptoms was 1.08 (95% CI = 0.89–1.32). Moreover, we found no evidence for nonlinearity (data not shown). However, compared to women who reported to have no symptoms of insomnia, the HR for women who reported to have all insomnia symptoms simultaneously was 2.38 (95% CI = 1.11–5.09) after multivariable adjustment.

In a separate analysis, we found no clear statistical evidence for any effect modification by BMI or by age (Tables S1 and S2, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A337).

In sensitivity analyses, the estimate remained essentially unchanged or became slightly stronger after exclusion of the first 3 years of follow-up and of 124 cases of breast cancer that occurred during this period. For insomnia symptoms, the exclusion of women who reported use of sleep medications/sedatives at baseline did not substantially change the results (data not presented).

DISCUSSION

In this large prospective study of 33,332 women among whom 862 had a diagnosis of invasive breast cancer during 15 years of follow-up, we observed no consistent associations between individual insomnia symptoms and breast cancer risk. Nonetheless, women who reported having all insomnia symptoms simultaneously seemed to be at more than twofold higher risk, compared to women without any insomnia symptoms.

Comparison With Previous Studies

Several epidemiologic studies have investigated the association between shift work and breast cancer risk. In a recent meta-analysis, the pooled adjusted relative risk for the association between "ever exposed to night shift work" and breast cancer was 1.19 (95% CI = 1.05–1.35) (11), suggesting a moderate increase in risk associated with nightly shift work.

However, much less is known about the association between insomnia and breast cancer risk. The Finnish Twin Study and two case-control studies conducted in Australia investigated the associations of some individual symptom components of insomnia but found no clear associations with breast cancer risk for any of the reported symptoms (31–33). The Women's Health Initiative study included a self-reported rating scale of insomnia symptoms. In that study, women who were above a predefined level of symptoms had a risk for breast cancer that did not differ from women who were below that symptom level (HR, 0.99; 95% CI = 0.93–1.05) (9).

In line with previous epidemiologic studies, we found no consistent increase in risk of breast cancer for women who reported one or two individual insomnia symptoms compared to women with no symptoms. Among women who reported having all the insomnia symptoms simultaneously, however, we observed a considerable increase. One might hypothesize that if only one or two aspects of sleep are compromised, other aspects can compensate, resulting in an overall satisfactory sleep functioning. For example, difficulty in falling asleep can be compensated by good maintenance of sleep and/or by highly restorative sleep. However, simultaneous problems of initiating and maintaining sleep and that of nonrestorative sleep may leave no room for compensation and thus lead to adverse health effects (34). We shall emphasize, however, that the findings from the latter analysis had low precision and a wide CI. To our knowledge, no previous study has examined breast cancer risk in those with all aspects of insomnia. Therefore, further investigations are clearly needed to confirm these findings. Interestingly, in a recent animal study, experimentally induced sleep disturbance increased the risk for breast cancer in mice (16), but generalizability of this finding to humans is not straightforward.

Potential Mechanisms for an Observed Association

A number of plausible biological models have been proposed to explain how insomnia could increase risk for breast cancer. One suggested possibility is that sleep disturbances might lead to obesity and subsequently increase breast cancer risk (13–15). However, we found no support for this possibility in our analysis, since adjustment for BMI did not affect the result. Another suggested possibility is that women who experience insomnia symptoms may have an impaired immune function that may be associated with increased breast cancer risk (21,22). It has also been suggested that insomnia may be associated with suppression of melatonin levels that in turn might increase estrogen production and subsequently lead to increased breast cancer risk (17,20,35,36).

Strengths and Limitations

The present study has several strengths. We followed a large population-based cohort of women of all ages over a long time, and in the analyses, we could adjust for a wide range of potentially confounding factors. In addition, retention to the study was high, and breast cancer follow-up was nearly complete, with only 0.1% of the population lost to follow-up due to emigration from Norway. The highly reliable registration of breast cancer cases in Norway minimized the possibility for misclassification of end points (37).

On the other hand, the study also has some limitations. First, data on sleep were self-reported and not validated by polysomnography. However, it is not routinely used

for diagnosing insomnia (38). The reason is that difficulty initiating or maintaining sleep and nonrestorative sleep are subjective symptoms and cannot easily be objectively measured. In fact, insomnia may be present even in the absence of polysomnographic signs of sleep disturbance (38). Data on sleep apnoea syndrome, a potential correlate of both insomnia and breast cancer (39), are not available in the HUNT study and therefore confounding due to sleep apnea could not be assessed. However, sleep apnea is strongly and positively associated with age and with BMI (40), and both these factors were closely accounted for in our analyses. Finally, these results are from a general population in Norway and can only be generalized to similar populations.

CONCLUSIONS

We found no evidence of an association between individual insomnia symptoms and subsequent risk for breast cancer. However, having all insomnia symptoms simultaneously, that is, nonrestorative sleep and difficulty of initiating and maintaining sleep, might be associated with a considerable risk increase. Ours is the first study that has examined the association between the combination of all insomnia symptoms and breast cancer risk. The findings are biologically plausible, but our statistical precision is low; large prospective studies are therefore warranted to confirm our results.

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REFERENCES

1. APA, American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.
2. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6:97–111.
3. Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: results of the 2003 National Sleep Foundation Sleep in America Survey. J Psychosom Res 2004;56:497–502.
4. Suls J, Green PA, Davidson KW. A biobehavioral [corrected] framework to address the emerging challenge of multimorbidity. Psychosom Med 2016;78:281–9.
5. Fiorentino L, Ancoli-Israel S. Insomnia and its treatment in women with breast cancer. Sleep Med Rev 2006;10:419–429.
6. Fiorentino L, Rissling M, Liu L, Ancoli-Israel S. The symptom cluster of sleep, fatigue and depressive symptoms in breast cancer patients: severity of the problem and treatment options. Drug Discov Today Dis Models 2011;8:167–173.
7. Costa AR, Fontes F, Pereira S, Gonçalves M, Azevedo A, Lunet N. Impact of breast cancer treatments on sleep disturbances—a systematic review. Breast 2014;23:697–709.
8. Tell D, Mathews HL, Janusek LW. Day-to-day dynamics of associations between sleep, napping, fatigue, and the cortisol diurnal rhythm in women diagnosed as having breast cancer. Psychosom Med 2014;76:519–528.
9. 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.
10. Fang HF, Miao NF, Chen CD, Sithole T, Chung MH. Risk of cancer in patients with insomnia, parasomnia, and obstructive sleep apnea: a nationwide nested case-control study. J Cancer 2015;6:1140–1147.
11. Wang F, Yeung KL, Chan WC, Kwok CC, Leung SL, Wu C, Chan EY, Yu IT, Yang XR, Tse LA. A meta-analysis on dose-response relationship between night shift work and the risk of breast cancer. Ann Oncol 2013;24:2724–2732.
12. Costa G, Haus E, Stevens R. Shift work and cancer—considerations on rationale, mechanisms, and epidemiology. Scand J Work Environ Health 2010;36:163–179.
13. Marshall NS, Glozier N, Grunstein RR. Is sleep duration related to obesity? A critical review of the epidemiological evidence. Sleep Med Rev 2008;12:289–298.
14. Knutson KL, Spiegel K, Penev P, Van Cauter E. The metabolic consequences of sleep deprivation. Sleep Med Rev 2007;11:163–178.
15. Percik R, Stumvoll M. Obesity and cancer. Exp Clin Endocrinol Diabetes 2009;117:563–566.
16. Van Dycke KC, Rodenburg W, van Oostrom CT, van Kerkhof LW, Pennings JL, Roenneberg T, van Steeg H, van der Horst GT. Chronically alternating light cycles increase breast cancer risk in mice. Curr Biol 2015;25:1932–1937.
17. Cos S, González A, Martinez-Campa C, Mediavilla MD, Alonso-González C, Sánchez-Barceló EJ. Estrogen-signaling pathway: a link between breast cancer and melatonin oncostatic actions. Cancer Detect Prev 2006;30:118–128.
18. Voordouw BC, Euser R, Verdonk RE, Alberda BT, de Jong FH, Drogendijk AC, Fauser BC, Cohen M. Melatonin and melatonin-progestin combinations alter pituitary-ovarian function in women and can inhibit ovulation. J Clin Endocrinol Metab 1992;74:108–117.
19. Schernhammer ES, Rosner B, Willett WC, Laden F, Colditz GA, Hankinson SE. Epidemiology of urinary melatonin in women and its relation to other hormones and night work. Cancer Epidemiol Biomarkers Prev 2004;13:936–943.
20. Haus EL, Smolensky MH. Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. Sleep Med Rev 2013;17:273–284.
21. Kryger MRT, Dement WC. Principles and Practice of Sleep Medicine Fourthed, Philadelphia: Elsevier Saunders; 2005.
22. Bovbjerg DH. Circadian disruption and cancer: sleep and immune regulation. Brain Behav Immun 2003;17(suppl 1): S48–S50.
23. Krokstad S, Langhammer A, Hveem K, Holmen TL, Midthjell K, Stene TR, Bratberg G, Heggland J, Holmen J. Cohort profile: the HUNT Study, Norway. Int J Epidemiol 2013;42:968–977.

24. Laugsand LE, Vatten LJ, Platou C, Janszky I. Insomnia and the risk of acute myocardial infarction: a population study. Circulation 2011;124:2073–2081.
25. Mykletun A, Stordal E, Dahl AA. Hospital Anxiety and Depression (HAD) scale: factor structure, item analyses and internal consistency in a large population. Br J Psychiatry 2001;179:540–544.
26. Bjelland I, Lie SA, Dahl AA, Mykletun A, Stordal E, Kraemer HC. A dimensional versus a categorical approach to diagnosis: anxiety and depression in the HUNT 2 study. Int J Methods Psychiatr Res 2009;18:128–137.
27. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–370.
28. Hernán MA, Hernández-Díaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. Am J Epidemiol 2002;155:176–184.
29. Rothman KJGS, Lash TL. Modern Epidemiology, vol. 359. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
30. Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff ML, Klint A, Køtlum JE, Olafsdóttir E, Pukkala E, Storm HH. NORDCAN—a Nordic tool for cancer information, planning, quality control and research. Acta Oncol 2010;49:725–736.
31. Girschik J, Heyworth J, Fritschi L. Self-reported sleep duration, sleep quality, and breast cancer risk in a population-based case-control study. Am J Epidemiol 2013;177:316–27.
32. Girschik J, Fritschi L, Erren TC, Heyworth J. Quantitative exposure metrics for sleep disturbance and their association with breast cancer risk. Cancer Causes Control 2013;24:919–28.
33. Verkasalo PK, Lillberg K, Stevens RG, Hublin C, Partinen M, Koskenvuo M, Kaprio J. Sleep duration and breast cancer: a prospective cohort study. Cancer Res 2005;65:9595–600.
34. Laugsand LE, Strand LB, Platou C, Vatten LJ, Janszky I. Insomnia and the risk of incident heart failure: a population study. Eur Heart J 2014;35:1382–93.
35. Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med 2001;344:276–85.
36. Blask DE. Melatonin, sleep disturbance and cancer risk. Sleep Med Rev 2009;13:257–64.
37. Larsen IK, Smastuen M, Johannesen TB, Langmark F, Parkin DM, Bray F, Moller B. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. Eur J Cancer 2009;45:1218–31.
38. Littner M, Hirshkowitz M, Kramer M, Kapen S, Anderson WM, Bailey D, Berry RB, Davila D, Johnson S, Kushida C, Loube DI, Wise M, Woodson BT, American Academy of Sleep Medicine; Standards of Practice Committe. Practice parameters for using polysomnography to evaluate insomnia: an update. Sleep 2003;26:754–60.
39. Chang WP, Liu ME, Chang WC, Yang AC, Ku YC, Pai JT, Lin YW, Tsai SJ. Sleep apnea and the subsequent risk of breast cancer in women: a nationwide population-based cohort study. Sleep Med 2014;15:1016–20.
40. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H, Smith PL. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. Proc Am Thorac Soc 2008;5:185–92.