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Original Contribution

Night-Shift Work and Breast Cancer Risk in a Cohort of Chinese Women

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Shift work involving disruption of circadian rhythms has been classified as a probable cause of human cancer by the International Agency for Research on Cancer, based on limited epidemiologic evidence and abundant experimental evidence. The authors investigated this association in a population-based prospective cohort study of Chinese women. At baseline (1996–2000), information on lifetime occupational history was obtained from 73,049 women. Lifetime night-shift exposure indices were created using a job exposure matrix. During 2002–2004, self-reported data on frequency and duration of night-shift work were collected. Hazard ratios and 95% confidence intervals, adjusted for major breast cancer risk factors, were calculated. During follow-up through 2007, 717 incident cases of breast cancer were diagnosed. Breast cancer risk was not associated with ever working the night shift on the basis of the job exposure matrix (adjusted hazard ratio = 1.0, 95% confidence interval: 0.9, 1.2) or self-reported history of night-shift work (adjusted hazard ratio = 0.9, 95% confidence interval: 0.7, 1.1). Risk was also not associated with frequency, duration, or cumulative amount of night-shift work. There were no indications of effect modification. The lack of an association between night-shift work and breast cancer adds to the inconsistent epidemiologic evidence. It may be premature to consider shift work a cause of cancer.

breast neoplasms; China; prospective studies; work schedule tolerance

Abbreviations: CI, confidence interval; HR, hazard ratio; IARC, International Agency for Research on Cancer.

The International Agency for Research on Cancer (IARC) has classified shift work that involves disruption of circadian rhythms a probable cause of human cancer (group 2A), on the basis of limited epidemiologic evidence and abundant experimental evidence (1). In Western countries, 15%–20% of the total workforce is estimated to be involved in night-shift work and other types of shift work (2, 3). Given this widespread exposure, the IARC classification could have far-reaching implications. Denmark is the first country to regard breast cancer as an occupational disease, granting compensation to breast cancer patients with a long history of night-shift work. This decision has been controversial, given that the existing epidemiologic data are based on a relatively small number of observational studies which have not produced a clear and consistent body of evidence (4, 5).

In a population-based prospective cohort study of over 70,000 ever-employed women in Shanghai, China, who provided information on lifetime occupational history and night-shift work, we assessed the association between shift work and breast cancer risk.

MATERIALS AND METHODS

Study population and data collection

The Shanghai Women's Health Study is a population-based prospective cohort study being conducted in Shanghai, China (6). All women aged 40–70 years in 7 representative urban communities of Shanghai identified through resident offices were eligible for inclusion. Between 1996 and 2000, 81,170 women were approached in person by trained interviewers, and 74,942 women were recruited, resulting in a participation rate of 92%. For the present analyses, women who had a history of cancer at study entry ($n = 1{,}576$), had never held a job outside the home ($n = 274$), or did not have complete data on work history ($n = 43$) were excluded.

The cohort was followed for the occurrence of cancer and other chronic diseases through a combination of biennial in-person interviews and annual record linkage to the Shanghai Cancer Registry and the Shanghai vital statistics database. Response rates for the first (2000–2002), second (2002–2004), and third (2004–2007) follow-up surveys were 99.8%, 98.7%, and 96.7%, respectively. All possible incident cancer cases were verified through home visits. Medical charts from the diagnostic hospital were reviewed to verify the diagnosis. The study was approved by the institutional review boards of the participating institutions in China and the United States.

In-person interviews were conducted at baseline by trained interviewers using a structured questionnaire to elicit information on demographic background, socioeconomic status, family history of cancer, reproductive factors, and lifetime occupational history. Written informed consent was obtained by the interviewer. Lifetime occupational histories included the name of the workplace, job title (including main duties and products), and years of starting and ending employment for each job held longer than 1 year. Each occupation was coded (3 digits) according to the 1982 Chinese manual of standard occupational and industry codes (7). Occupational physical activity was assessed using a job exposure matrix, which assigned jobs to categories with low, intermediate, and high sitting time. For each job in a subject's work history, the median amount of sitting time (1, 4, and 7 hours/day for low, moderate, and high, respectively) was multiplied by the number of years of working in that job. Average occupational sitting time was calculated by dividing the sum of these products by total years of employment.

Assessment of night-shift work

We assessed night-shift work by applying a job exposure matrix developed by an experienced Chinese industrial hygienist (S. X.) who was familiar with local industrial conditions. The job exposure matrix classified jobs in the occupational histories into 3 categories with increasing scores for night-shift work: 0 = no night-shift work; 1 = incidental night-shift work (e.g., reporters and army personnel); 2 = jobs likely to involve the night shift, but entailing working only part of the night or being on call (e.g., physicians and bakers); and 3 = jobs that probably involved all-night shifts (e.g., nurses, firemen, and certain production workers). These scores for individual jobs were used to calculate lifetime cumulative exposure by multiplying the years spent in each job by the score for that particular job, and then summing the product values over all jobs in a subject's work history. We calculated an average score by dividing this sum by the total number of years of employment. We computed lifetime number of years spent in jobs with possible night-shift work by summing the total number of years spent in jobs with a score higher than 0.

In addition, during the second follow-up (2002–2004), every participant was asked whether she had ever held a job involving night-shift work. Night-shift work was defined as starting work after 10 PM at least 3 times a month for over 1 year. Data on the average number of night shifts worked per week, the duration of shift work (years), and the years of starting and ending shift work were also collected. Cumulative night-shift work was calculated by multiplying the average number of night shifts per week by the duration of shift work.

Statistical analyses

All statistical analyses were performed in SAS, version 9.1 (SAS Institute Inc., Cary, North Carolina). The association between night-shift work and risk of breast cancer was evaluated using Cox proportional hazards regression (PROC PHREG) with age as the time scale and stratification by birth cohort (5-year intervals). Since the self-reported information on night-shift work was obtained during the second follow-up, this analysis was restricted to person-years and cases with incident breast cancer diagnosed after the second follow-up ($n = 69{,}982$, of whom 69,472 provided information on night-shift work).

Hazard ratios and 95% confidence intervals were calculated for subjects who had ever worked in a job involving the night shift. Frequency and duration of night-shift work, cumulative amount of night-shift work, and age at starting to work night shifts were investigated by means of categorical analysis based on tertiles among the exposed subjects. The association between cumulative night-shift work and breast cancer in subgroups was explored according to strata of menopausal status, age at first birth (<26 years vs. ≥26 years), educational level (middle school or less vs. high school or more), occupational physical activity (average sitting time at or above the median vs. below the median), body mass index (weight (kg)/height $(m)^2$; <23.7 vs. ≥23.7), alcohol consumption (yes/no), and energy intake (<1,644 kcal/day vs. ≥1,644 kcal/day).

Presented hazard ratios were adjusted for age, education, family history of breast cancer, number of pregnancies, age at first birth, and occupational physical activity. Other potential confounders, including age at menarche, menopausal status, body mass index, calorie intake, and nonoccupational physical activity, were examined but were found not to alter the risk estimates meaningfully and therefore were not included in the final model.

RESULTS

In total, 73,049 women without prevalent cancer at baseline had held at least 1 job outside the home. During an average follow-up period of 9.0 years, 717 women were newly diagnosed with an invasive malignant neoplasm of the breast (*International Classification of Diseases*, Ninth Revision, codes 162.0–162.9). Compared with the total cohort, a greater proportion of cases reported a high school education or more, a history of breast cancer in first-degree relatives, and a later age at first livebirth. Cases also tended to have lower levels of occupational and nonoccupational physical activity. Age, menopausal status, number of pregnancies, age at menarche, body mass index, and energy intake were comparable among cases and the total cohort (Table 1).

On the basis of the job titles in their occupational histories, 44% of the cohort were classified as having ever engaged in night-shift work. When results were adjusted for age only, breast cancer risks between 0.8 and 1.0 were observed among

Table 1. Baseline Characteristics of the Cohort by Breast Cancer Status, Shanghai Women's Health Study, 1996–2000

	Total Cohort (n = 73,049)		Breast Cancer Cases (n = 717)	
	Mean (SD)	%	Mean (SD)	%
Age at cohort entry, years	52.5 (9.1)		52.7 (8.8)	
Breast cancer in first-degree relative, %		2		4
Education, %				
Elementary school or lower		21		13
Middle school		37		32
High school		28		35
College or higher		14		19
Premenopausal[a], %		26		30
Age at menarche, years	14.9 (1.7)		14.8 (1.8)	
Age at first livebirth, years	25.9 (4.1)		26.8 (4.2)	
No. of pregnancies	2.8 (1.5)		2.6 (1.4)	
Body mass index[b]	24.0 (3.4)		24.2 (3.4)	
Total caloric intake, kcal/day	1,685.7 (407.3)		1,683.0 (374.6)	
Nonoccupational physical activity[c], MET-hours/week	106.6 (45.1)		102.9 (44.4)	
Occupational physical activity[d], hours/day spent sitting	3.39 (1.94)		3.80 (1.92)	

Abbreviation: SD, standard deviation; MET, metabolic equivalent.
[a] Information on menopausal status was updated during follow-up (last follow-up, 2004–2006).
[b] Weight (kg)/height (m)^2.
[c] Participation in exercise, household activities, and walking and cycling for transportation.
[d] Average sitting-time score based on the job exposure matrix (1, 4, or 7 hours/day) divided by the total (total lifetime work years).

women who had engaged in shift work as compared with those who had not (Table 2). None of the risk estimates reached statistical significance, and no consistent dose-response patterns were observed. After adjustment for additional potential confounders, the risk estimates were weakened to near unity. Because researchers in some previous studies (8–10) have reported an excess risk of breast cancer only after 20–30 years of employment in night-shift work, we also evaluated risk among long-term shift workers. In total, 16,549 and 6,526 women had worked in jobs classified as involving night-shift work for over 20 years and over 30 years, respectively. These women did not show an increased risk of breast cancer after adjustment for potential confounders (hazard ratio (HR) = 1.0 (95% confidence interval (CI): 0.8, 1.2) and HR = 1.1 (95% CI: 0.9, 1.5), respectively).

Self-reported information on night-shift work history was available for 69,472 women without cancer at the second follow-up. Of these women, 349 were diagnosed with breast cancer after an average follow-up period of 4.4 years. Of the 26% of the women who reported ever having worked night shifts, an inverse association with breast cancer risk was observed after adjustment for age only (Table 3). Women in the highest categories of duration and cumulative night-shift work and women who started night-shift work after age 30 years showed the greatest reductions in comparison with women who had never worked night shifts (HR = 0.6; $P \leq 0.05$ for all 3 associations). Adjustment for additional potential confounders resulted in risk ratios closer to unity that were not statistically significant. Working night shifts for over 20 years and over 30 years was reported by 5,056 and 1,715 women, respectively, and was not significantly associated with breast cancer risk (fully adjusted HRs were 0.7 (95% CI: 0.4, 1.2) and 0.9 (95% CI: 0.4, 2.0), respectively).

Sixty-eight percent of the women who reported ever working night shifts and 35% of the women who reported never working night shifts were classified as exposed on the basis of the job exposure matrix. The risk of breast cancer was not increased (fully adjusted HR = 0.9, 95% CI: 0.7, 1.3) for women who were classified as exposed on the basis of both a self-reported history of night-shift work and the occupational history (n = 12,437) in comparison with women who were classified as unexposed on the basis of both methods (n = 33,397).

Stratification of results according to menopausal status, age at first birth, educational level, occupational physical activity, body mass index, alcohol use, and energy intake revealed no significant associations between breast cancer risk and cumulative night-shift work on the basis of the job exposure matrix or self-reported history in subgroups (data not shown).

DISCUSSION

In this prospective, population-based cohort study of women in China, we found no evidence of an association

Table 2. Association Between a Score for Night-Shift Work Based on a Job Exposure Matrix[a] and Breast Cancer Risk Among 73,049 Women Without Incident Cancer at Baseline, Shanghai Women's Health Study[b]

	No. in Total Cohort	No. of Cases	Adjusted for Age		Fully Adjusted[c]	
			HR	95% CI	HR	95% CI
Ever working night shifts						
Never	41,164	423	1		1	
Ever	31,885	294	0.9	0.8, 1.1	1.0	0.9, 1.2
Average night-shift score						
0	41,164	423	1		1	
>0–≤1.29	10,507	102	1.0	0.8, 1.2	1.0	0.8, 1.2
>1.29–≤2.38	10,882	109	1.0	0.8, 1.2	1.1	0.9, 1.3
>2.38	10,496	83	0.8	0.6, 1.0	0.9	0.7, 1.2
P-trend				0.09		0.73
Duration of working in jobs with score >0, years						
0	41,164	423	1		1	
>0–≤14	10,569	108	1.0	0.8, 1.3	1.1	0.9, 1.3
>14–≤25	11,056	89	0.8	0.6, 1.0	0.9	0.7, 1.1
>25	10,260	97	0.9	0.7, 1.1	1.0	0.8, 1.3
P-trend				0.12		0.72
Lifetime cumulative night-shift score						
0	41,164	423	1		1	
>0–≤34	10,530	102	1.0	0.8, 1.2	1.0	0.8, 1.3
>34–≤66	11,473	103	0.9	0.7, 1.1	1.0	0.8, 1.2
>66	9,882	89	0.9	0.7, 1.1	1.0	0.8, 1.2
P-trend				0.15		0.84
Age at starting first job with score >0, years						
Never did shift work	41,164	423	1		1	
>26	10,055	87	0.8	0.7, 1.1	1.0	0.8, 1.2
>20–≤26	9,721	98	1.0	0.8, 1.2	1.0	0.8, 1.3
>0–≤20	12,109	109	0.9	0.7, 1.1	1.0	0.8, 1.2

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Each occupation in the occupational histories of the study participants was scored: 0 = no night-shift work; 1 = incidental night-shift work; 2 = jobs likely to involve the night shift, but entailing working only part of the night or being on call; and 3 = jobs probably involved all-night shifts. Lifetime cumulative scores were calculated by multiplying the years spent in each job by the score for that particular job, and then summing the product values over all jobs in a subject's work history. The average score was calculated by dividing this sum by the total years of employment.

[b] Follow-up extended from baseline (1996–2000) to December 2007, death, or the first diagnosis of incident cancer.

[c] Adjusted for age, education, family history of breast cancer, number of pregnancies, age at first birth, and occupational physical activity.

between night-shift work and breast cancer risk. The findings were similar regardless of whether the assessment of night-shift work was based on a job exposure matrix or self-reported information.

The designation of night-shift work as a probable cause of cancer by the IARC was primarily based on experimental evidence (1). In rodents, exposure to light at night reduced nocturnal melatonin concentrations, and removal of the pineal gland has been shown to increase the incidence or progression of (mammary) tumors (1, 11).

Relatively few epidemiologic studies have investigated the association between night-shift work and breast cancer. In 2 prospective cohort studies of nurses that incorporated specific questions on night-shift work, investigators reported elevated risks of breast cancer associated with engaging in night-shift work for over 20 years (8) and over 30 years (9). In a registry-linked case-control study conducted among

Table 3. Association Between Self-Reported Night-Shift Work and Breast Cancer Risk Among 69,472 Women Without Incident Cancer at the Second Follow-up, Shanghai Women's Health Study[a]

	No. in Total Cohort	No. of Cases	Adjusted for Age		Fully Adjusted[b]	
			HR	95% CI	HR	95% CI
Ever working night shifts						
Never	51,238	276	1		1	
Ever	18,234	73	0.8	0.6, 1.0	0.9	0.7, 1.1
Frequency (no. of night shifts per month)						
0	51,238	276	1		1	
>0–<8	2,681	8	0.5	0.3, 1.1	0.6	0.3, 1.2
8	10,475	45	0.8	0.6, 1.1	0.9	0.7, 1.3
>8	5,078	20	0.7	0.5, 1.1	0.9	0.5, 1.3
P-trend				0.03		0.29
Duration (years of working night shifts)						
0	51,238	276	1		1	
>0–≤5	6,055	25	0.8	0.5, 1.2	0.9	0.6, 1.3
>5–≤17	6,459	29	0.8	0.6, 1.2	0.9	0.6, 1.4
>17	5,720	19	0.6	0.4, 1.0	0.8	0.5, 1.2
P-trend				0.03		0.26
Cumulative exposure (total no. of night shifts)						
0	51,238	276	1		1	
>0–≤576	6,370	27	0.8	0.5, 1.2	0.9	0.6, 1.3
>576–≤1,632	5,924	28	0.9	0.6, 1.3	1.0	0.7, 1.5
>1,632	5,940	18	0.6	0.3, 0.9	0.7	0.4, 1.1
P-trend				0.02		0.17
Age at starting night-shift work, years						
Never did shift work	51,238	276	1		1	
>30	5,594	18	0.6	0.4, 1.0	0.7	0.5, 1.2
>21–≤30	5,768	25	0.8	0.5, 1.2	0.9	0.6, 1.3
>0–≤21	6,872	30	0.8	0.6, 1.2	0.9	0.6, 1.4

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] Follow-up extended from the second follow-up (2002–2004) to December 2007, death, or the first diagnosis of incident cancer.

[b] Adjusted for age, education, family history of breast cancer, number of pregnancies, age at first birth, and occupational physical activity.

nurses, which assigned exposure on the basis of type of hospital department, Lie et al. (10) also found an elevated risk of breast cancer associated with working night shifts for over 30 years. A population-based case-control study showed a nonsignificant increased risk for engaging in shift work for over 20 years (12). Findings for shorter durations of shift work are less consistent. Two population-based case-control studies of breast cancer using specific questions on night-shift work showed an elevated risk (13) and a reduced risk (14). In a population-based registry-linked case-control study with job exposure matrix assignments of full occupational history, Hansen (15) reported elevated breast cancer risk among night-shift workers, while a similar study with job exposure matrix assignments at 2 census years did not demonstrate such an association (16). Lastly, in a case-control study nested within a cohort of shipboard telegraph operators, Tynes et al. (17) reported a significant trend of increasing breast cancer risk with increasing duration of shift work among women over age 50 years only. Inconsistent findings from these studies may be explained, in part, by variations in definition of shift work and study design, potential recall bias, focus on a single profession versus multiple professions, and incomplete adjustment for confounding factors (1, 3, 18). A significantly increased incidence of breast cancer in comparison with the general population has also been observed in 6 out of 7 studies of flight attendants (18). However, those

studies lacked information on night-shift work and may have been confounded by exposure to cosmic radiation (1, 3).

To our knowledge, this is the first prospective population-based cohort study to have evaluated the role of shift work in cancer risk, allowing the evaluation of a wide range of occupations and socioeconomic groups. The prospective nature of the data collection tended to minimize recall bias, and the stable job histories in this population might have enhanced the accuracy of recall of occupational history. The cohort was large, with an adequate number of cases for studying the main effects of night-shift work. The high response rate reduced potential selection bias. Furthermore, detailed information on other potential risk factors was available for adjustment and exploration of risk in subgroups. Because of the long occupational histories in our cohort (average duration of 29 years), the long-term effects of working night shifts (i.e., for over 20 and over 30 years) could have been explored. However, the prevalences of women reporting having worked night shifts for such durations were relatively low (7% and 3%, respectively).

Another strength of our study was the use of complementary data on shift work based on occupational history (using a job exposure matrix) and self-reported night-shift work history. However, the accurate definition and assessment of relevant exposure remains a major complicating factor when studying night-shift work. It is unclear what aspects of night-shift work, including type, duration, direction, regularity, timing, and light intensity levels, may be associated with cancer. Consequently, inconsistent definitions of night-shift work have been used in epidemiologic studies with respect to the exact time interval to be considered the night shift, the minimum number of night shifts to be studied, and the evaluation of fixed night shifts versus rotating night shifts (3). Our questionnaire defined night-shift work as ''starting work after 10 PM at least 3 times a month,'' which approximately corresponds to the definition ''starting work after 7 PM at least once a week,'' which was used in 2 population-based case-control studies (13, 14). In contrast, the 2 nurse cohort studies only included rotating night shifts (8, 9). These studies, which were regarded as notable studies in the IARC evaluation (1), did show a positive association with breast cancer and may indicate that rotating night shifts are more disruptive than regular ''fixed'' shifts. Our questionnaire did not capture data on rotating versus fixed shifts and other unknown, potentially important aspects of night-shift work. Resulting misclassification of exposures might help to explain the lack of an association in this study and some of the other studies.

When using a job exposure matrix, it is difficult to take into account the frequency or timing of night shifts. The inclusion of all jobs with the potential for night-shift work in a job exposure matrix could also lead to overestimation of the true prevalence of night-shift work. In our study, 44% of the women had worked in jobs that were classified by the job exposure matrix as potentially involving night-shift work, while only 26% reported a history of night-shift work. Since the occupational histories were obtained prior to cancer diagnosis and assignment of night-shift work was conducted without knowledge of case status, the overestimation of exposure probably resulted in nondifferential misclassification of exposure, which generally tends to bias results towards the null. In our study, neither the job exposure matrix nor self-reported night-shift work revealed an association with breast cancer risk.

To our knowledge, this is the first study of night-shift work and breast cancer risk to have been carried out in a non-Western population. Breast cancer incidence rates in China have traditionally been low in comparison with Western countries, because of differences in diet, reproductive factors, and physical activity. Rising breast cancer incidence in China has been attributed to changes in these risk factors associated with the transition to a more ''Western'' lifestyle (19, 20). The reason for the lack of an association with breast cancer in this Chinese population remains unclear, although known breast cancer risk factors were carefully evaluated and adjusted for in our analyses. Recent work has shown ethnic variability in circadian ''clock'' gene variants (21). These findings raise the possibility of genetic differences in response to night-shift work. Our study cannot rule out this possibility, although the rapid increases in breast cancer incidence with an increasingly Westernized lifestyle suggest similarities in breast cancer etiology among Chinese and Western populations.

In conclusion, this large prospective study did not show an increased risk of breast cancer in relation to night-shift work, adding to the already inconsistent scientific evidence regarding the role of night-shift work in breast cancer development in humans. The inconsistency may be due to limited knowledge on specific aspects of shift work associated with cancer, such as timing, regularity, and light intensity, and suggests that it may be premature to label shift work a probable cause of human cancer.

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