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Sleep Quality, Duration and Breast Cancer Aggressiveness

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Abstract

Purpose—Epidemiological studies suggest that short sleep duration and poor sleep quality may increase breast cancer risk. However, whether sleep is associated with breast tumor aggressiveness characteristics has largely been unexplored.

Methods—The study included 4171 non-Hispanic whites (NHW) and 235 African Americans (AA) diagnosed with incident, primary, invasive breast cancer in the Women's Health Initiative (WHI) Observational Study (1994–2013). We used logistic regression to examine the association of baseline sleep (sleep duration, sleep quality, WHI Insomnia Rating Scale) with tumor grade, stage, hormone receptor status, HER2 status.

Results—In NHW, women who reported 6 hours of sleep/night were more likely to have tumors classified as regional/distant stage at diagnosis compared to women who slept 7–8 hours/night (adjusted odds ratio (OR): 1.25, 95% confidence interval (CI): 1.05–1.48). AA women who reported their typical night's sleep as 'average quality' or 'restless or very restless sleep' were more likely to be diagnosed with triple negative tumors than those who reported 'sound or restful' sleep (adjusted ORs: 2.91 (1.11, 7.63) and 3.74 (1.10, 12.77), respectively).

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Conflict of Interest Statement: The authors declare no potential conflicts of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conclusions—Our findings provide indications that aspects of sleep (sleep duration and quality), partially modifiable health behaviors, may be associated with development of aggressive tumor characteristics in postmenopausal women. The role of these sleep attributes may differ for NHW and AA women; however, further study in robust, racial diverse samples is needed. This study provides evidence that facets of sleep behavior are associated with the development of aggressive tumor features and these associations differ by race.

Keywords

sleep quality; sleep duration; breast cancer; subtype; disparities; race

Introduction

Sleep is a potentially modifiable health behavior increasingly recognized as being important for good health; both short and long sleep duration are associated with higher mortality [1]. Sleep deprivation is associated with increased risk of cancer [2]. Epidemiologic studies on shift work and breast cancer support an association of shift work and higher breast cancer risk in case control studies but have yielded inconsistent evidence from cohort studies [3–5]; this is hypothesized to be a result of shorter sleep duration, as 44% of night shift workers report short sleep duration versus 29% of day shift workers [6].

Other aspects of sleep outside of duration such as sleep quality may be more representative of circadian disruption, which effectively lowers circulating melatonin. Melatonin is recognized as an important player in circadian regulation, and has anti-inflammatory and immune-modulatory effects. Genes implicated in circadian rhythm are involved with DNA repair, as proteins associated with the biological clock are associated with checkpoints for DNA damage [7]. Sleep also exerts melatonin-independent benefits on the immune system [8]. Further, circadian disruption may impact breast cancer risk via increasing estrogen levels and altering estrogen receptor function [9].

Breast cancer is a clinically and etiologically heterogeneous disease, and risk factors may differentially contribute to the development of different tumor subtypes. Two studies in breast cancer cases only suggest that sleep may be associated with more aggressive breast cancers; among women who had estrogen receptor-positive tumors, sleep duration was inversely correlated with OncotypeDX, a recurrence score [10], and with higher tumor grade [11].

It is important to study sleep-breast cancer associations in all race/ethnic groups, because of the variability in both sleep duration and breast cancer risk by race/ethnicity. Particularly, African Americans have a higher rates of both long (>9 hours) and short sleep (<5 hours) compared to whites [12]. A recent study showed that black women with shorter sleep duration had a higher risk of ER-negative and PR-negative breast cancer [13]. Also, the higher incidence of aggressive breast tumors in African Americans and the potential for varying risk factors according to tumor type drives the current study.

To further characterize whether usual sleep behavior, inclusive of sleep duration and quality, is associated with the development of certain breast cancer attributes among non-Hispanic

whites and African Americans, we utilized the longitudinal follow-up and validated measures of sleep available in the Women's Health Initiative (WHI) Observational Study (OS). We hypothesized that women who developed aggressive breast cancers over the course of study follow-up would have reported shorter sleep duration and poorer sleep quality at WHI OS baseline than women who developed less aggressive breast cancers. Further, since African Americans have a higher incidence of hormone receptor negative tumors and poor sleep quality, we examined the association of sleep and breast cancer aggressiveness by race.

Methods

Study Population

Briefly, the Women's Health Initiative (WHI) includes 161,808 post-menopausal women aged 50–79 who participated in the clinical trials (N=68,132) or the observational study (OS) (N=93,676) [14]. Our study is restricted to 5,151 women who participated in the WHI OS and developed primary invasive breast cancer that was histologically-confirmed during follow-up through September 2013.

We excluded women with a history of breast cancer at WHI baseline (N=405), those missing information on sleep (N=78) or race/ethnicity (N=10). Based on our interest in exploring associations with sleep variables by race/ethnicity, we excluded women who self-identified as "Hispanic/Latina," "Asian/Pacific Islander," "Other" or "American Indian and Alaskan Natives" (N=258) because they accounted for less than 2% of the sample. In total, 4,406 women (n=4,171 non-Hispanic white and n=235 African American) women were included in our analyses. The WHI study protocol was approved by Institutional Review Boards at all participating institutions.

Sleep Measurement

At WHI baseline (1994–1998), a self-administered questionnaire was used to assess sleep behavior. Self-reported sleep duration was also obtained from self-administered questionnaires. Specifically, participants were asked: About how many hours of sleep did you get on a typical night during the past 4 weeks? Options included 5 hours or less, 6 hours, 7 hours, 8 hours, 9 hours and 10 or more hours.

The WHI Insomnia Rating Score (WHIIRS), is a validated composite sleep disturbance score ranging from 0–20 with higher numbers indicating greater insomnia [15, 16]. This score was calculated using responses from five questions about sleep behavior in the past 4 weeks pertaining to trouble falling asleep, waking up at night, early awakenings, trouble getting back to sleep after waking too early, and quality of a typical night's sleep (very sound or restful, sound or restful, average, restless, or very restless) [15].

Breast Cancer Subgroups

There were several variables collected and adjudicated by the WHI for breast cancer diagnoses to characterize breast tumors [17]. We evaluated the following tumor attributes: tumor stage at diagnosis, tumor-differentiation grade, estrogen receptor (ER) status, progesterone receptor (PR) status, and triple negative status. For tumor stage, we considered

the following categories: localized, regional, and distant. Tumor differentiation grade consists of the categories well, moderate, poor, and anaplastic. Triple negative status was classified from the results of the ER, PR, and HER2 results (i.e., negative for all expression of all three markers vs. positive for at least one marker). Those with missing tumor marker data were included in our overall sample, and individuals missing specific tumor markers were only excluded from those particular models. We obtained receptor status on 98% of cases for ER status, 95% of cases for PR status, and 75% of cases for HER2 status.

Covariates

Covariates of interest for the analysis that we included as potential confounders or effect modifiers include those associated with breast cancer risk. Variables were self-reported or derived from self-reported variables collected via a baseline questionnaire These included age at enrollment, postmenopausal hormone therapy use (current, former, never), smoking status (current, former, never), alcohol intake (non-drinker, former drinker, <1 drink/week, 1-<7 drinks/week and ≥7 drinks per week), household income (<$35,000, $35,000 to $74,999, and ≥$75,000), physical activity (MET-hours/week), several reproductive risk factors, mammogram frequency, and smoking (continuous pack years). We also included body mass index (BMI, measured in kg/m^2), which was measured during the WHI study visit by trained personnel according to standardized protocol.

Statistical Analyses

We evaluated all hypotheses with two-sided tests, and considered $p<0.05$ as statistically significant. We obtained descriptive statistics to characterize the WHI breast cancer cases stratified by race and identified differences in several pertinent variables. We also analyzed the associations between several pertinent variables and both sleep and tumor characteristics by race to identify potential confounding variables of the association of sleep and aggressiveness.

We utilized logistic regression models to test our main study hypotheses of the association of sleep variables with aggressive tumor characteristics. We examined four binomial logistic regression models with different dependent variables as indicators of tumor aggressiveness: regional/distant tumor stage, (vs. local stage), ER-negative status (vs. ER-positive), triple negative status (vs. not triple negative) and poor/anaplastic tumor grade (vs. well/moderately differentiated).

All logistic regression models were stratified by race. We adjusted for age, BMI, and hormone therapy use in all models, and additionally adjusted for smoking status, alcohol intake, household income, physical activity, and pack years of smoking. None of these variables was statistically significant and changed the point estimate by more than 10% to meet the definition of a confounding variable in our dataset.

However we adjusted for them to account for their known associations with sleep and breast cancer. We also examined BMI and hormone therapy use as potential effect modifiers and considered an interaction significant if p-interaction<0.10. We conducted sensitivity analysis to exclude women diagnosed with breast cancer in the first year of WHI follow-up (N=320)

for whom sleep may have been impacted due to underlying disease. All statistical analyses were conducted with SPSS Version 22.

Results

Table 1 shows the association of reproductive and tumor characteristics for non-Hispanic whites and African Americans. Non-Hispanic white cases were, on average, older at first birth and at menopause than African American cases in our sample, and were more likely to have used HT and have had a mammogram in the past two years. In terms of tumor characteristics, African American cases were more likely to have poorly differentiated, ER-negative, PR-negative, and triple negative tumors (all $p<0.001$).

Table 2 shows that African American women with breast cancer reported shorter sleep duration at WHI baseline than non-Hispanic white cases; 18% reported sleeping 5 or less hours per night compared to 5% of non-Hispanic whites ($p=0.001$). We observed no difference in the overall WHIIRS by race. With respect to individual components of WHIIRS, the distribution for African American cases was skewed more toward restless sleep compared to Non-Hispanic white cases. The differences are modest, with 15% of whites reporting very restless or restless sleep versus 18% of African Americans; $p=0.04$. Other components of WHIIRS did not differ significantly in distribution across case groups.

We present results for our analysis of the association between sleep variables and tumor stage (Table 3) or receptor status (Table 4). When formally evaluating possible confounders, no variables met our criteria of changing the odds ratios by more than 10% when age-adjusted. However we present two models adjusted for factors related to breast cancer and sleep duration and quality.

Among women with breast cancer, non-Hispanic whites who reported sleeping 6 hours/night were more likely to develop regional/distant stage tumors compared to women reporting sleeping 7–8 hours per night; adjusted OR (95% CI): 1.25 (1.05,1.48) (Table 3). We observed no statistically significant associations between other sleep variables and tumor stage in non-Hispanic white cases. Among the African American cases, regression models yielded no indication of an association between sleep attributes and tumor stage at diagnosis, although reporting restless/very restless sleep was suggestively associated with regional/distant stage at diagnosis. We found no evidence for associations of sleep duration or quality with breast tumor grade (data not shown).

Table 4 shows that among breast cancer cases, sleep duration, WHIIRS, and typical sleep quality were not associated with ER or PR status among non-Hispanic White or African Americans. Sleep behavior was not associated with ER, PR, or triple negative tumor status among non-Hispanic White cases. There was, however, a significant association between reported typical sleep quality and triple negative status among African American cases; women who reported average sleep quality had higher odds of developing triple negative tumors compared to those who reported sound or restful (or very sound or restful) typical sleep quality (adjusted OR=2.91, 95% CI: 1.11, 7.63). In addition, African American cases

who had restless or very restless sleep had higher odds of having triple negative tumors compared to the reference group (adjusted OR=3.74, 95% CI: 1.10, 12.77).

We conducted all sleep and tumor subtype analyses stratified by BMI and HT for non-Hispanic white cases only to investigate effect modification; we found no evidence of interaction. The sensitivity analysis excluding women diagnosed in the first year of WHI follow-up essentially had no impact on the findings.

Discussion

We examined the association between a prospective report of pre-diagnostic sleep quality, sleep duration, and breast cancer tumor aggressiveness in postmenopausal women who developed breast cancer over a mean 6.9 years (SD=4.6) of follow-up. We found a significant association between sleep duration and breast cancer stage in non-Hispanic white women; women with shorter sleep duration were more likely to have regional/distant tumors. Also, African American breast cancer cases who reported poorer sleep quality were more likely to develop triple negative tumors than cases who had reported sound or restful sleep.

Sleep quality and duration, while imperfect proxies for light at night and melatonin levels, may be directly associated with melatonin levels. Inadequate levels of the hormone melatonin, which is secreted from the pineal gland in the presence of darkness, may play a role in the association between sleep and breast cancer aggressiveness. Short sleep duration has been shown to increase circulating estrogen due to decreased melatonin secretion [18]; in fact, shift-workers secrete less melatonin than daytime workers, and experience higher circulating estrogen levels [19]. Further, results from a 2013 study suggest that night work for 20 years or more is associated with higher risk of ER-negative breast cancer [20].

Also important in the action and influence of melatonin on other physiologic processes is the abundance of melatonin receptors expressed. Findings from a recent study suggest that expression of the MT1 melatonin receptor is associated with lower stage and longer progression free survival, compared to women with MT1-negative tumors [21]. The authors observed a striking difference in MT1 expression; more African Americans had MT1-negative tumors compared to Caucasian women (49% vs. 12%) [21]. Although this study was restricted to those with triple negative tumors, these data further support a role of melatonin and the MT1 receptor whose regulatory effects include cell proliferation [22].

In addition to pathways involving hormones, short sleep duration has pro-inflammatory and immune-modulatory effects, possibly leading to the development of more aggressive breast tumors [11]. Circadian rhythm is involved in DNA repair, as proteins associated with the biological clock are associated with DNA damage checkpoints [7]. Defective pathways lead to increased cancer progression, genetic instability, and abnormalities in chromosomes [7]. These cancer-specific mechanisms support our findings that short sleep duration and poor sleep quality are associated with later stage and triple negative tumors. It is unclear why these associations appear to differ in non-Hispanic White and African American women

with breast cancer. Larger studies that include more robust samples of African Americans can provide more power to detect such associations, should they exist.

These WHI data have also previously been used to demonstrate that, among breast cancer patients, women who reported short sleep duration at baseline subsequently have significantly poorer breast cancer-specific survival (HR=1.46, 95% CI: 1.07–1.99) [23]. This finding helped to provide rationale for the current study. Further, there is consistency as we reported an association between sleep duration and stage at diagnosis among non-Hispanic white cases.

BMI is inversely associated with circulating urinary 6-sulphatoxymelatonin (melatonin's primary metabolite) [24–27] and sleep deficiency contributes to weight gain [28]. Sleep and circadian disturbances can alter both metabolic and endocrine functions, and may directly contribute to obesity, as evidence shows that shift workers have a higher incidence of metabolic abnormalities and obesity when compared to day shift workers [29]. While it is generally well accepted that obesity is a risk factor for postmenopausal breast cancer, we propose that dysfunctional sleep and/or altered circadian rhythm may represent a possible, partial upstream factor influencing obesity and postmenopausal breast cancer risk. While the rates of both obesity and aggressive breast tumors are higher in African Americans compared to whites, perhaps further studies can elucidate whether obesity is a mediator of the association of sleep disturbance and/or melatonin and breast cancer.

To date, there have been only two studies conducted on sleep and breast cancer tumor aggressiveness specifically, as opposed to studies of breast cancer risk. These studies have only measured sleep duration, not quality, and were not able to specifically examine differences by race. The first study found an association between mean self-reported sleep duration and tumor grade in 972 postmenopausal women, and reported an average of 7.16 hours of sleep/night for those with grade 1 tumors, 7.11 hours/night for those with grade 2 tumors, and 6.82 hours/night for those with grade 3 [11]. Although statistically insignificant, the same prior study found that those women with the longest sleep duration had the greatest proportion of stage 0 or 1 tumors (63.3% vs. <58.2%) compared to those in the shorter sleep duration groups [11]. We found no significant association between sleep duration and tumor grade; however, we did find that shorter sleep duration was associated with more advanced tumor stage at diagnosis among non-Hispanic white women with breast cancer. This discrepancy, finding an association with stage and null findings for grade are not surprising as these factors are independent prognostic factors [30]. In a second study on sleep and breast cancer aggressiveness, investigators found that sleep duration was inversely correlated with OncotypeDX score [31] in 101 women with ER+ stage I-III breast cancer [10]. The study included 90% Caucasians and 9% African Americans. Our study found no association between sleep quality or duration with ER or triple negative status (which takes HER2 into account) among non-Hispanic white cases, but did note an association between poor quality sleep and triple negative tumor status among African American women.

Our study has several strengths. By studying both sleep quality and sleep duration across different race groups, our study represents a more complete analysis of how sleep is associated with breast cancer tumor aggressiveness. The previous studies had sample sizes

of 101 and 972, and were limited to very small numbers for non-Caucasians. Our larger sample size provided us with greater statistical power to evaluate race-specific associations. Also, the study population is not restricted to any particular grade, or classification of breast cancer tumor, as previous studies have been, so all postmenopausal women with invasive breast cancer are represented. Differences in the distribution of tumor attributes across studies may also contribute to observed differences: 20.5% of cases included in the study by Khawaja et al. had stage 0, DCIS tumors [11], which were not included in our study, and all cases included in the study by Thompson et al. were ER+ [10], compared to only 85.8% (non-Hispanic white) and 67.9% (African American) in our study. These differences in distribution and inclusion may be partially responsible for the difference in findings. In addition to larger sample size and race-stratified analyses, the prospective design is an important strength of our study. Participants were queried about sleep behavior and demographics at baseline, so there is no issue of recall bias. Breast cancer outcomes were carefully assessed and adjudicated [17], so misclassification of outcome is likely to be low. Anthropometric measures were measured by medical professionals according to standardized protocol, reducing measurement error and bias resulting from self-report.

The limitations of our study also merit consideration. Although WHIIRS is a validated scale for measuring perceived insomnia, asking about sleep in the four weeks prior to WHI baseline may not capture the relevant window of exposure of sleep on the aggressiveness of breast cancer tumors. Lifetime sleep habits are not taken into account, therefore limiting the interpretations that can be made from the results. Also, sleep quality and sleep duration are both self-reported measures, which are subjective and are susceptible to bias. Adults tend to overestimate their sleep duration [32]. Self-reported sleep duration has been found to be only moderately correlated (r=0.47) with sleep duration measured by polysomnography or actigraphy [32]. We anticipate that these limitations would serve to attenuate the already significant results that we identified. Additionally, breast cancer aggressiveness has been shown to vary by menopausal status; however, in our study, we are limited to postmenopausal women. Therefore, our results are not generalizable to premenopausal women.

In summary, we examined the association between sleep quality, duration and breast cancer tumor aggressiveness among non-Hispanic white and African American postmenopausal women. Our results yield information of potential significance due to the high incidence of aggressive cancers in African Americans, and modifiability of sleep as a risk factor, provided other studies replicate our results. Since tumor aggressiveness affects one’s quality of life, chance of recurrence, and survival, the findings potentially have a large public health impact. We observed an association between sleep attributes and breast cancer tumor aggressiveness in the form of tumor stage in non-Hispanic whites, and triple negative status in African Americans. Further research is needed that utilizes more detailed characterization of sleep patterns and representation of larger samples of other race/ethnic groups.

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Table 1

Reproductive and tumor characteristics of invasive breast cancer cases (N=4,406).

Mean (SD) or N (%)	Non-Hispanic White N=4171	African-American N=235	P-value*
Age at first birth, yr (N=3722)			
<20	355 (10.5)	61 (33.9)	<0.001
20–29	2553 (75.3)	82 (45.6)	
≥30	368 (10.9)	15 (8.3)	
Never had term pregnancy	115 (3.4)	22 (12.2)	
Age at menarche, yr (N=4590)			
≤10	279 (6.7)	19 (8.1)	0.28
11–12	1771 (42.6)	93 (39.6)	
13–14	1748 (42.0)	95 (40.4)	
≥15	362 (8.7)	28 (11.9)	
Age at menopause, yr (N=4479)	48.9 (5.9)	46.9 (7.2)	<0.001
Time since menopause, yr (N=4479)	14.8 (8.95)	15.1 (9.86)	0.67
Hormone therapy use (N=4596)			
Never	1367 (32.8)	122 (51.9)	<0.0001
Past	535 (12.8)	40 (17.0)	
Current	2262 (54.3)	73 (31.1)	
Mammogram in past 2years (N=4486)			
No	395 (9.7)	39 (17.8)	0.001
Yes	3679 (90.3)	180 (82.2)	
Summary stage (N=4554)			
Localized	3121 (75.5)	167 (73.6)	
Regional	958 (23.2)	55 (24.2)	0.50
Distant	53 (1.3)	5 (2.2)	
Tumor-differentiation grade (N=4204)			
Well	1090 (28.5)	33 (16.5)	<0.0001
Moderate	1731 (45.3)	71 (35.5)	
Poor	920 (24.1)	89 (44.5)	
Anaplastic	78 (2.0)	7 (3.5)	
Lymph node involvement (N=4603)			
Yes	3124 (74.9)	169 (71.9)	0.17
No	1047 (25.1)	66 (28.1)	
ER-status (N=4302)			
Positive	3353 (85.8)	142 (67.9)	<0.0001
Negative	557 (14.2)	67 (32.1)	
PR-status (N=4239)			
Positive	2829 (73.4)	119 (58.0)	<0.0001
Negative	1027 (26.6)	86 (42.0)	
Her2/NEU Status (N=3307)			
Positive	426 (14.2)	26 (15.6)	0.34

Mean (SD) or N (%)	Non-Hispanic White N=4171	African-American N=235	P-value*
Negative	2581 (85.8)	141 (84.4)	
Triple Negative (N=3287)			
No	2705 (90.6)	128 (76.6)	<0.0001
Yes	282 (9.4)	39 (23.4)	

Table 2

Sleep characteristics of breast cancer cases (N=4406).

N (%)	Non-Hispanic White N=4171	African American N=235	P- value*
Sleep Duration			
≤5 hours	226 (5.4)	42 (17.9)	<0.0001
6	993 (23.8)	89 (37.9)	
7–8	2735 (65.7)	98 (41.7)	
≥9 hours	212 (5.1)	6 (2.6)	
Insomnia Rating Score (WHIIRS)			
0–3	1129 (27.1)	69 (29.4)	0.67
4–6	1188 (28.5)	68 (28.9)	
7–10	1067 (25.6)	52 (22.1)	
≥11	787 (18.9)	46 (19.6)	
Individual WHIIRS constituent variables:			
Trouble Falling			
Asleep			
Not in past 4 weeks	2358 (60.8)	150 (63.8)	0.52
Less than once a week	775 (18.6)	38 (16.2)	
1 or 2 times a week	498 (11.9)	25 (10.6)	
3 or more times a week	360 (8.6)	22 (9.4)	
Wake up several times a night			
Not in past 4 weeks	871 (20.9)	58 (24.7)	0.19
Less than once a week	720 (17.3)	31 (13.2)	
1 or 2 times a week	881 (21.1)	59 (25.1)	
3 or 4 times a week	752 (18.0)	37 (15.7)	
5 or more times a week	947 (22.7)	50 (21.3)	
Wake up earlier than planned			
Not in past 4 weeks	1699 (40.7)	106 (45.1)	0.55
Less than once a week	920 (22.1)	48 (20.4)	
1 or 2 times a week	807 (19.3)	38 (16.2)	
3 or 4 times a week	457 (11.0)	24 (10.2)	
5 or more times a week	288 (6.9)	19 (8.1)	
Have trouble getting back to sleep after waking up too early			
Not in past 4 weeks	1993 (47.8)	124 (52.8)	0.15
Less than once a week	878 (21.1)	40 (17.0)	
1 or 2 times a week	722 (17.3)	36 (15.3)	
3 or 4 times a week	366 (8.8)	17 (7.2)	
5 or more times a week	212 (5.1)	18 (7.7)	
Typical night's sleep			
Very restless	78 (1.9)	4 (1.7)	0.041
Restless	543 (13.0)	35 (14.9)	

N (%)	Non-Hispanic White N=4171	African American N=235	P- value*
Average	1747 (41.9)	109 (46.4)	
Sound or restful	1297 (31.1)	51 (21.7)	
Very sound or restful	506 (12.1)	36 (15.3)	

*P-value=differences between Non-Hispanic whites and African Americans using chi-square or t-tests.

Table 3

Associations of sleep duration, quality and tumor stage.

Sleep Variables	Non-Hispanic White OR (95% CI) for regional/distant versus local (N=4171)			African American OR (95% CI) for regional/distant versus local (N=235)		
	N	Model 1	Model 2	N	Model 1	Model 2
Sleep duration category						
≤5	218	1.06 (0.77–1.47)	1.06 (0.76–1.49)	41	1.19 (0.53–2.66)	1.32 (0.55–3.18)
6	975	**1.22 (1.04–1.45)**	**1.25 (1.05–1.48)**	85	0.75 (0.38–1.48)	0.81 (0.39–1.67)
7–8	2670	1.00 (Ref)	1.00 (Ref)	95	1.00 (Ref)	1.00 (Ref)
≥9	209	0.91 (0.65–1.28)	0.92 (0.65–1.30)	5	0.67 (0.07–6.35)	0.47 (0.04–5.06)
Insomnia Rating Score (WHIIRS)						
0–3	1101	1.00 (Ref)	1.00 (Ref)	67	1.00 (Ref)	1.00 (Ref)
4–6	1164	0.91 (0.75–1.10)	0.89 (0.73–1.09)	65	0.79 (0.36–1.73)	0.71 (0.31–1.66)
7–10	1045	0.94 (0.77–1.14)	0.90 (0.74–1.11)	49	0.62 (0.26–1.50)	0.70 (0.28–1.73)
≥11	766	0.88 (0.71–1.09)	0.85 (0.68–1.07)	45	1.08 (0.46–2.51)	1.25 (0.50–3.13)
Typical Sleep Quality						
Very sound or restful, or sound or restful	1763	1.00 (Ref)	1.00 (Ref)	84	1.00 (Ref)	1.00 (Ref)
Average quality	1707	1.00 (0.86–1.17)	0.97 (0.83–1.14)	104	1.00 (0.51–1.96)	1.02 (0.49–2.11)
Restless or very restless	606	0.90 (0.72–1.12)	0.86 (0.68–1.08)	38	1.80 (0.77–4.20)	2.14 (0.86–5.30)

Model 1 adjusted for age, BMI, and HT use.

Model 2 adjusted for Model 1 variables plus income, smoking status, pack years, alcohol intake, and physical activity.

Table 4

Association of sleep duration, quality and tumor characteristics stratified by race.

Sleep Variables	OR (95% CI) for ER-			OR (95% CI) for PR-			OR (95% CI) for Triple Negative		
	N	Model 1	Model 2	N	Model 1	Model 2	N	Model 1	Model 2
Non-Hispanic white invasive breast cancer cases (N=4171)									
Sleep duration									
≤5	207	0.90 (0.58–1.38)	0.91 (0.58–1.43)	203	1.17 (0.85–1.61)	1.16(0.83–1.62)	154	0.91 (0.51–1.61)	0.92(0.51–1.67)
6	929	1.11 (0.90–1.37)	1.13 (0.91–1.41)	916	1.04 (0.87–1.23)	(0.85–1.22)	696	(0.64–1.17)	(0.65–1.23)
7–8	2574	1.00 (Ref)	1.00 (Ref)	2540	1.00 (Ref)		1988	1.00 (Ref)	1.00 (Ref)
≥9	196	0.85 (0.55–1.33)	0.90 (0.58–1.41)	193	0.88 (0.62–1.24)	0.89 (0.63–1.27)	145	0.75(0.40–1.41)	0.77 (0.41–1.46)
Insomnia Rating Score (WHIIRS)									
0–3	1057	1.00 (Ref)	1.00 (Ref)	1041	1.00 (Ref)	1.00 (Ref)	825	1.00 (Ref)	1.00 (Ref)
4–6	1115	0.94 (0.74–1.19)	0.97 (0.76–1.24)	1099	1.02 (0.84–1.23)	1.06 (0.87–1.29)	864	1.04 (0.75–1.45)	1.05 (0.75–1.47)
7–10	1008	0.90 (0.70–1.16)	0.90 (0.69–1.16)	999	0.95 (0.78–1.16)	0.96 (0.78–1.18)	745	1.07 (0.76–1.50)	1.01 (0.71–1.43)
≥11	730	0.90 (0.69–1.18)	0.90 (0.68–1.20)	717	1.00 (0.81–1.24)	0.98 (0.78–1.23)	553	0.98 (0.67–1.43)	0.90 (0.61–1.34)
Typical Sleep Quality									
Very sound or restful, or sound or restful	1695	1.00 (Ref)	1.00 (Ref)	1663	1.00 (Ref)	1.00 (Ref)	1317	1.00 (Ref)	1.00 (Ref)
Average quality	1640	1.01 (0.83–1.23)	1.05 (0.86–1.28)	1625	1.01 (0.86–1.18)	1.02 (0.87–1.20)	1236	1.13 (0.87–1.47)	1.09 (0.83–1.44)
Restless or very restless	575	0.85 (0.64–1.13)	0.88 (0.65–1.18)	568	0.98 (0.78–1.22)	0.94 (0.75–1.19)	434	0.81 (0.54–1.21)	0.76 (0.50–1.16)
African American invasive breast cancer cases (N=235)									
Sleep duration									
≤5	37	1.02 (0.45–2.30)	1.12 (0.46–2.77)	35	1.89 (0.84–4.24)	1.89 (0.80–4.49)	30	1.61 (0.63–4.12)	1.47 (0.53–4.07)
6	79	0.59 (0.30–1.17)	0.64 (0.31–1.31)	79	0.86 (0.46–1.63)	0.86 (0.44–1.67)	63	0.50 (0.21–1.23)	0.46 (0.18–1.18)
7–8	88	1.00 (Ref)	1.00 (Ref)	87	1.00 (Ref)	1.00 (Ref)	69	1.00 (Ref)	1.00 (Ref)
≥9	5	0.98 (0.15–0.65)	0.73 (0.09–5.65)	4	1.15 (0.15–8.91)	0.76 (0.09–6.35)	5	0.60 (0.06–6.07)	0.39 (0.03–4.75)
Insomnia Rating Score (WHIIRS)									
0–3	62	1.00 (Ref)	1.00 (Ref)	61	1.00 (Ref)	1.00 (Ref)	50	1.00 (Ref)	1.00 (Ref)
4–6	61	1.04 (0.49–2.21)	0.95 (0.43–2.14)	59	1.59 (0.76–3.33)	1.90 (0.87–4.15)	49	0.68 (0.26–1.83)	0.67 (0.24–1.87)
7–10	46	0.55 (0.23–1.32)	0.63 (0.26–1.57)	45	1.38 (0.62–3.08)	1.78 (0.77–4.11)	36	0.70 (0.24–2.03)	0.64 (0.21–1.93)
≥11	40	0.85 (0.35–2.03)	0.90 (0.34–2.36)	40	1.18 (0.51–2.75)	1.36 (0.55–3.41)	32	1.51 (0.56–4.08)	1.54 (0.51–4.64)

Sleep Variables	N	OR (95% CI) for ER- Model 1	OR (95% CI) for ER- Model 2	N	OR (95% CI) for PR- Model 1	OR (95% CI) for PR- Model 2	N	OR (95% CI) for Triple Negative Model 1	OR (95% CI) for Triple Negative Model 2
Typical Sleep Quality									
Very sound or restful/sound or restful	62	1.00 (Ref)	1.00 (Ref)	77	1.00 (Ref)	1.00 (Ref)	62	1.00 (Ref)	1.00 (Ref)
Average quality	80	1.47 (0.76–2.86)	1.30 (0.64–2.64)	94	1.20 (0.64–2.24)	1.28 (0.66–2.47)	80	**3.11 (1.22–7.89)**	**2.91 (1.11–7.63)**
Restless/very restless	25	1.64 (0.68–3.97)	1.82 (0.69–4.81)	34	1.35 (0.59–3.13)	1.54 (0.62–3.81)	25	**4.29 (1.35–13.68)**	**3.74 (1.10–12.77)**

Model 1 is adjusted for age, BMI, and HT use.

Model 2 is adjusted for age, BMI, and HT use, as well as income, smoking status, pack years, alcohol intake, and physical activity.