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ORIGINAL ARTICLE

Nightshift work and fracture risk: the Nurses' Health Study

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Abstract
Summary Nightshift 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 nightshift 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 nightshift 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 nightshift 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 nightshift work.
Results Compared with women who never worked night shifts, 20+ years of nightshift work was associated with a significantly increased risk of wrist and hip fractures over 8 years of follow-up [RR=1.37, 95% confidence interval (CI), 1.04–1.80]. This risk was strongest among women with a lower body mass index (<24) who never used hormone replacement therapy (RR=2.36; 95% CI, 1.33–4.20). The elevated risk was no longer apparent with 12 years of follow-up after the baseline single assessment of nightshift work.
Conclusions Long durations of rotating nightshift work may contribute to risk of hip and wrist fractures, although the potential for unexplained confounding cannot be ruled out.

Keywords Hip fractures · Light exposure · Melatonin · Night work · Wrist fractures

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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].

Nightshift 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 nightshift 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 nightshift 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 2 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 fulltime or part time as a nurse and reported their years of nightshift 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), and 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).

Nightshift work

On the 1988 questionnaire, participants were asked, "What is the total number of years during which you worked rotating night shifts (at least three 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 4 years thereafter using a semiquantitative 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 nightshift work were not assessed after the 1988 report, we attempted to examine the extent of a lasting effect of nightshift work on fracture risk by analyzing three follow-up periods: 4 years (1988–1992), 8 years (1988–1996), and 12 years (1988–2000).

Cox proportional hazards models were used to compute relative risks for each upper category of years spent in nightshift work compared with those who never worked a nightshift 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 12 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 20 or more years of rotating nightshift work were somewhat older than those with fewer years. After adjusting for age, longer durations of nightshift 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 nightshift 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 4 years of follow-up after the 1988 shift work report, fracture risk was 43% greater for the nurses with 20 or more years of nightshift work compared with those who never worked this type of schedule. With 8 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 12 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 8-year follow-up (1988–1996) with the first occurrence of hip fracture as the outcome. Risk remained significantly

Table 1 Age-standardized characteristics of the study population of postmenopausal nurses at 1988 baseline by number of years spent working in rotating night shifts

	Years of rotating nightshift 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-h[a]/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[b] 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[c]	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

Values are means±SD or percentages and are standardized to the age distribution of the study population.
[a] Metabolic equivalents from recreational and leisure-time activities.
[b] Postmenopausal hormone replacement therapy.
[c] Number of children among parous women.

Table 2 Relative risks of wrist and hip fractures over 4, 8, and 12 years of follow-up among postmenopausal nurses by total number of years spent working in rotating night shifts as of 1988

	Years of rotating nightshift 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% CI.
[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.

elevated for the nurses with 20 or more years of nightshift 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 nightshifts and risk of wrist and hip fractures with 8 years of follow-up. Only BMI and HRT were possible modifiers, though their interactions with nightshift work were not statistically significant ($P_{\text{interaction}}$=0.32 and 0.10, respectively). Twenty or more years of nightshift 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 nightshift work was found when BMI and HRT use were combined ($P_{\text{interaction}}$=0.03). Twenty or more years of nightshift 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 sunshine exposure is the most important determinant of total 25(OH)D level; 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 8 years of follow-up, which may indicate that there is no lasting effect of night work or melatonin suppression on the bone or may be due to increasing inaccuracy in our exposure as participants accumulated years of nightshift work after 1988.

In the US, 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 lifestyle (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 lifestyle 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 nonlinear relationship between years of rotating nightshift 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 but 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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Conflicts of interest None.

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