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Night work and breast cancer risk in a general population prospective cohort study in The Netherlands

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ABSTRACT

Experimental studies in animals indicate that disruption of the circadian rhythm is carcinogenic, and night work has been suggested to be a probable breast cancer cause in humans. Findings among humans, however are inconsistent, often gathered with retrospective study designs, and only based on specific populations, such as nurses. We used data on night work collected in the Dutch Labor Force Surveys of 1996 until 2009, and individually linked these with National registers on hospital admission. Among 285,723 women without breast cancer at baseline, 2,531 had a hospital admission for breast cancer during an average of 7 years of follow up in the registers. Occasional and regular night work were not associated with the risk of hospital admission for breast cancer (adjusted hazard ratios 1.04; 95 % confidence interval 0.85–1.27, and 0.87; 0.72–1.05, respectively). Working more hours per week, or more years in a job entailing night work did not show increased breast cancer risks. Hazard ratios neither differed between nurses and women with other occupations. Our results show no association of night work with incident breast cancer, and suggest that night work generally does not increase the risk of breast cancer among women in the Dutch working population.

INTRODUCTION

In 2007, the International Agency for Research on Cancer (IARC) classified shift work that involves circadian disruption as a probable human carcinogen [1]. The mechanism by which night work may favor the induction or promotion of malignant tumors of the breast is multifactorial. Endocrinological and immunological changes due to circadian disruption, sleep loss, and/or melatonin suppression resulting from light-at-night may lead to an increased risk of endocrine tumors [2]. As about one in five workers in the European Union works at least one night per month, although more common among men (23 %) than among women (14 %) [3], an association between night work and breast cancer would have a significant public health impact. The IARC classification was based on sufficient evidence from animal studies and limited evidence from epidemiological studies in humans [1]. Kolstad [4] compatibly reported that the number of positive studies in humans was small, and with risk estimates that were only modestly increased. After these reviews, several new epidemiological studies were performed, and recently four meta analyses were published [5–8]. These meta analyses agree that the results of the individual studies are heterogeneous, and three indicate that this heterogeneity is explained in part by study design [5–7]. They show significantly higher pooled risks of breast cancer for night work exposure in case–control studies, but not in cohort studies. Recall bias is not expected in the case–control studies that used existing occupational records, but as suggested by Bonde et al. [9], it may have played a role in some of the case–control studies. The meta analyses differ, however, with respect to the approaches taken, and so do their main conclusions. Jia et al. [6] indicated that night work is associated with an increased risk of breast cancer, Kamdar et al. [7] demonstrated weak evidence to support the association, Iljaz et al. [5] indicated insufficient evidence for a link between night work and breast cancer, and Wang et al. [8] concluded that a positive dose–response relationship is likely. These inconsistent conclusions demonstrate that the scientific evidence for this relation is insufficient. According to the authors of the meta analyses, additional large-scale prospective investigations are needed, including diverse populations. The objective of the present large prospective study is therefore to add to the scientific evidence about the possible association between night work and breast cancer by investigating the general working population.

METHODS

Study sample and data collection

The study sample consisted of participants of the 14 Dutch Labor Force Surveys that were performed in the period 1996 until 2009. These Labor Force Surveys aimed to provide information on relations between people and the labor market. Each year, Statistics Netherlands randomly sampled persons aged 15 years and older from the national household registers, except for persons living in institutions or collective households. The annual samples consisted of approximately 118,000 individuals per year, resulting in a total sample of 828,121 men and 829,039 women. Record linkage of these Labor Force Survey data with national registers on hospital admission was carried out by Statistics Netherlands. An encrypted copy of the national identification number for Dutch residents was used to link the micro-data of each Labor Force Survey participant to the micro-data of individuals registered to have had a hospital admission. To avoid double counting, only the first survey data

were used from women who happened to participate in more than one Labor Force Survey.

The outcome variable of the present study was hospital admission due to breast cancer. The National Medical Registration (NMR) of the years 1996 through 2009 were used to identify women admitted to hospital due to breast cancer. In this NMR, hospital admissions for (part of) 1 day or more are registered, together with data on diagnosis and treatment. Almost all general and university hospitals, as well as several specialized hospitals in The Netherlands provide data to the NMR, which resulted in more than 95 % coverage in most of the years that were used for this study. ICD-9-CM primary diagnosis code 174 was used to identify women with breast cancer (174.0–174.6, 174.8, and 174.9). If a woman had had several hospital admissions due to breast cancer, the date of her first hospital admission was selected. Incident cases were defined as those hospital admissions due to breast cancer that occurred after enrolment in the study, i.e. after assessment of night work in the Labor Force Survey. Women who were hospitalized with breast cancer in 1996 or later, but before or in the same month as their enrolment in the study were excluded from all analyses, to reduce the risk of reversed causality and recall bias, as breast cancer diagnosis may affect night work engagement and recall.

All independent variables were derived from the Labor Force Survey. Statistics Netherlands collected these data by means of computer assisted personal interviewing. Prior to their inclusion, persons were informed about the Labor Force Survey aims and design, and that their data—for research purposes—might be coupled to other national data files. Participants with a paid job for 12 h per week or more were asked about working at night and about several other aspects of their current job. No detailed information on the working situation was asked from participants working <12 h per week.

Current exposure to night work was asked with the question: ‘Do you work at nights, meaning between midnight and 6 am?’. The answering options were ‘No’, ‘Yes, sometimes’, and ‘Yes, regularly’. The occupation of the participant at the time of study entry was classified according to the International Standard Classification of Occupations (ISCO) version 1988, and was subsequently categorized into six groups: managers and officials, professionals, technicians, clerks, service and sales workers, and other blue-collar workers. Contractual working hours were categorized into less than 24 h per week, 24–35 h per week, and 36 h per week or more. Job tenure was assessed and categorized into working 0–3, 4–9, 10–19, and 20 years or more on the current job.

Origin, based on the country of birth, was categorized into Dutch, Western immigrants, and non-Western immigrants. A question was also posed on whether children were living in the household or not. Educational level was categorized into high (International Standard Classification of Education version 1997 (ISCED level ≥ 5), intermediate (ISCED level 4), or low (ISCED level ≤ 3).

Data analyses

The Labor Force Survey data of each participant were individually linked to their hospital admission registrations, if present. Only women aged 15–64 years at the time of participating in the Labor Force Survey, and who had non-missing data on night work were selected (Fig. 1). χ^2 tests were used to analyze the differences between the night work categories in the proportion of women within a category of the demographic and job related characteristics. Cox proportional hazards regression

was used to evaluate the association of night work with hospital admission due to breast cancer. Analyses were performed both without and with adjustment for age, origin, children in the household, education, occupational group, contractual working hours, and job tenure. Women with missing data on one of these variables were excluded from all analyses to improve comparability of findings.

[FIGURE 1]

Separate analyses were also performed without the women who were admitted to hospital for breast cancer within 24 months after the assessment of night work. These analyses were performed to eliminate the bias that could occur if early symptoms of breast cancer may result in discontinuing night work. In addition, analyses were stratified by job tenure and contractual working hours to investigate if the relation between night work and breast cancer is stronger among women with potentially longer exposure duration or potentially higher exposure frequency. Since several previous studies included only nurses, we also performed analyses that were stratified by occupation (nurses or other).

RESULTS

In total, 285,723 women had complete data and were included in the analyses. Average duration of follow up was 6.9 years in the hospital admission registration (range 0.0–13.9 years), resulting in 2.0 million person-years of follow up. Table 1 shows that 10.4 % of the women reported occasional or regular night work at study entry. Breast cancer hospitalization was registered for 2,531 women (0.89 %). Baseline information on demographic, and job related characteristics of the study sample is presented in Table 2, separately for each category of night work exposure.

[TABLE 1][TABLE 2]

Table 3 shows the results of the bivariate and multivariate Cox regression analyses. Women with regular night work had a significantly lower risk of hospital admission for breast cancer in bivariate analyses compared to women who reported no night work [Hazard Ratio (HR) 0.79; 95 % CI 0.66–0.95]. Adjustment for age and the other factors, however, resulted in a somewhat higher and non-significant HR (0.87; 95 % CI 0.72–1.05). Occasional night work was not related to hospital admission for breast cancer.

[TABLE 3]

Age was a strong predictor of hospital admission for breast cancer in bivariate as well as multivariate analyses. Risks were 13-fold higher in women aged 51–64 years than in women aged 15–30 years. Origin, educational level, occupation, job tenure, and contractual working hours were significantly related to the risk of breast cancer in bivariate analyses, whereas the presence of children living in the household was not. Adjustment for covariates attenuated the Hazard Ratios, although also in multivariate analyses, women with a non-Western origin had a significantly reduced risk of hospital admission (HR 0.60; CI 0.46–0.79). Five hundred and eighty women had a hospital admission for breast cancer within 24 months after responding to the Labor Force Survey. Excluding these cases from the analyses, and therewith counteracting the effect that early symptoms of the disease

may have led to discontinuing night work, hardly affected the results. The multivariate HR for occasional night work and hospital admission changed from 1.04 to 1.03 (95 % CI 0.82–1.29), and the multivariate HR for regular night work changed from 0.87 to 0.86 (95 % CI 0.69–1.07).

In order to investigate whether the relation between night work and breast cancer risk is stronger among women with potentially longer exposure duration or potentially higher exposure frequency, multivariate analyses stratified by job tenure and contractual working hours were performed. Tables 4 and 5 show no significant associations between night work and hospital admission due to breast cancer within job tenure categories nor within contractual working hours categories. The interaction between job tenure as a continuous scale and night work was also not significant for both occasional and regular night work. Similarly, the interaction between contractual working hours as a continuous scale and night work was also not significant for both occasional night work and regular night work.

[table 4][table 5]Nurses were three times more likely to engage in occasional night work than non-nurses, and nine times more likely to engage in regular night work. Among nurses, 26 out of 2,057 with occasional night work developed breast cancer, 51 out of 8,029 nurses with regular night work developed breast cancer, and 105 out of 11,651 nurses who reported no night work developed breast cancer, resulting in no significant association between night work and the risk of hospital admission for breast cancer. Differences in Hazard Ratios between nurses and non-nurses were not significant, so no interaction was found between night work and being occupied as a nurse on the risk of hospital admission for breast cancer (Table 6).

[TABLE 6]

DISCUSSION

This large prospective study showed no association between occasional or regular night work and hospital admission for breast cancer among women in the general Dutch working population. In addition, job tenure and contractual work hours, as indicators of potentially longer exposure duration and potentially higher exposure frequency of night work, were not associated with higher breast cancer risks. Comparison with the four other prospective studies published to date [10–13] shows that our findings differ from the relatively small study on women sampled from several branches [10], and the two cohort studies that included only nurses [12, 13]. In these two studies on nurses, increased risks of breast cancer were found for those who worked at nights for more than 20 or 30 years [12, 13]. Our findings, however, are in line with the single other large study in the general population [11]. In that Asian cohort no overall nor exposure response association was found, which resulted in discussions about east–west differences in response to being exposed to light at night [14]. The null association of the current cohort study, conducted in a Western country, does not support such a hypothesis on east–west differences. We investigated whether night work was associated with a higher risk of breast cancer among nurses, but did not find a significantly increased risk. The differences between the findings from these two studies and our findings may be related to the duration of exposure to night work. Due to the small numbers of cases in our study, however, we were not able to investigate the risk in nurses with a longer tenure—we only investigated the risk in nurses and non-nurses associated with any exposure.

Recent case–control studies indicated that the intensity and disruptiveness of night shifts might play an important role in the relation between night work and breast cancer [15–17]. Lie et al. showed that breast cancer risk might be related to the number of consecutive night shifts. They found no increased risk for long-term exposure to ≥ 3 night shifts per month, but significantly elevated breast cancer risk for working in jobs including ≥ 6 consecutive night shifts [16]. In the present study, we had no data on the number of consecutive shifts. For two reasons the prevalence of working ≥ 6 consecutive night shifts may be smaller in our study than in most other studies published in this field, possibly explaining the null findings. First, the assessment of night work in our study was measured from 1996 to 2009, and referred to the current exposure, whereas the assessment of night work in most other studies was performed before 1995, and referred to life time exposure. As the number of nights worked in succession has generally decreased over the past decades, and there has been a change to faster and also to forward rotating shift schedules [2, 18, 19], we expect less circadian disruption, and less sleep deprivation among exposed women in our study. Second, the proportion of women working on part time contracts is high in The Netherlands compared to other countries. Three out of four women employed in The Netherlands have a part time job, which is more than two times the European average [20]. This makes it less likely for women included in our study to have worked many consecutive nights. Our analyses stratified by contractual working hours, however, gave no indication of an increased risk of breast cancer associated with night work in women who work more hours per week than average. To our knowledge, this is the largest prospective study on night work and incident breast cancer performed to date. The two million person years at risk resulted in a sufficient number of hospital admissions for breast cancer to obtain small confidence intervals. This large number of cases also enabled, in an additional analysis, the exclusion of women with a hospital admission that occurred within 2 years following the assessment of night work. This exclusion minimized the potential risk of bias that may occur if early symptoms of breast cancer reduce night work participation. Exclusion of these cases, however, did not increase the Hazard Ratios. The large data set and the large number of incident hospital admissions also enabled the investigation of interactions with potential exposure duration and potential exposure frequency. We found that the association between night work and breast cancer was not increased in women working more hours per week, nor in women who were working for more years on the same job. Therefore, no indication of a potential exposure response association was found. It should be noted, however, that combining current night work and job tenure to obtain a proxy for life time exposure to night work may result in exposure misclassification.

The large general sample of women, representative for the Dutch working population, coupled to the national hospital admission registration, strengthens the generalizability of our findings. The prospective design by linkage of the Labor Force Survey data with the high quality national registration of hospital admissions resulted in reliable outcome data, and diminished the risk of recall bias, that may have played a role in some of the case–control studies [9]. A disadvantage of large prospective studies, however, is generally the absence of precise measurements, and of indicators that have been suggested to be relevant more recently. As such, in our study only a single measure of current exposure to night work was available. It has been indicated, however, that the shift system, the number of years on a particular

non-day shift schedule, and the shift intensity may be key to describe relevant exposure [21]. Furthermore, the covariates that were included in our multivariate models may not have adjusted for all confounding. It has been shown that women who work at night are substantially different from women who work during the day, and many of these differences have previously been suggested to put night workers at increased risk of cancer [22]. In particular in our study, the presence of children living in the household was a suboptimal proxy for parity, as children living in the household is not equivalent to biologically having children. Furthermore, the presence of children in the household usually decreases among women above the age of 45 years, as their children start living on their own. As breast cancer risk increases with age, this may explain why our breast cancer relative risk estimates for children living in the household were not significant, and not in line with previous research [23]. Overall, however, other prospective studies suggest that the risk estimates of night work may hardly be affected by additional adjustment for factors that are considered relevant, such as a family history of breast cancer, age at menarche, number of pregnancies, age at first birth, menopausal status, hormone replacement therapy, and lifestyle habits [11–13].

In conclusion, this large prospective study found no significant relation of night work with incident hospitalization for breast cancer among women in the general Dutch working population. Potentially longer exposure duration and potentially higher exposure frequency to night shift work also did not result in higher relative risks. This study adds to the current knowledge base on night work and breast cancer, and indicates that there is not a strong relation between night work and breast cancer in the examined population.

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Conflict of interest

The authors declare that they have no conflict of interest.

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TABLES

Table 1 Incidence of breast cancer hospitalization during study follow up for women with, and those without night work at baseline (N = 285,723)

	Night work			
	No (89.6 %)	Occasional (3.7 %)	Regular (6.7 %)	Total
Breast cancer hospital admission				
No	253,588	10,561	19,043	283,192
Yes	2,312	102	117	2,531
Incidence	0.90 %	0.96 %	0.61 %	0.89 %

Table 2 Baseline characteristics of the study sample by night work exposure level

	Night work			
	No	Occasional	Regular	Total
	255,900 (89.6 %)	10,663 (3.7 %)	19,160 (6.7 %)	285,723 (100 %)
Age				
15–30	28.2 % ▼	28.3 %	33.1 % ▲	28.5 %
31–40	29.2 % ▼	30.5 % ▲	29.9 %	29.3 %
41–50	27.1 % ▲	27.4 %	26.1 % ▼	27.0 %
51–64	15.5 % ▲	13.8 % ▼	10.9 % ▼	15.1 %
Origin				
Dutch	86.8 % ▼	87.2 %	88.4 % ▲	87.0 %
Western	7.8 % ▲	8.1 %	6.8 % ▼	7.8 %
Non-Western	5.3 % ▲	4.7 % ▼	4.8 % ▼	5.3 %
Children in household				
No	41.7 %	41.3 %	42.5 % ▲	41.7 %
Yes	58.3 %	58.7 %	57.5 % ▼	58.3 %
Education				
Low	25.6 % ▲	16.4 % ▼	14.9 % ▼	24.5 %
Intermediate	40.1 % ▼	44.3 % ▲	51.6 % ▲	41.1 %
High	34.3 % ▼	39.4 % ▲	33.5 % ▼	34.4 %
Occupation				
Managers and officials	7.4 % ▼	14.6 % ▲	6.1 % ▼	7.5 %
Professionals	20.1 % ▲	21.9 % ▲	18.1 % ▼	20.0 %
Technicians	21.0 % ▼	29.5 % ▲	43.0 % ▲	22.8 %
Clerks	21.7 % ▲	4.5 % ▼	4.5 % ▼	19.9 %

	Night work			
	No	Occasional	Regular	Total
Service and sales workers	18.3 %▼	21.0 %▲	21.1 %▲	18.6 %
Other blue collar	11.5 %▲	8.5 %▼	7.3 %▼	11.1 %
Job tenure (years)				
0–3	39.3 %▲	35.9 %▼	36.2 %▼	39.0 %
4–9	29.4 %▼	30.1 %	31.2 %▲	29.5 %
10–19	20.9 %▼	21.9 %▲	22.1 %▲	21.0 %
20+	10.4 %▼	12.2 %▲	10.5 %	10.5 %
Contractual working hours				
12–23 h per week	35.2 %▲	28.0 %▼	28.8 %▼	34.5 %
24–35 h per week	33.8 %▼	33.4 %	38.0 %▲	34.1 %
36+ h per week	31.0 %▼	38.6 %▲	33.3 %▲	31.4 %

▼▲: $p < 5\%$, for differences between proportions in different categories of night work

Table 3 Crude and multivariate adjusted associations between baseline characteristics and breast cancer hospital admission (N = 285,723)

	Hospital admission (2,531 cases)			
	Unadjusted		Adjusted^a	
	HR	95 % CI	HR	95 % CI
Night work				
No	Ref.		Ref.	
Occasional	1.04	0.86–1.27	1.04	0.85–1.27
Regular	0.79	0.66–0.95	0.87	0.72–1.05
Age				
15–30	Ref.		Ref.	
31–40	4.64	3.85–5.59	4.52	3.73–5.48
41–50	9.86	8.25–11.79	9.57	7.94–11.53
51–64	13.47	11.21–16.19	12.76	10.48–15.54
Origin				
Dutch	Ref.		Ref.	
Western	1.01	0.87–1.17	0.92	0.79–1.06
Non-Western	0.47	0.36–0.61	0.60	0.46–0.79
Children in household				
No	Ref.		Ref.	
Yes	1.00	0.93–1.08	0.99	0.91–1.09

	Hospital admission (2,531 cases)			
	Unadjusted		Adjusted^a	
	HR	95 % CI	HR	95 % CI
Education				
Low	Ref.		Ref.	
Intermediate	0.87	0.79–0.96	1.08	0.97–1.20
High	1.05	0.95–1.15	1.10	0.97–1.25
Occupation				
Managers and officials	Ref.		Ref.	
Professionals	0.82	0.70–0.95	0.91	0.77–1.07
Technicians	0.77	0.66–0.89	1.00	0.86–1.17
Clerks	0.74	0.64–0.86	0.99	0.85–1.16
Service and sales workers	0.58	0.50–0.68	0.85	0.72–1.01
Other blue collar	0.70	0.59–0.83	0.90	0.76–1.08
Job tenure (years)				
0–3	Ref.		Ref.	
4–9	1.43	1.29–1.59	1.00	0.90–1.12
10–19	2.07	1.87–2.30	1.07	0.96–1.19
20+	3.00	2.66–3.38	1.11	0.98–1.26
Contractual working hours				
12–23 h per week	Ref.		Ref.	
24–35 h per week	0.95	0.87–1.04	1.05	0.96–1.15
36+ h per week	0.73	0.66–0.81	1.05	0.94–1.17

HR hazard ratio, CI confidence interval, Ref. reference group

^aAdjusted for all factors included in this Table

Table 4 Multivariate adjusted associations between night work and incident hospital admission for breast cancer by job tenure (N = 285,723)

	Proportion at baseline (%)	0–3 years (N = 111,424) (684 cases)		4–9 years (N = 84,431) (684 cases)		10–19 years (N = 59,998) (708 cases)		20+ years (N = 29,870) (455 cases)		P value of trend ^a
		HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	
Night work										
No	89.6	Ref.		Ref.		Ref.		Ref.		
Occasional	3.7	1.05	0.70–1.57	1.05	0.71–1.55	1.21	0.85–1.73	0.78	0.48–1.28	0.66
Regular	6.7	0.70	0.47–1.04	0.94	0.66–1.34	0.91	0.65–1.28	0.95	0.62–1.45	0.26

Adjusted for all factors included in Table 3, except for job tenure

HR hazard ratio, CI confidence interval, Ref. reference group

^aInteraction between job tenure as a continuous scale and night work

Table 5 Multivariate adjusted associations between night work and incident hospital admission for breast cancer by contractual working hours (N = 285,723)

	Proportion at baseline (%)	12–23 h/week (N = 98,570) (985 cases)		24–35 h/week (N = 97,445) (853 cases)		36+ h/week (N = 89,708) (693 cases)		P value of trend ^a
		HR	95 % CI	HR	95 % CI	HR	95 % CI	
Night work								
No	89.6	Ref.		Ref.		Ref.		
Occasional	3.7	1.32	0.95–1.85	0.88	0.61–1.26	1.00	0.71–1.41	0.27
Regular	6.7	1.10	0.81–1.49	0.77	0.56–1.06	0.79	0.54–1.14	0.20

Adjusted for all factors included in Table 3, except for contractual working hours

HR hazard ratio, CI confidence interval, Ref. reference group

^aInteraction between contractual working hours as a continuous scale and night work