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Original Contribution

Night Work and Breast Cancer Risk Among Norwegian Nurses: Assessment by Different Exposure Metrics

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Associations between night work and breast cancer risk were investigated in a nested case-control study within a cohort of 49,402 Norwegian nurses. A total of 699 (74%) of the live cases diagnosed in 1990–2007 and 895 (65%) controls, cancer free at the time of sampling, were interviewed about work history and potential risk factors. The odds ratios for risk of breast cancer in relation to different exposure metrics were estimated by multivariate unconditional logistic regression models. No increase of risk was found after long duration of work by nurses working ≥3 night shifts per month. Small, nonsignificantly increased risks were observed for exposure to ≥30 years in hospitals or other institutions (odds ratio (OR) = 1.1), ≥12 years in schedules including night work (OR = 1.3), ≥1,007 night shifts during the lifetime (OR = 1.2), and lifetime average number of ≥4 night shifts per month (OR = 1.2). Nonsignificantly increased risks of breast cancer were observed in nurses who worked ≥5 years with ≥4 (OR = 1.4) and ≥5 (OR = 1.6) consecutive night shifts. Significantly increased risks were seen in nurses who worked ≥5 years with ≥6 consecutive night shifts (OR = 1.8, 95% confidence interval: 1.1, 2.8). The results suggest that risk may be related to number of consecutive night shifts.

breast neoplasms; case-control studies; chronobiology phenomena; Norway; nurses; risk

Abbreviations: CI, confidence interval; OR, odds ratio.

Breast cancer is the most common cancer in women in Western societies. Shift work, implying exposure to light at night and the subsequent reduction in the synthesis of the hormone melatonin, has been suggested as a contributing cause of this cancer (1). In 2007, the International Agency for Research on Cancer classified shift work that involves disruption of circadian rhythms as a probable human carcinogen, 2A (2), on the basis of limited evidence from epidemiologic studies and sufficient evidence from animal models. The inconsistent results from the epidemiologic studies might partly be due to different designs and to shortcomings, such as crude assessment of shift and night work characteristics and incomplete adjustment for confounding factors. Previous studies have characterized night work mainly by duration of work in jobs including night shifts. Studies considering additional factors characterizing shift systems, such as length of shift cycle, direction of shift cycle, start time of the work shifts, and number of nights worked in succession, have been requested (3).

The aspects of night work that might be associated with breast cancer risk have not been sufficiently understood. It has been hypothesized, however, that night work may influence cancer risk through sleep deprivation, circadian disruption, and depression of the hormone melatonin through exposure to light at night. Work schedules with longer sequences of consecutive night shifts increase circadian desynchronization (3).

Some studies indicate that nurses have an increased risk of breast cancer (4–6). The objective of the present study, which was based on a Norwegian cohort of nurses (5), was to examine the relation of shift work and breast cancer risk, including detailed evaluation of different exposure metrics of night-shift work.

MATERIALS AND METHODS

Study population

A cohort of 49,402 female nurses who graduated from a 3-year nursing school between 1914 and 1985 was established in 2004, on the basis of information from the Norwegian Board of Health's registry of nurses, as has been described in detail previously (5).

A nested case-control study was carried out within this cohort. First-occurrence breast cancer cases were identified by linkage to the Cancer Registry of Norway by the 11-digit personal identification number given to all Norwegians alive in 1960 or later. The Cancer Registry of Norway has virtually complete records of all individual cases of cancer in the Norwegian population since January 1, 1953 (7). The coding of cancer is based on a modified version of the *International Classification of Diseases*, Seventh Revision (ICD-7), until 1993 and from that time forward on the *International Classification of Diseases for Oncology*, Second Edition (ICD-O-2). Cases were included if diagnosed during the period from January 1990 through December 2007, aged 35–74 years at diagnosis, and alive by February 2009. Of the 1,132 cases diagnosed in 1990–2007, 943 were alive and included in the study. For each diagnostic year, cases were grouped into eight 5-year age strata (35–39, 40–44, . . ., 65–69, and 70–74 years), and the proportion in each stratum was calculated. Controls were frequency matched within each 5-year age stratum for each diagnostic year (1990, 1991, . . ., 2006, 2007) among the nurses in the cohort without breast cancer prior to that specific year and alive by February 2009 (i.e., according to the incidence density method). For each diagnostic year, 50% more controls than cases were selected in each age stratum. The study was approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics.

Data collection

Information about the study was first published in the journal of the Nurses' Association of which most nurses (>85%) are members. In order to minimize the risk of recall bias, (e.g., that the cases might exaggerate their shift work experience compared with the controls), the study was designed to investigate a broader spectrum of work-related factors possibly related to breast cancer risk. A few weeks before the telephone interviews started, all cases and controls received an information letter, including a declaration-of-consent form and a checklist for work history. All women who had ever held a job as a nurse during at least 1 year were requested to participate in a telephone interview. From April to June 2009, trained interviewers at Statistics Norway interviewed all women who had given a written or an oral consent. Interviewers did not have a priori information about the case-control status of the nurses. They used a structured questionnaire that included detailed questions on work and other known or potential breast cancer risk factors that might confound the association between night work and breast cancer risk. Lifetime occupational history included information on years of starting and ending employment for each job held longer than 1 year, type of work site (hospital, other institution, others), whether performing radiographic procedures (no, sporadic performance of radiographic procedures, daily performance of radiographic procedures), and type of work schedule (only days, only nights, both days and nights). A ''night shift'' was defined as a shift that lasted from at least 12 PM until 6 AM, alhough the shift may start earlier or end later. This is the normal night shift in Norway. The number of night shifts per month and the number of consecutive night shifts were asked for jobs including night work. Work history and other time-related variables were truncated at the year of diagnosis for the cases and year of selection for the controls and hereafter called year of diagnosis for both cases and controls.

Twelve nurses who had never held a job as a nurse for as much as 1 year were excluded. Altogether, 74% of the primary breast cancer cases identified and alive (699/943) and 65% of the controls (895/1,384) were interviewed and included in the study.

Assessment of night work

Different exposure metrics of night work were computed on the basis of work history (Table 1). If nothing else is stated, the term ''night work'' in this study includes working periods from rotating, as well as permanent, night schedules and includes the work of permanent night workers. To evaluate the influence of permanent night work, we performed separate analyses, excluding nurses who worked only at night as permanent night workers (11%); these odds ratios were then compared with the overall odds ratios when including all night workers, in order to evaluate the difference.

The average number of night shifts per month was imputed for jobs reported to include night shifts if the average number was missing (10% of night-shift jobs) or for jobs where the reported average number exceeded 16 (1% of night-shift jobs). For imputation, we applied the average number of night shifts per month in jobs that started during the same 5-year period (before 1960, 1960–1964,. . ., 1995–1999, 2000 and after) and in the same kind of work site (hospital, other institution, others). The imputed number of night shifts per month varied from 4.5 to 7.0. The reference category, in all but one analysis, consists of nurses who never worked at night after graduation from the nursing school. However, all women in this study had some exposure to night work during the 3 years at a nursing school.

Confounder assessment

The following covariates were evaluated as possible confounders: age at menarche, parity, breast cancer in mother/sister, use of oral contraceptives, hormonal treatment during the recent 5 and recent 2 years before diagnosis, body mass index at age 18 years and time of diagnosis, weight gain >10 kg from age 18 years to diagnosis, age at diagnosis, period of diagnosis, alcohol consumption and tobacco use, and duration of daily, occupational exposure to x-rays. A variable was included as a confounder if the chi-square test showed an association with night work, or if inclusion of the variable in the analysis changed the risk estimate by 10% or more.

Table 1. Names and Definitions of Selected Exposure Metrics of Night Work for Norwegian Nurses, Including 699 Breast Cancer Cases Diagnosed in 1990–2007 and 895 Controls

Name of Exposure Metric	Definition
Duration of employment in hospitals or other institutions	Sum of years spent in such institutions[a]
Duration of work in schedules including ≥3 night shifts per month	Sum of years spent in jobs including a minimum of 3 night shifts per month
Duration of work in schedules including night work	Sum of years spent in jobs including either permanent night work or rotating night shifts
Cumulative no. of lifetime night shifts	Sum over all jobs (no. of years spent in a job including night work multiplied by 12 months and by average no. of night shifts per month)
Lifetime average no. of night shifts per month	Cumulative no. of lifetime night shifts divided by total no. of months of employment
Duration of work in schedules including a minimum of 3–7 consecutive night shifts	For nurses who ever worked a minimum of 3–7 consecutive night shifts for <5 years and ≥5 years[b]

[a] Surrogate measure used in a previous study of Norwegian nurses (9).
[b] The remaining nurses were categorized according to ever or never having worked night shifts.

Ten nurses reported age at menopause lower than 30 years. For 5 of them, the age at menopause was altered to the reported year of starting postmenopausal hormones. For the remaining 5 nurses, age at menopause was coded as missing. Of 36 nurses who did not report age at menopause, 11 nurses aged ≥60 years at the time of diagnosis were categorized as postmenopausal. The year of starting or stopping was missing for 13 jobs but was imputed for 8 of these jobs, on the basis of the year of starting and stopping for the jobs preceding and following the actual one.

Statistical methods

The relative risks of breast cancer were estimated as odds ratios with 95% confidence intervals by using multivariable unconditional logistic regression models.

In addition to the matching variables age at diagnosis (35–49, 50–59, 60–69, 70–75 years) and period of diagnosis (1990–1994, 1995–1999, 2000–2004, 2005–2007), the covariates parity (nulliparous, 1–2, ≥3 children), breast cancer in mother and/or sister (no/yes), and alcohol consumption at the time of diagnosis (<2 times per week, ≥2 times per week) were entered in the final model. Adding other variables did not lead to substantial changes in the risk estimates.

When categorizing the continuous variables ''duration of work in schedules including night work'' and ''cumulative number of lifetime night shifts,'' we chose the third quartile among the controls (i.e., 12 years, 1,007 nights) as the cut-off point for the highest exposure category.

For the other variables, the cut-off point of the highest category was chosen to secure a reasonable number of observations in that category. Potential differences by time and life periods were evaluated by restricting exposure to the time period before 1970 and before age 40 years. As some studies have reported different risks for pre- and postmenopausal women (8), separate analyses were made for the postmenopausal group. Furthermore, analyses including only recently diagnosed cases from 2004 to 2007 were performed, to evaluate any effect of exclusion of deceased cases.

Two-sided P values of less than 0.05 were considered to indicate statistical significance. Trend tests were performed on the basis of categorical classification. All statistical analyses were carried out by using STATA, release 11, statistical software (StataCorp LP, College Station, Texas).

RESULTS

Table 2 shows the distribution of established and possible risk factors by case-control status. Previously identified risk factors for breast cancer are confirmed, for example, early menarche, a lower number of childbirths, breast cancer in mother or sister, and hormonal treatment use within the recent years before diagnosis. Sixty-seven percent of the cases and 66% of the controls were postmenopausal at the time of diagnosis.

The average number of jobs and of jobs involving night work was 4.8 and 2.0, respectively, among the cases and 4.5 and 1.9 among the controls. The prevalence of ever having worked a night shift was 85% in cases and 84% in controls.

Results from multivariate regression analyses of 4 previously used exposure metrics (8–11) adjusted for age and time of diagnosis are presented in Table 3, with and without adjustment for parity, family history of breast cancer, and alcohol consumption. A nonsignificant decreased risk was observed in the highest exposure group of ''duration of work in schedules including ≥3 night shifts per month'' (odds ratio (OR) = 0.8). Odds ratios from 1.1 to 1.3 were observed in the highest exposure category for the other exposure metrics in that table, after adjustment for all potential confounders. Imputation for missing values of average monthly number of night shifts resulted in slightly lower estimates as compared with no imputation. No significant trend was observed by increasing exposure in any of these analyses.

Table 4 displays the risk estimates for breast cancer by duration of work in schedules including a minimum number of 3–7 consecutive night shifts. Significantly increased odds ratios were observed among nurses who worked a minimum of 5 years in schedules with ≥6 (OR = 1.8) and ≥7 (OR = 1.7) consecutive night shifts, respectively. A

Table 2. Characteristics of Female Norwegian Nurses, Including 699 Breast Cancer Cases Diagnosed in 1990–2007 and 895 Controls

Characteristic	Cases		Controls		*P* Value
	Mean (SD)	%	Mean (SD)	%	
Age at stop time, years[a]	54.4 (7.7)		54.5 (7.9)		0.82[b]
Menarche before age 12 years		10.1		6.4	0.01[c]
Age at menarche, years	13.5 (1.4)		13.3 (1.3)		0.03[b]
Nulliparous		13.0		13.0	0.97[c]
No. of children	2.4 (0.9)		2.6 (1.04)		0.00[c]
Age at first birth, years[d]	26.8 (4.2)		26.5 (4.0)		0.15[b]
Age at first birth ≥30 years[d]		23.9		20.0	0.09[c]
First degree family history of breast cancer		18.9		8.8	0.00[c]
Ever use of oral contraceptives or IUD		43.7		40.8	0.24[c]
Postmenopausal at stop time[a]		66.9		65.7	0.64[c]
Age at menopause ≥55 years[e]		9.8		8.6	0.47[c]
Age at menopause, years[e]	48.8 (4.8)		48.5 (4.7)		0.36[b]
Body mass index of ≥25 at age 18 years[f]		5.7		5.0	0.52[c]
Body mass index of ≥25 at stop time[a,f]		33.9		31.2	0.25[c]
Recent hormonal treatment use 5 years before diagnosis[e]		40.0		34.7	0.04[c]
Recent hormonal treatment use 2 years before diagnosis[e]		35.0		27.0	0.01[c]
Alcohol consumption at stop time[a] at least twice/week		7.5		5.1	0.05[c]
Ever smoked		47.2		42.2	0.05[c]
Daily exposure to x-rays		17.9		14.2	0.05[c]

Abbreviations: IUD, intrauterine device; SD, standard deviation.
[a] Stop time, year of diagnosis for cases and year of selection for controls.
[b] Derived from analysis of variance.
[c] Derived from the chi-square test.
[d] Among the parous women only.
[e] Among the postmenopausal women only.
[f] Body mass index, weight (kg)/height $(m)^2$.

significant, positive trend was found with increasing duration in jobs including a minimum of 6 or 7 consecutive night shifts ($P_{trend} = 0.01$ and 0.05, respectively).

The risk estimate for all nurses was found to be similar in the following subgroups, when using the exposure metric "minimum 5 years with ≥6 consecutive nights": postmenopausal nurses (OR = 1.8, 95% confidence interval (CI): 1.1, 3.0); nurses, excluding permanent night workers (OR = 1.6, 95% CI: 1.0, 2.6); and the cases diagnosed during 2004–2007 (OR = 1.7, 95% CI: 0.8, 3.8). Risk estimates did not change when the exposure was limited to the time period before 1970 or age <40 years.

DISCUSSION

When applying different previously used exposure metrics for night work, we found that estimates showed a slight (10%–30%) but nonsignificant increase of risk for breast cancer in the highest exposure categories. By using consecutive night shifts as the exposure parameter, we observed significantly elevated breast cancer risks in the range of 1.7–1.8 in nurses who worked 5 or more years in jobs including ≥6 consecutive night shifts, compared with nurses who never worked night shifts. To our knowledge, this is the first study to reveal an association between a higher number of consecutive night shifts and breast cancer risk.

The study is based on a large cohort of nurses educated from 1950 to 1984 and includes a high number of breast cancer cases. Compulsory reporting of all cancer cases to the national cancer registry made it possible to identify all breast cancer cases in the cohort for the period 1990–2007. However, several validity questions have to be addressed.

The study is based on living, prevalent cases. Selection bias might affect the results when deceased cases are excluded. However, a subanalysis of cases diagnosed in 2004–2007 showing approximately the same estimates as for all suggests that it is unlikely that the inclusion of long-term survivors has biased the results. Although the participation rate is considered fairly high in both groups, differential recruitment between groups, together with the 9% higher response rate among cases than controls, might also have contributed to selection bias. Responders and nonresponders were, however, similar with respect to socioeconomic status, occupation, age distribution, and sex.

A detailed occupational history with information on lifetime night work experience and data on well-known and suspected risk factors was obtained by telephone interviews.

Table 3. Odds Ratios of Breast Cancer for Norwegian Nurses, Including 699 Breast Cancer Cases Diagnosed in 1990–2007 and 895 Controls by Selected Exposure Metrics

Exposure Metric	No. of Cases	No. of Controls	OR[a]	95% CI	OR[b]	95% CI
Duration of employment in hospitals and other institutions						
<1 year	23	29	1.0		1.0	
1–14 years	303	400	1.0	0.5, 1.7	0.9	0.5, 1.7
15–29 years	287	370	1.0	0.6, 1.7	0.9	0.5, 1.7
≥30 years	86	96	1.1	0.6, 2.1	1.1	0.6, 2.0
P_{trend}[c]				0.48		0.66
Duration of work in schedules including ≥3 night shifts per month						
Never night work	102	148	1.0		1.0	
Never ≥3 nights per month	28	27	1.5	0.8, 2.7	1.4	0.8, 2.6
1–14 years	390	489	1.2	0.9, 1.5	1.2	0.9, 1.6
15–29 years	152	182	1.2	0.9, 1.7	1.2	0.9, 1.7
≥30 years	27	49	0.8	0.5, 1.3	0.8	0.5, 1.4
P_{trend}[c]				0.85		0.69
Duration of work in schedules including night work						
Never night work	102	148	1.0		1.0	
1–11 years	410	523	1.1	0.9, 1.5	1.2	0.9, 1.5
≥12 years	187	224	1.2	0.9, 1.7	1.3	0.9, 1.8
P_{trend}[c]				0.25		0.17
Cumulative no. of lifetime night shifts						
Never night work	102	148	1.0		1.0	
<1,007 night shifts	396	504	1.1	0.9, 1.5	1.2	0.9, 1.6
≥1,007 night shifts	201	243	1.2	0.9, 1.6	1.2	0.9, 1.7
P_{trend}[c]				0.29		0.24
Lifetime average no. of night shifts per month						
Never night work	102	148	1.0		1.0	
<4 night shifts per month	415	505	1.2	0.9, 1.6	1.2	0.9, 1.6
≥4 night shifts per month	182	242	1.1	0.8, 1.5	1.2	0.8, 1.6
P_{trend}[c]				0.76		0.51

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Odds ratios adjusted for age (35–49, 50–59, 60–69, 70–75 years) and period of diagnosis (1990–1994, 1995–1999, 2000–2004, 2005–2007).

[b] Odds ratios adjusted for age (35–49, 50–59, 60–69, 70–75 years), period of diagnosis (1990–1994, 1995–1999, 2000–2004, 2005–2007), parity (0, 1–2, ≥3 children), family history of breast cancer in mother or sister (no/yes), and frequency of alcohol consumption at time of diagnosis (maximum 1 time/week, ≥2 times/week).

[c] Calculated by using the category number of the exposure variable as a continuous variable.

Such interview data are particularly subject to recall bias. In Norway, over the last years, there has been an increasing public concern about night work and breast cancer risk. In order to minimize the risk of cases and controls reporting exposures differently on the basis of their status as either case or control, we designed the study to investigate a broader spectrum of work-related factors possibly related to breast cancer risk. In addition, no difference was found between cases and controls on duration in jobs reported to include night work but where number of consecutive night shifts was missing. Still, we cannot exclude that information bias may have contributed to the results observed.

A variety of potential confounders were identified in the present study, among them ionizing radiation. However, no major confounding was observed by occupational exposure to x-rays or by any other variable. By studying one profession only, the problem of other potential confounders was reduced. In the final models, age, period of diagnosis, parity, family history of breast cancer, and alcohol consumption were included as covariates. Among the validity issues addressed, we consider potential recall bias as the greatest threat to the associations observed in this study. On the other hand, nondifferential misclassification of exposure, together with the lack of a completely unexposed reference category, may have biased risk estimates toward unity.

Previous studies evaluating the association between breast cancer and night work differ with respect to classification of the duration of night work, with cutpoints for the highest categories varying from 3.1 to 30 years. In 5 studies (8–12), long duration of night work was associated with

Table 4. Odds Ratios of Breast Cancer for Norwegian Nurses, Including 699 Breast Cancer Cases Diagnosed in 1990–2007 and 895 Controls, by Exposure to Night Work, Expressed as Duration of Work Including a Minimum of 3–7 Consecutive Night Shifts

Exposure Metric	No. of Cases	No. of Controls	OR[a]	95% CI	OR[b]	95% CI
Duration of work in schedules including a minimum of 3 consecutive night shifts						
Never worked nights	102	148	1.0		1.0	
Never worked 3 consecutive nights	125	126	1.4	1.0, 2.0	1.4	1.0, 2.1
Worked <5 years with ≥3 consecutive nights	194	250	1.1	0.8, 1.5	1.1	0.8, 1.6
Worked ≥5 years with ≥3 consecutive nights	278	371	1.1	0.8, 1.5	1.1	0.8, 1.5
P_{trend}[c]				0.79		0.92
Duration of work in schedules including a minimum of 4 consecutive night shifts						
Never worked nights	102	148	1.0		1.0	
Never worked 4 consecutive nights	306	398	1.1	0.8, 1.5	1.1	0.8, 1.5
Worked <5 years with ≥4 consecutive nights	160	205	1.1	0.8, 1.6	1.2	0.8, 1.6
Worked ≥5 years with ≥4 consecutive nights	131	144	1.3	0.9, 1.9	1.4	0.9, 1.9
P_{trend}[c]				0.13		0.10
Duration of work in schedules including a minimum of 5 consecutive night shifts						
Never worked nights	102	148	1.0		1.0	
Never worked 5 consecutive nights	386	501	1.1	0.8, 1.5	1.1	0.8, 1.5
Worked <5 years with ≥5 consecutive nights	137	172	1.2	0.8, 1.6	1.2	0.8, 1.7
Worked ≥5 years with ≥5 consecutive nights	74	74	1.4	1.0, 2.2	1.6	1.0, 2.4
P_{trend}[c]				0.10		0.05
Duration of work in schedules including a minimum of 6 consecutive night shifts						
Never worked nights	102	148	1.0		1.0	
Never worked 6 consecutive nights	414	542	1.1	0.8, 1.5	1.1	0.8, 1.5
Worked <5 years with ≥6 consecutive nights	119	148	1.2	0.8, 1.7	1.2	0.8, 1.7
Worked ≥5 years with ≥6 consecutive nights	64	57	1.6	1.0, 2.5	1.8	1.1, 2.8
P_{trend}[c]				0.04		0.02
Duration of work in schedules including a minimum of 7 consecutive night shifts						
Never worked nights	102	148	1.0		1.0	
Never worked 7 consecutive nights	430	594	1.1	0.9, 1.5	1.1	0.9, 1.5
Worked <5 years with ≥7 consecutive nights	109	145	1.1	0.8, 1.6	1.1	0.8, 1.6
Worked ≥5 years with ≥7 consecutive nights	58	53	1.6	1.0, 2.5	1.7	1.1, 2.8
P_{trend}[c]				0.11		0.05

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Odds ratios adjusted for age (35–49, 50–59, 60–69, 70–75 years) and period of diagnosis (1990–1994, 1995–1999, 2000–2004, 2005–2007).

[b] Odds ratios adjusted for age (35–49, 50–59, 60–69, 70–75 years), period of diagnosis (1990–1994, 1995–1999, 2000–2004, 2005–2007), parity (0, 1–2, ≥3 children), family history of breast cancer in mother or sister (no/yes), and frequency of alcohol consumption at time of diagnosis (maximum 1 time/week, ≥2 times/week).

[c] Calculated by using the category number of the exposure variable as a continuous variable.

increased risks. Schernhammer et al. (8) studied the association between night work and breast cancer among nurses participating in the Nurses' Health Study and followed up in 1988–1998. Based on a question in 1988 regarding how many years in total the woman had worked rotating night shifts with at least 3 nights per month, a significant increase of risk (relative risk = 1.36) was found for the longest exposure (≥30 years), compared with never working such shifts. In the Nurses' Health Study II (12), premenopausal nurses who reported ≥20 years of rotating night shifts showed a significant increase of breast cancer risk (relative risk = 1.79) compared with nurses who never worked night shifts. In a German population-based case-control study, Pesch et al. (10) found a nonsignificant increase (OR = 1.66) of risk among women employed ≥20 years in shift work. In a previous study of Norwegian nurses (9), a significantly elevated risk was found among nurses who had worked for 30 years or more in hospitals and other

institutions (OR = 2.21, 95% CI: 1.10, 4.45). This result was not replicated in the present study, when applying the same surrogate measure of exposure (OR = 1.1, 95% CI: 0.6, 2.0). The cases of the 2 studies were, however, diagnosed at different time periods: during 1960–1982 in the former study versus 1990–2007 in the present. Thus, the different results may be due to the progressive change of shift systems observed in many countries in recent decades, from traditionally slow-rotating to faster-rotating systems (3). Prior to 1970, shift schedules for Norwegian nurses often included 7–14 consecutive night shifts in addition to day shifts, and night shifts of 12 hours' duration were quite common. In the present study, no significant association was found between duration of work including night shifts (OR = 1.3 for ≥12 years including night work; OR = 0.8 for ≥30 years of work in schedules including ≥3 night shifts per month). The range of years worked for ≥5 years in schedules with both ≥6 and ≥7 consecutive night shifts was 5–39 years (mean, 11.4 years for ≥6; mean, 11.0 years for ≥7 consecutive night shifts). In a recent population-based cohort study of Chinese women (11), no increase or a nonsignificantly decreased hazard ratio of breast cancer was found by duration of night work. As ethnic variability has been discovered in clock gene variants (13), potentially genetic differences in response to night shift work may explain some of the difference, in addition to the differences in diet and reproductive factors (11).

Risk estimates by the exposure metric, ''cumulative number of lifetime night shifts,'' were slightly but nonsignificantly elevated in the present study (OR = 1.2) among nurses who worked ≥1,007 night shifts. Compared with women never working at night, Pesch et al. (10) observed an odds ratio of 1.73 (95% CI: 0.71, 4.22) in women who worked ≥807 night shifts, and Pronk et al. (11) found a risk ratio of 0.7 (95% CI: 0.4, 1.1) in women exposed to >1,632 night shifts. Using the exposure categories of Pesch et al. (10) and Pronk et al. (11) in the present study resulted in an odds ratio of 1.2 (95% CI: 0.9, 1.7) among Norwegian nurses exposed to ≥807 night shifts and an odds ratio of 1.3 (95% CI: 0.9, 1.9) among Norwegian nurses exposed to >1,632 night shifts (not shown). The inconsistent findings from these studies may be explained by different study designs, variation in definition and distribution of night shift work (depending on country and period), and unstable estimates in some studies due to a low number of cases.

In the present study, risk estimates by ''lifetime average number of night shifts per month'' were slightly but nonsignificantly elevated in exposed nurses compared with nurses who never worked at night. The 2 exposure metrics, ''cumulative number of lifetime night shifts'' and ''lifetime average number of night shifts per month,'' were both based on information on average number of night shifts per month for each job. Because the length of a nurse's work cycle usually exceeds 4 weeks, the monthly average number of night shifts may have been incorrectly reported and estimated. In the present study, the number of consecutive night shifts was probably easier to recall than the number of night shifts per month. A high number of nights worked in succession, usually in addition to morning and afternoon shifts, was probably exhausting, with great implications for social life. Thus, the number of consecutive night shifts is presumably the most informative exposure metric in this study. Because nurses often change their shift schedules during their working life because of changing jobs or organizational changes, duration of work in schedules with a minimum number of consecutive nights seems to be the most optimal exposure metric, including information on both intensity and duration of night work. The observed significant increase of risk in the highest exposed group (OR = 1.81 for ≥5 years in schedules including 6 consecutive night shifts), combined with a positive trend, supports an association between night work and breast cancer. Slowly rotating night shift systems include longer sequences of consecutive night shifts, thereby causing increased circadian misalignments or desynchronization of many biologic functions, including sleep (3). The more successive nights of work, the more disruption of sleep (14).

In summary, this study suggests that breast cancer risk may be related to the number of consecutive night shifts. Because this is the first study to assess the impact of number of consecutive night shifts, the association needs to be replicated in other studies. In addition to epidemiologic studies, further research is needed to establish the pathways and mechanisms mediating the possible effects of shift work in breast cancer risk, including individual factors such as genetic variations of clock genes.

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