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Article

Rotating Nightshift Work and Hematopoietic Cancer Risk in US Female Nurses

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Abstract

Background: Nightshift work is a plausible risk factor for hematologic cancer, but epidemiological evidence remains sparse, especially for individual subtypes. We prospectively examined the association of rotating nightshift work with hematopoietic cancer risk.

Methods: This cohort study included US women from the Nurses' Health Study (NHS: n = 76 846, 1988–2012) and Nurses' Health Study II (NHSII: n = 113 087, 1989–2013). Rotating nightshift work duration was assessed at baseline (both cohorts) and cumulatively updated (NHSII). Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for overall hematopoietic cancer and specific histologic subtypes. All statistical tests were two-sided.

Results: We documented 1405 (NHS) and 505 (NHSII) incident hematopoietic cancer cases during follow-up. In NHS, compared with women who never worked rotating nightshifts, longer rotating nightshift work duration was associated with an increased risk of overall hematopoietic cancer ($HR_{1–14y} = 0.93$, 95% CI = 0.83 to 1.04; $HR_{\geq 15y} = 1.28$, 95% CI = 1.06 to 1.55; $P_{trend} = .009$). In NHSII, results were similar though not statistically significant ($HR_{1–14y} = 0.99$, 95% CI = 0.82 to 1.21; $HR_{\geq 15y} = 1.41$, 95% CI = 0.88 to 2.26; $P_{trend} = .47$). In the subtype analyses in the NHS, the association of history of rotating nightshift work with risk of diffuse large B-cell lymphoma varied by duration ($HR_{1–14y} = 0.71$, 95% CI = 0.51 to 0.98; $HR_{\geq 15y} = 1.69$, 95% CI = 1.07 to 2.67; $P_{trend} = .01$) compared with those who never worked rotating nightshifts. Women reporting a longer history of rotating nightshifts also had suggestive (statistically nonsignificant) increased risks of overall non-Hodgkin lymphoma ($HR_{\geq 15y} = 1.19$, 95% CI = 0.95 to 1.49), Hodgkin lymphoma ($HR_{\geq 15y} = 1.32$, 95% CI = 0.43 to 4.06), and multiple myeloma ($HR_{\geq 15y} = 1.42$, 95% CI = 0.85 to 2.39).

Conclusions: Longer duration (≥15 years) of rotating nightshift work was associated with increased risks of overall and several subtypes of hematopoietic cancer.

The global disease burden of hematopoietic cancer is substantial (1). In the United States, major classes of hematopoietic cancer are projected to account for 10% of new cancer diagnoses and 9.4% of all cancer deaths in 2019 (2). With few established risk factors, the impact of circadian disruption and other critical risk behaviors that may result from nightshift work (3–5) has been suggested to be involved in the etiology of several specific hematopoietic cancers (6–12). However, epidemiological evidence regarding the relationship between night (shift) work and risk of overall hematopoietic cancer (13) and its component classes or histologic subtypes remains inconclusive (13–17). Moreover, no prior study has investigated potential heterogeneity across major non-Hodgkin lymphoma subtypes.

Shift work is increasingly prevalent in our 24/7 societies (3,18–20), currently affecting approximately 20% of the global workforce (21,22). In the United States, 25–50% of health-care, protective, and transportation services entail shift work (23). Shift work has been associated with a wide spectrum of health consequences (3,24) and is currently classified by the International Agency for Research on Cancer (IARC) as a probable carcinogen (group 2A) (18,22,25,26). Among shift work schedules, nightshifts are most disruptive to regular sleep cycles and hence the circadian clock (18,25,27).

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With their detailed assessments of rotating nightshift work and well-documented demographics, anthropometric data, lifestyle information, and medical records, the Nurses' Health Study (NHS) (28–31) and Nurses' Health Study II (NHSII) (31) cohorts are unparalleled for investigations regarding the health impacts of rotating nightshift work and have previously been referred to by IARC as highly reliable human evidence (25,32–34). We prospectively examined the association of rotating nightshift work with hematopoietic cancer risk in these two large cohorts, investigating potential heterogeneity across major histologic subtypes of hematopoietic cancer.

Methods

Study Population

Details of the NHS and NHSII have been described previously (28–31). Briefly, they are ongoing cohort studies of US female registered nurses. NHS began in 1976 (28–31), when 121 700 participants aged 30–55 years were enrolled, and NHSII in 1989 (31), enrolling 116 429 participants between 25 and 42 years of age. Biennial self-administered questionnaires were used to update detailed information on anthropometric data, lifestyle characteristics, medical history, newly diagnosed diseases, and disease outcomes. Diet was assessed quadrennially via semiquantitative food-frequency questionnaires. Response rates exceeding 90% have been achieved. The study protocol was approved by the Institutional Review Board of the Brigham and Women's Hospital (Boston, MA) and those of participating registries as required. Informed consent from participants was indicated by the completion and return of the questionnaires. We used 1988 as baseline for the NHS and 1989 for NHSII, when rotating nightshift work history was first assessed. Participants who reported no information on rotating nightshift work at baseline, who were diagnosed with any cancer, or died before baseline, and those with missing information on age were excluded, leaving 76 846 women in NHS and 113 087 in NHSII for inclusion.

Ascertainment of Rotating Nightshift Work

NHS participants reported their total number of years of rotating nightshift work (defined as at least 3 nights/mo in addition to evenings and days) in 1988, with "never, 1–2, 3–5, 6–9, 10–14, 15–19, 20–29, and ≥30 years" as the prespecified response categories. NHSII participants were first queried about lifetime rotating nightshift work history in 1989, using the same definition, with "never, 1–2, 3–5, 6–9, 10–14, 15–19, and ≥20 years" as the prespecified response categories and with regular updates thereafter (for each 2-year cycle in prespecified categories of months) (35,36). In final analyses, we classified participants into three categories by their total duration of rotating nightshift work (never, 1–14, and ≥15 years) (37). For NHSII, we used both baseline and cumulatively updated assessments of lifetime rotating nightshift work history.

Ascertainment of Hematopoietic Cancer Cases and Participant Deaths

Physician-diagnosed incident cancer events were reported by participants via biennial questionnaires. With their permission, medical records and pathology reports were accessed to confirm diagnoses of hematopoietic cancer; if medical records were unavailable, we referred to state cancer registries. We used the World Health Organization (WHO) classification system and International Lymphoma Epidemiology Consortium guidelines (38–40) to determine histologic subtypes of lymphomas based on morphology and immunophenotype. Classification of chronic lymphocytic leukemia or small lymphocytic lymphoma and follicular lymphoma does not rely on immunophenotype information, and thus those histologic types could be identified by morphology alone (38). Diagnoses of multiple myeloma were identified based on criteria specified by the International Myeloma Working Group (41). For diagnoses in very early years with no available immunophenotyping information, we used the proposed translation from previous classification systems to the current WHO standard (38,40). Participant deaths were ascertained through the National Death Index, postal authorities, or next-of-kin reporting (42,43).

Ascertainment of Covariates

We considered age, race, cumulative average body mass index (BMI), alcohol consumption, physical activity, smoking status, pack-years of smoking, daily energy intake, and current regular aspirin or nonsteroidal anti-inflammatory drug (NSAID) use as potential confounders in analyses. Participants biannually or quadrennially updated bodyweight (which we used to calculate BMI), physical activities (metabolic equivalent of tasks [MET] scores were assigned to every specific type of physical activity, and total physical activity in MET-h/wk was calculated) (44), smoking status, pack-years of smoking, dietary habits (total calories intake and alcohol intake), and history of aspirin and other NSAIDs use. Height and race were assessed once. The validity and reproducibility of self-reported information have previously been described (44–49).

Statistical Analysis

Person-years of follow-up accrued from the return date of the baseline questionnaire until the date of any cancer diagnosis reported, death recorded, or the end of follow-up period, whichever arrived earliest. We estimated age- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for hematopoietic cancer risk using Cox proportional hazard models conditioning on age and questionnaire cycle across categories of rotating night work duration. Women who never worked rotating nightshifts served as the reference group in all analyses. Considering that assessments of shift work exposure differed by cohort (single assessment in NHS vs cumulatively updated in the NHSII), models were presented separately for each cohort. Tests for linear trend were performed by assigning the midpoint values to rotating nightshift work duration categories (never, 1–14, and ≥15 years) and modeling these values as a continuous variable. The assumption of proportionality was verified using interactions between the exposure of interest (nightshift work) and the (log-)time scale.

The outcomes included incident cases of hematopoietic cancer in both cohorts. To investigate potential heterogeneity across major subclasses and histologic subtypes, we also performed subtype analysis in the NHS. Within the limits of subtype-specific sample sizes, we were able to conduct separate analyses only for overall non-Hodgkin lymphoma, overall T- and B-cell non-Hodgkin lymphoma (in aggregate), a few common histologic types of B-cell non-Hodgkin lymphoma (diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia or small lymphocytic lymphoma), multiple myeloma, Hodgkin lymphoma (in aggregate),

and myeloid leukemias (also in aggregate). We were unable to conduct subtype- or subgroup-specific analyses in NHSII because of limited power. Because most of the NHS participants were close to their retirement age (and hence, close to stopping rotating nightshift work) when reporting lifetime shiftwork history at baseline, we performed secondary analyses specifically among those aged older than 60 years and 60 years and younger in 1988, respectively.

In multivariable models, we controlled for age (continuous, months), follow-up cycle (each 2-year interval), race (white, black, others), cumulative average BMI (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), alcohol consumption (0, 0.1–4.9, 5–14.9, ≥15 g/d), physical activity (≤8, 8.1–16, 16.1–24, >24 MET-h/wk), smoking status (never, current, past smoker), pack-years of smoking (0, 0.1–4.9, 5–14.9, ≥15 pack-years), daily energy intake (kcal/d, in quintiles), and current regular aspirin or NSAID use (>2 tablets/wk). Time-varying covariates were updated biennially or quadrennially in models. Missing data were carried forward from the latest valid data in previous follow-up cycles to minimize missing information of these repeatedly measured variables. For the remaining missing values of categorical covariates after replacement, we created and included missing indicators in the models.

We conducted data analyses using SAS statistical software, version 9.4 (SAS Institute Inc). All tests were two-sided, and *P* value less than .05 was considered statistically significant.

Results

Population Characteristics

A total of 1405 incident hematopoietic cancer case patientes were documented during 1 538 485 person-years of follow-up in NHS and 505 case patients during 2 541 133 person-years of follow-up in NHSII. In NHS, compared with those reporting no history of rotating nightshift work, women with longer duration of rotating nightshift work were more likely to be older, had a higher BMI, reported higher levels of total energy intake, and were more likely to be current smokers and regular users of aspirin and other NSAIDs. They also engaged in more physical activities and reported lower alcohol intake. Similarly, in NHSII, women with longer history of rotating nightshift work also tended to be older, had a higher BMI, had higher energy intake, and were more likely to report being regular users of aspirin and other NSAIDs and more physically active. However, they were less likely to be Caucasian and consumed more alcohol. No other appreciable variation was observed (Table 1).

Rotating Nightshift Work and Overall Hematopoietic Cancer Risk

In multivariable analyses in the NHS, compared with women who never worked rotating nightshifts, longer duration of rotating nightshift work was associated with higher risk of overall hematopoietic cancer ($HR_{1–14y}$ = 0.93, 95% CI = 0.83 to 1.04; $HR_{≥15y}$ = 1.28, 95% CI = 1.06 to 1.55; P_{trend} = .009). This association was more robust among participants aged 60 years and younger at baseline ($HR_{1–14y}$ = 0.95, 95% CI = 0.83 to 1.09; $HR_{≥15y}$ = 1.42, 95% CI = 1.12 to 1.82; P_{trend} = .005) but was attenuated among those older than 60 years ($HR_{1–14y}$ = 0.89, 95% CI = 0.73 to 1.07; $HR_{≥15y}$ = 1.09, 95% CI = 0.81 to 1.46; P_{trend} = .50) (Table 2).

In NHSII, we observed a similar but not statistically significant positive association between duration of rotating nightshift work and overall hematopoietic cancer risk. In multivariable-adjusted analyses, compared with the reference group, risk of overall hematopoietic cancer was statistically nonsignificantly elevated among women with longer baseline rotating nightshift work history ($HR_{1–14y}$ = 0.87, 95% CI = 0.73 to 1.04; $HR_{≥15y}$ = 1.15, 95% CI = 0.59 to 1.26; P_{trend} = .25) and cumulative updated rotating nightshift work history ($HR_{1–14y}$ = 0.99, 95% CI = 0.82 to 1.21; $HR_{≥15y}$ = 1.41, 95% CI = 0.88 to 2.26; P_{trend} = .47) (Table 3).

Rotating Nightshift Work and Specific Hematopoietic Cancer Risk

In multivariable analyses in the NHS, the association of history of rotating nightshift work with risk of diffuse large B-cell lymphoma appeared to vary by duration (compared with women never working shifts, $HR_{1–14y}$ = 0.71, 95% CI = 0.51 to 0.98; $HR_{≥15y}$ = 1.69, 95% CI = 1.07 to 2.67; P_{trend} = .01). In addition, rotating nightshift work duration was associated with suggestive (but not statistically significant) increases in risk of overall non-Hodgkin lymphoma ($HR_{1–14y}$ = 0.88, 95% CI = 0.77 to 1.00; $HR_{≥15y}$ = 1.19, 95% CI = 0.95 to 1.49; P_{trend} = .15), Hodgkin lymphoma ($HR_{1–14y}$ = 0.90, 95% CI = 0.46 to 1.75; $HR_{≥15y}$ = 1.32, 95% CI = 0.43 to 4.06; P_{trend} = .63), multiple myeloma ($HR_{1–14y}$ = 1.35, 95% CI = 1.00 to 1.82; $HR_{≥15y}$ = 1.42, 95% CI = 0.85 to 2.39; P_{trend} = .20), and myeloid leukemias ($HR_{1–14y}$ = 1.20, 95% CI = 0.82 to 1.76; $HR_{≥15y}$ = 1.22, 95% CI = 0.64 to 2.33; P_{trend} = .57). There was no positive association between rotating nightshift work and risk of T-cell lymphoma, overall B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia. When restricting to those aged 60 years and younger at baseline, we observed stronger effects of rotating nightshift work on the risks of T-cell lymphoma, diffuse large B-cell lymphoma, Hodgkin lymphoma, multiple myeloma, and myeloid leukemias (Tables 4 and 5).

Discussion

In this study, we observed an increased hematopoietic cancer risk with longer duration of rotating nightshift work and potential subtype heterogeneity. These findings add to existing evidence in support of a carcinogenic effect of rotating nightshift work.

Our study corroborates the previously observed higher risk of overall non-Hodgkin lymphoma (14,15) and myeloid leukemia among male night workers (13). In contrast, our findings conflict with other prior reported null findings on overall hematopoietic cancer (13), overall lymphatic cancer (13), and multiple myeloma (13) among night workers or nightshift workers, and higher risk of chronic lymphocytic leukemia among rotating nightshift workers (16). Additionally, we reported an increased risk of diffuse large B-cell lymphoma among rotating nightshift workers and a suggestive positive association for multiple myeloma and Hodgkin lymphoma, whereas we observed no positive association for other B-cell lymphoma types or T-cell lymphoma. Whereas most hematopoietic cancer endpoints had no association with a shorter duration history of rotating nightshift work, we observed borderline inverse associations of diffuse large B-cell lymphoma and chronic lymphocytic leukemia risk in women reporting up to 14 years of shift work. To our knowledge, ours is the first study to examine these individual B-cell lymphoma endpoints in relation to rotating nightshift work. Of note, evidence from prior studies may have been affected by their study design [eg, retrospective studies (13,15,16), relatively

Table 1. Age and age-adjusted baseline characteristics of study population in NHS and NHSII across rotating nightshift work duration*,†,‡

	Duration of rotating nightshift work (≥3 nightshifts/mo)							
	NHS (1988, n = 76 846)				NHSII (1989, n = 113 087)			
Characteristic	Never	1–14 y	15–29 y	≥30 y	Never	1–5 y	6–14 y	≥15 y
No. (%)	31 060 (41.42)	40 104 (52.19)	4321 (5.62)	1361 (1.77)	42 978 (38.00)	55 234 (48.84)	13 655 (12.07)	1220 (1.08)
Age, mean (SD), y	54.31 (7.17)	54.75 (7.13)	56.13 (6.91)	60.36 (4.60)	34.76 (4.70)	34.52 (4.75)	35.53 (4.02)	39.22 (2.53)
Race, %								
White	97.86	97.53	96.34	97.56	93.36	92.01	91.29	80.85
Black	1.19	1.50	2.25	1.48	1.41	1.99	2.25	2.57
Other	0.95	0.96	1.41	0.95	5.22	6.00	6.46	16.57
BMI, mean (SD), kg/m^2	25.33 (4.79)	25.62 (4.90)	26.97 (5.51)	26.60 (5.19)	23.90 (4.88)	24.00 (4.97)	24.95 (5.61)	26.22 (6.84)
Smoking status, %								
Never smoked	45.70	43.37	42.01	41.56	67.15	64.79	61.27	57.60
Past smoker	36.79	37.98	32.80	33.74	20.54	21.81	21.92	18.06
Current smoker	17.51	18.65	25.19	24.70	12.31	13.39	16.81	24.34
Smoking, mean (SD)[§], pack-years	23.07 (19.54)	23.21 (19.44)	26.13 (20.00)	26.20 (20.09)	11.35 (8.22)	11.23 (8.17)	11.75 (8.16)	13.08 (8.01)
Physical activity, mean (SD), MET-h/wk[‖]	14.64 (20.90)	15.95 (21.86)	16.15 (21.85)	19.31 (28.44)	22.75 (34.28)	25.76 (37.56)	27.70 (40.18)	42.27 (64.23)
Alcohol intake, mean (SD), g/d	6.13 (10.63)	6.27 (10.72)	5.25 (10.54)	5.53 (9.75)	2.99 (5.99)	3.22 (6.17)	3.06 (5.86)	3.27 (8.12)
Total energy intake, mean (SD), kcal/d	1745.83 (519.21)	1782.40 (526.24)	1789.22 (555.76)	1781.38 (562.94)	1770.36 (539.75)	1798.88 (549.32)	1809.78 (568.07)	1846.80 (534.87)
Regular use of aspirin, >2 tablets/wk, %	32.57	33.49	35.39	35.61	10.96	11.12	12.55	9.95
Regular use of other NSAIDs, >2 tablets/wk, %	17.92	18.59	21.60	21.35	17.83	19.75	22.74	20.07

*Women with a history of any cancer at baseline and those who reported no information on rotating nightshift work were excluded. BMI = body mass index; MET = metabolic equivalent task; NHS = Nurses' Health Study; NHSII = Nurses' Health Study II; NSAIDs = nonsteroidal anti-inflammatory drugs.

†Percentages are of nonmissing values.

‡Percentages may not add to 100% after rounding.

§Cumulative among smokers.

‖Weekly energy expenditure in MET-h/wk from recreational and leisure-time physical activity.

Table 2. Rotating nightshift work and overall hematopoietic cancer risk in the NHS*

Cohort	Rotating nightshift work exposure			P_{trend}§
	Never	1–14 y	≥15 y	
NHS baseline history of shift work				
Cases	570	694	141	
Incidence rate per 100 000 person-years	90.77	86.50	130.34	
Age-adjusted model, HR (95% CI)†	1.00 (Referent)	0.93 (0.83 to 1.04)	1.28 (1.06 to 1.54)	.009
MV-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.93 (0.83 to 1.04)	1.28 (1.06 to 1.55)	.009
NHS baseline history of shift work (among women aged >60 y in 1988)				
Cases	202	249	58	
Incidence rate per 100 000 person-years	144.19	128.88	156.33	
Age-adjusted model, HR (95% CI)†	1.00 (Referent)	0.89 (0.73 to 1.07)	1.09 (0.81 to 1.46)	.50
MV-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.89 (0.73 to 1.07)	1.09 (0.81 to 1.46)	.50
NHS baseline history of shift work (among women aged ≤60 y in 1988)				
Cases	368	445	83	
Incidence rate per 100 000 person-years	75.43	73.05	117.88	
Age-adjusted model, HR (95% CI)†	1.00 (Referent)	0.95 (0.83 to 1.09)	1.42 (1.12 to 1.81)	.005
MV-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.95 (0.83 to 1.09)	1.42 (1.12 to 1.82)	.005

*A total of 1405 hematopoietic cancer cases were documented during 24 years of follow-up (1988–2012) in the NHS (baseline n = 76 846). CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent task; MV = multivariable; NHS = Nurses' Health Study.
†Adjusted for age (continuous, months) and follow-up cycle (each 2-year interval).
‡Adjusted for age (continuous, months), follow-up cycle (each 2-year interval), race (white, black, others), cumulative average body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), alcohol consumption (0, 0.1–4.9, 5–14.9, ≥15 g/d), physical activity (≤8, 8.1–16, 16.1–24, >24 MET-h/wk), smoking status (never smoker, current smoker, past smoker), pack-years of smoking (0, 0.1–4.9, 5–14.9, ≥15 pack-years), daily energy intake (kcal/d, in quintiles), and current regular aspirin or use of nonsteroidal anti-inflammatory drugs (>2 tablets/wk).
§P_{trend} was calculated using the midpoint of each category of rotating shift work duration in years.

Table 3. Rotating nightshift work and overall hematopoietic cancer risk in the NHSII*

Cohort	Rotating nightshift work exposure			P_{trend}§
	Never	1–14 y	≥15 y	
NHSII baseline history of shift work				
Cases	208	288	9	
Incidence rate per 100 000 person-years	21.49	18.62	33.74	
Age-adjusted model, HR (95% CI)†	1.00 (Referent)	0.87 (0.73 to 1.04)	1.18 (0.60 to 2.32)	.25
MV-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.87 (0.73 to 1.04)	1.15 (0.59 to 2.26)	.25
NHSII updated shift work				
Cases	152	333	20	
Incidence rate per 100 000 person-years	19.53	19.51	35.42	
Age-adjusted model, HR (95% CI)†	1.00 (Referent)	1.00 (0.83 to 1.21)	1.46 (0.91 to 2.33)	.40
MV-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.99 (0.82 to 1.21)	1.41 (0.88 to 2.26)	.47

*A total of 505 hematopoietic cancer cases were documented during 24 years of follow-up (1989–2013) in the NHSII (baseline n = 113 087). CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent task; MV = multivariable; NHSII = Nurses' Health Study II.
†Adjusted for age (continuous, months) and follow-up cycle (each 2-year interval).
‡Adjusted for age (continuous, months), follow-up cycle (each 2-year interval), race (white, black, others), cumulative average body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), alcohol consumption (0, 0.1–4.9, 5–14.9, ≥15 g/d), physical activity (≤8, 8.1–16, 16.1–24, >24 MET-h/wk), smoking status (never smoker, current smoker, past smoker), pack-years of smoking (0, 0.1–4.9, 5–14.9, ≥15 pack-years), daily energy intake (kcal/d, in quintiles), and current regular aspirin or use of nonsteroidal anti-inflammatory drugs (>2 tablets/wk).
§P_{trend} was calculated using the midpoint of each category of rotating shift work duration in years.

limited power (15,16)], imprecise assessment of type and duration of nightshift work (and therefore likely exposure misclassification) (13,14,17), diagnostic challenges (the reliability of the diagnosis of cancer subtypes in historic cohorts) (13,50), and/or incomplete control for potential covariates (13,14,16).

A higher risk of hematopoietic cancers among nightshift workers may appear biologically plausible. Mechanisms that have linked shift work to the risk of non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, and leukemias may include melatonin suppression (51,52), alterations in expression levels and/or polymorphisms of clock genes (6–9,53–56), and subsequent deregulation of many clock-associated biological processes (6–9,51–56). In addition, individuals experiencing shiftwork are more likely to expose themselves to various altered lifestyle factors (3,57), some of which (eg, smoking) have been associated with increased risk of specific hematopoietic cancers (eg, Hodgkin lymphoma and non-Hodgkin lymphoma), though we carefully adjusted for smoking history (10–12). Immune dysregulation, inflammation, survival-favoring DNA mutations, and prematurely halted hematopoiesis have varying degrees of importance to the different classes or subtypes of hematopoietic cancers. Some of these mechanisms would be

Table 4. Rotating nightshift work and risk of specific hematopoietic cancers in the NHS*,†

	Baseline history of rotating nightshift work			
NHS	Never	1–14 y	≥15 y	P_{trend}‖
Overall non-Hodgkin lymphoma				
Cases	410	473	94	
Incidence rate per 100 000 person-years	65.29	58.95	86.89	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.88 (0.77 to 1.00)	1.18 (0.94 to 1.48)	.16
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.88 (0.77 to 1.00)	1.19 (0.95 to 1.49)	.14
T-cell lymphoma				
Cases	21	23	4	
Incidence rate per 100 000 person-years	3.34	2.87	3.70	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.85 (0.47 to 1.54)	0.92 (0.31 to 2.71)	.87
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.83 (0.46 to 1.51)	0.96 (0.32 to 2.85)	.93
Overall B-cell lymphoma				
Cases	323	360	67	
Incidence rate per 100 000 person-years	51.43	44.87	61.93	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.84 (0.72 to 0.98)	1.08 (0.83 to 1.41)	.61
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.84 (0.72 to 0.98)	1.09 (0.84 to 1.43)	.56
Diffuse large B-cell lymphoma				
Cases	76	70	26	
Incidence rate per 100 000 person-years	12.10	8.72	24.03	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.70 (0.51 to 0.97)	1.67 (1.06 to 2.63)	.02
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.71 (0.51 to 0.98)	1.69 (1.07 to 2.67)	.01
Follicular lymphoma				
Cases	63	93	10	
Incidence rate per 100 000 person-years	10.03	11.59	9.24	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	1.14 (0.83 to 1.58)	0.85 (0.43 to 1.66)	.67
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	1.14 (0.83 to 1.58)	0.82 (0.41 to 1.62)	.60
Chronic lymphocytic leukemia				
Cases	109	112	16	
Incidence rate per 100 000 person-years	17.36	13.96	14.79	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.77 (0.59 to 1.00)	0.77 (0.45 to 1.30)	.27
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.77 (0.59 to 1.00)	0.81 (0.48 to 1.37)	.36
Hodgkin lymphoma				
Cases	17	19	4	
Incidence rate per 100 000 person-years	2.71	2.37	3.70	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.89 (0.46 to 1.71)	1.36 (0.45 to 4.11)	.59
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.90 (0.46 to 1.75)	1.32 (0.43 to 4.06)	.63
Multiple myeloma				
Cases	67	119	19	
Incidence rate per 100 000 person-years	10.67	14.83	17.56	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	1.34 (0.99 to 1.81)	1.45 (0.87 to 2.42)	.17
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	1.35 (1.00 to 1.82)	1.42 (0.85 to 2.39)	.20
Myeloid leukemias				
Cases	45	70	12	
Incidence rate per 100 000 person-years	7.17	8.72	11.09	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	1.21 (0.83 to 1.76)	1.30 (0.68 to 2.47)	.44
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	1.20 (0.82 to 1.76)	1.22 (0.64 to 2.33)	.57

*Within the limits of subtype-specific sample sizes, we were able to conduct separate analyses for overall non-Hodgkin lymphoma, overall T- and B-cell non-Hodgkin lymphoma (in aggregate), a few common histologic types of B-cell non-Hodgkin lymphoma (diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia or small lymphocytic lymphoma), multiple myeloma, Hodgkin lymphoma (in aggregate), and myeloid leukemias (also in aggregate). CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent task; MV = multivariable; NHS = Nurses' Health Study.

†A total of 1405 hematopoietic cancer cases were documented during 24 years of follow-up (1988–2012) in the NHS.

‡Adjusted for age (continuous, months) and follow-up cycle (each 2-year interval).

§Adjusted for age (continuous, months), follow-up cycle (each 2-year interval), race (white, black, others), cumulative average body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), alcohol consumption (0, 0.1–4.9, 5–14.9, ≥15 g/d), physical activity (≤8, 8.1–16, 16.1–24, >24 MET-h/wk), smoking status (never smoker, current smoker, past smoker), pack-years of smoking (0, 0.1–4.9, 5–14.9, ≥15 pack-years), daily energy intake (kcal/d, in quintiles), and current regular aspirin or use of nonsteroidal anti-inflammatory drugs (>2 tablets/wk).

‖P_{trend} was calculated using the midpoint of each category of rotating shift work duration in years.

Table 5. Rotating nightshift work and risk of specific hematopoietic cancers in the NHS among women aged 60 years or younger at baseline (1988)*,†

NHS	Baseline history of rotating nightshift work			P_{trend}‖
	Never	1–14 y	≥15 y	
Overall non-Hodgkin lymphoma				
Cases	265	312	51	
Incidence rate per 100 000 person-years	54.31	51.22	72.43	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.92 (0.78 to 1.08)	1.20 (0.88 to 1.62)	.29
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.92 (0.78 to 1.08)	1.19 (0.88 to 1.62)	.29
T-cell lymphoma				
Cases	13	15	3	
Incidence rate per 100 000 person-years	2.66	2.46	4.26	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.91 (0.43 to 1.91)	1.41 (0.41 to 5.00)	.60
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.91 (0.43 to 1.94)	1.47 (0.41 to 5.27)	.56
Overall B-cell lymphoma				
Cases	207	241	36	
Incidence rate per 100 000 person-years	42.43	39.56	51.13	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.91 (0.75 to 1.10)	1.11 (0.77 to 1.58)	.65
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.91 (0.75 to 1.09)	1.12 (0.78 to 1.60)	.62
Diffuse large B-cell lymphoma				
Cases	50	47	15	
Incidence rate per 100 000 person-years	10.25	7.72	21.30	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.74 (0.50 to 1.10)	1.81 (1.01 to 1.26)	.04
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.74 (0.50 to 1.11)	1.91 (1.06 to 3.46)	.03
Follicular lymphoma				
Cases	42	63	6	
Incidence rate per 100 000 person-years	8.61	10.34	8.52	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	1.18 (0.80 to 1.75)	0.88 (0.37 to 2.09)	.84
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	1.19 (0.80 to 1.76)	0.83 (0.35 to 1.99)	.74
Chronic lymphocytic leukemia				
Cases	66	79	7	
Incidence rate per 100 000 person-years	13.53	12.97	9.94	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.93 (0.67 to 1.28)	0.68 (0.31 to 1.48)	.32
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.92 (0.67 to 1.28)	0.71 (0.32 to 1.55)	.37
Hodgkin lymphoma				
Cases	12	13	3	
Incidence rate per 100 000 person-years	2.46	2.13	4.26	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	0.90 (0.41 to 1.98)	1.89 (0.53 to 6.81)	.34
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	0.88 (0.40 to 1.95)	1.69 (0.46 to 6.23)	.44
Multiple myeloma				
Cases	40	71	13	
Incidence rate per 100 000 person-years	8.20	11.66	18.46	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	1.37 (0.93 to 2.02)	2.07 (1.10 to 3.88)	.03
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	1.39 (0.94 to 2.05)	1.99 (1.05 to 3.76)	.04
Myeloid leukemias				
Cases	25	39	7	
Incidence rate per 100 000 person-years	5.12	6.40	9.94	
Age-adjusted model, HR (95% CI)‡	1.00 (Referent)	1.25 (0.75 to 2.07)	1.81 (0.78 to 4.20)	.17
MV-adjusted model, HR (95% CI)§	1.00 (Referent)	1.23 (0.74 to 2.04)	1.73 (0.73 to 4.07)	.21

*Within the limits of subtype-specific sample sizes, we were able to conduct separate analyses for overall non-Hodgkin lymphoma, overall T- and B-cell non-Hodgkin lymphoma (in aggregate), a few common histologic types of B-cell non-Hodgkin lymphoma (diffuse large B-cell lymphoma, follicular lymphoma, and chronic lymphocytic leukemia or small lymphocytic lymphoma), multiple myeloma, Hodgkin lymphoma (in aggregate), and myeloid leukemias (also in aggregate). BMI = body mass index; CI = confidence interval; HR = hazard ratio; MET = metabolic equivalent task; MV = multivariable; NHS = Nurses' Health Study.

†A total of 896 hematopoietic cancer cases were documented during 24 years of follow-up (1988–2012) in the NHS among women aged 60 years or younger at baseline.

‡Adjusted for age (continuous, months) and follow-up cycle (each 2-year interval).

§Adjusted for age (continuous, months), follow-up cycle (each 2-year interval), race (white, black, others), cumulative average body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), alcohol consumption (0, 0.1–4.9, 5–14.9, ≥15 g/d), physical activity (≤8, 8.1–16, 16.1–24, >24 MET-h/wk), smoking status (never smoker, current smoker, past smoker), pack-years of smoking (0, 0.1–4.9, 5–14.9, ≥15 pack-years), daily energy intake (kcal/d, in quintiles), and current regular aspirin or use of nonsteroidal anti-inflammatory drugs (>2 tablets/wk).

‖P_{trend} was calculated using the midpoint of each category of rotating shift work duration in years.

particularly relevant to the pathogenesis of a given histologic type of hematopoietic cancer, such as diffuse large B-cell lymphoma or any of the types with suggestive findings. Whether circadian disruption or its physiologic sequelae influence known pathways of lymphomagenesis or leukemogenesis, which differ somewhat across types of hematologic cancer and have not yet been definitively linked to melatonin suppression, remains to be explored.

Our study has several strengths. First, it represents the largest prospective study investigating the association of rotating nightshift work duration with hematopoietic cancer risk to date. Second, we were able to adequately control for a wide range of covariates (42–49,53). Third, detailed medical records and pathology reports of hematopoietic cancer cases were accessed, allowing us to examine heterogeneity across several major classes and histologic subtypes using the modern WHO and International Lymphoma Epidemiology classification schemes (38–41). Particularly, we were able to investigate heterogeneity across several specific B-cell non-Hodgkin lymphoma subtypes for the first time, to our knowledge. The high follow-up rate attained (exceeding 90%) minimizes bias because of the differential exposure and outcome experience for participants lost to follow-up. Last, the high homogeneity of our study participants (female, all health-care professionals) ensured data quality and minimized certain confounding (eg, socioeconomic status, educational attainment), and thus further enhanced the internal validity.

Of note, the associations observed in this study could have been underestimated for several reasons. First, in our study, assessments of exposure differed by cohort. Cumulative assessments of rotating nightshift work history were available in NHSII only. By contrast, in NHS, where we had enough power to perform histologic subtype analyses, our assessment of rotating nightshift work history was crudely measured (assessed only once, at baseline, when participants were mostly close to retirement age). This inevitable underestimation of lifetime exposure in the NHS could have attenuated the effect estimates towards the null. Second, misreporting of exposure may exist in some instances. We asked nurses about their history of working rotating nightshifts; however, their history of permanent night work was not separately queried. Some of the participants working on a permanent nightshift work schedule may have misunderstood this question and consequently inadvertently misclassified themselves as never working rotating nightshifts (reference group) (18,25,58,59). Third, "health-related selection" (60,61) or the so-called "healthy worker effect" (62,63) may exist. Specifically, nurses who were able to accumulate a longer history of working rotating nightshifts may be healthier in nature compared with those working permanent day and night routines, or those switching back from rotating nightshifts to other schedules. This could have also caused underestimation of the effect of our exposure. For example, women with a history of autoimmune disease (a risk factor for some types of lymphoid malignancy) (64,65) may have been less likely to accumulate longer durations of rotating nightshift work.

Several limitations of this study should also be noted. First, the assessments of rotating nightshift work in our cohorts are self-reported, and we lack information on intensity of nightshifts and number of consecutive nightshifts. Second, though extensive multivariable analyses have been conducted, the possibility for residual uncontrolled confounding always remains. We lacked information on family history of hematopoietic cancer, exposure to pesticides and other putative environmental or occupational risk factors (eg, radiation and chemotherapeutical drugs), and history of oncogenic infections. Third, our study participants are not randomly sampled from the US female population but are all health-care professionals of predominantly European ancestry, thus precluding generalizability of current conclusions to other demographic groups (18,24,26,59,66). Finally, we had relatively limited power for the analysis of individual histologic subtypes, which hampered detection of statistically significant associations and precluded separate analyses of individual subtypes for Hodgkin lymphoma, T-cell non-Hodgkin lymphoma, less common types of B-cell non-Hodgkin lymphoma, and myeloid leukemias. Moreover, U-shaped associations were observed for several specific subtypes. The possibility that these associations were observed by chance cannot be ruled out, and these results must therefore be interpreted with caution.

Collectively, our study adds timely evidence suggesting rotating nightshift work as a potential risk factor for hematopoietic cancers. Importantly, our findings suggest that rotating nightshift work may be associated with several, but not with all, types of hematopoietic cancer, underscoring the need for additional investigation in larger populations with reliable classification of individual histologic subtypes. Further prospective investigations are needed to confirm current findings. It will also be critical to consider refined shift work assessments in future research. Specifically, documentation of several major domains of occupational history (ie, shift system, shift intensity, and shift duration) is needed, as has been recommended in the report from an IARC Monographs Working Group (18). In addition, studies in model systems are warranted to elucidate the precise mechanisms by which rotating nightshift work affects hematopoietic cancer risk, especially with regard to the apparent heterogeneity across various histologic subtypes observed in our study.

In conclusion, this prospective cohort study suggests that among US female nurses, longer duration (≥15 years) of rotating nightshift work is associated with increased risk of overall and several types of hematopoietic cancer and that the association may be heterogeneous across histologic subtypes. Our conclusion should be interpreted with caution in light of mechanistic and epidemiological evidence and warrants further validation by large prospective investigations in diverse populations and with more detailed rotating nightshift work assessments.

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YZ, BMB, and ESS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ESS designed research; YZ conducted research and performed statistical analysis; YZ and BMB analyzed and interpreted the data; YZ wrote the article; BMB, KP, ESZ, ACE, and ESS performed critical revision of the manuscript for important intellectual content; all authors read and approved final content.

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