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NIGHT SHIFT WORK AND FRACTURE RISK: THE NURSES' HEALTH STUDY

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Abstract

Summary—Night shift work suppresses melatonin production and has been associated with an increased risk of major diseases including hormonally related tumors. Experimental evidence suggests that light at night acts through endocrine disruption, likely mediated by melatonin. To date, no observational study has addressed the effect of night work on osteoporotic fractures, another condition highly sensitive to sex steroid exposure. Our study, to our knowledge the first to address this question, supports the hypothesis that night shift work may negatively affect bone health, adding to the growing list of ailments that have been associated with shift work.

Introduction—We evaluated the association between night shift work and fractures at the hip and wrist in postmenopausal nurses.

Methods—The study population was drawn from Nurses' Health Study participants who were working full or part time in nursing in 1988 and had reported their total number of years of rotating night shift work. Through 2000, 1,223 incident wrist and hip fractures involving low or moderate trauma were identified among 38,062 postmenopausal women. We calculated multivariate relative risks (RR) of fracture over varying lengths of follow-up in relation to years of night shift work.

Results—Compared with women who never worked night shifts, 20+ years of night shift work was associated with a significantly increased risk of wrist and hip fractures over eight years of follow-up (RR = 1.37, 95% confidence interval [CI], 1.04–1.80). This risk was strongest among women with a lower BMI (<24) who never used hormone replacement therapy (RR = 2.36; 95% CI, 1.33–4.20). The elevated risk was no longer apparent with twelve years of follow-up after the baseline single assessment of night shift work.

Conclusions—Long durations of rotating night shift work may contribute to risk of hip and wrist fractures, although the potential for unexplained confounding cannot be ruled out.

Keywords

writs fractures; hip fractures; light exposure; melatonin; night work

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INTRODUCTION

Laboratory evidence that visible light, including artificial light, can acutely suppress melatonin generated novel hypotheses proposing that the diminished function of the pineal gland and a suppression of melatonin levels might promote the development of cancer in humans [1–4]. Night shift work, through exposure to artificial light at night, has subsequently been linked with decreased circulating melatonin levels in humans [5] and increasing risks of cancer and other major diseases [6]. The primary mode of action through which melatonin is thought to influence health is endocrine disruption [7].

Almost 40 years ago, it was proposed that melatonin affects calcium metabolism [8,9]. Subsequent studies described more direct effects of melatonin on the bone via estrogen suppression and consequent inhibition of osteoclastic activity [10]. More speculatively, antioxidant effects of melatonin in relation to free-radical generation of osteoclast activity have also been described as a potentially bone protecting mechanism [11]. The physiologic decline in melatonin secretion through menopause and with age lends further support to a link between melatonin suppression and postmenopausal osteoporosis [9]. Finally, diurnal changes in bone turnover are suggestive of a role of melatonin in osteoporosis [12–15].

To further evaluate the endocrine disruptive potential of night work, we set out to evaluate the effect of night shift work on osteoporotic fractures, another condition highly sensitive to estrogen exposure. To date, no observational study has been published that evaluates the effect of night work on risk of osteoporotic fractures. Because data on night shift workers are particularly sparse, the Nurses' Health Study (NHS) provides a unique opportunity to prospectively assess this association.

METHODS

Study Population

The NHS cohort was formed in 1976 when 121,700 female registered nurses, 30 to 55 years of age, responded to an initial mailed questionnaire. The women provided a medical history and information on risk factors related to cancer, heart disease, and other health conditions. Follow-up questionnaires have been mailed every two years to identify incident diseases and to update and expand information on participants. Deaths are reported by family members or the postal service and are confirmed through the National Death Index. The NHS was approved by the Institutional Review Board of the Brigham and Women's Hospital in Boston.

We began our analysis in 1988 with participants of the NHS who were working full-time or part-time as a nurse and reported their years of night shift work on the questionnaire (n = 48,120). Women were excluded from the study population for the following reasons: prevalent diagnosis of cancer (n = 3,043); previous hip or wrist fracture (n = 1,166), no response to any subsequent questionnaire on which incident fractures were reported (n = 279); not Caucasian (n = 1,227). Women entered analysis when postmenopausal, hence the 1988 baseline study population of 21,859 grew to include 38,062 women through 2000.

Wrist and Hip Fractures

Participants were asked to report all previous hip and wrist fractures (date, bone site, and circumstances leading to fracture) in 1982 and incident fractures were reported on subsequent biennial questionnaires. Cases in this study included only the first occurrence of a fracture at the distal radius (Colles' fractures) or proximal femur that was caused by low or moderate trauma (e.g., slipping on ice, falling from the height of a chair). Fractures due to high trauma (e.g., skiing, falling down a flight of stairs) were excluded from analysis (about 15% of the reports).

Night Shift Work

On the 1988 questionnaire, participants were asked, "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?" Response categories were never, 1–2, 3–5, 6–9, 10–14, 15–19, 20–29, and 30 or more years. No other assessments of shift work were available from any of the subsequent questionnaires. Categories with sparse response were combined in analysis.

Risk Factors for Fractures

Body weight and time spent in recreational and leisure-time activities were assessed on all biennial questionnaires during the follow-up period of this investigation. At each assessment, body mass index (BMI) was calculated using height reported in 1976, and physical activity was converted into metabolic equivalents. Both variables were updated in analyses with an average of all previously reported data. Smoking status and daily cigarette consumption, menopausal status and use of hormone replacement therapy (HRT), use of thiazide diuretics, and incident diagnoses of osteoporosis were also assessed on the biennial questionnaires, and these data were updated in analyses with newly reported information. Diet was first ascertained in 1980 and at least every four years thereafter using a semi-quantitative food frequency questionnaire, from which daily intakes of calcium, vitamin D, protein, retinol, alcohol, and caffeine were calculated. In analyses, intakes were updated with an average from all previously reported diets. Parity was reported on questionnaires through 1984, when few participants were still bearing children, and a subsequent assessment in 1996 was used to confirm final parity.

Statistical Analysis

Each participant contributed person-time from the return date of her 1988 questionnaire or the questionnaire on which she first reported being postmenopausal until the occurrence of a hip or wrist fracture, a cancer diagnosis, failure to respond to any subsequent questionnaire on which incident fractures would be reported, death, or end of follow-up. Though years spent in night shift work were not assessed after the 1988 report, we attempted to examine the extent of a lasting effect of night shift work on fracture risk by analyzing three follow-up periods: four years (1988–1992), eight years (1988–1996), and twelve years (1988–2000).

Cox proportional hazards models were used to compute relative risks for each upper category of years spent in night shift work compared with those who never worked a night shift schedule. Multivariate models were adjusted for age in months and all other assessed risk factors for hip and wrist fracture. Years spent working rotating night shifts up until 1988 was applied to the entire follow-up period, whereas current data on fracture risk factors were used to allocate person-time to the appropriate category for each variable at the beginning of every 2-year follow-up cycle.

RESULTS

Over twelve years of follow-up, 1,223 fracture cases (1,047 wrist, 176 hip) were identified in the study population. The median age at fracture was 62.2 for the wrist and 64.9 for the hip. Characteristics of the study population at 1988 baseline by total years spent working in rotating night shifts are shown in Table 1. The nurses with twenty or more years of rotating night shift work were somewhat older than those with fewer years. After adjusting for age, longer durations of night shift work were associated with higher BMI, more activity, and less likelihood of using hormone replacement therapy (Table 1). Dietary intakes and the other risk factors did not differ appreciably by years of night shift work.

The relative risks (RR) of wrist and hip fractures over increasing years spent working in rotating night shifts are shown in Table 2. There was little confounding by the other fracture risk factors

as evidenced by the similarity of results from the models adjusted only for age and 2-year questionnaire cycles and the full multivariate-adjusted models. Over four years of follow-up after the 1988 shift work report, fracture risk was 43% greater for the nurses with twenty or more years of night shift work compared with those who never worked this type of schedule. With eight years of follow-up and a greater number of fracture cases, the elevated risk became statistically significant (RR = 1.37, 95% confidence interval (CI), 1.04–1.80). With twelve years of follow-up after the shift work assessment, an association with wrist and hip fractures was no longer evident.

As expected, wrist fractures were far more common than hip fractures in this study. Therefore, we reanalyzed the eight-year follow-up (1988–1996) with the first occurrence of hip fracture as the outcome. Risk remained significantly elevated for the nurses with twenty or more years of night shift work (RR = 2.02, 95% CI, 1.03–3.93).

We examined whether any of the factors listed in Table 1 modified the association between years spent working rotating night shifts and risk of wrist and hip fractures with eight years of follow-up. Only BMI and HRT were possible modifiers, though their interactions with night shift work were not statistically significant ($P_{interaction}$ = 0.32 and 0.10, respectively). Twenty or more years of night shift work was associated with significantly increased fracture risks among the nurses with a BMI < 24 kg/m^2 (RR = 1.63, 95% CI, 1.11–2.39) and among those who never used HRT (RR = 1.70, 95% CI, 1.15–2.53), whereas no associations were observed among the nurses with a BMI ≥ 24 kg/m^2 (RR = 0.97, 95% CI, 0.62–1.52) or among those who ever used HRT (RR = 1.13, 95% CI, 0.73–1.73). A significant interaction with night shift work was found when BMI and HRT use were combined ($P_{interaction}$=0.03). Twenty or more years of night shift work was associated with a significantly increased fracture risk among the nurses who never used HRT and had a BMI < 24 kg/m^2 (RR = 2.36, 95% CI, 1.33–4.20) but not among those who ever used HRT and had a higher BMI (RR = 1.07, 95% CI, 0.54–2.12).

DISCUSSION

In this large and, to our knowledge, first observational study of shift work and postmenopausal fractures, the risk of fractures was modestly elevated in the women who had worked for 20 or more years on rotating night shifts, compared with those who reported never having worked rotating night shifts. This risk appeared significantly stronger among leaner women without any HRT use. The results from this study are compatible with a possible endocrine disruptive effect of night-time light exposure, likely through the melatonin pathway.

Exposure to light at night has repeatedly been shown to profoundly suppress melatonin levels, particularly in women [16,17]. Because experimental studies suggest that melatonin influences bone metabolism [9], we speculate that the modest effects of night work on fracture risk in our study provides further support for a link between melatonin suppression and osteoporosis. Our observation that fracture risk was higher in lean women and in those without HRT use (both presumably states of comparatively low estrogen environments) could indicate that otherwise high estrogen levels might override the modest, independent effects of melatonin on bone metabolism.

Because of vitamin D's role in bone health, and the potential for lower vitamin D levels among long-term night workers, identifying an independent effect of melatonin suppression in night workers is difficult. However, we had prospective information on vitamin D intake from foods and supplements in our cohort, and adjusting for these covariates did not alter our estimates substantially. While food frequency questionnaires, as used in the current study, have been shown to reflect plasma 25(OH)D levels reasonably well [r = 0.35; [18]], data of elderly people [19,20] suggest that sun shine exposure is the most important determinant of total 25(OH)D

level and therefore, in subjects with low sun exposure, total 25(OH)D level might constitute a better marker of dietary intake of vitamin D. It is therefore possible that, despite the fact that we were able to adjust for a number of important risk factors for osteoporosis including vitamin D intake, there may still be residual confounding for which we were unable to account.

Although we did not validate self-reported duration of rotating night shifts, it is likely that these reports are reliable. Other self-reports have been highly accurate in this cohort [21], and previous validations of similar questions (e.g. use of electric blankets) [22] have shown reasonable reproducibility. Moreover, the prospective design of our study eliminates recall bias. On the other hand, we were limited by our single shift work assessment in drawing inferences about the latency period between rotating shift work and an osteoporotic fracture because we did not ascertain current shift-work status. This made it difficult to assess the direct effects of night work on fracture risk beyond a reasonably small number of years of follow-up. In our analysis, the risk we observed diminished beyond eight years of follow-up, which may indicate that there is no lasting effect of night work (or melatonin suppression, respectively) on the bone, or maybe due to increasing inaccuracy in our exposure as participants accumulated years of night shift work after 1988.

In the U.S., a significant portion of nurses worked on permanent nightshifts during the period of our investigation [23]. If these nurses classified themselves as never working on rotating shifts, such misclassification could have biased our results towards the null: while circadian disruption is also prevalent in permanent night workers [24], it is more severe in rotating shift workers and they would therefore remain at the highest overall risk. However, we did not query permanent night work and are therefore unable to address this.

Another potential bias that might have occurred in our data is what could be referred to as an “unhealthy shift worker effect” [25]. If persons with factors for a less healthy life style (such as workers from lower socioeconomic status) tend to choose to do shift work and these factors are associated with fracture risk, this bias could lead to an overestimation of the true association. However, the excess risk associated with longer durations of shift work persisted after controlling for known life-style factors, such as physical activity, smoking, and diet. Nonetheless, we were limited by our one-timed assessment of night work and it is therefore possible that the non-linear relationship between years of rotating night shift work and fracture risk reflects this potential for uncontrolled confounding.

In conclusion, working on rotating night shifts was associated with a moderately increased risk of osteoporotic fractures among postmenopausal nurses in our cohort. The findings from our study are novel and require confirmation. Moreover, because night work has become so common in developed countries, future studies about light exposure and endocrine disruption are needed. Not only should these studies assess the relation of light exposure to other endocrine related conditions, they should also consider the risks in men. Finally, strategies to reduce the potentially negative health effects of rotating night work need to be considered, including shift schedule optimization.

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References

1. Cohen M, Lippman M, Chabner B. Role of pineal gland in aetiology and treatment of breast cancer. Lancet 1978;312:814–816. [PubMed: 81365]

2. Kerenyi NA, Pandula E, Feuer GM. Oncostatic effects of the pineal gland. Drug Metab Drug Interact 1990;8:313–319.

3. Stevens RG. Electric power use and breast cancer: a hypothesis. Am J Epidemiol 1987;125:556–561. [PubMed: 3548332]

4. 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;90:941–943. [PubMed: 14997186]

5. Burch JB, Yost MG, Johnson W, Allen E. Melatonin, sleep, and shift work adaptation. J Occup Environ Med 2005;47:893–901. [PubMed: 16155474]

6. Arendt J. Melatonin and human rhythms. Chronobiol Int 2006;23:21–37. [PubMed: 16687277]

7. Sanchez-Barcelo EJ, Cos S, Mediavilla D, Martinez-Campa C, Gonzalez A, Alonso-Gonzalez C. Melatonin-estrogen interactions in breast cancer. J Pineal Res 2005;38:217–222. [PubMed: 15813897]

8. Kiss J, Banhegyi D, Csaba G. Endocrine regulation of blood calcium level. II. Relationship between the pineal body and the parathyroid glands. Acta Med Acad Sci Hung 1969;26:363–370. [PubMed: 5380805]

9. Cardinali DP, Ladizesky MG, Boggio V, Cutrera RA, Mautalen C. Melatonin effects on bone: experimental facts and clinical perspectives. J Pineal Res 2003;34:81–87. [PubMed: 12562498]

10. Suzuki N, Hattori A. Melatonin suppresses osteoclastic and osteoblastic activities in the scales of goldfish. J Pineal Res 2002;33:253–258. [PubMed: 12390509]

11. Melhus H, Michaelsson K, Holmberg L, Wolk A, Ljunghall S. Smoking, antioxidant vitamins, and the risk of hip fracture. J Bone Miner Res 1999;14:129–135. [PubMed: 9893075]

12. Heshmati HM, Riggs BL, Burritt MF, McAlister CA, Wollan PC, Khosla S. Effects of the circadian variation in serum cortisol on markers of bone turnover and calcium homeostasis in normal postmenopausal women. J Clin Endocrinol Metab 1998;83:751–756. [PubMed: 9506720]

13. Hassager C, Risteli J, Risteli L, Jensen SB, Christiansen C. Diurnal variation in serum markers of type I collagen synthesis and degradation in healthy premenopausal women. J Bone Miner Res 1992;7:1307–1311. [PubMed: 1466255]

14. Greenspan SL, Dresner-Pollak R, Parker RA, London D, Ferguson L. Diurnal variation of bone mineral turnover in elderly men and women. Calcif Tissue Int 1997;60:419–423. [PubMed: 9115158]

15. Ostrowska Z, Kos-Kudla B, Swietochowska E, Marek B, Kajdaniuk D, Gorski J. Assessment of the relationship between dynamic pattern of nighttime levels of melatonin and chosen biochemical markers of bone metabolism in a rat model of postmenopausal osteoporosis. Neuro Endocrinol Lett 2001;22:129–136. [PubMed: 11335889]

16. Graham C, Cook MR. Examination of the melatonin hypothesis in women exposed at night to EMF or bright light. Environ Health Perspect 2001;109:501–507. [PubMed: 11401762]

17. Travlos GS, Wilson RE, Murrell JA, Chignell CF, Boorman GA. The effect of short intermittend light exposures on the melatonin circadian rhythm and NMU-induced breast cancer in female F344/N rats. Toxicol Pathol 2001;29:126–136. [PubMed: 11215676]

18. Jacques PF, Sulsky SI, Sadowski JA, Phillips JC, Rush D, Willett WC. Comparison of micronutrient intake measured by a dietary questionnaire and biochemical indicators of micronutrient status. Am J Clin Nutr 1993;57:182–189. [PubMed: 8424386]

19. Newton HM, Sheltawy M, Hay AW, Morgan B. The relations between vitamin D2 and D3 in the diet and plasma 25OHD2 and 25OHD3 in elderly women in Great Britain. Am J Clin Nutr 1985;41:760–764. [PubMed: 2984915]

20. Lips P, van Ginkel FC, Jongen MJ, Rubertus F, van der Vijgh WJ, Netelenbos JC. Determinants of vitamin D status in patients with hip fracture and in elderly control subjects. Am J Clin Nutr 1987;46:1005–1010. [PubMed: 3687818]

21. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. Am J Epidemiol 1986;123:894–900. [PubMed: 3962971]

22. Laden F, Neas LM, Tolbert PE, Holmes MD, Hankinson SE, Spiegelman D, Speizer FE, Hunter DJ. Electric blanket use and breast cancer in the Nurses' Health Study. Am J Epidemiol 2000;152:41–49. [PubMed: 10901328]

23. Bureau of Labor Statistics Workers on Flexible and Shift Schedules in 2004 Summary. http://www.bls.gov/news.release/flex.nr0.htm

24. Folkard S, Monk TH, Lobban MC. Short and long-term adjustment of circadian rhythms in 'permanent' night nurses. Ergonomics 1978;21:785–799. [PubMed: 729546]

25. McMichael AJ. Standardized mortality ratios and the "healthy worker effect": Scratching beneath the surface. J Occup Med 1976;18:165–168. [PubMed: 1255276]

Table 1

Age-standardized characteristics [a] of the study population of postmenopausal nurses at 1988 baseline by number of years spent working in rotating night shifts.

	Years of Rotating Night Shift Work				
	Never (n=8,980)	**1–2 years (n=4,703)**	**3–9 years (n=4,987)**	**10–19 years (n=1,882)**	**≥ 20 years (n=1,307)**
Age, years	56.5 ± 5.2	56.0 ± 5.1	56.7 ± 5.0	56.8 ± 5.1	58.0 ± 4.8
Body mass index, kg/m^2	24.1 ± 5.7	24.0 ± 5.5	24.4 ± 5.8	24.7 ± 6.4	25.1 ± 6.7
Activity, met-hours[b]/week	12.5 ± 14.3	13.5 ± 14.7	13.9 ± 15.1	14.2 ± 16.9	14.6 ± 16.3
Current smoker, %	21	20	22	26	25
HRT[c] user, %	37	38	36	34	28
Thiazide diuretic user, %	15	14	15	17	17
Osteoporosis diagnosis, %	6	5	6	7	6
Nulliparous, %	5	6	7	5	6
Parity[d]	3.4 ± 1.6	3.4 ± 1.6	3.3 ± 1.6	3.4 ± 1.6	3.4 ± 1.8
Calcium, mg/day	916 ± 351	917 ± 340	918 ± 342	911 ± 327	898 ± 337
Vitamin D, µg/day	8.2 ± 5.5	8.1 ± 5.4	8.2 ± 5.2	8.2 ± 5.1	8.3 ± 5.5
Protein, g/day	74 ± 12	74 ± 11	75 ± 11	74 ± 12	74 ± 12
Retinol, µg/day	1368 ± 1269	1395 ±1380	1403 ±1323	1436 ± 1277	1449 ± 1416
Alcohol, g/day	6.6 ± 10.0	6.4 ± 9.7	6.5 ± 9.8	5.8 ± 9.5	5.4 ± 9.5
Caffeine, mg/day	353 ± 218	352 ± 216	364 ± 219	385 ± 226	391 ± 241

[a] Values are means ± standard deviation or percentages and are standardized to the age distribution of the study population.

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

[c] Postmenopausal hormone replacement therapy.

[d] Number of children among parous women.

Table 2

Relative risks of wrist and hip fractures over four, eight, and twelve years of follow-up among postmenopausal nurses by total number of years spent working in rotating night shifts as of 1988.

	Years of Rotating Night Shift Work				
	never	**1–2 years**	**3–9 years**	**10–19 years**	**≥ 20 years**
1988–1992 Follow-up					
Wrist/Hip Fractures	127/16	72/11	57/3	26/4	29/2
Person-years	36754	19325	20341	7496	5127
Age-adjusted RR[a] (95% CI[b])	1.00	1.16 (0.88–1.53)	0.75 (0.55–1.01)	1.04 (0.70–1.54)	1.43 (0.96–2.11)
Multivariate RR[c] (95% CI[b])	1.00	1.18 (0.89–1.55)	0.74 (0.55–1.01)	1.03 (0.69–1.53)	1.43 (0.96–2.13)
1988–1996 Follow-up					
Wrist/Hip Fractures	280/36	167/25	130/17	63/9	54/10
Person-years	84005	44814	46076	16837	10909
Age-adjusted RR[a] (95% CI[b])	1.00	1.17 (0.98–1.40)	0.83 (0.68–1.01)	1.13 (0.87–1.46)	1.35 (1.03–1.77)
Multivariate RR[c] (95% CI[b])	1.00	1.19 (0.99–1.42)	0.83 (0.68–1.01)	1.12 (0.87–1.46)	1.37 (1.04–1.80)
1988–2000 Follow-up					
Wrist/Hip Fractures	434/74	246/40	205/34	96/15	66/13
Person-years	137596	74136	74552	26881	16613
Age-adjusted RR[a] (95% CI[b])	1.00	1.07 (0.93–1.24)	0.85 (0.73–0.99)	1.11 (0.90–1.36)	1.10 (0.86–1.40)
Multivariate RR[c] (95% CI[b])	1.00	1.08 (0.93–1.25)	0.86 (0.73–1.00)	1.11 (0.90–1.36)	1.11 (0.87–1.42)

[a] Relative risk adjusted for age and questionnaire cycle.

[b] 95% confidence interval.

[c] Relative risk adjusted for age, body mass index, physical activity, smoking status, hormone replacement therapy use, thiazide diuretic use, diagnosis of osteoporosis, and daily intakes of calcium, vitamin D, and alcohol.