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Associations Among Rotating Night Shift Work, Sleep, and Skin Cancer in Nurses' Health Study II Participants

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Abstract

Background—Night shift work and sleep duration have been associated with breast and other cancers. Results from the few prior studies of night shift work and skin cancer risk have been mixed and not fully accounted for other potentially important health-related variables (e.g., sleep characteristics). This study evaluated the relationship between rotating night shift work and skin cancer risk and included additional skin cancer risk factors and sleep-related variables.

Methods—The current study used data from 74,323 Nurses' Health Study (NHS) II participants. Cox proportional hazards models were used to estimate multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for skin cancers across categories of shift work and sleep duration.

Results—Over 10 years of follow-up, 4308 BCC, 334 SCC and 212 melanoma cases were identified. Longer duration of rotating night shifts was associated with a linear decline in risk of BCC (HR=0.93, 95% CI: 0.90-0.97 per 5-year increase). Shift work was not significantly associated with either melanoma (HR=1.02, 95% CI: 0.86-1.21) or SCC (HR=0.92, 95% CI: 0.80-1.06). A short sleep duration (≤6 hours per day) was associated with lower risks of melanoma (HR=0.68, 95% CI: 0.46-0.98) and BCC (HR=0.93, 95% CI: 0.86-1.00) compared with the most common report of 7 hours. SCC was not associated with duration of sleep (HR=0.94, 95% CI: 0.83-1.06).

Conclusions—Longer duration of rotating night shift work and shorter sleep duration were associated with lower risk of some skin cancers. Further research is needed to confirm and identify the mechanisms underlying these associations.

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Keywords

rotating night shift work; sleep; skin cancer

Introduction

Night shift work, involving work during the evening or night hours, is one factor that has gained attention in its potential association to cancer. It has been hypothesized that greater susceptibility to cancer in shift workers involves the exposure to light at night and ensuing melatonin suppression.[1-4] The majority of investigations have focused on the relationship between shift work and breast cancer. However, emerging evidence implicates shift work in the development of other cancers including skin cancer, e.g.[2] Given melatonin's antimutagenic and oncostatic properties, and its presence in the skin,[2] melatonin alteration may be associated with skin cancer risk among shift workers.

Results from the two prior studies that investigated the relationship between shift work and skin cancer were mixed with one study finding no association between shift work and skin cancer[5] and another finding a longer duration of shift work was with a lower risk of skin cancer.[4] Several limitations preclude definitive interpretations of the findings from these studies. First, neither study assessed participant sleep-related variables such as sleep duration, which may be a more proximal influence on melatonin. However, a recent study found no clear relationship between sleep duration and melanoma.[6] Second, information regarding participant chronotype (an attribute reflecting morningness or eveningness) could help to account for individual differences in response to shift work (i.e., evening types may be better equipped to tolerate shift work when compared to morning types). Moreover, the definition of shift work in the study by Schwartzbaum and colleagues[5] can be subjected to criticism regarding potential misclassification, potentially nullifying any existing associations. In sum, it is premature to draw conclusions regarding the interactions among shift work, melatonin levels, and skin cancer.

Accordingly, the aim of the current study was to investigate the association between shift work and skin cancer incidence (melanoma, squamous cell carcinoma [SCC], and basal cell carcinoma [BCC]) using the large, longitudinal NHSII dataset. In order to further extend the work of Schernhammer and colleagues,[4] a variety of potential covariates were examined including demographic variables, skin cancer risk factors, sleep-related variables, and other health-related variables. Given that shift workers often obtain insufficient amounts of sleep,[7] we also sought to examine the degree to which sleep duration may be associated with skin cancer risk, both independent of, and in association with, shift work. In the current study, both markers of sleep quantity and circadian desynchrony were examined for to parse out which variable(s), if any, account for, or protect against, cancer risk.

Methods

Sample

The NHSII is a prospective cohort study established in 1989, when 116,430 US registered female nurses ages 25-42 who resided in 14 states completed initial questionnaires on their medical histories and health-related exposures. Updated information was obtained by mailed questionnaires biennially. Details of this cohort have been described previously.[8] The protocol for this study was approved by the Institutional Review Board at Brigham and Women's Hospital in Boston MA. The participants' completion and return of the self-administered questionnaire was considered informed consent.

The base population of this investigation was formed by 82,100 participants, who reported their daily hours of sleep in 2001 and years of working rotating night shifts on questionnaires between 1989 and 2001. We excluded women with a previous report of any cancer before 2001 and those of African American, Asian, or Hispanic ethnicity (5% of the population) due to differing inherent risks of skin cancer, leaving 74,323 in the study population.

Measures

Rotating night shift work—Information on total years during which the nurse had worked on rotating night shifts was available from the 1989 questionnaire. Specifically the question was: "What is the total number of years during which you worked rotating night shifts (at least 3 nights/month in addition to days or evenings in that month)?" The pre-specified response categories were: " Never; 1-2 years; 3-5 years; 6-9 years; 10-14 years; 15-19 years; 20 years or more". The information was updated in 1991, 1993, 1997, 2001 and 2005. The 1991, 1993, and 1997 questionnaires collected information about the total number of months during which the nurse had worked rotating night shifts in the past 2 years with pre-specified response categories: none, 1–4, 5–9, 10–14, 15–19, and ≥ 20. In 2005, data on the duration of rotating night shifts in both 2001–2003 and 2003–2005 were collected. We assigned and added together midpoint values in years (or months) and calculated and used the total number of years having worked various types of shifts as the primary exposure variable. We collapsed the data of rotating night shift into five categories: never, < 2, 2-5.9, 6-9.9, and ≥10 years. On the 2001 questionnaire, participants specified the years (never, before 1989, 1989-1994, 1995-2001+) in which they worked permanent night shifts for six or more months.

Sleep duration—Women reported their average number of hours of sleep over a 24-hour period on the 2001 questionnaire; response categories were <5, 5, 6, 7, 8, 9, 10+ hours. A prior NHS study had found that a single questionnaire-based report of sleep duration correlated highly with sleep duration recorded in daily diaries (r=0.79).[9] We collapsed these categories based on the sample distribution by grouping women into categories of ≤6, 7, 8, and ≥9 hours of sleep per 24-hour period.

Skin cancer incidence—Participants reported cancer diagnoses biennially. With their permission, pathological records were obtained and reviewed by physicians to confirm

diagnoses for melanoma and SCC. Information on melanoma from tumor registries was used when medical records could not be obtained. Only confirmed cases of invasive melanoma and invasive SCC were included in the analyses. Medical records were not obtained for self-reported cases of BCC, but previous reports have demonstrated the high validity of self-report of BCC, with more than 90% confirmed by histopathology records in the NHSI.[10]

Covariates

Age and marital status were assessed. Women also reported their economic status on a scale of 1 to 10 when compared to others in the U.S.

Skin cancer risk factors assessed included first degree family history of melanoma, number of blistering sunburns between ages 15 and 20, skin reaction after two hours of sun exposure without sunscreen as a child/adolescent, number of nevi/moles on legs, natural hair color at age 20, average hours per week spent in the sun during summer months at ages 25-35, frequency of use of artificial tanning at ages 25-35, and average annual ultraviolet radiation reaching the earth's surface at the participant's residence.

Perceived sleep duration adequacy, frequency of daytime sleepiness, snoring, and symptoms of restless leg syndrome were assessed in 2001. Chronotype was assessed in 2009 when women reported whether they were a morning-type or evening-type of person.

Body mass index, smoking status, alcohol intake, metabolic equivalents from leisure-time physical activity, menopausal status, postmenopausal hormone use, and years of oral contraceptive use were all assessed biennially. Diet quality assessed with the Alternate Healthy Eating Index was assessed every four years.[11]

Statistical Analysis

Each participant contributed person-time from the return date of the 2001 baseline questionnaire. In the melanoma analyses, participants were censored at date of melanoma diagnosis, death, or end of follow-up on June 1, 2011. In analyses of SCC and BCC, women were further censored at date of diagnosis of SCC or BCC or last questionnaire response since questionnaire reports were critical for identifying these outcomes.

We used Cox proportional hazards models to compute hazard ratios (HR) of melanoma, SCC, and BCC with 95% confidence intervals (CI) within categories of sleep and shift work. Models were rerun with continuous exposure data to test for linearity. P for linear trend was calculated based on the median of collapsed shift work categories. Women did not contribute person-time in follow-up cycles in which shift work data were missing. All models were conditioned on months of age and questionnaire cycle to account for age and time. Multivariable-adjusted RRs were calculated from models adjusted simultaneously for covariates. We controlled for and assessed the potential contributions of a variety of other variables (demographics, skin cancer risk factors, other sleep-related variables, other health-related variables) that are known to be or could potentially be associated with skin cancer incidence, but because none of them altered our results, we did not retain them in our main models. In analyses, shift work duration was updated in 2003 and 2005 and other covariates used time-varying data when available. Multiplicative interactions between exposures were

calculated using the Wald test for continuous data. Statistical tests were two-sided and significance was determined by $P<0.05$.

Results

Among the 74,323 women who formed the 2001 baseline population for this analysis, a total of 4,854 incident cases of skin cancer were documented during 10 years of follow-up, comprising 4,308 BCC, 334 SCC, and 212 melanoma cases.

The age-adjusted characteristics of the study population at baseline are reported in Table 1 by rotating shift work duration and in Table 2 by sleep duration. Women with longer durations of rotating night shift work or shorter hours of sleep were more likely to be current smokers and to report inadequate sleep, and they were less likely to live in an area with high UV-B flux, report a high economic status, and use hormone therapy if postmenopausal. Women with longer durations of rotating night shift work were also less likely to be married, more likely to snore and had a higher BMI on average. Those who slept 9 or more hours daily reported less physical activity, and both short and long sleep durations were associated with more frequent sleepiness during the day.

In multivariable analyses, a longer duration of working rotating night shifts was associated with a statistically significant linear decline in risk of BCC, with a 7% decrease in risk for every 5 years of shift work (HR=0.93, 95% CI 0.90-0.97; Ptrend < 0.001 (Table 3). In the categorical analysis, risk was 17% lower in women who had worked for 10 or more years on rotating night shifts (HR=0.83, 95% CI 0.74-0.94) and also in women who worked for 6-9.9 years (HR=0.83, 95% CI 0.75-0.93) compared with women who never worked rotating night shifts. Results from the simple age-adjusted model were comparable to those from the multivariable model, indicating that confounding by covariates was minimal. Shift work was not significantly associated with either melanoma or SCC, though case counts in the longer duration categories were low, limiting statistical power. For SCC, we did observe non-significant lower risks in the longer rotating night shift work categories and a non-significant 8% lower risk for every 5 years of work (HR=0.92, 95% CI 0.80-1.06), consistent with what we observed for BCC.

We conducted two additional analyses to see how timing of shift work in relation to BCC diagnosis might impact the inverse association we observed between the two. In the first analysis, we found a lower risk of BCC in women who currently reported shift work (HR=0.86, 95% CI 0.75-0.99) than for women who had not reported it for twelve or more years (HR=0.93, 95% CI 0.87-1.00) in comparison with those who never engaged in shift work. In the second analysis, we found a lower risk of BCC per five years of shift work that was reported after 1989 (HR=0.89, 95% CI 0.83-0.96) than for women who only reported shift work before 1989 (HR=0.98, 95% CI 0.91-1.05). Though these results indicate that an inverse association between shift work and BCC might attenuate with longer time between the two, the differences are small and confidence intervals overlap.

Women who reported 6 or fewer hours of sleep daily had a 36% lower risk of melanoma (HR=0.64, 94% CI 0.46-0.98) and a 7% lower risk of BCC (HR=0.93, 95% CI 0.86-1.00) in

the multivariable model that included rotating night shift work compared with those who reported sleeping for 7 hours, the most common sleep duration in the cohort. SCC was not associated with duration of sleep.

To limit the potential for misclassification if women with permanent night work did not classify themselves as “rotating” night shift workers, but rather, as women without any rotating night shift work (thereby erroneously contributing to our reference group), we reran the multivariable models for rotating night shift work and risk of each skin cancer excluding women who reported that they had ever engaged in permanent night shift work (n=31,623). We did not observe any meaningful differences in this sensitivity analysis. We also examined associations between rotating night shift work and sleep and risk of melanoma and SCC in separate analyses for sun-exposed (head, neck, arms, lower legs) and non-sun-exposed (trunk, buttocks, thighs) cancer sites and again did not observe any meaningful differences in results (data not shown).

In further secondary analyses, we examined the associations of rotating night shift work and sleep with each skin cancer outcome stratified by hair color (red vs brown/black), chronotype (morning vs night type person), UV-B availability at residence (≤113 vs >113 R-B units), and BMI (<25 v ≥ 25). We also examined the associations of rotating night shift work with each skin cancer outcome stratified by sleep duration and the associations of sleep duration stratified by shift work duration. The only significant difference was by hair color for rotating night shift work and BCC ($P_{interaction}$=0.02). Specifically, longer durations of rotating night shift work were associated with a significant linear decrease in risk of BCC for women with brown or black hair color (Table 4), such that risk decreased by 9% for every 5 year increase in duration of shift work (HR=0.91, 95% CI 0.87-0.96) whereas rotating night shift work was not associated with BCC in women with red or blonde hair (HR=1.00, 95% CI 0.92-1.08).

Discussion

In this 10-year prospective study, a longer duration of working rotating night shifts was associated with a significantly lower risk of BCC in women with black or brown hair color. There was a similar non-significant trend for SCC but no evidence of an association for melanoma. With regard to sleep, a shorter duration was associated with a significantly lower risk of melanoma and BCC but not SCC. This is in contrast to a study using NHS, NHS II, and Health Professionals Follow-Up Study data, which found no association between sleep duration and melanoma risk.[6] However, the current study controlled for many more variables than the previous one, which provided little detail about methods and analyses.

Some of the potential mechanistic variables that could contribute to the associations among rotating night shift work, sleep, and skin cancer in the current study include UV exposure, obesity, immune dysfunction, inflammation, and melatonin. Despite its being the primary risk factor for skin cancer, we were unable to find evidence showing that UV exposure is a major factor in these associations (e.g., women who do more shift work spend less time in the sun). Lower residential UVB flux during adulthood was associated with longer duration of rotating shift work and shorter sleep duration. Adult residential UVB flux does not

account for UV exposure or protection behavior in childhood or adulthood.[12] However, we controlled for such UV-related variables in the analyses. Moreover, separate analyses of associations with UV exposed and non-exposed body sites did not demonstrate meaningful differences compared to our main analyses. Additionally, the association between longer rotating shift work and BCC was significant for women with dark but not light hair. Individuals with light hair (and skin) are genetically at greater risk of skin cancer than individuals with dark hair, which contributes to risk above and beyond later environmental and behavioral exposures.[13]

Obesity is a well-established cancer risk factor, including for skin cancer.[14,15] However, higher BMI was associated with longer rotating shift work, which was associated with a *lower* risk of BCC in the current study, and stratifying by BMI did not alter study findings. Immune dysfunction and inflammation are also cancer risk factors. These are associated with longer shift work and shorter sleep,[16-18] which were associated with *lower* skin cancer risk in the current study.

Melatonin possesses antioxidant and anti-carcinogenic properties in general and specifically in relation to skin cells and UV exposure. Thus, one would expect lower melatonin levels to be associated with higher skin cancer incidence. Melatonin is produced in the dark, inhibited by retinal exposure to light, and helps regulate circadian rhythms. Lower melatonin levels are associated with longer shift work and shorter sleep.[19,20] We did assess for melatonin supplementation in the current study, but the prevalence was less than 2%. It is possible that melatonin is also associated with hair pigmentation, but this potential association is not well-understood.[21]

The fact that the association with rotating shift work did not emerge for melanoma is interesting. This may be due to either the biological differences between melanomas and non-melanomas or low power. We previously examined the relationship between rotating night shift work and skin cancers using data from the first NHS.[4] Findings were similar to the current study in that the longer an individual worked rotating night shifts, the lower their risk of skin cancer. However, lower melanoma risk in particular was associated with longer rotating shift work in the NHS study. In that paper, we postulated that our results may demonstrate that while high levels of melatonin may be protective among individuals functioning within their natural circadian rhythms, those with circadian desynchrony may be protected by the opposite, i.e. melatonin suppression. However, in the prior analysis, we were unable to control for sleep-related variables. A melatonin mechanism is likely complex and dependent on a variety of factors such as the exact nature of shift work at specific critical ages, melatonin production in the pineal gland versus the skin, or an interaction between melatonin and other factors such as melanin (skin and hair pigmentation),[4] which were unable to be assessed directly in the current study.

Strengths of the study are the large sample and longitudinal nature of the data. A limitation is that only nurses (all of whom were women) were included, who may differ in some way from the general population. Another limitation is that some of the data were reported long ago (e.g., shift work for some only reported at baseline) and may no longer be accurate, were reported retrospectively for long periods of time (e.g., UV exposure during childhood),

or were reported in limited detail (e.g., shift work only captures total duration, not variability of on and off rotation schedules; average 24-hour sleep duration was only assessed in 2001). There may have also been underreporting of skin cancer. Additionally, key variables were assessed for different time periods among women of different ages, and we do not know exactly when the critical periods are for the contribution of environmental and behavioral skin cancer risk factors. Finally, there was modest power for some analyses.

Conclusions

The current study contributes to the literature on the association between shift work, sleep, and cancer. Though there is some evidence for an association between long-term night shift work and an increased risk of breast cancer, data from research investigating a potential association with cancers at other sites have been limited and inconsistent.[22] A meta-analysis investigating the association between sleep duration and cancer risk (skin cancer was not included) found a positive association for colorectal cancer and a negative association for hormone-related cancers such as those of the breast.[23] However, a recent study found no clear relationship between sleep duration and melanoma.[6] In the current study, we controlled for menopausal status and hormone use. Thus, there may be another mechanism involved in the association among shift work, sleep, and skin cancer for which we did not account, or we are unable to identify a complex interplay of mechanistic variables. For example, a more comprehensive comparison of the effects of rotating versus permanent night shift work might offer some clarification. Future studies could involve biometric assessment of melatonin, and/or immune, inflammatory, or metabolic biomarkers.

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What this paper adds

- Results from the few prior studies of night shift work and skin cancer risk have been mixed and not fully accounted for other potentially important health-related variables (e.g., sleep characteristics).
- Longer duration of rotating night shift work and shorter sleep duration were associated with lower risk of some skin cancers.
- Further research is needed to confirm and identify the mechanisms underlying these associations.

Table 1

Age-adjusted characteristics of the study population at 2001 baseline by rotating night shift duration

Variables					
Duration of rotating night shift work (years)	**0**	**<2**	**2-5.9**	**6-9.9**	**≥10**
Proportion of Sample (%)	**29**	**27**	**24**	**11**	**9**
Age, years[a]	47.05 ± 4.60	46.64 ± 4.73	46.22 ± 4.70	46.27 ± 4.58	47.22 ± 4.28
Body Mass Index, kg/m^2	25.66 ± 4.89	25.85 ± 4.98	26.22 ± 5.09	26.76 ± 5.30	27.21 ± 5.33
Physical activity, MET-hours/week[b]	19.22 ± 21.66	19.47 ± 21.55	20.33 ± 22.66	20.35 ± 22.73	20.15 ± 22.96
Alcohol intake, g/day	3.87 ± 7.04	4.07 ± 7.28	4.14 ± 7.30	3.98 ± 7.34	3.52 ± 6.64
Alternate Health Eating Index[c]	47.82 ± 10.69	47.74 ± 10.78	47.91 ± 10.63	47.68 ± 10.81	47.14 ± 10.72
Sleep, ≤ 6 hours over a 24-hour period, %	25	27	31	33	40
First degree relative history of melanoma, %	11	11	12	12	12
Red or blonde hair, %	20	20	20	20	17
Moles, ≥ 10 on lower legs, %	15	15	14	14	13
Artificial tanning, ≥ 6 times/year at ages 25-35, %	3	3	3	3	3
Time spent in sun, ≥ 5 hours/week at ages 25-35, %	43	43	44	44	45
Severe sunburns, ≥ 6 at ages 15-20, %	9	10	11	10	11
Skin sensitivity to burning[d], %	42	41	41	41	41
Annual UV-B flux at residence, ≥ 145 R-B units[e], %	26	23	21	19	16
Sleep not usually adequate, %	46	48	51	52	57
Sleepy ≥4 days/week, %	11	12	12	13	14
Snore most nights, %	14	15	17	18	19
Restless legs syndrome	2	2	2	2	2
Current smoker, %	7	8	10	10	12
Married, %	82	82	79	76	75
In top 20 percent of economic ladder[f], %	12	12	11	10	9
Oral contraceptive use, ≥ 8 years, %	22	22	22	22	22
Current use of postmenopausal hormones[g], %	66	64	64	62	59

Values are means ± SD or percentages and are standardized to the age distribution of the study population

[a]Value is not age-adjusted

[b]Metabolic equivalents from recreational and leisure-time activities

[c]Score of 0-100 measuring adherence to a dietary pattern most predictive of disease risk

[d]Skin reaction after two or more hours in the sun without sunscreen on a bright sunny day during childhood and adolescence (none/some redness, burn, painful/blistering burn)

[e]Measured in Robertson-Berger units (count×10^{-4})

[f]Self-reported economic status compared to others

[g]Calculated among postmenopausal women only

Table 2

Age-adjusted characteristics of the study population at 2001 baseline by sleep duration

Variables				
Amount of sleep over a 24-hour period (hours)	**≤6**	**7**	**8**	**≥ 9**
Proportion of sample (%)	**29**	**43**	**23**	**5**
Age, years[a]	46.92 ± 4.57	46.66 ± 4.66	46.61 ± 4.70	46.44 ± 4.68
Body Mass Index, kg/m^2	26.62 ± 5.29	25.89 ± 4.96	25.77 ± 4.91	26.39 ± 5.24
Physical activity, MET-hours/week[b]	19.69 ± 22.89	19.88 ± 21.64	20.35 ± 22.23	16.83 ± 20.83
Alcohol intake, g/day	3.57 ± 6.86	4.01 ± 6.84	4.35 ± 7.70	4.33 ± 8.66
Alternate Health Eating Index[c]	47.18 ± 10.68	47.91 ± 10.62	48.23 ± 10.82	47.49 ± 11.06
Rotating night shift work, ≥10 years, %	12	7	6	7
First degree relative history of melanoma, %	12	11	11	13
Red or blonde hair, %	19	20	20	21
Moles, ≥ 10 on lower legs, %	14	15	15	15
Artificial tanning, ≥ 6 times/year at ages 25-35, %	3	3	3	3
Time spent in sun, ≥ 5 hours/week at ages 25-35, %	43	44	44	45
Severe sunburns, ≥ 6 at ages 15-20, %	10	10	10	11
Skin sensitivity to burning[d], %	41	42	40	42
Annual UV-B flux at residence, ≥ 145 R-B units[e], %	20	22	24	26
Sleep not usually adequate, %	81	48	18	21
Sleepy ≥4 days/week, %	18	10	8	21
Snore most nights, %	17	15	15	20
Restless legs syndrome	3	2	2	4
Current smoker, %	11	8	7	8
Married, %	75	81	83	78
In top 20 percent of economic ladder[f], %	8	12	14	13
Oral contraceptive use, ≥ 8 years, %	23	22	21	22
Current use of postmenopausal hormones[g], %	60	66	65	69

Values are means ± SD or percentages and are standardized to the age distribution of the study population

[a]Value is not age-adjusted

[b]Metabolic equivalents from recreational and leisure-time activities

[c]Score of 0-100 measuring adherence to a dietary pattern most predictive of disease risk

[d]Skin reaction after two or more hours in the sun without sunscreen on a bright sunny day during childhood and adolescence

[e]Measured in Robertson-Berger units (count$\times 10^{-4}$)

[f]Self-reported economic status compared to others

[g]Calculated among postmenopausal women only

Table 3

Risk of skin cancer by rotating night shift work and sleep duration 2001-2011 among women in Nurses' Health Study II.

Skin Cancer			Person-years	Number of case subjects	Age-adjusted Hazard Ratio (95% Confidence Interval)[a]	Multivariable Model Hazard Ratio (95% Confidence Interval)[b]
Melanoma						
	Years on rotating night shift					
		Never	195,698	67	1.00 (referent)	1.00 (referent)
		< 2	185,319	54	.86 (.60, 1.23)	.85 (.59, 1.22)
		2-5.9	164,389	45	.83 (.57, 1.21)	.84 (.57, 1.23)
		6-9.9	76,144	28	1.11 (.71, 1.73)	1.13 (.72, 1.77)
		≥10	64,556	18	.86 (.51, 1.45)	.95 (.55, 1.61)
	per 5 years				.99 (.84, 1.17)	1.02 (.86, 1.21)
	Hours per night of sleep					
		≤ 6	196,562	44	.64 (.45, .92)	.68 (.46, .98)
		7	292,182	100	1.00 (referent)	1.00 (referent)
		8	160,869	60	1.09 (.79, 1.51)	1.12 (.80, 1.56)
		≥9	36,394	8	.64 (.31, 1.31)	.64 (.31, 1.34)
	per 1 hour				1.14 (1.00, 1.30)	1.12 (0.96, 1.30)
Basal Cell Carcinoma						
	Years on rotating night shift					
		Never	180,825	1333	1.00 (referent)	1.00 (referent)
		< 2	171,484	1179	.94 (.87, 1.02)	.93 (.86, 1.01)
		2-5.9	152,152	1032	.95 (.88, 1.03)	.96 (.88, 1.04)
		6-9.9	70,873	416	.82 (.73, .92)	.83 (.75, .93)
		≥10	59,310	348	.79 (.70, .89)	.83 (.74, .94)
	per 5 years				.92 (.88, .95)	.93 (0.90, .97)

Skin Cancer			Person-years	Number of case subjects	Age-adjusted Hazard Ratio (95% Confidence Interval)[a]	Multivariable Model Hazard Ratio (95% Confidence Interval)[b]
	Sleep Duration					
		≤ 6	182,096	1117	.89 (.82, .96)	.93 (.86, 1.00)
		7	270,200	1904	1.00 (referent)	1.00 (referent)
		8	148,947	1075	1.03 (.95, 1.11)	1.03 (.95, 1.11)
		≥ 9	33,401	212	.92 (.80, 1.06)	.95 (.82, 1.09)
	per 1 hour				1.04 (1.01, 1.07)	1.03 (.99, 1.06)
Squamous Cell Carcinoma						
	Years on rotating night shift					
		Never	181,704	106	1.00 (referent)	1.00 (referent)
		< 2	172,281	93	.95 (.72, 1.26)	.94 (.71, 1.24)
		2-5.9	152,832	74	.89 (.66, 1.20)	.86 (.63, 1.16)
		6-9.9	71,151	34	.86 (.58, 1.26)	.85 (.57, 1.26)
		≥10	59,512	27	.77 (.50, 1.17)	.81 (.53, 1.25)
	per 5 years				.91 (.79, 1.04)	.92 (.80, 1.06)
	Sleep Duration					
		≤ 6	182,851	97	1.00 (.77, 1.29)	1.07 (.82, 1.41)
		7	271,436	145	1.00 (referent)	1.00 (referent)
		8	149,642	79	1.01 (.77, 1.33)	.97 (.73, 1.28)
		≥ 9	33,552	13	.73 (.41, 1.28)	.73 (.41, 1.31)
	per 1 hour				.97 (.88, 1.08)	.94(.83, 1.06)

[a] Age-adjusted models include both shiftwork and hours of sleep duration.

[b] Covariates included in the multivariable model: years of shift work (≤2, 2-5.9, 6-9.9, ≥10), hours of sleep per night (≤6, 7, 8, ≥9), sleep adequacy (yes/no), sleepy days per week (none, 1-3, 4-6, 7), snoring (never, occasionally, few, most, every night per week), restless legs syndrome (yes/no), family history of melanoma (yes/no), hours spent in sun per week ages 25-35 (< 1, 2-4, ≥5), number of severe sunburns from ages 15 to 20 (none, 1, 2, 3-4, 5-9, ≥10), sunburn severity after ≥2 hours in the sun during childhood (no reaction, some redness, burn, painful burn/blisters), artificial tanning frequency per year ages 25-35 (never, 1-2, 3-5, 6-11, ≥12 per year), annual UV at residence (< 104, 104-112, 113-119, 120-144, ≥145 R-B units), moles on lower legs (1-2, 3-4, 5-9, 10-14, 15-20, ≥21), natural hair color in adolescence (red, blonde, light brown, dark brown, black), marital status (single, married, divorced/separated/widow), financial status on 10-rung ladder (top rungs 9-10, rungs 7-8, rungs 5-6, bottom

rungs 1-4), Body Mass Index kg/m^2 (BMI; <22, 22-24.9, 25-28.9, ≥29), physical activity (metabolic equivalents from recreational and leisure-time activities (MET) hours/week: < 3, 3-8.9, 9-17.9, 18-26.9, 27-41.9, ≥42), smoking status (never, past, current), menopausal status (premenopausal, postmenopausal, dubious menopause), postmenopausal hormones (no use, past use, current use), oral contraceptive use (never, < 4 yrs, 4 to < 8 yrs, ≥8 years), g/day alcohol intake (none, > 0 to < 5; 5 to < 10, ≥10); Alternate Healthy Eating Index (0-29, 30-39, 40-49, 50-59, 60-100).

Table 4

Risk of basal cell carcinoma by rotating night shift work 2001-2011 stratified by hair color among women in Nurses' Health Study II.

Hair Color		Person-years	Number of case subjects	Multivariable Model Hazard Ratio (95% Confidence Interval)[a]
Red/Blonde				
Years on rotating night shift				
	Never	34,071	315	1.00 (referent)
	< 2	34,138	285	.89 (.75, 1.05)
	2-5.9	29,696	257	.99 (.83, 1.17)
	6-9.9	14,116	119	.95 (.76, 1.18)
	≥10	10,366	92	.94 (.74, 1.20)
per 5 years				1.00 (.92, 1.08)
Brown/Black				
Years on rotating night shift				
	Never	140,172	962	1.00 (referent)
	< 2	135,674	883	.95 (.87, 1.04)
	2-5.9	115,910	730	.95 (.86, 1.05)
	6-9.9	52,586	273	.80 (.70, .92)
	≥10	42,369	220	.80 (.69, .92)
per 5 years				.91 (.87, .96)

[a]Covariates included in the multivariable model: years of shift work (≤2, 2-5.9, 6-9.9, ≥10), hours of sleep per night (≤6, 7, 8, ≥9), sleep adequacy (yes/no), sleepy days per week (none, 1-3, 4-6, 7), snoring (never, occasionally, few, most, every night per week), restless legs syndrome (yes/no), family history of melanoma (yes/no), hours spent in sun per week ages 25-35 (< 1, 2-4, ≥5), number of severe sunburns from ages 15 to 20 (none, 1, 2, 3-4, 5-9, ≥10), sunburn severity after ≥2 hours in the sun during childhood (no reaction, some redness, burn, painful burn/blisters), artificial tanning frequency per year ages 25-35 (never, 1-2, 3-5, 6-11, ≥12 per year), annual UV at residence (< 104, 104-112, 113-119, 120-144, ≥145 R-B units), moles on lower legs (1-2, 3-4, 5-9, 10-14, 15-20, ≥21), , marital status (single, married, divorced/separated/widow), financial status on 10-rung ladder (top rungs 9-10, rungs 7-8, rungs 5-6, bottom rungs 1-4), Body Mass Index kg/m^2 (BMI; <22, 22-24.9, 25-28.9, ≥29), physical activity (metabolic equivalents from recreational and leisure-time activities (MET) hours/week: < 3, 3-8.9, 9-17.9, 18-26.9, 27-41.9, ≥42), smoking status (never, past, current), menopausal status (premenopausal, postmenopausal, dubious menopause), postmenopausal hormones (no use, past use, current use), oral contraceptive use (never, < 4 yrs, 4 to < 8 yrs, ≥8 years), g/day alcohol intake (none, > 0 to < 5; 5 to < 10, ≥10); Alternate Healthy Eating Index (0-29, 30-39, 40-49, 50-59, 60-100).