DOI: 10.1093/jnci/djr044
Advance Access publication on February 18, 2011.

Rotating Night Shifts and Risk of Skin Cancer in the Nurses' Health Study

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Manuscript received July 26, 2010; revised January 14, 2011; accepted January 20, 2011.

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Night shift work is associated with increased risk of several cancers, but the risk of skin cancer among night shift workers is unknown. We documented 10 799 incident skin cancers in 68 336 women in the Nurses' Health Study from June 1988 to June 2006 and examined the relationship between rotating night shifts and skin cancer. We used Cox proportional hazard models, adjusted for confounding variables (phenotypic and established risk factors of skin cancer), and performed stratified analysis to explore the modifying effect of hair color. Working 10 years or more on rotating night shifts was associated with a 14% decreased risk of skin cancer compared with never working night shifts (age-standardized incidence rate: 976 per 100 000 person-years (PY) vs 1070 per 100 000 PY, respectively; adjusted hazard ratios = 0.86, 95% confidence interval = 0.81 to 0.92, P_{trend} < .001). This association was strongest for cutaneous melanoma; working 10 years or more of rotating night shifts was associated with 44% decreased risk of melanoma, after adjustment for melanoma risk factors (age-standardized incidence rate: 20 per 100 000 PY vs 35 per 100 000 PY, respectively; adjusted hazard ratios = 0.56, 95% confidence interval = 0.36 to 0.87, P_{trend} = .005). Hair color, a surrogate for an individual's susceptibility to skin cancer, was a statistically significant effect modifier for the observed associations; darker-haired women had the lowest risk ($P_{interaction}$ = .02).

J Natl Cancer Inst 2011;103:602–606

Melatonin has antimutagenic and oncostatic activity, and light exposure during night shift work can induce desynchrony in circadian rhythms and reduced melatonin production (1,2). Shift work is therefore thought to have important health impacts (3), and a growing body of literature provides evidence to link night shift work with increased risk of several malignancies, including breast (4–13), endometrial (14), prostate (15,16), and colorectal cancers (17), and non-Hodgkin lymphoma (18). With the exception of Parkinson disease (PD) (19), night shift work has also been associated with increased risk of chronic nonmalignant diseases such as gastrointestinal disorders, cardiovascular disease, and diabetes (3).

To examine whether night shift work is associated with an increased risk of skin cancers, as hypothesized by Kvaskoff and Weinstein (20), we used data from the Nurses' Health Study (21–23), a large prospective study of nurses in the United States. We calculated hazard ratios (HRs) and 95% confidence intervals (CIs) using Cox proportional hazard models. To examine the proportional hazard assumption, we constructed interaction terms between rotating night shift work and calendar year and used likelihood ratio tests to assess the significance of these interaction terms. We performed stratified analysis to explore the modifying effect of hair color—as a proxy for phenotypic predisposition of skincancer—on the association between night shift work and skin cancer. To obtain *P* values for the tests of interaction, we performed likelihood ratio tests. All statistical tests were two-sided.

In 1982, we collected information from Nurses' Health Study participants on natural hair color at age 20, history of painful sunburn that blistered, childhood or adolescent tendency to tan after repeated sun exposure, and childhood or adolescent tendency to burn after 2 hours or more of sunlight exposure. The information on number of melanocytic nevi larger than 3 mm in diameter located on limbs was collected in 1986. First-degree family history of melanoma (parents and siblings) was asked in 1982 and updated in 1992, 1996, and 2000. In a 2008 questionnaire, we asked how many hours per week (2–5, 6–10, and ≥11) were spent outdoors in direct sunlight in the middle of the day in summer months, including work and recreation at different age intervals (25–35, 36–59, and ≥ 60 years), and educational levels (high school, college, and nursing school).

Among the 68 336 women who formed the baseline population for this analysis, a total of 10 799 incident cases of skin cancer were documented during 18 years of follow-up, comprising 9632 basal cell carcinoma (BCC), 849 squamous cell carcinoma (SCC), and 318 melanoma case patients (Supplementary Table 1, available online). Women who reported having melanoma, SCC, BCC, or any other cancer before 1988 were excluded. The analysis was restricted to non-Hispanic white women because the number of case subjects in the other racial/ethnic categories was small.

Higher duration of working rotating nightshifts was associated with a statistically significantly lower risk of skin cancer (P_{trend} < .001) overall (Table 1). Women who had worked for more than 10 years on rotating night shifts had a 14% lower risk of skin cancer compared with never night shift workers (multivariable HR = 0.86, 95% CI = 0.81 to 0.92). The age-standardized incidence rates of skin cancer were 976 per 100 000 person-years among those with 10+ years of rotating night shifts and 1070 per 100 000 person-years among those who never worked rotating night shifts, translating into 8% fewer cases. When follow-up was restricted to 10 years (1988–1998), assuming a shorter induction period for skin cancer, results remained largely unchanged (multivariable HR = 0.90, 95% CI = 0.82 to 0.98, P_{trend} = .02). When we examined the effect of night shift work on different types of skin cancer, although the risk for each skin cancer was reduced, the strongest association was observed for melanoma. Working 10 years

or more of rotating night shifts was associated with a 44% decreased risk of melanoma, after adjustment for melanoma risk factors (multivariable HR = 0.56, 95% CI = 0.36 to 0.87, P_{trend} = .005) (Table 1). The age-standardized incidence rates of melanoma were 20 per 100 000 person-years among those with 10+ years of rotating night shifts and 35 per 100 000 person-years among those who never worked rotating night shifts translating into 57% fewer cases.

As a phenotypic proxy for a woman's predisposition to skin cancer, we stratified our analysis by natural hair color. The inverse association between 10 years or more of rotating night shift work and all skin cancers was strongest among women with black or dark brown hair color (Table 2), and the test for interaction was statistically significant ($P_{interaction}$ = .02). We observed no effect modification by sunlight exposure level at baseline geographic residence or body location of skin cancer (available for melanoma and SCC only).

Our findings are in contrast with evidence from previous studies (4–18,27), which suggested that lower levels of melatonin among night shift workers attributable to longer duration of exposure to artificial light at night, could be responsible for the positive associations with the risk of cancers other than melanoma observed in these studies (1). Experimental studies provide strong evidence for some general oncostatic properties of melatonin both in vivo and in vitro (28). Melatonin, which is synthesized not only in the pineal gland but also in other locations such as the skin (29), has been reported to reduce the growth of cell lines of malignant melanoma as well as other tumors (29–36). However, effects may vary by melatonin concentration. In one study, low (or "physiological") melatonin concentrations appeared to inhibit melanoma cell proliferation in vitro, whereas higher levels of melatonin had either no effect on melanoma cell growth or exerted stimulatory activity (30). In another study, pharmacological doses of melatonin were associated with increased melanoma cell proliferation, but lower doses had no (not even a protective) effect (37). Finally, nocturnal melatonin supplementation in mice that were exposed to constant light was associated with increased melanoma progression, whereas it had the opposite effect when administered under light–dark conditions (30). This last result supports the hypothesis that the effects of melatonin are dependent on photoperiod and time of day (physiologically higher levels at night), and genetic factors may also play a role in interindividual variation in absolute amount of physiological peak melatonin production during the night. Thus, although higher melatonin levels might be beneficial in individuals with stable circadian rhythms, in night workers, melatonin suppression may be more beneficial, perhaps especially among those with physiologically high peak melatonin production (which might be related to skin phenotype). There is some evidence suggesting that melatonin has an important role in hair physiology (38) and that dark hair is associated with higher tryptophan/melatonin levels (39). Another mechanistic explanation might pertain to melanin. Melatonin might be suppressed to a greater extent in those with high innate eumelanin levels if melatonin suppression were somehow associated with higher eumelanin activity (40).

To our knowledge, only one study to date, a Scandinavian register-based cohort study (41), has attempted to examine the risk of melanoma associated with shift work. That study, which did not report an association between night work and melanoma risk, was based on only 11 case subjects (41). Several studies of airline personnel reported a higher risk of melanoma related to this occupation (42,43), but whether the increased risk is more likely attributable to exposure to cosmic radiation, circadian disruption, or the lifestyle of airline personnel currently remains unclear (44).

Night shift workers have also been reported to be at higher risk of several non malignant chronic diseases, although PD has been an exception. Chen et al. (19) reported a 50% lower risk of PD among women who worked 15 years or more of rotating night shifts compared with those who never worked rotating night shifts (19). Notably, evidence has been accumulating to support a decreased risk of cancer among PD patients with the important exception of skin cancers, specifically melanoma (45,46). Gao et al. (47,48) reported a twofold increased risk of PD associated with fair hair color, a strong phenotypic risk factor of melanoma (47), and a family history of melanoma in a first-degree relative (HR = 1.85, 95% CI = 1.2 to 2.8) (48). Based on these findings, it appears possible that PD and melanoma share common genetic or environmental risk factors (49), hich might be influenced by circadian disruption (as encountered during night work).

Our study had several limitations. The question about shift work was asked only once and may have been misclassified in some instances; however, because of the prospective nature of our analyses, we expect any resulting bias only toward the null. Even though we adjusted for all known or suspected risk factors for skin cancer, the possibility for uncontrolled

CONTEXTS AND CAVEATS

Prior knowledge

Night shift work has been associated with increased risk of several cancers, but the risk of skin cancer for shift workers is unknown.

Study design

A total of 10 799 incident cases of melanoma and basal cell and squamous cell carcinoma were documented among women in the Nurses' Health study between June 1988 and June 2006. Women who worked in night shifts for 10 years or more were compared with those who worked in night shifts for shorter periods or never.

Contribution

Working 10 years or more on rotating night shifts was associated with a statistically significantly decreased risk of skin cancer. Women with darker hair color, a surrogate for an individual's susceptibility to skin cancer, had the lowest risk.

Implications

The inverse association between the risk of skin cancer and both longer durations of night shift work and darker hair color suggests that both genetic and environmental factors may act in melatonin suppression during night work.

Limitations

The question about shift work was asked only once and may have been misclassified in some instances. Details of ultraviolet light exposure could not be considered and may be confounding variables.

From the Editors

Table 1. Risk of skin cancer by rotating night shift work among 68336 women in the Nurses' Health Study*

Years on rotating night shift	Person-years	No. of case subjects	Age-adjusted HR (95% CI)	Multivariable model 1†, HR (95% CI)	Multivariable model 2†, HR (95% CI)
Skin cancer					
Never	413727	4426	1.0 (referent)	1.0 (referent)	1.0 (referent)
1–2 y	246014	2653	1.02 (0.97 to 1.07)	1.01 (0.96 to 1.05)	1.02 (0.97 to 1.07)
3–5 y	167774	1875	0.99 (0.94 to 1.05)	0.97 (0.92 to 1.02)	1.01 (0.96 to 1.07)
6–9 y	68474	698	0.91 (0.84 to 0.99)	0.89 (0.82 to 0.96)	0.88 (0.81 to 0.96)
≥10 y	117507	1147	0.84 (0.78 to 0.89)	0.82 (0.77 to 0.87)	0.86 (0.81 to 0.92)
P_{trend}‡			<.001	<.001	<.001
Melanoma					
Never	416272	147	1.0 (referent)	1.0 (referent)	1.0 (referent)
1–2 y	247545	79	0.91 (0.69 to 1.19)	0.89 (0.68 to 1.18)	0.89 (0.68 to 1.18)
3–5 y	168816	50	0.83 (0.60 to 1.14)	0.80 (0.58 to 1.10)	0.83 (0.60 to 1.15)
6–9 y	68858	18	0.72 (0.44 to 1.18)	0.68 (0.42 to 1.11)	0.65 (0.40 to 1.06)
≥10 y	118144	24	0.57 (0.37 to 0.87)	0.54 (0.35 to 0.83)	0.56 (0.36 to 0.87)
P_{trend}‡			.007	.003	.005
SCC					
Never	416088	363	1.0 (referent)	1.0 (referent)	1.0 (referent)
1–2 y	247434	207	0.97 (0.82 to 1.15)	0.96 (0.81 to 1.13)	0.96 (0.81 to 1.14)
3–5 y	168744	137	0.88 (0.72 to 1.07)	0.85 (0.70 to 1.04)	0.89 (0.73 to 1.08)
6–9 y	68825	55	0.87 (0.65 to 1.15)	0.84 (0.63 to 1.12)	0.84 (0.63 to 1.11)
≥10 y	118099	87	0.76 (0.60 to 0.96)	0.74 (0.59 to 0.94)	0.79 (0.63 to 1.00)
P_{trend}‡			.02	.01	.04
BCC					
Never	414194	3916	1.0 (referent)	1.0 (referent)	1.0 (referent)
1–2 y	246272	2367	1.03 (0.98 to 1.08)	1.01 (0.96 to 1.07)	1.03 (0.98 to 1.08)
3–5 y	167942	1688	1.01 (0.95 to 1.07)	0.98 (0.93 to 1.04)	1.03 (0.97 to 1.09)
6–9 y	68537	625	0.93 (0.85 to 1.01)	0.90 (0.82 to 0.98)	0.90 (0.82 to 0.97)
≥10 y	117600	1036	0.86 (0.80 to 0.92)	0.84 (0.78 to 0.90)	0.88 (0.82 to 0.94)
P_{trend}‡			<.001	<.001	.001

* 103613 of the women returned the 1988 questionnaire, which included the question about night work. The population for this study consisted of the 85197 (82.2%) of the respondents who answered the question on night work. Women who did not answer the shift work question on the 1988 questionnaire did not substantially differ from respondents in terms of their risk profile. A total of 10799 incident skin cancer case subjects, comprising 9632 BCC, 849 SCC, and 318 melanoma case subjects, were diagnosed in the base population between June 1, 1988, and May 31, 2006. Women who reported having melanoma, SCC, BCC, or any other cancer before 1988 were excluded. The analysis was restricted to non-Hispanic white women because the number of case subjects in the other racial/ethnic categories was small. A total of 68336 women remained to form the baseline population for this analysis, and 1013497 person-years of follow-up were accrued from 1988 to 2006. Skin cancers were defined as having occurred during the period between June 1, 1988, and May 31, 2006. Nurses who reported the occurrence of SCC and melanoma were asked for permission to review their medical records, and skin cancer was confirmed through review of these records. Medical records were not obtained for self-reported BCC. A validation study demonstrated that >90% of self-reported BCC among nurses were confirmed by histopathological findings (24,25). Reviews of medical records were conducted by investigators without knowledge of exposure. BCC = basal cell carcinoma; CI = confidence interval; HR = hazard ratio; SCC = squamous cell carcinoma.

† Multivariable model 1: relative risk adjusted for age in 1 year increments, and phenotypic and established risk factors of skin cancer including hair color at 20 years of age (red, blond, light brown, dark brown, and black), family history of skin cancer (yes, no), child and adolescence tendency to burns (some redness, burn, and painful burn/blisters), number of palpable moles on arms and legs (1–2, 3–5, 6–9, and ≥10), and lifetime severe sunburns that blistered (1–2, 3–5, 6–9, and ≥10); to control as finely as possible for confounding by age, calendar time, and any possible two-way interactions between these two time scales, we stratified analyses jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle. Multivariable model 2: additional adjustment for residence ultraviolet exposure level (low, middle, and high) (26) at birth, and at 15 and 30 years of age, average hours of sun exposure per week (2–5, 6–10, and ≥11 h/wk) at 25–35, 36–59, and ≥60 years of age. Complete-subject analyses were used to handle missing values. In 1988, the study participants were asked how many years in total they had worked rotating night shifts, which was defined as at least three nights per month in addition to days or evenings in that month. Data on lifetime years worked on rotating nightshift until 1988 was gathered in eight prespecified categories: never, 1–2, 3–5, 6–9, 10–14, 15–19, 20–29, and ≥30 years.

‡ *P* value for continuous linear term by two-sided Wald test. Tests of trends across categories of exposure were calculated by treating the levels of exposure as a continuous variable by assigning each category a midpoint and reporting the Wald statistics for the covariate.

confounding remains. For example, a possible source of bias in our study was residual confounding as a result of nondifferential misclassification of variables related to ultraviolet light. However, in analyses stratified by residence, ultraviolet light exposure level at baseline, and by location of skin cancer, we found no important effect modification. Thus, actual sun exposure appears less likely to play a role in the observed inverse association between night shift work and skin cancer risk. The strengths of our study include large size, prospective nature, detailed information on location of skin cancers, and a detailed history of sun exposure in participants, as well as regularly updated information on confounders.

In conclusion, we found lower risks of skin cancer in women with longer durations of rotating night shift work. Because the risks of all three skin cancers that we examined (melanoma, SCC, and BCC) were lower, and no effect modification by history of sunlight exposure was apparent, the role of sun seems to be negligible in these associations. That the inverse association was

Table 2. Risk of skin cancer by rotating night shift work among 68 336 women in the Nurses' Health Study stratified by hair color*

Years on rotating night shift	Dark brown/black hair color		Light brown hair color		Red/blonde hair color	
	No. of case subjects	Multivariable HR† (95% CI)	No. of case subjects	Multivariable HR (95% CI)	No. of case subjects	Multivariable HR (95% CI)
Melanoma						
Never	52	1.0 (referent)	56	1.0 (referent)	31	1.0 (referent)
1–9 y	41	0.61 (0.40 to 0.93)	59	0.91 (0.63 to 1.32)	28	0.72 (0.43 to 1.20)
≥10 y	5	0.30 (0.12 to 0.75)	9	0.61 (0.30 to 1.24)	6	0.58 (0.24 to 1.40)
P_{trend}‡		.006		.17		.21
SCC						
Never	143	1.0 (referent)	124	1.0 (referent)	65	1.0 (referent)
1–9 y	162	0.90 (0.72 to 1.14)	132	0.89 (0.70 to 1.15)	77	1.03 (0.74 to 1.45)
≥10 y	26	0.58 (0.38 to 0.88)	33	0.91 (0.61 to 1.34)	18	0.87 (0.51 to 1.49)
P_{trend}‡		.01		.61		.61
BCC						
Never	1496	1.0 (referent)	1405	1.0 (referent)	688	1.0 (referent)
1–9 y	1682	0.93 (0.87 to 1.00)	1750	1.07 (1.00 to 1.15)	881	1.03 (0.93 to 1.14)
≥10 y	365	0.79 (0.70 to 0.89)	375	0.93 (0.83 to 1.04)	192	0.93 (0.79 to 1.10)
P_{trend}‡		<.001		.22		.39

* With prospective follow-up in 1988–2006 and with total of 10 799 skin cancer case subjects. BCC = basal cell carcinoma; CI = confidence interval; HR = hazard ratio; SCC = squamous cell carcinoma.

† Multivariable relative risk adjusted for age in 1 year increments, and phenotypic and established risk factors of skin cancer including family history of skin cancer (yes, no), child and adolescence tendency to burns (some redness, burn, and painful burn/blisters), number of palpable moles on arms and legs (1–2, 3–5, 6–9, and ≥10), and lifetime severe sunburns that blistered (1–2, 3–5, 6–9, and ≥10), residence ultraviolet exposure level (low, middle, and high) (26) at birth, and at 15 and 30 years of age, average hours of sun exposure per week (2–5, 6–10, and ≥ 11 h/wk) at 25–35, 36–59, and 60 years or more of age.

‡ *P* value for continuous linear term by two-sided Wald test. Tests of trends across categories of exposure were calculated by treating the levels of exposure as a continuous variable by assigning each category a midpoint and reporting the Wald statistics for the covariate.

strongest among women with dark hair raises the possibility for several mechanistic explanations, including a genetic component that may affect both the extent of melatonin suppression during night work and skin cancer risk.

References

1. Stevens RG. Electric power use and breast cancer: a hypothesis. *Am J Epidemiol.* 1987; 125(4):556–561.
2. Schernhammer ES, Schulmeister K. Melatonin and cancer risk: does light at night compromise physiologic cancer protection by lowering serum melatonin levels? *Br J Cancer.* 2004;90(5):941–943.
3. Knutsson A. Health disorders of shift workers. *Occup Med (Lond).* 2003;53(2):103–108.
4. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst.* 2001;93(20):1557–1562.
5. Hansen J. Light at night, shiftwork, and breast cancer risk. *J Natl Cancer Inst.* 2001;93(20): 1513–1515.
6. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst.* 2001;93(20): 1563–1568.
7. Megdal SP, Kroenke CH, Laden F, Pukkala E, Schernhammer ES. Night work and breast cancer risk: a systematic review and meta-analysis. *Eur J Cancer.* 2005;41(13): 2023–2032.
8. Schernhammer ES, Kroenke CH, Laden F, Hankinson SE. Night work and risk of breast cancer. *Epidemiology.* 2006;17(1): 108–111.
9. Pukkala E, Auvinen A, Wahlberg G. Incidence of cancer among Finnish airline cabin attendants. *BMJ.* 1995;311(7006):649–652.
10. Rafnsson V, Sulem P, Tulinius H, Hrafnkelsson J. Breast cancer risk in airline cabin attendants: a nested case-control study in Iceland. *Occup Environ Med.* 2003;60(11): 807–809.
11. Tynes T, Hannevik M, Andersen A, Vistnes A, Haldorsen T. Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control.* 1996;7(2): 197–204.
12. Hansen J. Increased breast cancer risk among women who work predominantly at night. *Epidemiology.* 2001;12(1):74–77.
13. Kloog I, Haim A, Stevens RG, Barchana M, Portnov BA. Light at night co-distributes with incident breast but not lung cancer in the female population of Israel. *Chronobiol Int.* 2008;25(1):65–81.
14. Viswanathan AN, Hankinson SE, Schernhammer ES. Night shift work and the risk of endometrial cancer. *Cancer Res.* 2007; 67(21):10618–10622.
15. Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. *Epidemiology.* 2007;18(1):182–183.
16. Kubo T, Ozasa K, Mikami K, et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. *Am J Epidemiol.* 2006;164(6):549–555.
17. Schernhammer ES, Laden F, Speizer FE, et al. Night-shift work and risk of colorectal cancer in the nurses' health study. *J Natl Cancer Inst.* 2003;95(11):825–828.
18. Lahti TA, Partonen T, Kyyronen P, Kauppinen T, Pukkala E. Night-time work predisposes to non-Hodgkin lymphoma. *Int J Cancer.* 2008;123(9):2148–2151.
19. Chen H, Schernhammer E, Schwarzschild MA, Ascherio A. A prospective study of night shift work, sleep duration, and risk of Parkinson's disease. *Am J Epidemiol.* 2006; 163(8):726–730.
20. Kvaskoff M, Weinstein P. Are some melanomas caused by artificial light? *Med Hypotheses.* 2010;75(3):305–311.
21. Colditz GA, Stampfer MJ, Willett WC, et al. Reproducibility and validity of self-reported menopausal status in a prospective cohort study. *Am J Epidemiol.* 1987;126(2):319–325.
22. Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study. *N Engl J Med.* 1991;325(11):756–762.
23. Colditz GA, Manson JE, Hankinson SE. The Nurses' Health Study: 20-year contribution to the understanding of health among women. *J Womens Health.* 1997;6(1):49–62.
24. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol.* 1986;123(5):894–900.

25. Hunter DJ, Colditz GA, Stampfer MJ, Rosner B, Willett WC, Speizer FE. Diet and risk of basal cell carcinoma of the skin in a prospective cohort of women. *Ann Epidemiol.* 1992; 2(3):231–239.
26. Qureshi AA, Laden F, Colditz GA, Hunter DJ. Geographic variation and risk of skin cancer in US women. Differences between melanoma, squamous cell carcinoma, and basal cell carcinoma. *Arch Intern Med.* 2008;168(5):501–507.
27. Pesch B, Harth V, Rabstein S, et al. Night work and breast cancer—results from the German GENICA study. *Scand J Work Environ Health.* 2010;36(2):134–141.
28. Vijayalaxmi, Thomas CR Jr, Reiter RJ, Herman TS. Melatonin: from basic research to cancer treatment clinics. *J Clin Oncol.* 2002;20(10):2575–2601.
29. Slominski A, Tobin DJ, Zmijewski MA, Wortsman J, Paus R. Melatonin in the skin: synthesis, metabolism and functions. *Trends Endocrinol Metab.* 2008;19(1):17–24.
30. Otalora BB, Madrid JA, Alvarez N, Vicente V, Rol MA. Effects of exogenous melatonin and circadian synchronization on tumor progression in melanoma-bearing C57BL6 mice. *J Pineal Res.* 2008;44(3):307–315.
31. Fischer TW, Zmijewski MA, Zbytek B, et al. Oncostatic effects of the indole melatonin and expression of its cytosolic and nuclear receptors in cultured human melanoma cell lines. *Int J Oncol.* 2006;29(3):665–672.
32. Yerneni LK, Jayaraman S. Pharmacological action of high doses of melatonin on B16 murine melanoma cells depends on cell number at time of exposure. *Melanoma Res.* 2003;13(2):113–117.
33. Cos S, Garcia-Bolado A, Sanchez-Barcelo EJ. Direct antiproliferative effects of melatonin on two metastatic cell sublines of mouse melanoma (B16BL6 and PG19). *Melanoma Res.* 2001;11(2):197–201.
34. el-Domeiri AA, Das Gupta TK. Reversal by melatonin of the effect of pinealectomy on tumor growth. *Cancer Res.* 1973;33(11): 2830–2833.
35. Ghosh BC, el-Domeiri AA, Das Gupta TK. Effect of melatonin on hamster melanoma. *Surg Forum.* 1973;24:121–122.
36. Narita T, Kudo H. Effect of melatonin on B16 melanoma growth in athymic mice. *Cancer Res.* 1985;45(9):4175–4177.
37. Izykowska I, Gebarowska E, Cegielski M, et al. Effect of melatonin on melanoma cells subjected to UVA and UVB radiation in in vitro studies. *In Vivo.* 2009;23(5):733–738.
38. Fischer TW. [The influence of melatonin on hair physiology]. *Hautarzt.* 2009;60(12): 962–972.
39. Bertazzo A, Biasiolo M, Costa CV, Cardin de Stefani E, Allegri G. Tryptophan in human hair: correlation with pigmentation. *Farmaco.* 2000;55(8):521–525.
40. Scherer D, Kumar R. Genetics of pigmentation in skin cancer—a review. *Mutat Res.* 2010;705(2):141–153.
41. Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health.* 2007;33(5):336–343.
42. Buja A, Mastrangelo G, Perissinotto E, et al. Cancer incidence among female flight attendants: a meta-analysis of published data. *J Womens Health (Larchmt).* 2006;15(1):98–105.
43. Buja A, Lange JH, Perissinotto E, et al. Cancer incidence among male military and civil pilots and flight attendants: an analysis on published data. *Toxicol Ind Health.* 2005;21(10): 273–282.
44. Langner I, Blettner M, Gundestrup M, et al. Cosmic radiation and cancer mortality among airline pilots: results from a European cohort study (ESCAPE). *Radiat Environ Biophys.* 2004;42(4):247–256.
45. Olsen JH, Friis S, Frederiksen K, McLaughlin JK, Mellemkjaer L, Moller H. Atypical cancer pattern in patients with Parkinson's disease. *Br J Cancer.* 2005;92(1):201–205.
46. Olsen JH, Friis S, Frederiksen K. Malignant melanoma and other types of cancer preceding Parkinson disease. *Epidemiology.* 2006;17(5):582–587.
47. Gao X, Simon KC, Han J, Schwarzschild MA, Ascherio A. Genetic determinants of hair color and Parkinson's disease risk. *Ann Neurol.* 2009;65(1):76–82.
48. Gao X, Simon KC, Han J, Schwarzschild MA, Ascherio A. Family history of melanoma and Parkinson disease risk. *Neurology.* 2009;73(16): 1286–1291.
49. Fiala KH, Whetteckey J, Manyam BV. Malignant melanoma and levodopa in Parkinson's disease: causality or coincidence? *Parkinsonism Relat Disord.* 2003;9(6):321–327.

Funding

National Institute of Health CA87969 (PI: Hankinson, S.E.,) and the Department of Dermatology, Brigham and Women's Hospital.

Notes

The funders did not have any involvement in the design of the study; the collection, analysis, and interpretation of the data; the writing of the article; or the decision to submit the article for publication.

E. S. Schernhammer: funding, data collection, analysis, interpretation, and article preparation; P. Razavi: data analysis and article preparation; T. Y. Li: data analysis and article preparation; A. A. Qureshi: article interpretation and preparation; J. Han: data collection and analysis and article interpretation and preparation.

We are indebted to the participants of the Nurses' Health Study for their dedication to this study. We thank the following state cancer registries for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, Wyoming.

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