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Sleep and survival among women with breast cancer: 30 years of follow-up within the Nurses' Health Study

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Background: Breast cancer is a leading cause of cancer death in women. Sleep has been linked with mortality among cancer-free population; however, its association with survival among women with breast cancer is understudied.

Methods: Breast cancer patients ($N = 3682$) reported their average sleep duration post diagnosis. Subsamples also provided their pre-diagnosis sleep duration ($n = 1949$) and post-diagnosis sleep difficulties ($n = 1353$). Multivariate Cox models estimated hazard ratios (HR) and confidence intervals (CI) of all-cause, breast cancer, and non-breast cancer mortality.

Results: At diagnosis, the mean age was 64.9 years and 91.7% were stage I or II. Women sleeping $\geqslant 9$ h per night post diagnosis had a strong higher risk of all-cause (multivariate HRs: MV-HR = 1.37, CI = 1.10–1.71), breast cancer (MV-HR = 1.46, CI = 1.02–2.07), and non-breast cancer mortality (MV-HR = 1.34, CI = 1.01–1.79), compared to women sleeping 8 h per night. Increased sleep duration post diagnosis (*vs* unchanged) and regular sleep difficulties (*vs* rare/none) were associated with a strong elevated risk of all-cause mortality ($\text{MV-HR}_{\text{increased duration}} = 1.35$, CI = 1.04–1.74; $\text{MV-HR}_{\text{regular difficulties}} = 1.49$, CI = 1.02–2.19) and a moderate greater risk of breast cancer and non-breast cancer mortality.

Conclusions: Various facets of sleep were associated with higher all-cause mortality risk. If replicated, these findings support evaluation of breast cancer patients' sleep duration and difficulties to identify those at risk for poorer outcomes.

Breast cancer is the most common cancer in women worldwide (Center *et al*, 2011). In 2016, ~246 660 new cases and 40 450 deaths occurred in the USA (American Cancer Society, 2016a). Regardless of disease stage and position on the cancer trajectory, from diagnosis, through treatment and survivorship, women with breast cancer are likely to report poor sleep quality, in a higher proportion than what is generally reported among the general population (Savard and Morin, 2001; Fiorentino and Ancoli-Israel, 2006; Colagiuri *et al*, 2011; Mosher and Duhamel, 2012) and by patients with other cancer sites (Garrett *et al*, 2011; Savard *et al*, 2011). Further, they experience shorter sleep duration compared with healthy, age-matched women (Silberfarb *et al*, 1993; Carpenter *et al*, 2004; Fiorentino and Ancoli-Israel, 2006). Disrupted sleep among cancer patients may be related to their

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emotional response to diagnosis and treatment side effects (e.g., pain, fatigue; Savard and Morin, 2001; Trudel-Fitzgerald *et al*, 2013) and will frequently be reported for several years following diagnosis and treatment (Savard *et al*, 2011; Zhou and Recklitis, 2014).

There is increasing interest in better understanding the role of sleep in carcinogenesis (Erren *et al*, 2016). For instance, some studies have suggested that short and long sleep duration are associated with increased cancer incidence (Jiao *et al*, 2013; Luojus *et al*, 2014; Xiao *et al*, 2016), though others have revealed null findings (Sturgeon *et al*, 2012; Girschik *et al*, 2013; Vogtmann *et al*, 2013; Qian *et al*, 2015) or inverse associations (Sigurdardottir *et al*, 2012; Zhao *et al*, 2013). Similarly, the emerging literature on sleep quality (e.g., difficulties falling/staying asleep, early awakening) and cancer risk has been mixed (Kripke *et al*, 2002; Sigurdardottir *et al*, 2013; Erren *et al*, 2015; Fang *et al*, 2015; Sen *et al*, 2016). With regard to mortality, self-reported sleep duration (Cappuccio *et al*, 2010; Shen *et al*, 2016), changes in sleep duration (Ferrie *et al*, 2007) and poor sleep quality (Dew *et al*, 2003) are associated with increased risk of all-cause death among the general population. However, less is known about their role in cancer survival. In a recent research where self-reported sleep characteristics were collected 7.5 years (median) before cancer diagnosis, short sleep duration, alone or combined with frequent snoring, was related to increased breast cancer mortality, whereas sleep quality was unrelated (Phipps *et al*, 2016). However, given the role of cancer-related factors (e.g., psychological distress, side effects of treatments) in insomnia development (Savard and Morin, 2001) and the sustained high rates of insomnia among breast cancer patients in the first year following diagnosis (Savard *et al*, 2011), considering the role of sleep characteristics after breast cancer diagnosis in relation to future mortality risk is warranted. Preliminary actigraph data from advanced stage breast cancer patients suggested that poor sleep efficiency assessed up to 7 years post diagnosis was associated with cancer-specific mortality over a 10-year follow-up period (Palesh *et al*, 2014). Albeit informative, these studies have not considered mortality unrelated to breast cancer, an important outcome on its own. To our knowledge, no prior epidemiological study has examined the extent to which self-reported sleep duration or difficulties assessed the first years following a breast cancer diagnosis, as well as changes in sleep duration from pre- to post diagnosis are related to all-cause, breast cancer and non-breast cancer mortality over up to 30 years of follow-up. Therefore, we investigated these associations in a large cohort of women with non-metastatic breast cancer. Specifically, we hypothesised that shorter and longer sleep duration, increase and decrease in sleep duration, as well as sleep difficulties, would be related to higher mortality risk.

MATERIALS AND METHODS

Participants. The Nurses' Health Study comprises 121 700 female nurses who were enroled in 1976 (ages 30–55 years; Willett *et al*, 1987). They completed biennial questionnaires on demographic characteristics, lifestyle, medical history, and newly diagnosed medical conditions, with a response rate of >85% per questionnaire (Bao *et al*, 2016). All women who reported having a diagnosis on biennial questionnaires were asked for permission to review their pathology reports and medical records by a study physician to confirm the diagnosis and assess tumour characteristics (e.g., stage). Women who reported their sleep duration within the 4 years following an invasive breast cancer diagnosis ($N=3767$) were eligible for this study; questions were assessed in 1986, 2000, 2002, and 2008. We excluded participants who reported a cancer before their breast cancer diagnosis (except non-melanoma skin cancer; $n=49$) or stage IV diagnosis given the low 5-year relative survival (American Cancer Society, 2016b; $n=36$), yielding an analytic sample of 3682 cases. To explore the association of changes in sleep duration from pre- to post diagnosis with mortality, a subsample of women was identified ($n=1949$) who completed multiple questionnaires (e.g., 1986 and 2000) assessing sleep and diagnosed with breast cancer between two time points. Another subsample consisted of women who completed the sleep difficulties measure, only queried in 2000, in the 4 years following their diagnosis ($n=1353$). The study protocol was approved by the institutional review board of the Brigham and Women's Hospital in Boston, MA, and the human investigations were performed after approval. Informed consent was obtained from all participants.

Measures. To assess average sleep duration, participants were queried about their 'total hours of actual sleep in a 24-hour period' with the following responses: ⩽5, 6, 7, 8, 9, 10, or ⩾11 h. In this cohort, self-reported average time spent sleeping has been found highly correlated with sleep duration as assessed by sleep diaries (Spearman $r=0.79$; $P<0.0001$) and reproducible over time assessments (sleep duration reported in 2000 and 2002 within a 1 h deviation: Cohen's κ statistic = 0.81; Patel *et al*, 2004). Because of small numbers, participants who reported ⩽5 or 6 h of sleep were grouped together for the current analyses, as were those with ⩾9 h of sleep. When comparing sleep duration before *vs* after diagnosis, women were categorised as sleeping either ⩾1 h less (decrease), ⩾1 h more (increase), or no change. Sleep difficulties were assessed using the following question: 'How much of the time during the past 4 weeks did you have difficulty falling asleep or staying asleep?', with responses ranging from 'all of the time' to 'none of the time.' In this study, categories were collapsed to regularly (all or most of the time), occasionally (a good bit or some of the time), and rarely/never (a little or none of the time).

On the basis of similar prior work conducted in this cohort and other samples (Kwan *et al*, 2013; Patel *et al*, 2004; Phipps *et al*, 2016; Xiao *et al*, 2016), relevant covariates included demographics (marital status (married or in a relationship, divorced, separated, or widowed), highest attained educational level (registered nurse (RN), bachelor, graduate degree), census tract income (continuous, in $)), cancer- and health-related variables (year of diagnosis (continuous), age at diagnosis (continuous), time between date of diagnosis and report of sleep (continuous)), stage (I, II, III), type of surgery (lumpectomy, mastectomy), chemotherapy (yes/no), radiation therapy (yes/no), hormone therapy (yes/no), prevalent diabetes or heart disease (yes/no), hormone use and reproductive history (oral contraceptive use (OC; ever/never), number of pregnancies (continuous), family history of breast cancer (yes/no), menopause status (pre-/postmenopausal), postmenopausal hormone use (PMH, never/past/current user)), and other behavioural variables (body mass index (BMI, kg m^{-2}; ⩽25, 25.1–28.9, ⩾29), alcohol consumption (g per day; ⩽6/>6; Kwan *et al*, 2013), pack-years of smoking (continuous), caffeine (mg per day; quintiles), calories intake (kcal per day; quintiles), physical activity (metabolic equivalent task, MET-h per week; 3, 3–8.9, 9–14.9, 15–23.9, ⩾24)) (Holmes *et al*, 2005). For exploratory analyses, a composite binary score of depression was created using a Boolean OR operator approach (Pan *et al*, 2011) based on self-reported depressive symptoms (Ware and Sherbourne, 1992), physician-diagnosed depression, and antidepressant use whenever these information was available between 1986 and 2008. Cancer-related variables (i.e., year of diagnosis, age at diagnosis, stage, and treatments) were extracted from participants' medical records. Nurses' educational level was assessed on the 1992 questionnaire. All other covariates were self-reported on the same questionnaire in which women completed the sleep duration measurement (i.e., within 4 years post diagnosis).

Deaths were reported by next of kin and postal authorities or identified through the National Death Index, leading to 98% mortality follow-up (Rich-Edwards *et al*, 1994). Physicians ascertained cause of death from death certificates, supplemented as needed by medical records. Underlying cause of death was assigned according to the International Classification of Diseases, Eighth Revision (ICD-8; World Health Organization, 1967).

Statistical analyses. Cox proportional hazards regression models were used to assess the hazard ratios (HR) and 95% confidence intervals (CI) of mortality among breast cancer patients, from date of diagnosis to the end of follow-up (June 2012) or death, whichever came first. The relationship of sleep variables (i.e., post-diagnosis sleep duration, change in sleep duration from pre- to post diagnosis, and post-diagnosis sleep difficulties) with mortality was examined in three sets of nested models. An initial model adjusted for cancer- and health-related variables (listed above). Given that information on cancer treatment was only available for 54.9–66.5% of the analytic sample ($N = 3682$), we also included in this first model a binary missing indicator for each oncologic treatment (yes/no). We then added demographics and hormone-related variables including reproductive history and the fully adjusted model included behaviour-related covariates. To assess the non-linear association of sleep duration and difficulties with mortality outcomes, we calculated *P*-values for non-linear trend across categories of sleep duration and difficulties, using a quadratic term for the sleep variables. In the models using changes from pre- to post diagnosis as the exposure, we further adjusted for pre-diagnosis sleep duration. Sleep variables were assessed in relation to all-cause death, breast cancer death, and non-breast cancer death as distinct outcomes of interest. Because only one subtype of death could occur for each participant (i.e., breast cancer *vs* non-breast cancer death), a competing risks framework was also used (Wang *et al*, 2016): using the cause-specific proportional hazards models, we tested for heterogeneity to assess whether the associations of sleep with both breast cancer and non-breast cancer death were statistically different. Kaplan–Meier curves were also implemented to depict the relation of sleep duration categories with all-cause, breast cancer, and non-breast cancer mortality.

Stratified analyses explored potential effect modifiers of the association between sleep duration and mortality and the likelihood ratio tests were performed, when relevant, to verify statistical significance. Specifically, stratification by age at diagnosis ($n_{>65\ \text{years}} = 1736$ *vs* $n_{\leqslant 65\ \text{years}} = 1946$), as well as post-diagnosis physical activity levels (using the median; $n_{\leqslant 8.5\ \text{MET-h per week}} = 1843$

Table 1. Age-standardised characteristics of 3682 breast cancer participants at post diagnosis (at sleep assessment)

	Hours of sleep per night			
	⩽6 h ($n = 965$)	7 h ($n = 1234$)	8 h (reference) ($n = 1100$)	⩾9 h ($n = 383$)
Age, mean (s.d.)[a]	67.2 (9.2)	66.0 (9.6)	67.6 (8.9)	69.3 (8.6)
Census tract income[b]	64 (25)	65 (25)	64 (24)	63 (24)
Duration of OC use (years)	1.7 (3.2)	2.0 (3.4)	2.1 (3.6)	1.8 (3.4)
Caffeine intake (mg per day)	171.3 (168.7)	172.9 (163.3)	174.7 (167.0)	161.9 (161.6)
Total caloric intake (kcal per day)	1684 (528)	1699 (521)	1723 (527)	1761 (534)
Physical activity (met-h per week)	14.9 (19.7)	15.5 (18.2)	14.8 (19.0)	13.5 (18.6)
BMI (kg m^{-2})	26.9 (5.3)	26.1 (5.0)	26.5 (5.1)	27.1 (5.6)
Alcohol intake (g per day)	5.6 (10.5)	5.3 (9.5)	6.0 (11.4)	6.6 (13.5)
Time between diagnosis and sleep assessment (years)	1.7 (1.1)	1.7 (1.1)	1.8 (1.2)	1.7 (1.1)
Education (RN degree), %	75.9	69.9	71.9	78.2
Married/in a relationship	69.6	72.5	76.2	76.2
Ever parous	91.1	93.7	93.1	94.3
Postmenopausal	95.3	94.9	94.9	94.8
Ever used PMH	56.6	61.1	61.5	57.3
Family history of breast cancer	24.4	21.6	23.1	19.3
Prevalent diabetes or heart disease	12.8	12.6	13.6	15.4
Current smoker	7.8	9.3	9.2	8.1
Cancer stage I	65.3	65.5	65.8	61.2
Cancer stage II	28.4	26.1	24.9	27.6
Cancer stage III	6.3	8.4	9.3	11.2
Mastectomy	49.6	46.8	45.8	49.2
Chemotherapy	45.5	42.8	45.3	44.2
Radiation therapy	68.9	71.0	72.4	68.8
Hormone therapy	80.9	83.2	82.5	73.2
ER+ or PR+	86.8	83.8	84.6	80.9

Abbreviations: BMI = body mass index; ER+ = estrogen-receptor-positive; OC = oral contraception; PMH = postmenopausal hormones; PR+ = progesterone-receptor-positive; RN = registered nurse. Values are means (s.d.) or percentages and are standardised to the age distribution of the study population. Values of polytomous variables may not sum to 100% due to rounding. Percentages of oncologic treatments (i.e., mastectomy, chemotherapy, radiation therapy, and hormone therapy) are from women without missing information on these variables. Sample includes women who received a breast cancer diagnosis and completed either the 1986, 2000, 2002, or 2008 sleep assessment within 4 years after being diagnosed.
[a]Value is not age adjusted.
[b]Census tract income is in thousands of dollars.

vs $n_{>8.5\ \text{MET-h per week}} = 1839$), snoring ($n_{\text{never to occasionally}} = 2061$ *vs* $n_{\text{a few nights per week to every night}} = 1208$), and depression status ($n_{\text{depressed}} = 559$ *vs* $n_{\text{non-depressed}} = 2319$) was examined. In the subsample of women who completed both the sleep duration and sleep difficulties item in 2000 ($n = 1353$), models using sleep duration as the exposure were stratified by sleep difficulties ($n_{\text{regularly/occasionally}} = 550$ *vs* $n_{\text{rarely/never}} = 803$) given prior work suggesting an interaction effect on health-related outcomes (Carroll *et al*, 2015).

In distinct sensitivity analyses we excluded: (1) women diagnosed 1 and 2 year(s), before the sleep assessment, separately, to minimise effects of various oncologic treatments on sleep ($n_{\text{1-year lag}} = 1126$; $n_{\text{2-year lag}} = 1971$); (2) women who died 1 year following the sleep assessment to adjust for advanced disease that could impact sleep and survival and to account for reverse causation (i.e., undiagnosed morbidity/advanced disease might influence sleep subsequently and also directly affect mortality; $n = 77$); (3) women categorised as depressed ($n = 559$). Additional sensitivity analyses adjusted for sleep difficulties in models using sleep duration as the exposure and vice versa; supplemental models were further adjusted for prior history of shift work (Lin *et al*, 2015), snoring (Phipps *et al*, 2016), and sleep/anxiety medication (Kripke *et al*, 2002). Because results from all sensitivity analyses were largely similar to our main analyses, for the sake of parsimony only the main models are presented here. All analyses were conducted using SAS software version 9.4 (Cary, NC, USA) with a two-sided *P*-value of 0.05.

RESULTS

At the time of diagnosis, women were on average 64.9 years old (s.d. = 9.3) and almost all (88.3%) postmenopausal. At the time of sleep measure completion (on average 1.7-year post diagnosis, s.d. = 1.1), the majority were married (73.2%), had an RN degree as their highest attained educational level (72.8%), and few reported diagnoses of diabetes or heart disease (13.3%). Nearly a quarter reported a family history of breast cancer (22.6%), and most had an early stage cancer (stages I or II: 91.7%). The distribution of variables across sleep duration categories is presented in Table 1.

Among the complete sample of 3682 women, there were 976 deaths, including 412 breast cancer and 564 non-breast cancer deaths, over the follow-up period (median 11 years between diagnosis and death). Compared to women who reported sleeping 8 h per night on average, those who slept ⩾9 h had a strong higher risk of all-cause (HR = 1.45, CI = 1.16–1.80), breast cancer (HR = 1.49, CI = 1.05–2.10), and non-breast cancer mortality (HR = 1.40, CI = 1.05–1.87) in the initial models adjusting for cancer- and health-related variables (Table 2). The strength of the relationship was fairly robust to the inclusion of demographics, hormone-, and behaviour-related variables in the multivariate models (MV-$HR_{\text{all-cause}} = 1.37$, CI = 1.10–1.71 (Figure 1); MV-$HR_{\text{breast cancer}} = 1.46$, CI = 1.02–2.07 (Supplementary Figure 1); MV-$HR_{\text{non-breast cancer}} = 1.34$, CI = 1.01–1.79 (Supplementary Figure 2). No statistical association was observed between the other sleep duration categories and any cause of mortality (Table 2), although the estimates mirrored a U-shaped association with shorter sleep duration being associated with a small elevated risk of mortality. Accordingly, the *P*-values for the test of non-linearity were statistically or marginally significant in all fully adjusted models ($P \leqslant 0.12$).

Table 3 displays the associations between change in sleep duration from pre- to post diagnosis and mortality ($n = 1949$; 381 all-cause, 132 breast cancer, 249 non-breast cancer deaths). Women whose sleep duration increased after diagnosis were at a strong greater risk of all-cause mortality (MV-HR = 1.35,

Table 2. Association between post-diagnosis sleep duration and mortality ($N = 3682$)

	Model 1		Model 2		Model 3	
Hours of sleep per night (deaths/N)	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**
All-cause deaths (976 deaths)						
⩽6 h (257/965)	1.03	(0.87–1.22)	1.01	(0.86–1.20)	1.05	(0.88–1.24)
7 h (315/1234)	0.97	(0.82–1.14)	0.96	(0.82–1.13)	1.00	(0.85–1.18)
8 h (292/1100)	*1 (reference)*					
⩾9 h (112/383)	**1.45**	**(1.16–1.80)**	**1.40**	**(1.12–1.74)**	**1.37**	**(1.10–1.71)**
P-value for non-linear trend	**0.0008**		**0.009**		**0.02**	
Breast cancer deaths (412 deaths)						
⩽6 h (100/965)	1.07	(0.82–1.40)	1.10	(0.84–1.44)	1.13	(0.86–1.48)
7 h (143/1234)	1.09	(0.86–1.39)	1.07	(0.84–1.36)	1.10	(0.86–1.40)
8 h (124/1100)	*1 (reference)*					
⩾9 h (45/383)	**1.49**	**(1.05–2.10)**	**1.46**	**(1.03–2.07)**	**1.46**	**(1.02–2.07)**
P-value for non-linear trend	0.13		0.11		0.12	
Non-breast cancer deaths (564 deaths)						
⩽6 h (157/965)	1.03	(0.83–1.28)	0.98	(0.79–1.23)	1.01	(0.81–1.27)
7 h (172/1234)	0.90	(0.73–1.11)	0.89	(0.72–1.10)	0.90	(0.73–1.12)
8 h (168/1100)	*1 (reference)*					
⩾9 h (67/383)	**1.40**	**(1.05–1.87)**	**1.37**	**(1.03–1.83)**	**1.34**	**(1.01–1.79)**
P-value for non-linear trend	**0.003**		**0.02**		**0.03**	

Abbreviations: BMI = body mass index; CI = confidence intervals; HR = hazard ratio; OC = oral contraceptive; PMH = postmenopausal hormone. Model 1: year of diagnosis, age at diagnosis, time since diagnosis, cancer stage, surgery, chemotherapy, radiation therapy, hormone therapy, prevalent diabetes or heart disease, missing indicators for oncologic treatments. Model 2: Model 1 + age, marital status, education level, income, OC use, number of pregnancies, family history of breast cancer, menopausal status, PMH use. Model 3: Model 2 + BMI, alcohol consumption, smoking, caffeine, calories intake, physical activity. Sample includes women who received a breast cancer diagnosis and completed either the 1986, 2000, 2002, or 2008 sleep duration assessment ⩽4 years after. Bold characters indicate statistically significant results. Italic characters indicate the reference group.

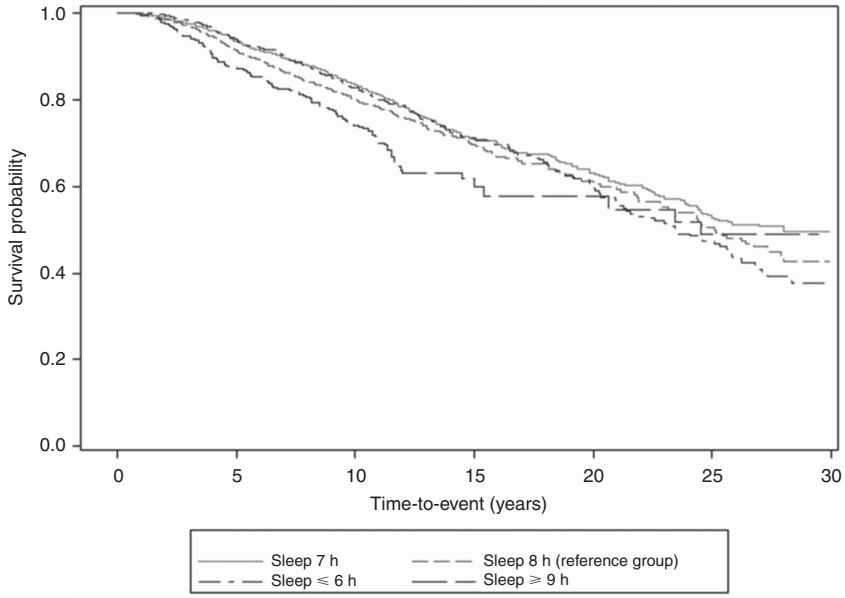

Figure 1. Kaplan–Meier curves for all-cause mortality in relation to sleep duration categories.

CI = 1.04–1.74) than those who reported no change. Breast cancer and non-breast cancer death were associated with sleep duration increases with a similar magnitude (MV-$HR_{breast\ cancer}$ = 1.29, CI = 0.84–2.00; MV-$HR_{non\text{-}breast\ cancer}$ = 1.32, CI = 0.96–1.82; competing risk analyses, P = 0.97), but power was more limited. Compared to women who reported no change, those with at least 1 h decrease in sleep duration did not clearly exhibit a greater mortality risk, except for non-breast cancer mortality (MV-$HR_{all\text{-}cause}$ = 1.26, CI = 0.97–1.65; MV-$HR_{breast\ cancer}$ = 0.89, CI = 0.55–1.45; MV-$HR_{non\text{-}breast\ cancer}$ = 1.42, CI = 1.02–1.96; competing risk analyses, P = 0.09).

The relationship of sleep difficulties with mortality was only strong for all-cause deaths in the subsample of 1353 participants (Table 4; 366 all-cause, 119 breast cancer, and 247 non-breast cancer deaths). Specifically, compared to women who reported rare or no sleep difficulties, those who regularly struggled falling or staying asleep had a greater all-cause mortality risk (MV-HR = 1.49, CI = 1.02–2.19). Although breast cancer death was suggestively related to experiencing regular sleep difficulties (MV-HR = 1.78, CI = 0.94–3.36), non-breast cancer death was not associated (MV-HR = 1.38, CI = 0.85–2.26) and these two associations were not statistically different (competing risk analyses, P = 0.68). No associations were noted between occasional sleep difficulties and mortality, and none of the P-values for non-linear trend were statistically significant (Table 4).

Stratified analyses revealed that neither age at diagnosis, nor levels of physical activity or snoring post diagnosis were effect modifiers of the association between sleep duration and mortality; null results were also noted for the interaction of sleep difficulties with sleep duration (results not shown). However, among women with post-diagnosis depression status information (n = 2878), differences emerged among short sleepers: those with ⩽6 h of sleep per night who were non-depressed post diagnosis (n = 2319; 152 breast cancer deaths) had a strong reduced breast cancer mortality risk (MV-$HR_{non\text{-}depressed}$ = 0.48, CI = 0.30–0.76), whereas those who were depressed (n = 559; 48 breast cancer deaths) had a suggestively higher risk (MV-$HR_{depressed}$ = 2.30, CI = 0.99–5.31, $P_{interaction}$ < 0.01), compared to their respective counterparts who slept 8 h per night. The impact of depression status was only observed with breast cancer death for women who slept ⩽6 h per night; no statistical interaction effects were found for sleep duration of 7 or 9 h, nor other causes of death.

DISCUSSION

We found that women with breast cancer who sleep at least 9 h have a 37, 46, and 34% greater risk of all-cause, breast cancer, and non-breast cancer mortality, respectively, than those who sleep 8 h; no associations were observed for sleep durations <8 h. An increase in sleep duration from pre- to post diagnosis, compared to no change, was associated with a 35% higher risk of all-cause death. Furthermore, women who reported regular sleep difficulties had a 49% increased risk of all-cause mortality, compared to women without such frequent difficulties.

Overall, research has been inconsistent in relating sleep with incident breast cancer and very limited as it relates to breast cancer survival. The increased mortality observed among long sleepers is consistent with recent meta-analyses that demonstrated an association between sleep duration, and all-cause and cardiovascular death in the general population (Cappuccio *et al*, 2010; Shen *et al*, 2016). However, the elevated breast cancer mortality risk for longer duration (⩾9 h) is particularly novel. Various mechanisms of the long sleep duration–mortality relationship have been proposed, including sleep fragmentation, lack of physiological challenge (e.g., exercise), depression, and underlying disease processes (e.g., sleep apnoea, heart disease; Grandner and Drummond, 2007). Several of these mechanistic factors may actually serve as confounders/effect modifiers (e.g., depression, sleep apnoea, fatigue) rather than being true mediators (e.g., lack of physiological challenge, shortened photoperiod) (Stamatakis and Punjabi, 2007). In the current study, sleep fragmentation was indirectly assessed by adjusting for sleep difficulties in sensitivity analyses, whereas physical activity and prevalent diabetes/heart disease, and snoring (as a proxy for sleep apnoea) were considered as confounders and effect modifiers. Further models stratified by depression status post diagnosis and sensitivity analyses excluded women who were depressed when the sleep measures were queried. Thus, the robustness of our findings for all mortality outcomes supports the possible role of long sleep duration on mortality among breast cancer patients. Despite adjustment for health behaviours and cancer-related factors, which tended to be less favourable among women of this sample reporting ⩾9 h per night compared to their counterparts (e.g., greater alcohol intake, lower

Table 3. Association between change in sleep duration from pre- to post diagnosis and mortality ($N = 1949$)

	Model 1		Model 2		Model 3	
Change in sleep duration (deaths/N)	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**
All-cause deaths (381 deaths)						
No change (123/824)	*1 (reference)*					
Decrease (104/477)	1.29	(0.99–1.68)	1.26	(0.96–1.64)	1.26	(0.97–1.65)
Increase (144/648)	**1.41**	**(1.10–1.81)**	**1.41**	**(1.10–1.82)**	**1.35**	**(1.04–1.74)**
Breast cancer deaths (132 deaths)						
No change (49/824)	*1 (reference)*					
Decrease (28/477)	0.90	(0.56–1.45)	0.87	(0.54–1.41)	0.89	(0.55–1.45)
Increase (55/648)	1.30	(0.85–1.98)	1.29	(0.84–1.98)	1.29	(0.84–2.00)
Non-breast cancer deaths (249 deaths)						
No change (84/824)	*1 (reference)*					
Decrease (76/477)	**1.49**	**(1.08–2.04)**	**1.43**	**(1.03–1.97)**	**1.42**	**(1.02–1.96)**
Increase (89/648)	**1.44**	**(1.06–1.97)**	**1.46**	**(1.07–2.00)**	1.32	(0.96–1.82)

Abbreviations: BMI = body mass index; CI = confidence intervals; HR = hazard ratio; OC = oral contraceptive; PMH = postmenopausal hormone. Model 1: year of diagnosis, age at diagnosis, time since diagnosis, cancer stage, surgery, chemotherapy, radiation therapy, hormone therapy, prevalent diabetes or heart disease, missing indicators for oncologic treatments, sleep duration pre-diagnosis. Model 2: Model 1 + age, marital status, education level, income, OC use, number of pregnancies, family history of breast cancer, menopausal status, PMH use. Model 3: Model 2 + BMI, alcohol consumption, smoking, caffeine, calories intake, physical activity. Sample includes women who completed either the 1986 & 2000 or 2002 & 2008 sleep duration assessments and who received their breast cancer in between these two time points. Bold characters indicate statistically significant results. Italic characters indicate the reference group.

Table 4. Association between post-diagnosis difficulties initiating or maintaining sleep and mortality ($N = 1353$)

	Model 1		Model 2		Model 3	
Sleep difficulties (deaths/N)	**HR**	**(95% CI)**	**HR**	**(95% CI)**	**HR**	**(95% CI)**
All-cause deaths (366 deaths)						
Rarely/never (210/803)	*1 (reference)*					
Occasionally (123/442)	1.07	(0.85–1.33)	1.04	(0.83–1.30)	1.05	(0.84–1.32)
Regularly (33/108)	1.40	(0.96–2.04)	**1.48**	**(1.01–2.16)**	**1.49**	**(1.02–2.19)**
P-value for non-linear trend	0.58		0.24		0.25	
Breast cancer deaths (119 deaths)						
Rarely/never (65/803)	*1 (reference)*					
Occasionally (41/442)	1.08	(0.73–1.61)	1.09	(0.73–1.62)	1.09	(0.72–1.63)
Regularly (13/108)	1.55	(0.84–2.86)	1.62	(0.87–3.03)	1.78	(0.94–3.36)
P-value for non-linear trend	0.57		0.48		0.37	
Non-breast cancer deaths (247 deaths)						
Rarely/never (145/803)	*1 (reference)*					
Occasionally (82/442)	1.04	(0.79–1.37)	1.00	(0.76–1.32)	1.00	(0.76–1.32)
Regularly (20/108)	1.37	(0.85–2.21)	1.41	(0.87–2.28)	1.38	(0.85–2.26)
P-value for non-linear trend	0.65		0.30		0.32	

Abbreviations: BMI = body mass index; CI = confidence intervals; HR = hazard ratio; OC = oral contraceptive; PMH = postmenopausal hormone. Model 1: year of diagnosis, age at diagnosis, time since diagnosis, cancer stage, surgery, chemotherapy, radiation therapy, hormone therapy, prevalent diabetes or heart disease, missing indicators for oncologic treatments. Model 2: Model 1 + age, marital status, education level, income, OC use, number of pregnancies, family history of breast cancer, menopausal status, PMH use. Model 3: Model 2 + BMI, alcohol consumption, smoking, caffeine, calories intake, physical activity. Sample includes women who completed the 2000 sleep difficulties assessment (only available at this time point) and who were diagnosed with breast cancer ⩽4 years before (i.e., between 1996 and 2000). Bold characters indicate statistically significant results. Italic characters indicate the reference group.

proportion of ER+ or PR+ receptors), long sleep could duration could still reflect an underlying health condition. Nonetheless, by corroborating results obtained from non-cancer/healthier populations, these results are consistent with prior literature suggesting that the mechanism of elevated risk among long sleepers is not limited to a single organ system or condition; rather it may impair health function globally (Kripke *et al*, 2002; Patel *et al*, 2004).

Short sleep duration was not statistically associated with all mortality outcomes in the overall sample, although the estimates mirrored the U-shaped association that has been observed among varied populations (Cappuccio *et al*, 2010; Shen *et al*, 2016) and additional trend analyses suggested such non-linear association. Unlike recent work (Phipps *et al*, 2016), snoring did not alter the relationship of short sleep duration with mortality, which could be related to the timing of assessment (pre- *vs* post-cancer diagnosis). However, a strong relationship for short sleep was noted among non-depressed *vs* depressed women. Of note, the number of deaths per level of sleep duration was relatively small in these stratified analyses (models with depressed women: $n_{deaths} = 8–36$), leading to less stable estimates with wider CIs. Hence, the moderating impact of depression in the relationship of sleep duration with mortality should be interpreted cautiously and warrants replication. Moreover, increased sleep duration from pre- to post diagnosis was associated with 38% elevated all-cause mortality risk. Such additional hours of sleep, regardless of pre-diagnosis sleep duration, may reflect the patient's psychological and/or

physiological response to the cancer diagnosis and treatments. For instance, fatigue is a common side effect of cancer treatment, thus patients are often told to rest in order to recuperate (Ancoli-Israel *et al*, 2001). Although napping seems beneficial in the short term, such behaviour may disrupt the sleep-wake schedule over time and serve as a precipitating factor for the development of insomnia (Savard and Morin, 2001; Trudel-Fitzgerald *et al*, 2013), a sleep disorder that may continue to impact health function well after the patient has ended treatment (Zhou and Recklitis, 2014).

One of the most commonly reported complaints in oncology is poor sleep quality, seen in up to 70% of non-metastatic breast cancer patients within the first months following diagnosis (Fiorentino and Ancoli-Israel, 2006; Savard *et al*, 2011; Palesh *et al*, 2013). Chronically poor sleep may influence cancer outcomes through impaired immune function (Sephton and Spiegel, 2003; Lange *et al*, 2010), metabolic pathways leading to obesity (Mullington *et al*, 2009; Buxton *et al*, 2012), and altered melatonin release (Blask, 2009). The current results identified a statistically higher risk of all-cause mortality in women reporting regular sleep difficulties compared to those who reported little or none. These novel findings suggest that beyond sleep duration, sleep difficulties should be considered to fully understand how patients' health may be impacted. Two previous prospective cohort studies documented no association between sleep quality and breast cancer incidence (Girschik *et al*, 2013; Vogtmann *et al*, 2013), whereas recent work suggested that experiencing several, but not single, insomnia symptoms was related to increased risk (Sen *et al*, 2016). As deficient sleep- and age-related physical declines are often intertwined (Zee and Turek, 2006), poor sleep may exacerbate underlying diseases processes leading to worse health outcomes in breast cancer patients, whereas cancer-free individuals may not be affected to the same extent.

The current study has some limitations. First, because the assessment of sleep variables was self-reported, and the study design is observational, it is impossible to conclude whether sleep duration and difficulties are causally related to future mortality risk in breast cancer patients (Stamatakis and Punjabi, 2007; Kurina *et al*, 2013). The relationship might also be bidirectional, where declining health may foster longer sleep, as the individual is less able/willing to get out of bed (Grandner and Drummond, 2007). However, our sample did not encompass stage IV cancer cases and our main results were largely unchanged in the sensitivity analyses addressing reverse causation, thus lowering the likelihood of this issue. Next, the majority of the sample were Non-Hispanic White of similar socioeconomic status, limiting the generalisability of the results. Furthermore, using missing indicators for each oncologic treatment may yield biased estimates, although models without such indicators suggested similar increased risk among the subset of women with treatment information. Finally, additional confounders/mediators (e.g., sleep apnoea, altered immune functioning, shortened light exposure, fatigue; Grandner and Drummond, 2007) were not available for these analyses, but should be considered in future work.

To our knowledge, this is the first prospective study to explore the effects of self-reported sleep duration, changes in sleep duration from pre- to post diagnosis, and sleep difficulties, all assessed within 4 years after diagnosis (mean of 1.7-year post diagnosis), on future mortality risk in non-metastatic breast cancer patients. This novel research conducted among a large sample of women using a prospective design with up to 30 years of follow-up suggests that longer sleep duration ($\geqslant 9$ h), increased sleep duration from pre- to post diagnosis, and sleep difficulties are associated with all-cause mortality. From a research perspective, the mechanisms underscoring these associations should be explored. If these results are replicated in future work, it will be important to evaluate breast cancer patients for long and changing sleep duration, in addition to sleep difficulties in the clinical setting, to identify patients who may be at risk for poor outcomes.

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CONFLICT OF INTEREST

The authors assume full responsibility for analyses and interpretation of these data.

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