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The current knowledge of the association between night-shift work and hematological cancers is scarce. This large population-based epidemiological study brings new evidence about the effect of night-shift work on the risk of leukemia and lymphoma.

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Key terms: cancer; case–control study; circadian disruption; hematological cancer; Hodgkin lymphoma; JEM; job-exposure matrix; leukemia; multiple myeloma; night work; night worker; night-shift work; non-Hodgkin lymphoma; Nordic; shift work; shift worker

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Night-shift work and hematological cancers: a population based case–control study in three Nordic countries

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Objective The aim of this case–control study was to assess the effect of night-shift work on the risk of hematological cancers.

Methods The study included 39 371 leukemia, 56 713 non-Hodgkin lymphoma, 9322 Hodgkin lymphoma, and 26 188 multiple myeloma cases diagnosed between 1961 and 2005 in Finland, Sweden, and Iceland. Five controls for each case were selected from the Nordic Occupational Cancer Study (NOCCA) cohort, matched by year of birth, sex and country. Night-shift exposure was assessed by using the NOCCA job-exposure matrix (JEM). Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated from conditional logistic regression models.

Results Overall, night work was not associated with a risk of hematological cancers. We observed a small but non-significantly increased risk for leukemia (OR 1.07, 95% CI 0.99–1.16), especially for acute myeloid leukemia (OR 1.15, 95% CI 0.97–1.36) among workers exposed to a high level of cumulative night work exposure. Night work exposure was not associated with lymphatic cancers and multiple myeloma.

Conclusion This study did not support associations between night-shift work and hematological cancers.

Key terms circadian disruption; night work; night worker; shift work; shift worker; JEM; job-exposure matrix; leukemia; Hodgkin lymphoma; non-Hodgkin lymphoma; multiple myeloma.

In 2007, the International Agency for Research on Cancer (IARC) classified shift-work that involves circadian disruption as probably carcinogenic to humans (group 2A) based on sufficient evidence from animal studies and limited evidence from eight studies of human breast cancer (1). Since then, epidemiological studies have provided further evidence on an association between night-shift work and the risk of breast cancer (2) and other cancers including, leukemia and lymphomas (3–6).

A potential carcinogenic effect of night-shift work is believed to result mainly from the disruption of circadian rhythms, decreased secretion of the pineal gland hormone melatonin and sleep deprivation (7, 8). Melatonin may have a more direct effect on the development of cancer through its growth-inhibitory and oncostatic properties (9). It may inhibit cell proliferation and induce apoptosis in human acute leukemia and lymphoma cells (10). Serum melatonin levels were significantly lower in chronic lymphocytic leukemia (CLL) subjects compared to healthy control subjects (11). Furthermore, alteration in expression levels and polymorphisms in several clock genes have been associated with lymphoma and CLL eti-

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ology and prognosis (11, 12–14). This evidence suggests that the disruption of circadian rhythm and/or decreased levels of melatonin may be associated with an increased risk of hematological cancers.

We aimed to assess an association between night work and hematological cancers in a large study based on job history obtained from population censuses and data from three reliable Nordic cancer registries.

Methods

The source population was the Nordic Occupational Cancer Studies (NOCCA) cohort. The NOCCA cohort consists of 14.9 million persons from Finland, Iceland, Norway, Sweden and Denmark who participated in one or more population censuses in 1960, 1970, 1980/81, and/or 1990 (15). The current case–control study was nested within the Finnish, Swedish and Icelandic part of the NOCCA cohort. We did not have access to individual level data from Denmark and Norway.

Incident cases of leukemia, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL) and multiple myeloma (MM), diagnosed between 1961 and 2005 in Finland, Sweden, and Iceland and who did not have a previous history of cancer, were identified from the cancer registries of these countries. Out of the leukemia cases, categories of acute myeloid leukemia (AML) and CLL were separated for specific analyses. The Finnish Cancer Registry includes cancers diagnosed since 1953. It is based on reports from clinical and pathological departments, private clinics, general practitioners and death registry records. The Cancer Registry of Iceland started in 1955, and case notifications are based on reports from pathology laboratories complemented by information from cytology and hematology laboratories, hospitals, health centers and deaths certificates. In Sweden, the Cancer Registry was established in 1958, and case reporting is based on reports from hospitals, pathologists and private practitioners (16).

For each case, five controls who were alive and did not have a history of cancer prior to the date of diagnosis of the case ("index date"), were randomly selected from the NOCCA cohort. Controls were individually matched to cases by country, sex, and year of birth. Study participants were ≥20 years at index date, and they had at least one census record before that date.

The job history of the study participants was available from computerized census records from the 1960, 1970, 1980 and 1990 censuses in Sweden; the 1970, 1980 and 1990 censuses in Finland; and the 1981 census in Iceland. Census questionnaires were self-administered and included questions related to economic activity, occupation, and industry. They were completed by the heads of households for all members of households in Finland and Sweden. In Iceland, each member of household who was ≥17 years old personally completed a questionnaire.

Occupations in Finland and Sweden were coded according to the Nordic Occupational Classification (NYK) (17), a Nordic adaptation of the International Standard of Classification of Occupations (ISCO) from 1958 (18). In Iceland, a national adaptation of the ISCO-68 (19) was originally used for occupational coding. Icelandic codes were also converted to ISCO-58 to homogenize the occupational coding system in all Nordic countries.

Night-shift work exposure estimates for each study participant were assigned by using the NOCCA job-exposure matrix (NOCCA-JEM). The NOCCA-JEM was developed by a Nordic expert panel based on the concept of the Finnish job-exposure matrix (FINJEM) (20).

Assessment of night-shift work in the NOCCA-JEM was based on the Quality of Work Life Survey 1990 from Finland (21). The proportion of night-shift work in a given job was assessed based on the question "How is your working time arranged?". The three response options were: (i) regular daytime work; (ii) two-shift work, regular evening work, or weekend work or other irregular working hours that do not include night work; and (iii) regular or irregular three-shift work, or regular night-time work. We used the proportion (P) of respondents to the latter as an indicator of probability of night work in each job, eg, P=0.44 for midwives and 0.16 for airline pilots. We categorized the probability of night work into ≤0.10, 0.11–0.50, and >0.50 categories for the main analysis.

In this study, we had no direct information on the duration of work, including night-shift work. Therefore, employment was assumed to start at age 20 and end at either 65 years or the index date, whichever came first. If a person had different occupations in different censuses, we assumed that he/she changed an occupation midway between two consecutive censuses. The duration of night work was multiplied by the probability of the exposed person in a given job to calculate the cumulative night-shift work. Hence, for a midwife with 10 years of exposure, the estimated cumulative night work was 4.4 years (0.44×10 years). Cumulative night-shift work was categorized into unexposed, low, moderate, and high exposure levels, which refer to 0, 1–10, 11–20, and >20 years, respectively.

Selection of co-factors for the final main effect models was based on the "purposeful variable selection" method (22). In this method, co-factors are selected through a step-by-step procedure involving univariate and multivariate analyses, and only those factors that significantly contribute to the final main effect models are selected.

We estimated the cumulative exposure for co-factors by multiplying the duration of exposure by the probability of exposed persons and average annual exposure (L). The final main effect models included cumulative benzene, formaldehyde and ionizing radiation exposure because they significantly contributed to the fit of the models.

We estimated odds ratios (OR) and 95% confidence intervals (95% CI) by using conditional logistic regression models. We treated ordinal levels of categorical night work exposure as continuous variables to test for the significance of the dose–response relationship (P-trend). The significance of interaction between night work exposure and sex was assessed by using analysis of variance.

We conducted sensitivity analyses to assess the robustness of the main findings. We conducted analyses stratified by sex and age (≤50 and >50 years). We also used the duration of night work as an alternative exposure metric to the probability of night work and cumulative night work. Finally, we used 5, 10, and 15-year lag-times for cumulative night work, assuming the most recent exposures may not be related to the etiology of cancer.

All analyses were conducted by using R for Windows version 3.3.3 statistical software.

Results

The study included 9158 AML, 16269 CLL, 39371 all leukemias, 56713 NHL, 9322 HL, and 26188 MM cases (table 1). More than 65% of hematological cancer cases were from Sweden, while only less than 1% were from Iceland. Hematological cancer was more common among men than women, particularly for CLL (60.5% men versus 39.5% women) and HL (59.6% men versus 40.4% women). The highest median age was observed for CLL (71 years) and the lowest for HL (57 years).

Table 2 shows results for the probability of night work. We did not observe an association between the probability of night work and hematological cancers. There were no large sex-specific differences between OR estimates.

Table 3 shows the results for cumulative night work. A small non-significantly increased OR of all leukemias was observed for high level cumulative night-shift work exposure (OR 1.07, 95% CI 0.99–1.16). This risk seemed to be restricted to AML (OR 1.15, 95% CI 0.97–1.36). The AML risk was increased for men (OR 1.31, 95% CI 1.07–1.60) but not women (OR 0.90, 95% CI 0.66–1.21) for the high cumulative exposure category, and this difference was statistically significant (P-value for interaction 0.01). We did not observe an increased risk of lymphomas or MM. There was no dose–response pattern in the risk estimates (table 3). The results for cumulative night work from the main analysis did not materially change in lag-time analysis (supplementary tables A and B, www.sjweh.fi/show_abstract.php?abstract_id=3705).

Finally, we did not observe any increased risk of hematological cancers for the duration of night work exposure (supplementary table C www.sjweh.fi/show_abstract.php?abstract_id=3705).

Discussion

In this population based case–control study, we assessed the effect of night work exposure on the risk of leukemia, AML, CLL, NHL, HL, and MM. The results did not provide any clear evidence for associations between night work and hematological cancers. A sig-

Table 1. Selected demographic characteristics of incident cases of acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), all leukemia types combined (leukemia), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM) in the Nordic Occupational Cancer Study (NOCCA) cohort during 1961–2005.

Characteristics	AML (9158)	CLL (16 269)	Leukemia (39 371)	HL (9322)	NHL (56 713)	MM (26 188)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Country						
Finland	3099 (33.8)	4353 (26.8)	11 372 (28.9)	2817 (30.2)	18 367 (32.4)	7009 (26.8)
Iceland	114 (1.2)	118 (0.7)	362 (0.9)	95 (1.0)	455 (0.8)	212 (0.8)
Sweden	5945 (64.9)	11 798 (72.5)	27 637 (70.2)	6410 (68.8)	37 891 (66.8)	18 967 (72.4)
Sex						
Men	4646 (50.7)	9837 (60.5)	22 210 (56.4)	5558 (59.6)	29 990 (52.9)	13 776 (52.6)
Women	4512 (49.3)	6432 (39.5)	17 161 (43.6)	3764 (40.4)	26 723 (47.1)	12 412 (47.4)
Age at diagnosis						
≤40	481 (5.3)	77 (0.5)	1313 (3.3)	2277 (24.4)	2070 (3.6)	211 (0.8)
41–60	2221 (24.3)	2869 (17.6)	8748 (22.2)	3096 (33.2)	15 031 (26.5)	5431 (20.7)
61–80	5093 (55.6)	10 443 (64.2)	23 132 (58.8)	3496 (37.5)	31 902 (56.3)	16 813 (64.2)
≥80	1363 (14.9)	2880 (17.7)	6178 (15.7)	453 (4.9)	7710 (13.6)	3733 (14.3)
Mean (median)	66 (68)	70 (71)	67 (69)	55 (57)	66 (68)	69 (70)

Table 2. Odds ratios (OR) and 95% confidence intervals (95% CI) for acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), all leukemia types combined (leukemia), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM) in relation to probability of night work. Probability of night-work was equal to the proportion of exposed workers in a given job.

Probability of night-work	Male					Female					Total				
	Case	Control	OR [a]	95% CI	P-trend	Case	Control	OR [a]	95% CI	P-trend	Case	Control	OR [a]	95% CI	P-trend
AML[b]					0.02					<0.01					0.02
≤0.10	3495	17 385	1.00			3729	18 166	1.00			7224	35 551	1.00		
0.11–0.50	925	4725	0.97	0.90–1.05		513	2949	0.84	0.75–0.93		1438	7674	0.92	0.86–0.98	
>0.50	226	1120	1.00	0.87–1.17		270	1445	0.90	0.78–1.03		496	2565	0.95	0.86–1.05	
CLL[b]					0.27					0.75					0.28
≤0.10	7458	37 044	1.00			5369	26 768	1.00			12 827	63 812	1.00		
0.11–0.50	1895	9648	0.97	0.92–1.03		698	3575	0.97	0.89–1.06		2593	13 223	0.97	0.93–1.02	
>0.50	484	2493	0.96	0.87–1.06		365	1817	1.00	0.89–1.13		849	4310	0.98	0.91–1.06	
Leukemia[b]					0.74					0.17					0.25
≤0.10	16 859	84 049	1.00			14 277	70 695	1.00			31 136	154 744	1.00		
0.11–0.50	4249	21 602	0.98	0.94–1.02		1869	10 205	0.90	0.86–0.95		6118	31 807	0.95	0.92–0.98	
>0.50	1102	5399	1.02	0.95–1.09		1015	4905	1.02	0.95–1.10		2117	10 304	1.02	0.97–1.07	
HL[b]					0.11					<0.01					<0.01
≤0.10	4290	21 158	1.00			3223	15 688	1.00			7513	36 846	1.00		
0.11–0.50	1018	5319	0.94	0.87–1.02		409	2372	0.83	0.74–0.94		1427	7691	0.90	0.85–0.96	
>0.50	250	1313	0.94	0.82–1.08		132	760	0.84	0.69–1.01		382	2073	0.90	0.81–1.01	
NHL[b]					0.13					0.33					0.07
≤0.10	22 866	113 885	1.00			22 810	113 473	1.00			45 676	227 358	1.00		
0.11–0.50	5769	28 952	0.99	0.96–1.02		2930	15 397	0.95	0.91–0.99		8699	44 349	0.98	0.95–1.00	
>0.50	1355	7113	0.94	0.89–1.01		983	4745	1.03	0.96–1.11		2338	11 858	0.98	0.94–1.03	
MM[b]					0.43					0.16					0.15
≤0.10	10 689	53 219	1.00			10 863	54 043	1.00			21 552	107 262	1.00		
0.11–0.50	2468	12 537	0.98	0.93–1.03		1186	6121	0.96	0.90–1.03		3654	18 658	0.97	0.93–1.01	
>0.50	619	3124	0.99	0.90–1.08		363	1896	0.95	0.84–1.07		982	5020	0.97	0.91–1.04	

[a] Adjusted for cumulative benzene, formaldehyde and ionizing radiation. ≤0.10 category was used as a reference.
[b] P-values for sex-exposure interaction: AML 0.06; CLL 0.88; leukemia 0.05; HL 0.13; NHL 0.04; MM 0.82.

nificantly increased risk was observed for AML among men exposed to high cumulative night work, but not women. Although, this difference was statistically significant, there was no dose–response pattern in the risk estimates. Furthermore, we did not observe sex-specific differences for the probability of night work. This suggests that the observed sex-specific differences may be a chance finding.

Current evidence on the association between night-shift work and hematological cancers is scarce. A significantly increased risk of NHL was observed among men from Canada (OR 2.31, 95% CI 1.48–3.61), but without a dose–response pattern (5). In a study of Finnish men based on the same JEM as used in the present study, exposure to a high category of cumulative night work with a 10-year lag-time showed a risk ratio of 1.28 (95% CI 1.03–1.59) for NHL (3). In our study, the risk of NHL among men for the corresponding exposure was 1.06 (95% CI 0.96–1.17), and analysis restricted to Finnish men yielded an OR of 1.17 (95% 0.98–1.40). Likewise, as in Lahti et al (3), the risk of NHL among women was the highest for a moderate exposure level. Inconsistencies between the studies may be explained by differences in the study designs, analytic approaches and study populations.

An increased risk of leukemia (ratio of standardized incidence ratios [SIR_r] =3.21, 95% CI 1.20–10.05) but not NHL was observed in a study of German chemical workers (4). However, this result could be due to exposures to chemicals, eg, benzene, or by chance due to the small number of leukemia cases (16 observed cases in shift workers and 6 observed cases in day workers). We observed only a small non-significant increase of leukemia risk for moderate and high exposure levels, though without any dose–response pattern (table 1).

In a population based case–control study in Spain, working night-shifts was not associated with an increased risk of CLL (OR 1.06, 95% CI 0.78–1.45). However, a long duration of night shifts (>20 years) was statistically significantly positively associated with CLL (OR 1.77, 95% CI 1.14–2.74) (6). This is inconsistent with our results, where a long duration of night-shift work was not associated with a CLL risk (OR 0.99, 95% CI 0.94–1.04 for exposure duration >20 years) (supplementary table C). However, this inconsistency may occur because the duration of night work in our study was less precisely assessed.

Our case–control study covered virtually all incident cases of hematological cancers diagnosed between 1961 and 2005 in Finland, Iceland and Sweden. When data from cancer registries of Finland and Iceland were compared to hospital discharge reports in linkage studies,

Table 3. Odds ratios (OR) and 95% confidence intervals (95% CI) for acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), all leukemia types combined (leukemia), Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM) in relation to cumulative night work.

Cumulative night-work	Male					Female					Total				
	Case	Control	OR [a]	95% CI	P-trend	Case	Control	OR [a]	95% CI	P-trend	Case	Control	OR [a]	95% CI	P-trend
AML					0.31					0.03					0.53
Unexposed	3471	17 395	1.00			3724	18 225	1.00			7195	35 620	1.00		
Low	930	4672	0.99	0.92–1.08		571	3234	0.85	0.77–0.94		1501	7906	0.93	0.88–0.99	
Moderate	118	675	0.88	0.72–1.07		165	817	0.98	0.83–1.17		283	1492	0.94	0.82–1.07	
High	127	488	1.31	1.07–1.60		52	284	0.90	0.66–1.21		179	772	1.15	0.97–1.36	
CLL					0.29					0.98					0.38
Unexposed	7438	36 954	1.00			5361	26 767	1.00			12 799	63 721	1.00		
Low	1846	9382	0.98	0.92–1.03		743	3799	0.97	0.89–1.06		2589	13 181	0.98	0.93–1.02	
Moderate	291	1482	0.97	0.86–1.11		233	1116	1.05	0.90–1.21		524	2598	1.00	0.91–1.11	
High	262	1367	0.95	0.83–1.09		95	478	0.99	0.79–1.24		357	1845	0.96	0.86–1.08	
Leukemia					0.44					0.89					0.51
Unexposed	16 801	84 045	1.00			14 261	70 870	1.00			31 062	154 915	1.00		
Low	4144	20 982	0.99	0.95–1.03		2050	10 940	0.93	0.88–0.98		6194	31 922	0.97	0.94–0.99	
Moderate	670	3227	1.04	0.95–1.13		601	2870	1.04	0.95–1.14		1271	6097	1.04	0.98–1.11	
High	595	2796	1.06	0.97–1.17		249	1125	1.10	0.96–1.26		844	3921	1.07	0.99–1.16	
HL					0.90					0.18					0.43
Unexposed	4345	21 672	1.00			3268	16 160	1.00			7613	37 832	1.00		
Low	1012	5110	0.99	0.91–1.06		479	2586	0.91	0.82–1.02		1491	7696	0.96	0.90–1.02	
Moderate	113	591	0.96	0.78–1.17		13	48	1.42	0.76–2.64		126	639	0.98	0.81–1.19	
High	88	417	1.06	0.84–1.34		4	26	0.80	0.28–2.30		92	443	1.04	0.83–1.30	
NHL					0.92					0.26					0.62
Unexposed	22 901	114 286	1.00			22 856	113 900	1.00			45 757	228 186	1.00		
Low	5593	28 355	0.98	0.95–1.02		3696	18 874	0.97	0.94–1.01		9289	47 229	0.98	0.96–1.01	
Moderate	833	4096	1.02	0.94–1.10		126	587	1.08	0.89–1.31		959	4683	1.02	0.95–1.09	
High	663	3113	1.03	0.95–1.12		45	254	0.88	0.65–1.22		708	3467	1.02	0.94–1.11	
MM					0.65					0.43					0.45
Unexposed	10 694	53 344	1.00			10 865	54 190	1.00			21 559	107 534	1.00		
Low	2354	11 883	0.99	0.94–1.04		1469	7460	0.98	0.92–1.04		3823	19 343	0.98	0.95–1.02	
Moderate	387	1918	1.01	0.90–1.13		52	268	0.97	0.72–1.31		439	2186	1.00	0.90–1.11	
High	341	1735	0.98	0.87–1.10		26	142	0.92	0.60–1.39		367	1877	0.97	0.87–1.09	

[a] Odds ratios were adjusted for cumulative benzene, formaldehyde and ionizing radiation. Unexposed group was used as a reference category.
[b] P-values for sex-exposure interaction: AML 0.01; CLL 0.90; leukemia 0.27; HL 0.41; NHL 0.74; MM 0.98.

99% completeness of the registry data was observed in both countries. Studies linking death certificates with the Swedish cancer registry data also demonstrated reasonably high completeness and accuracy. However, 18% of leukemia cases were missing in Sweden because the cancer registry in this country did not use death certificates as an information source (16). This could bias our results only if the completeness of leukemia cases would differ in exposure groups, which is unlikely.

Another advantage was the accuracy of occupational classification. Previous validity studies demonstrated high accuracy of occupational classifications based on census records in the Nordic countries (23).

The main limitation of this study was the potential exposure misclassification due to the lack of detailed night-shift exposure information on study participants. The NOCCA-JEM can group occupations only to probability of exposure to night-shift work, and cannot account for exposure variations between and within jobs and over changing ages. Previous studies demonstrated that the frequency of night-shift work (particularly a high number of consecutive shifts) maybe an important predictor of its carcinogenic effect (24, 25). These studies also showed that night-shift exposure intensity is dependent on age, that is, it is more common among younger workers (26). Such exposure details are not captured by NOCCA-JEM. However, age-specific sensitivity analysis in this study did not yield differences with the main results. In addition, we expect that true frequency of night-shift work in the highest exposure category is markedly larger than in the unexposed category. Therefore, we may have observed an increased risk of hematological cancers at least in the high exposure category if one truly existed.

Limited job history data in this study could be another reason for exposure misclassification. Annual job histories of study participants were not available, and therefore, they were imputed from census records by assuming the person changed occupations midway between available censuses. This assumption was the weakest for persons with high occupational mobility, and for Iceland because annual job history for entire the working career was based on a single census from 1981. However, the Icelandic part of the data constituted only

<1% of the overall study population, and excluding it from the main analysis did not change the main findings. In addition, previous studies demonstrated low occupational mobility in the Nordic countries, particularly among men and in occupations requiring higher education (15, 23). Therefore, limited job history is less likely to strongly bias the main results in this study.

In conclusion, this large study based on JEM and nationwide cancer registry data did not support associations between night-shift work exposure and leukemia, AML, CLL, NHL, HL, and MM as seen in some previous studies. Further studies with more detailed night work assessment are needed to produce more precise risk estimates for hematological cancers.

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Ethical approval

As this study was register-based, neither ethical committee review nor informed consent from the study subjects was required.

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Conflict of interest

The authors declare no conflict of interest.

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