ORIGINAL ARTICLE

Nested case–control study of night shift work and breast cancer risk among women in the Danish military

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ABSTRACT

Objectives Growing but limited evidence suggests that night shift work is associated with breast cancer. The authors conducted a nationwide case–control study nested within a cohort of 18 551 female military employees born in 1929–1968 to investigate the risk for breast cancer after night shift work and to explore the role of leisure time sun exposure and diurnal preference.

Methods The authors documented 218 cases of breast cancer (1990–2003) and selected 899 age-matched controls from the cohort by incidence density sampling. Information on shift work, sun exposure habits, diurnal preference and other potential confounders was obtained from a structured questionnaire. ORs were estimated by multivariate conditional logistic regression.

Results Overall, the authors observed an adjusted OR of 1.4 (95% CI 0.9 to 2.1) among women with ever compared with never night shifts. The RR for breast cancer tended to increase with increasing number of years of night shift work (p=0.03) and with cumulative number of shifts (p=0.02),with a neutral risk for fewer than three night shifts per week. The OR for the group with the highest tertile of cumulative exposure was 2.3 (95% CI 1.2 to 4.6). The most pronounced effect of night shift work on breast cancer risk was observed in women with morning chronotype preference and intense night shifts (OR=3.9, 95% CI 1.6 to 9.5). Night shift workers tended to sunbathe more frequently than day workers.

Conclusions The results indicate that frequent night shift work increases the risk for breast cancer and suggest a higher risk with longer duration of intense night shifts. Women with morning preference who worked on night shifts tended to have a higher risk than those with evening preference.

What this paper adds

- A working group convened by the International Agency for Research on Cancer in October 2007 classified shift work that involves circadian disruption as probably carcinogenic to humans (group 2A) and called for new studies.
- Previous studies were limited in particular by focusing primarily on one profession (nursing), lacking information about potential confounders or effect modifiers, including sun exposure (vitamin D), and diurnal preference (morning or evening).
- Our results show a higher risk for breast cancer associated with longer duration of intense night shifts and a neutral risk for only one or two night shifts per week. Women on night shifts tended to sunbathe more frequently than day workers. Therefore, our results do not support that less sun exposure in night workers may explain the observed increased breast cancer risk. Women with morning preference tended in general to have a lower risk for breast risk than those with evening preference, whereas women with morning preference who worked on night shifts tended to have a higher risk than those with evening preference. These results warrant further study.

INTRODUCTION

The invention of electric light about 130 years ago made it possible to extend day activities and to work at night. About 10%–20% of the workforce in Europe and the USA now have night work schedules, and there seems to be increasing night work worldwide.[1 2] Night work can disrupt circadian rhythms, suppress production of the pineal hormone melatonin and result in sleep deprivation, all of which affect hundreds of metabolic and physiological processes, including hormone production, cell cycling and apoptosis, which in turn may increase the initiation, progression and growth of human tumours, including breast cancer.[3 4] During the past decade, evidence has emerged that night shift work may increase the risk for breast cancer, and there is increasing insight into the potential biological mechanisms.[4 5] An expert group convened by the International Agency for Research on Cancer concluded that shift work that involves circadian disruption is probably carcinogenic to humans, on the basis of limited evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of exposure to light during the daily dark period.[6 7]

So far, the most consistent associations between shift work and breast cancer have been found for a single profession, nursing.[8–12] Nurses, however, may have common risk factors for breast cancer (eg, exposure to radiation, stress or chemicals); investigations of other professions are warranted. Furthermore, it has been suggested that some of the increased risk for breast cancer among night workers might be due to less exposure of the skin to the sun,[5 13] resulting in inadequate vitamin D, which in some studies has been associated with an

increased risk for breast cancer.[14] Finally, it has been suggested that shift work may affect chronotypes differently (ie, in people who prefer the morning and those who prefer the evening) and that the increased risk of night workers for breast cancer may be due to self-selection of people with evening preference, who might be genetically more susceptible to breast cancer than those with a morning preference.[15 16]

As part of a larger study of occupational and non-occupational exposures and risks for cancer in the Danish military, we investigated night shift work and female breast cancer risk, including, as a new approach, the potential effects of sun exposure habits and diurnal preference.

MATERIALS AND METHODS

Study population

A cohort of all military employees in Denmark was established from the files of the nationwide pension fund, adherence to which has been compulsory for all wage earners aged 16–66 years since 1964.[17] The pension fund retains information on all individuals employed in all companies in Denmark, including start and end dates, company name and an eight-digit company registration number. Each resident of Denmark is assigned a unique10-digit personal identification number by the Central Person Register, which has been in use since 1968[18] and includes date and place of birth, current and past addresses, civil status and date of death, immigration or disappearance. Using the Danish military's company registration number, we identified all women born between 1929 and 1968 who had ever been employed in any division of the Danish military between 1 April 1964 and 31 December 1999, who were alive on 1 January 1990 (in order to secure a relatively high proportion of cancer survivors) and were 75 years old or younger at the time of completing the questionnaire (in order to reduce the likelihood of age-related memory problems). In total, 18 551 women fulfilled these criteria.

All 329 cases of primary breast cancer (ICD-7 170) in 1990–2003 were documented from the files of the nationwide Danish Cancer Registry by use of the Central Person Registry number.[19] The Cancer Registry, which was initiated in 1942, is regarded as virtually complete and contains diagnoses classified by an extended Danish version of the International Classification of Diseases, revision 7, and date of diagnosis.[19] In total, 218 women who had had breast cancer (66%) were still alive and living in Denmark at the time of interview (between March 2005 and December 2006). We received mandatory permission from the treating hospitals to contact 210 (96%) of these live cases. We chose 899 live potential female controls at random from the cohort by incidence density sampling and approximately frequency matched (1:4) them with cases on the distribution of 1-year groups of birth years. The current address of each potential participant was retrieved from the Central Person Register, which is updated daily.[18]

Exposure assessment

A 28-page postal structured questionnaire elicited information on all jobs held for at least 1 year and on specific exposures in the military (eg, firing ammunition indoors and outdoors, use of chemical warfare agents), other occupational exposures in and outside the military (eg, night shift work, asbestos), lifestyle factors (eg, tobacco smoking, alcohol drinking, sun exposure habits, reproductive history), educational level (years at school and highest job level) and diurnal preference (morning, evening, neither).If a woman did not reply, reported only one job or filled in the questionnaire only partly, she was telephoned up to 10 times (morning, afternoon, evening and weekend) for about 3 weeks after the invitation letter and encouraged to fill in the questionnaire or to participate in a telephone interview based on the same questionnaire. The trained telephone interviewers were blinded to case or control status. For the women who did not answer the questionnaire and could not be contacted by telephone, the postal address and vital status were retrieved from the Central Person Register and a repeat postal invitation was sent. Overall, the questionnaire was completed in 141 (67%) cases and by 551 (61%) controls.

Night shift work was defined as working for at least 1 year during hours beginning after 17:00 and ending before 9:00, not including overtime. This includes exposure to artificial light after midnight, when melatonin normally peaks in healthy people.[20] In this definition, permanent and rotating night shifts were assessed as one entity. We recorded first calendar year, total duration (1–2, 3–5, 6–9, 10–15, 15–19, 20–29 and ≥30 years) and the average number (continuous) of such shifts per week in periods with night work. We did not separate out night shift work with the military from that outside. Cumulative exposure (ie, lifetime number of night shifts) was calculated as the average number of night shifts per week multiplied by the midpoint of the upper and lower boundaries of the duration of shift work categorised in the questionnaire. Tertiles for exposed controls were used as cut-off points in the analyses.

Occupational exposure to radar equipment in the military, including potential exposure to electromagnetic fields (EMF), which have been the subject of intense debate in the media as a cause of cancer, was used as an indicator of recall bias. A woman was classified as exposed to EMF if she gave a positive answer to at least one of two questions: "Have you operated radar equipment?" and "Have you used surveillance equipment in operating theatres?"

Statistical analysis

Associations between night shift work and risk for breast cancer were analysed in multivariate logistic regression models conditional on age in 5-year groups at the date of completion of the questionnaire (<50, 50–54, 55–59, 60–64, 65–69 and 70–75 years). The reference group was women with <1 year of night work. RR was estimated as ORs and their 95% CIs by use of the statistical package STATA, revision 11.

Potential confounders were evaluated in univariate analyses based on Student t test for continuous variables and χ^2test for categorical variables: length of education (7, 8–9, 10, >10 years), body mass index (<25, ≥25 kg/m^2), alcohol drinking (cumulative, ever, never), menopausal status (pre, post), use of hormone replacement therapy (never, 1–5, ≥6 years), use of contraceptives (never, 1–9, ≥10 years), occupational exposure to radar or EMF (yes/no), occupational physical activity (no, light, heavy), satisfactory influence on job (yes/no), too high a workload and work pace (yes/no), age at menarche (<11, 11–14, ≥14 years), age at menopause (<45, 45–49, 50–54, ≥55 years), number of childbirths (0, 1–2, ≥3), tobacco smoking (0, 1–10, ≥10 years, never, current, previous, continuous) and occasional sun exposure (never/rare, at least once weekly/always). In the final models, we included, in addition to night shift work variables, the following variables with univariate p values ≤0.15: hormone replacement therapy (0.003), number of childbirths (0.15), age at menarche (0.02), length of education (0.01), occasional sun-bathing (0.01) and tobacco smoking status (0.15). Inclusion of the other variables did not change the risk estimates substantially (table 1).

χ^2test was used to evaluate differences in the (categorical) exposures of night shift workers and non-night shift workers, with a 5% level of significance (table 1).

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Table 1 Characteristics of study participants by cases and controls and lifetime night shift work status, including univariate ORs

	Cases					Controls					Univariate	
	No night shift work (N=89)		Night shift work (N=43)			No night shift work (N=361)		Night shift work (N=144)				
Characteristic	**No.**	**%**	**No.**	**%**	**p Value***	**No.**	**%**	**No.**	**%**	**p Value***	**OR**	**p Value†**
Education (years)												
7	15	17	7	16	0.96	63	18	35	24	0.24	1	0.01
8–9	16	18	9	21		73	20	21	15		1.2	
10	29	33	13	30		124	35	49	34		1.4	
>10	26	29	14	33		97	27	38	26		2.0	
Body mass index (kg/m^2)												
<25	51	58	20	49	0.38	197	55	77	53	0.89	1	0.85
≥25	37	42	21	51		144	40	58	40		1.0	
Age at menarche (years)												
<11	15	17	3	7	0.14	34	10	15	10	0.63	1	0.02
11–14	44	49	38	88		298	82	114	79		0.6	
≥14	9	10	2	5		29	8	15	10		0.6	
Age at menopause (years)												
<45	4	4	3	7	0.51	30	8	16	6	0.62	1	0.16
45–50	21	21	8	19		73	20	28	19		1.7	
50–55	22	22	6	14		54	15	21	15		2.3	
≥55	2	2	2	5		12	3	2	2		2.0	
Childbirths												
None	13	15	9	21	0.58	36	10	16	11	0.90	1	0.15
1–2 children	53	60	22	51		227	63	91	63		0.6	
≥3 children	23	26	12	28		93	26	37	26		0.6	
Oral contraceptive use (years)												
Never	35	39	16	37	0.74	133	37	44	31	0.13	1	0.82
1–10	30	34	18	42		132	37	67	47		0.9	
≥10	21	24	9	21		77	21	27	19		1.1	
Hormone replacement therapy use (years)												
Never	71	79	32	74	0.46	324	86	124	86	0.47	1	0.003
1–5 years	8	9	7	16		24	8	12	8		1.5	
≥6 years	10	11	4	9		13	4	8	6		2.3	
Satisfactory job influence												
No	15	17	10	23	0.44	59	16	24	17	0.99	1	0.52
Yes	70	79	32	74		292	81	118	82		0.9	
High workload and work pace												
No	55	62	15	35	0.02	203	42	61	42	0.03	1	0.35
Yes	30	34	25	58		150	59	82	57		1.2	
Physical activity at work												
Light	59	66	28	65	0.51	257	71	87	60	0.03	1	0.38
Heavy	19	19	12	28		96	27	52	36		0.8	
Alcohol consumption (≥1 unit/week; 1 unit=12 g alcohol)												
Never	7	8	4	9	0.78	42	12	12	8	0.78	1	0.35
Ever	82	92	39	91		319	88	132	91		1.2	
Tobacco smoking												
Never	24	27	12	28	0.83	132	37	46	32	0.64	1	0.15
Former	29	33	12	28		97	27	42	29		1.3	
Current	36	36	19	44		129	36	54	38		1.4	
1–10 years	26	7	12	8	0.56	26	7	12	8	0.89	1.5	0.25
>10 years	190	53	82	57		190	53	82	57		1.4	
Occupational exposure to radar or electromagnetic fields (EMF)												
Never	818	99	31	7	<0.001	351	97	133	92	<0.01	1	0.39
Ever	1	1	11	26		10	3	11	8		1.2	
Occasional sunbathing frequency												
Never/rare	60	67	27	63	0.54	207	57	61	42	0.003	1	0.01
Always/at least once weekly	28	31	16	37		152	42	81	56		0.6	
Diurnal preference												
Morning	38	43	18	42	0.31	222	62	66	46	0.002	1	0.02
Evening	25	28	17	39		66	18	45	31		1.9	
Neither	24	27	8	19		72	20	32	22		1.6	

Numbers may not add up owing to missing values.
*Pearson χ^2test.
†Wald χ^2test.

As the participation of cases and controls was only modest, we performed a rough sensitivity analysis to determine what difference in the participation of day workers (not exposed to night shifts) between cases and controls would be needed to negate the overall results. This analysis was based on the 30 cases and 77 controls who reported night shift work for at least 6 years and the 101 cases and 428 controls who reported primarily day work (reference).[21 22]

RESULTS

Table 1 shows the characteristics of the 132 cases and 505 controls with and without a reported night shift work history. No significant differences were seen for most variables, but significantly more controls with night shift worker than controls with day work had more physical activity at work, a greater workload and work pace, and more frequent exposure to EMF and the sun; furthermore, more control night shift workers had an evening preference. In cases, only occupational exposure to radar or EMF and high workload and work pace was significantly more frequent in night shift workers than in day workers.

Table 2 shows the ORs for breast cancer by ever versus never night shift work, three categories of duration of night shift work, by tertiles of cumulative exposure to night shift work and by combinations of duration and frequency of night shift work. Overall, we observed an adjusted OR of 1.4 (0.9 to 2.1). An approximately twofold increase in the OR for breast cancer was seen for women with at least 6 years of night shift work (p for trend=0.03). An increasing OR was also observed with increasing cumulative night shift work, with an adjusted OR of 2.3 (1.2 to 4.6) in the tertile with the highest exposure (p for trend=0.02). An increased risk for breast cancer was observed only for women with at least three night shifts per week for at least 6 years (p for trend=0.02).

The adjusted OR for breast cancer was 1.8 (1.2 to 2.9) for evening preference and 1.6 (1.0 to 2.7) for mixed preference in comparison with morning preference (data not shown). Table 3 shows the adjusted ORs for breast cancer after night shift work by diurnal preference. Women with morning preference and cumulative night shift work over the median had an OR of 3.9 (1.6 to 9.5), while that of women with evening preference was 2.0 (0.7 to 5.8); no increase in risk was found for the small group with mixed preference.

The adjusted ORs for breast cancer after occasional frequent sun exposure and potential occupational exposure to EMF were 0.8 (0.4 to 1.0) and 1.1 (0.4 to 2.4), respectively (data not shown).

The sensitivity analysis for potential selection bias showed that the crude OR of 1.7 (1.0 to 2.7) obtained when comparing cases and controls with fewer than 6 years of night shift work with those with more shift work would be fully negated (OR=1) if the selection bias factor was 1.65 and the selection probabilities of exposed cases and exposed controls were 0.76 and 0.45, respectively, given the approximately same selection probability (0.62) in the reference group. This indicates that controls working on night shifts would be approximately half as likely (0.5=10×257/59×95) to participate as night shift working cases.

DISCUSSION

We found that the risk for breast cancer tended to increase with increasing years of night shift work and cumulative night shift work, after adjustment for potential confounders. As a whole, these result are consistent with those of most previous studies, including two large, independent prospective cohorts of nurses in the USA,[8 9] three nested case–control studies of Norwegian and Danish nurses[10–12] and five case–control studies of other female shift workers in Denmark, Germany, Norway and the

Table 2 Relative risks for breast cancer among female military employees after night shift work by different metrics

	Cases* (N=141)		Controls* (N=551)			
Night shift work characteristic	**n**	**%**	**n**	**%**	**OR† (95% CI)**	**OR‡ (95% CI)**
Never	89	63	361	66	1 (Reference)	1 (Reference)
Ever	43	31	144	26	1.3 (0.8 to 2.0)	1.4 (0.9 to 2.1)
Duration (years§)						
Never	88	63	361	66	1 (Reference)	1 (Reference)
1–5.9	13	9	67	12	0.9 (0.5 to 1.7)	0.9 (0.4 to 1.7)
6–14.9	18	13	48	9	1.6 (0.9 to 3.0)	1.7 (0.9 to 3.2)
≥15	12	9	29	5	1.8 (0.9 to 3.7)	2.1 (1.0 to 4.5)
p For trend					0.06	0.03
Cumulative¶						
Never	82	58	351	64	1 (Reference)	1 (Reference)
<416	9	6	48	9	0.8 (0.4 to 1.8)	0.8 (0.4 to 1.9)
416–1560	14	10	48	9	1.4 (0.7 to 2.7)	1.4 (0.7 to 2.9)
>1560	17	12	43	8	1.9 (1.0 to 3.5)	2.3 (1.2 to 4.6)
p For trend					0.05	0.02
Duration and frequency (per week)						
Never	82	58	351	64	1 (Reference)	1 (Reference)
1–2 times; all durations	15	11	65	12	1.0 (0.5 to 1.9)	1.0 (0.5 to 1.9)
≥3 times; 1–5.9 years	9	6	48	9	0.9 (0.4 to 2.0)	1.1 (0.5 to 2.3)
≥3 times; 6–14.9 years	11	8	30	5	1.8 (0.8 to 3.8)	2.1 (1.0 to 4.8)
≥3 times; ≥15 years	9	6	16	3	2.4 (1.0 to 5.6)	2.5 (1.0 to 6.6)
p For trend					0.06	0.02

*Numbers may not add up owing to missing values.
†Adjusted for age.
‡Adjusted for age, hormone replacement therapy (0, 1–5, ≥6 years), number of childbirths (0, 1–2, ≥3), age at menarche (<11, 11–14, ≥14 years), years of education (7, 8–9, 10, ≥11), occasional sunbathing frequency (never/rare vs always/more than weekly) and tobacco smoking status (never, current, former).
§Regardless of number per week.
¶Based on tertiles for exposed controls.

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Table 3 Risk for breast cancer with night shift work and diurnal preference

Diurnal preference	Cumulative night shift work*	Cases† (N=141)	Controls† (N=551)	OR‡ (95% CI)
Morning	Never	36	216	1 (Reference)
	<884	6	34	1.3 (0.5 to 3.7)
	≥884	12	30	3.9 (1.6 to 9.5)
Evening	Never	21	65	1 (Reference)
	<884	5	21	0.8 (0.2 to 3.0)
	≥884	10	21	2.0 (0.7 to 5.8)
Neither (morning, evening)	Never	23	69	1 (Reference)
	<884	4	15	1.0 (0.3 to 4.0)
	≥884	3	17	0.7 (0.1 to 3.0)

*Years × times/year (median for exposed controls). Cut-off point based on median for exposed controls.
†Numbers may not add up owing to missing values.
‡Adjusted for age, hormone replacement therapy (0, 1–5, ≥6 years), number of childbirths (0, 12, ≥3), age at menarche (<11–14, ≥14 years), length of education (7, 8–9, 10, ≥11 years), occasional sunbathing frequency (never/rare vs always/more than weekly) and tobacco smoking status (never, current, former).

USA.[10 23–26] Three other studies, however, reported no association between night shift work and breast cancer.[27–29] Further supporting evidence of an increased risk between breast cancer and night shift comes from studies of flight attendants; however, these can also be exposed to and jet lag ionising radiation.[7] Interpretation of the latter studies is, however, limited because of lack of information on work schedules and insufficient control for confounding.

We observed a neutral risk for breast cancer associated with any duration of night shift work among women with only one or two shifts per week. This is consistent with the observation that one or two night shifts will not change the timing of melatonin production and thereby not initiate circadian disruption,[30] and partly consistent with the finding of a recent study on nurses in which an increased risk for breast cancer was seen only for women with at least four consecutive shifts.[11]

Various partly overlapping mechanisms have been suggested to be involved in breast carcinogenesis after shift work.[4 31] Exposure to light at night, depending on the duration, timing, intensity and wavelength,[32] acutely decreases production of the 'darkness hormone' melatonin in the pineal gland[20 33] and may delay or advance this biological signal for timing and duration of the night.[34] Depressed melatonin levels in turn may influence the initiation and growth of breast cancer cells[35]; lower levels of melatonin have been found in women with breast cancer than in those without in some but not all prospective studies.[36] Furthermore, night shift work can result in sleep deprivation,[37] disruption of communication between the 'master clock' in the suprachiasmatic nuclei and peripheral molecular clocks,[3] aberrant expression in clock genes[38] and epigenetic alteration of circadian genes,[39 40] all of which may be involved in breast carcinogenesis.[1]

A polymorphism in the *PER3* gene appears to be associated with evening preference[41] and probably also with increased breast cancer risk.[42] A novelty of our study was the inclusion of diurnal preference in analyses of shift work and risk for breast cancer. We observed, after adjustment for shift work, that women with evening preference tended to have a higher risk than those with morning preference. It has been reported previously that people with evening preference are more frequently selected for night jobs than those with morning preference because of a better capacity for coping.[2] Women with a genetically determined evening preference might therefore have a higher risk for breast cancer, which might at least partly explain the higher risk observed in night workers. Women with morning preference who work at night might, however, be more sensitive to circadian disruption[43] and thereby be at increased risk.[38] Interestingly, the OR for breast cancer of shift workers in our study tended to be higher in women with morning preference than in those with evening preference, suggesting that the latter may better tolerate night work. We assessed diurnal preference from a single question, which may have resulted in imprecision, although it has been shown that answers to a similar single question on diurnal preference correlated well with answers on more comprehensive questionnaires.[44] In any event, it will be important to test our results in future studies. If they are confirmed, diurnal preference should be taken into account in selecting people for night shift work.

Another new aspect of the present study was the inclusion of information on sunbathing habits (self-reported 'occasional frequent sun exposure'). We observed a weak overall protective effect of frequent sun exposure on breast cancer risk, in line with the vitamin D hypothesis.[14] Women on night shifts reported more frequent sun exposure than those with day work, who are usually not exposed to the sun at indoor work places on weekdays. Therefore, the increased risk for breast cancer of night shift workers in our study cannot be explained by less exposure to the sun. If this observation in a subgroup of Danish women is true for other populations who work on night shifts, the effect of shift work might have been underestimated in previous studies, although the hypothesis that sun exposure decreases breast cancer risk is somewhat controversial. Information on sunbathing should be considered in future studies of shift work and breast cancer in order to clarify this issue.

The advantages of the present study include a well-defined cohort based on complete routinely collected data on employment and identification of virtually all breast cancer cases in the high-quality Danish Cancer Registry.[19] Furthermore, we were able to adjust for major potential confounders for breast cancer, although this changed the results only marginally. Finally, although we were investigating a different population from those in previous studies of shift workers and breast cancer, the overall results are similar.[7]

All retrospective studies suffer from potential recall bias. We attempted to minimise such bias by focusing on occupational exposures in the military in general, with no mention of shift work in the introductory letter; furthermore, this question was only one of 32 questions on occupational and non-occupational exposures. Moreover, data collection was completed before the International Agency for Research on Cancer evaluation in October 2007[7] and thus before the most intensive part of the public debate in the media. Finally, reported exposure to radar and EMF was not significantly associated with risk for breast cancer, as observed in the majority of studies, although this issue

has been heavily debated.[45] This may also indicate that reporting bias in our study is not a major problem.

The modest participation rates of cases and controls (67% and 61%) might be a limitation if the night shift workers were more willing to participate than day workers and if this probability was different for cases as opposed to controls, which would result in over estimated risk. In a sensitivity analysis, we roughly estimated that shift working controls would have to be twice as likely to refuse to participate as shift working cases in order to negate the observed OR entirely. This seems unlikely, although not impossible. In contrast, a 'healthy worker effect', whereby workers who experienced health problems or felt uncomfortable with shift work tended to leave such work,[46] that was stronger for night workers than for day workers would bias the OR for breast cancer towards the null.

As this study is based on live prevalent cases of breast cancer, the results may not necessarily pertain to more aggressive, fatal breast cancers. Furthermore, exclusion of 111 (33%) deceased cases from the cohort might have introduced selection bias if the cases were more exposed to shift work than controls and if cases with night shift work were more likely to die than those without night shift work due to generally poorer survival. This would result in an underestimated risk.

In conclusion, this study gives further support to the hypothesis that night shift work increases the risk for breast cancer. In contrast, this study does not support the hypothesis that female night shift workers sunbathe less frequently than day workers. The observation that women with night work and morning preference (who may be less tolerant of night shift work) tend to have a higher risk for breast cancer than similar women with evening preference warrants further exploration in larger studies.

Contributors JH and CFL have contributed to the study regarding: (1) conception and design or analysis and interpretation of data (2) drafting the article or revising it critically for important intellectual content and (3) final approval of the version to be published. JH and CFL have designed and planned the study and developed the protocol. CFL made the data collection. JH and CFL made the statistical analyses. JH and CFL interpreted the final data analyses and JH wrote the manuscript.

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