American Journal of Epidemiology

Vol. 186, No. 5
DOI: 10.1093/aje/kwx140
Advance Access publication:
August 3, 2017

Original Contribution

Rotating Night-Shift Work and the Risk of Breast Cancer in the Nurses' Health Studies

Lani R. Wegrzyn, Rulla M. Tamimi, Bernard A. Rosner, Susan B. Brown, Richard G. Stevens, A. Heather Eliassen, Francine Laden, Walter C. Willett, Susan E. Hankinson, and Eva S. Schernhammer*

* Correspondence to Dr. Eva S. Schernhammer, Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, MA 02115 (e-mail: eva.schernhammer@channing.harvard.edu).

Initially submitted April 27, 2016; accepted for publication October 20, 2016.

In 2007, the International Agency for Research on Cancer declared shift work that involved circadian disruption to be a "probable" carcinogen (group 2A), noting that human evidence was limited. Using data from 2 prospective cohort studies, the Nurses' Health Study (1988–2012; $n = 78,516$) and Nurses' Health Study II (1989–2013; $n = 114,559$), we examined associations between rotating night-shift work and breast cancer risk. In the 2 cohorts, there were a total of 9,541 incident invasive breast malignancies and 24 years of follow-up. In the Nurses' Health Study, women with 30 years or more of shift work did not have a higher risk of breast cancer (hazard ratio (HR) = 0.95, 95% confidence interval (95% CI): 0.77, 1.17; P for trend = 0.63) compared with those who never did shift work, although follow-up occurred primarily after retirement from shift work. Among participants in the Nurses' Health Study II, who were younger than participants in the other cohort, the risk of breast cancer was significantly higher in women with 20 years or more of shift work at baseline, reflecting young-adult exposure (HR = 2.15, 95% CI: 1.23, 3.73; P for trend = 0.23), and was marginally significantly higher for women with 20 years or more of cumulative shift work when we used updated exposure information (HR = 1.40, 95% CI: 1.00, 1.97; P for trend = 0.74). In conclusion, long-term rotating night-shift work was associated with a higher risk of breast cancer, particularly among women who performed shift work during young adulthood. Further studies should explore the role of shift work timing on breast cancer risk.

breast cancer; circadian rhythm; estrogen receptor; progesterone receptor; work schedule tolerance

Abbreviations: CI, confidence interval; ER, estrogen receptor; ER–, estrogen receptor–negative; ER+, estrogen receptor–positive; HR, hazard ratio; IARC, International Agency for Research on Cancer; MHT, menopausal hormone therapy; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II; PR, progesterone receptor; PR–, progesterone receptor–negative; PR+, progesterone receptor–positive.

Breast cancer is the most common cancer among women worldwide (1). The noticeably higher prevalence in industrialized nations compared with developing countries suggests that environmental aspects of modern society may play an important role in breast cancer etiology (2). Disruption of the circadian system by exposure to light during the environmental nighttime hours, such as that seen with occupational night-shift work schedules, has been hypothesized to influence carcinogenesis through suppression of melatonin, modulation of sex hormones, or alteration of the expression of peripheral clock genes (3–6). Supporting epidemiologic studies, as well as strong mechanistic data from animal studies, led the International Agency for Research on Cancer (IARC) to classify night-shift work that involves circadian disruption as probably carcinogenic to humans (group 2A) in 2007 (7).

Since the IARC report, 5 meta-analyses with varying approaches and conclusions have been published in an effort to summarize the growing literature on the association between night-shift work and breast cancer risk. He et al. (8), Wang et al. (9), and Jia et al. (10) found moderately increased risks of breast

cancer associated with night-shift work, reporting pooled estimates in the range of 1.19–1.20. The overall estimate from Kamdar et al. (11) was similar in magnitude but was marginally significant. On the basis of only case-control studies, Ijaz et al. (12) reported a 9% increase in the risk of breast cancer for every 5 years of night-shift work, and He et al. reported a 16% increase in the risk of breast cancer for every 10 years of shift work (8). In each of the meta-analyses, the authors cited significant heterogeneity across studies, with differing results by type and quality of study. For all, there was insufficient evidence from cohort studies alone to draw a conclusion about the relationship of shift work and breast cancer risk.

Of the 3 cohort studies published since the IARC decision, there were 2 in which investigators found statistically significant positive associations (13, 14) and 1 in which they found no evidence of an association (15). However, the studies were limited by their small sample sizes (in Knutsson et al., $n = 4{,}036$; in Åkerstedt et al., $n = 13{,}656$) or short follow-up time (in Pronk et al., <5 years for self-reported shift-work exposure).

The analyses from the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS2) were among the few cohort study analyses with prospectively collected data on shift-work exposure that informed the 2007 IARC decision (16, 17). With double the follow-up time and twice as many cases of breast cancer, we are now able to investigate timing of risk, as well as breast cancer tumor markers.

METHODS

The NHS was established in 1976 when 121,701 female registered nurses who were 30–55 years of age returned a mailed questionnaire with detailed information about their lifestyles, occupational and environmental exposures, medication use, and medical conditions. The NHS2 was established in 1989 when 116,430 female registered nurses who were 25–42 years returned a similar questionnaire. Participants in both cohorts have provided updated information biennially thereafter, and the cumulative follow-up in the cohorts is greater than 90%. Both studies are currently ongoing. The Institutional Review Board of Brigham and Women's Hospital (Boston, Massachusetts) approved both studies, and all participants provided informed consent through the return of the initial questionnaire.

Exposure assessment

Rotating night-shift work duration was assessed through self-reported answers to the following question: "What is the total number of years during which you worked rotating night shifts (at least 3 nights/month in addition to days/evenings in that month)?" Data were collected in 1988 for the NHS and in 1989 for the NHS2. In the NHS2, a cumulative shift-work measure was determined by adding baseline history to subsequently updated shift-work information (obtained from a question about the total number of months having worked rotating night shifts in the prior years) collected in 1991, 1993, 1997, 2001, 2005, and, for a subset or women with e-mail addresses who were sent an online questionnaire, in 2007 ($n = 35{,}418$; 34% of participants active in 2007). In addition, the 2001 questionnaire contained a question about shift work in the period of 1995–1997. Answers were very similar to those given on the 1997 questionnaire (Pearson's $r = 0.53$, $P < 0.0001$), indicating that recall of shift-work information was reasonably comparable to information collected in real time. Shift-work information was carried forward for 1 questionnaire cycle in cases of missing data. After that, participants were excluded from analyses until information was again provided (i.e., they contributed person-time only as long as exposure status was captured). Of those asked about current shift-work exposure in 2007, only 8% were still working rotating night shifts. Therefore, for 2009 and subsequent cycles in which shift-work duration was not assessed, zero shift work was assumed.

Outcome assessment

Breast cancer cases were identified as having occurred during the period from June 1, 1988, to June 1, 2012 in the NHS and from June 1, 1989, to June 1, 2013 in the NHS2. Nurses who reported breast cancer were asked for permission for investigators to review their medical records, and breast cancer was confirmed through review of these records. When medical records were unavailable, participants with breast cancer were included in the analyses if their diagnoses were corroborated during a phone interview or via written confirmation from the subject. Approximately two-thirds of the deaths among cohort members were reported to us by next of kin or the postal system in response to follow-up questionnaires. In addition, we searched the National Death Index to identify deaths among the nonrespondents from each 2-year questionnaire. Only confirmed invasive breast cancers (i.e., excluding breast cancer in situ) were included in these analyses.

For secondary analyses of breast cancer by hormone receptor status, estrogen receptor (ER) and progesterone receptor (PR) status were determined using immunohistochemical staining of tumor tissue. The procedures for breast cancer tissue collection, tissue microarray construction, and staining and reading for tumor markers has been described in detail elsewhere (18). When tissue microarray results were unavailable, medical record documentation of ER and PR status was used instead.

Study population for analysis

At baseline (1988 in the NHS and 1989 in the NHS2), there were 103,415 participants in the NHS and 116,430 in the NHS2. Of these, participants with prior cancers except nonmelanoma skin cancer (NHS: 7,957 (8%); NHS2: 1,050 (1%)) and those who did not answer the initial shift-work history question (NHS: 16,942 (16%); NHS2: 581 (<1%)) were excluded. The remaining data sets for analysis comprised 78,516 women aged 42–67 years in the NHS and 114,559 women aged 25–42 years in the NHS2.

Statistical analyses

Cox proportional hazards models were used to calculate hazard ratios and 95% confidence intervals over the entire follow-up period. Because assessments of shift-work exposure differed by cohort (i.e., not updated in NHS; updated in NHS2), models are presented separately for each cohort. Women were categorized according to the duration of rotating night-shift work (NHS: none, 1–14 years, 15–29 years, or ≥30 years; NHS2: none, 1–9 years, 10–19 years, or ≥20 years). All models were simultaneously adjusted for age in

months and time period in 2-year intervals. Participants were censored at the time of breast cancer diagnosis, diagnosis of other cancer (except nonmelanoma skin cancer), or death, whichever came first. Multivariable models were adjusted for the following breast cancer risk factors and possible confounders of the association between shift work and breast cancer: height (inches), current body mass index and body mass index at age 18 years (weight in kilograms divided by height in meters squared), adolescent body size (assessed using pictograms, with scores ranging from 1 to 9), age at menarche and at first birth, parity, breastfeeding history, type of menopause, age at menopause, menopausal hormone therapy (MHT) use, duration of use of estrogen-only MHT, duration of use of combined estrogen and progesterone MHT, first-degree family history of breast cancer, history of benign breast disease, alcohol consumption (g/day), physical activity level (metabolic equivalent-hours/week), and current mammography use. All variables except for height and duration of MHT use by type were included in multivariable-adjusted models as categorical variables with missing indicators. Less than 1% of participants were missing information on height; those participants were excluded. Women with missing information on duration of MHT use by type were given the value of 0 months of MHT use. Body mass index was carried forward for 1 questionnaire cycle to fill in some missing data (3% missing in the NHS and 7% missing in the NHS2 after carrying forward).

We performed tests for trend with continuous exposure measures, using the midpoint of shift-work duration categories and truncating the highest category. All *P* values are 2-sided, and values less than 0.05 were considered statistically significant. SAS software, version 9.3 (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses.

Secondary analyses

Because similar main analyses with approximately half the follow-up time have been previously published (16, 17), we stratified by follow-up time period to separate early versus late associations of rotating night-shift work with breast cancer risk (i.e., ≤10 vs. >10 years of follow-up). To investigate the relationship of breast cancer risk with recency of night-shift work exposure in the NHS2, we ran models using an exposure of never, current, or past shift work with time since stopping shift work. For women who reported shift work at baseline but not thereafter, we assigned a baseline time since stopping by subtracting an assumed start of rotating night-shift work (21 years of age) and duration of reported exposure (lower bound category value, as the most conservative approach) from their current age. We also stratified by menopausal status and breast cancer hormone receptor status of tumors (ER+/PR+, ER+/PR−, or ER−/PR−) (19). Cases of other or missing subtypes were treated as censored events in this competing risks analysis. Wald tests for interaction were used for stratified analyses. The likelihood ratio test was used to test for heterogeneity among the results by ER and PR status. Using NHS2 data, we ran models to assess the relationship between breast cancer and shift-work duration accrued before and after first pregnancy (≥ 6 months of gestation) and before and after menopause. The measures of shift work before and after each life "event" were treated as continuous variables and included in the models together to determine the associations independent of the other measure. For these pregnancy and menopause analyses, we excluded women who were parous ($n = 81,529$) and postmenopausal ($n = 2,720$) at baseline in 1989 because shift work reported at baseline could not be attributed to either time period. To account for possible bias due to differential mammography screening, we performed a secondary analysis using inverse probability weighting by predicted mammography use (20).

RESULTS

During 24 years of follow-up, we documented 9,541 total invasive breast cancers (5,971 in the NHS and 3,570 in the NHS2), with a median time to breast cancer event of 13 years in the NHS and 14 years in the NHS2. The distributions of age-adjusted baseline characteristics of the NHS and NHS2 cohorts across categories of shift work are shown in Table 1. Briefly, participants in the NHS sample were roughly 20 years older than those in the NHS2, and those in the highest shift-work category were approximately 6 years older than those with no shift-work exposure in both cohorts. In addition, compared with those who had never done shift work, women with the highest levels of shift work at baseline in both cohorts (≥30 years in the NHS, ≥20 years in the NHS2) were heavier, more likely to have had menarche before age 12 years, and more likely to be current smokers (with more pack-years of smoking) but consumed less alcohol. They also had lower percentages with benign breast disease, although this could be because of their lower mammography use.

Table 2 shows the relationship between rotating night-shift work and breast cancer risk. In the NHS, we observed no association between duration of rotating night-shift work and breast cancer risk (for ≥30 years vs. 0 years, multivariable-adjusted hazard ratio (HR) = 0.95, 95% confidence interval (CI): 0.77, 1.17; *P* for trend = 0.63). By contrast, in the NHS2, 20 years or more of rotating night-shift work at baseline was associated with a significantly higher risk of breast cancer (for ≥20 years at baseline vs. 0 years, multivariable-adjusted HR = 2.15, 95% CI: 1.23, 3.73; *P* for trend = 0.23). Women with 20 years or more of cumulative rotating night-shift work exposure had a marginally significant higher risk of breast cancer (for ≥20 years of cumulative shift work vs. 0 years, multivariable-adjusted HR = 1.40, 95% CI: 1.00, 1.97; *P* for trend = 0.74).

Stratification by follow-up period in the NHS2 cohort showed a statistically significant higher risk of breast cancer during the first 10 years of follow-up, whereas a small increasing trend in risk was seen in the NHS cohort (see Table 3). No significant positive associations were observed in either cohort after more than 10 years of follow-up. The interaction of shift work with follow-up time period was statistically significant for NHS participants (*P* for interaction = 0.03)

In the NHS2, we observed no significant associations of breast cancer risk with current or past shift work or with different times since stopping working night shifts as compared with never doing shift work (for current shift work, multivariable-adjusted HR = 0.89, 95% CI: 0.78, 1.02; for <10 years since stopping shift work, multivariable-adjusted HR = 0.88, 95% CI: 0.78, 1.00; for 10–19 years since stopping, multivariable-adjusted HR = 1.05, 95% CI: 0.95, 1.16; for ≥20 years since stopping, multivariable-adjusted HR = 1.08, 95% CI: 0.99, 1.19). Shift-work duration accrued before

Table 1. Age-Adjusted Baseline Characteristics by Categories of Rotating Night-Shift Work Duration in the Nurses' Health Study ($n = 78,516$), 1988, and Nurses' Health Study II ($n = 114,559$), 1989

Characteristic	Years of Rotating Night-Shift Work by Study															
	NHS								NHS2							
	None ($n = 31,746$)		1–14 ($n = 40,966$)		15–29 ($n = 4,424$)		≥30 ($n = 1,380$)		None ($n = 43,529$)		1–9 ($n = 65,783$)		10–19 ($n = 5,085$)		≥20 ($n = 162$)	
	Mean (SD)[a]	%[a]	Mean (SD)[a]	%[a]	Mean (SD)[a]	%[a]	Mean (SD)[a]	%[a]	Mean (SD)[a]	%[a]	Mean (SD)[a]	%[a]	Mean (SD)[a]	%[a]	Mean (SD)[a]	%[a]
Age, years	54.3 (7.2)		54.7 (7.1)		56.1 (6.9)		60.4 (4.6)		34.8 (4.7)		34.6 (4.7)		37.2 (3.4)		41.0 (2.4)	
Height, inches	64.5 (2.4)		64.5 (2.4)		64.4 (2.5)		64.5 (2.5)		64.9 (2.6)		64.9 (2.6)		64.9 (2.7)		63.9 (2.9)	
BMI[b]	25.3 (4.8)		25.6 (4.9)		27.0 (5.5)		26.6 (5.2)		23.9 (4.9)		24.1 (5.1)		25.3 (5.9)		24.8 (5.8)	
BMI[b] at age 18 years	21.2 (2.9)		21.3 (3.0)		21.9 (3.4)		21.9 (3.7)		21.2 (3.2)		21.3 (3.4)		22.0 (4.1)		21.3 (4.2)	
Childhood body size[c]	2.4 (1.3)		2.4 (1.3)		2.4 (1.4)		2.3 (1.4)		2.6 (1.2)		2.6 (1.2)		2.7 (1.3)		2.6 (1.3)	
Adolescent body size[c]	2.7 (1.2)		2.7 (1.2)		2.7 (1.3)		2.7 (1.3)		2.9 (1.1)		2.9 (1.1)		3.0 (1.2)		2.7 (1.2)	
Menarche before age 12 years		22		23		24		30		24		25		29		35
Ever use of OCs		49		49		46		44		83		83		83		57
Nulliparous		5		6		6		6		28		32		36		42
No. of children[d]	3.2 (1.5)		3.1 (1.5)		3.2 (1.6)		3.2 (1.6)		2.1 (0.9)		2.0 (0.9)		2.1 (0.9)		2.0 (0.7)	
Age at first birth, years[d]	24.9 (3.2)		25.3 (3.4)		24.9 (3.5)		25.3 (3.1)		25.2 (4.0)		25.7 (4.1)		25.3 (4.1)		23.0 (3.5)	
Ever breastfed[d]		47		49		47		43		48		46		39		32
Postmenopausal		67		68		70		86		2		2		3		4
Menopause because of surgery[e]		41		42		44		40		93		92		96		88
Current MHT use[e]		35		35		29		29		83		79		84		82
Age at menopause, years[e]	48.8 (4.8)		48.7 (4.8)		48.3 (4.7)		48.4 (4.3)		37.7 (4.3)		37.5 (4.7)		37.4 (3.6)		40.4 (0.8)	
First-degree family history of breast cancer		11		11		11		12		6		6		5		2
History of benign breast disease		37		38		34		30		28		29		27		17
Current smoker		17		19		25		25		12		13		19		23
Pack-years of smoking[f]	23.1 (19.5)		23.2 (19.4)		26.1 (20.0)		26.2 (20.0)		11.4 (8.2)		11.3 (8.2)		11.8 (8.3)		12.3 (7.6)	
Alcohol consumption, g/day	6.1 (10.6)		6.3 (10.7)		5.3 (10.5)		5.5 (9.7)		3.0 (6.0)		3.2 (6.1)		2.9 (6.1)		1.3 (4.4)	
Physical activity, MET-hours/week	14.6 (20.8)		16.0 (21.9)		16.1 (21.7)		19.3 (28.3)		22.7 (34.2)		26.0 (37.9)		32.8 (48.4)		25.7 (56.2)	
Nurse's educational level of bachelor's or higher[g]		31		30		24		22		N/A		N/A		N/A		N/A
Husband's educational level of college or higher[h]		55		56		42		49		80		83		80		90
Ever had a mammogram		77		76		70		72		38		37		34		29

Abbreviations: BMI, body mass index; MET, metabolic equivalent; MHT, menopausal hormone therapy; N/A, not applicable; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II; OC, oral contraceptive.
[a] Values are standardized to the age distribution of the study population.
[b] Weight (kg)/height $(m)^2$.
[c] Body size was recalled using pictures of body outlines that were numbered 1–9 from leanest to fattest.
[d] Among parous women only.
[e] Among postmenopausal women only.
[f] Among smokers only.
[g] Collected in 1992 for NHS only.
[h] Among married or widowed women only (collected in 1992 for NHS; collected in 1999 for NHS2).

Table 2. Associations of Duration of Rotating Night-Shift Work and Invasive Breast Cancer During 24 Years of Follow-up in the Nurses' Health Study, 1988–2012, and the Nurses' Health Study II, 1989–2013

Exposure Measure	No. of Cases	No. of Person-Years	Age Adjusted		Multivariable Adjusted[a]		
			HR	95% CI	HR	95% CI	*P* for Trend
NHS rotating night-shift work history, years	5,971	1,568,438[b]					0.63
None	2,382	640,594	1.00	Referent	1.00	Referent	
1–14	3,162	817,778	1.03	0.98, 1.09	1.01	0.96, 1.07	
15–29	331	84,887	1.02	0.91, 1.14	1.06	0.94, 1.19	
≥30	96	25,178	0.92	0.75, 1.13	0.95	0.77, 1.17	
NHS2 1989 baseline rotating night-shift work history, years	3,570	2,570,855					0.23
None	1,318	978,847	1.00	Referent	1.00	Referent	
1–9	2,071	1,475,921	1.06	0.99, 1.13	1.05	0.98, 1.13	
10–19	168	112,752	0.94	0.80, 1.10	1.00	0.85, 1.17	
≥20	13	3,335	1.83	1.05, 3.17	2.15	1.23, 3.73	
NHS2 cumulative rotating night-shift work (updated), years[c]	3,188	2,214,524[b]					0.74
None	950	675,209	1.00	Referent	1.00	Referent	
1–9	2,002	1,384,743	1.03	0.96, 1.12	1.04	0.96, 1.12	
10–19	201	140,868	0.90	0.77, 1.05	0.94	0.81, 1.10	
≥20	35	13,705	1.29	0.92, 1.81	1.40	1.00, 1.97	

Abbreviations: CI, confidence interval; HR, hazard ratio; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II.

[a] Multivariable-adjusted models were adjusted for the following covariates: age (months), height (inches; continuous), body mass index (weight (kg)/height (m)^2; <18.5, 18.5–24.9, 25.0–29.9, or ≥30), body mass index at age 18 years (<18.5, 18.5–24.9, 25.0–29.9, or ≥30), adolescent body size (average of diagram scores at ages 10 and 20 years; 1.0, 1.5–2.0, 2.5–3.0, 3.5–4.0, or ≥4.5), age at menarche (<12, 12–13, or ≥14 years), age at first birth and parity combined (for NHS: nulliparous, age <25 years and 1–2 children, age <25 years and ≥3 children, age 25–29 years and 1–2 children, age 25–29 years and ≥3 children, age ≥30 years and 1–2 children, or age ≥30 years and ≥3 children; for NHS2: nulliparous, parous age <25 years, parous age 25–29 years, or parous age ≥30 years), breastfeeding (for NHS: none, 1–11 months, or ≥12 months; for NHS2: none, 1–12 months, or >12 months), type of menopause and age at menopause combined (premenopausal, naturally postmenopausal at age <45 years, naturally postmenopausal at age ≥45 years, surgically postmenopausal at age <45 years, or , surgically postmenopausal at age ≥45 years), menopausal hormone therapy use (never, past, or current), duration of use of menopausal hormone therapy with estrogen alone (months; continuous), duration of use of estrogen and progesterone menopausal hormone therapy (months; continuous), first-degree family history of breast cancer (yes or no), history of benign breast disease (yes or no), alcohol consumption (0.0, 0.1–14.0, 14.1–28.0, or >28 g/day), physical activity level (≤8.0, 8.1–16.0, 16.1–24.0, or >24 metabolic equivalent-hours/week), and current mammography use (yes or no). All categorical covariates were included in models with missing indicators.

[b] Values do not sum to the total because of rounding.

[c] In the NHS2, analyses using updated data on duration of shift work excluded participants during the cycles in which they were missing information on shift work exposure, resulting in fewer cases and person-years than in analyses using history of shift work reported at baseline in 1989.

and after first pregnancy (modeled as continuous in years) was not associated with breast cancer risk (for shift work accrued before pregnancy, multivariable-adjusted HR = 1.01, 95% CI: 0.99, 1.03; $P = 0.23$; for shift work accrued after pregnancy, multivariable-adjusted HR = 0.93, 95% CI: 0.84, 1.02; $P = 0.12$).

The interaction of shift work with menopausal status was not significant ($P = 0.17$), and duration of shift work accrued before and after menopause (modeled as continuous in years) was not associated with breast cancer risk in the NHS2 (for shift work accrued before menopause, multivariable-adjusted HR = 1.00, 95% CI: 0.99, 1.01; $P = 0.90$; for shift work accrued after menopause, multivariable-adjusted HR = 0.98, 95% CI: 0.90, 1.06; $P = 0.54$). We also saw no evidence of heterogeneity by ER and PR status (in the NHS, P for heterogeneity = 0.18; in the NHS2, baseline P for heterogeneity = 0.48 and cumulative P for heterogeneity = 0.70) (see Web Table 1, available at https://academic.oup.com/aje), but the association with ER+/PR+ breast cancer was statistically significant in the NHS2 cumulative shift-work analysis (for ≥20 years of cumulative shift work vs. 0 years,

Table 3. Associations of Duration of Rotating Night-Shift Work and Invasive Breast Cancer, Stratified by Follow-up Period, in the Nurses' Health Study, 1988–2012, and the Nurses' Health Study II, 1989–2013

Exposure Measure	Follow-up ≤10 Years							Follow-up >10 Years							Multivariable *P* for Interaction
	No. of Cases	No. of Person-Years	Age Adjusted		Multivariable Adjusted[a]		*P* for Trend	No. of Cases	No. of Person-Years	Age Adjusted		Multivariable Adjusted[a]		*P* for Trend	
			HR	95% CI	HR	95% CI				HR	95% CI	HR	95% CI		
NHS rotating night-shift work history, years	2,598	735,599					0.04	3,373	819,920					0.25	0.03
None	977	298,701	1.00	Referent	1.00	Referent		1,405	336,729	1.00	Referent	1.00	Referent		
1–14	1,415	383,622	1.11	1.02, 1.21	1.09	1.00, 1.18		1,747	427,392	0.97	0.91, 1.05	0.96	0.89, 1.03		
15–29	146	40,739	1.03	0.86, 1.23	1.07	0.90, 1.28		185	43,381	1.01	0.87, 1.18	1.05	0.90, 1.23		
≥30	60	12,537	1.23	0.95, 1.60	1.26	0.97, 1.64		36	12,418	0.65	0.47, 0.91	0.68	0.49, 0.95		
NHS2 1989 baseline rotating night-shift work history, years	1,116	1,084,864					0.71	2,454	1,452,478					0.24	0.85
None	416	412,724	1.00	Referent	1.00	Referent		902	553,730	1.00	Referent	1.00	Referent		
1–9	637	622,782	1.03	0.91, 1.17	1.02	0.90, 1.15		1,434	833,620	1.07	0.98, 1.16	1.07	0.98, 1.16		
10–19	57	47,867	0.94	0.71, 1.24	0.96	0.73, 1.27		111	63,327	0.94	0.77, 1.14	1.01	0.83, 1.24		
≥20	6	1,491	2.13	0.95, 4.80	2.35	1.04, 5.31		7	1,801	1.63	0.77, 3.45	1.95	0.92, 4.15		
NHS2 cumulative rotating night-shift work (updated), years[b]	1,034	977,132					0.75	2,154	1,213,546[c]					0.89	0.73
None	341	321,600	1.00	Referent	1.00	Referent		609	346,804	1.00	Referent	1.00	Referent		
1–9	621	602,095	0.98	0.86, 1.12	0.97	0.85, 1.11		1,381	767,303	1.06	0.96, 1.16	1.07	0.97, 1.18		
10–19	60	50,481	0.92	0.70, 1.21	0.94	0.71, 1.23		141	88,801	0.90	0.74, 1.07	0.95	0.79, 1.14		
≥20	12	2,956	1.99	1.11, 3.56	2.13	1.19, 3.81		23	10,637	1.10	0.72, 1.66	1.19	0.78, 1.81		

Abbreviations: CI, confidence interval; HR, hazard ratio; NHS, Nurses' Health Study; NHS2, Nurses' Health Study II.

[a] Multivariable-adjusted models were adjusted for the following covariates: age (months), height (inches; continuous), body mass index (weight (kg)/height (m)^2; <18.5, 18.5–24.9, 25.0–29.9, or ≥30), body mass index at age 18 years (<18.5, 18.5–24.9, 25.0–29.9, or ≥30), adolescent body size (average of diagram scores at ages 10 and 20 years; 1.0, 1.5–2.0, 2.5–3.0, 3.5–4.0, or ≥4.5), age at menarche (<12, 12–13, or ≥14 years), age at first birth and parity combined (for NHS: nulliparous, age <25 years and 1–2 children, age <25 years and ≥3 children, age 25–29 years and 1–2 children, age 25–29 years and ≥3 children, age ≥30 years and 1–2 children, or age ≥30 years and ≥3 children; for NHS2: nulliparous, parous age <25 years, parous age 25–29 years, or parous age ≥30 years), breastfeeding (for NHS: none, 1–11 months, or ≥12 months; for NHS2: none, 1–12 months, or >12 months), type of menopause and age at menopause combined (premenopausal, naturally postmenopausal at age <45 years, naturally postmenopausal at age ≥45 years, surgically postmenopausal at age <45 years, or , surgically postmenopausal at age ≥45 years), menopausal hormone therapy use (never, past, or current), duration of use of menopausal hormone therapy with estrogen alone (months; continuous), duration of use of estrogen and progesterone menopausal hormone therapy (months; continuous), first-degree family history of breast cancer (yes or no), history of benign breast disease (yes or no), alcohol consumption (0.0, 0.1–14.0, 14.1–28.0, or >28 g/day), physical activity level (≤8.0, 8.1–16.0, 16.1–24.0, or >24 metabolic equivalent-hours/week), and current mammography use (yes or no). All categorical covariates were included in models with missing indicators.

[b] In the NHS2, analyses using updated data on duration of shift work excluded participants during the cycles in which they were missing information on shift work exposure, resulting in fewer cases and person-years than in analyses using history of shift work reported at baseline in 1989.

[c] Values do not sum to the total because of rounding.

multivariable-adjusted HR = 1.62, 95% CI: 1.07, 2.45). Combining the highest 2 categories of shift work also showed no significant heterogeneity by ER and PR status (in the NHS, *P* for heterogeneity = 0.21; NHS2 baseline *P* for heterogeneity = 0.46; NHS2 cumulative *P* for heterogeneity = 0.54). Further, in analyses stratified by ER status and PR status separately, we saw similar and statistically significant associations with ER+ and PR+ tumors separately for 20 years or more of cumulative shift work in the NHS2 (for ER+ breast cancer, multivariable-adjusted HR = 1.50, 95% CI: 1.01, 2.22; for PR+ breast cancer, multivariable-adjusted HR = 1.57, 95% CI: 1.04, 2.37).

The results from analyses in which we used inverse probability weighting for mammographic screening were not substantially different from the main results from analyses in which we used traditional model adjustment for current mammography use (in the NHS, for ≥30 years vs. 0 years, unweighted multivariable-adjusted HR = 0.97 and weighted multivariable-adjusted HR = 1.00; in the NHS2, for ≥20 years at baseline vs. 0 years, unweighted multivariable-adjusted HR = 2.60 and weighted multivariable-adjusted HR = 2.55; in the NHS2, for ≥20 cumulative years vs. 0 years, unweighted multivariable-adjusted HR = 1.41 and weighted multivariable-adjusted HR = 1.51).

DISCUSSION

In our previously published analyses of the relationship between rotating night-shift work and breast cancer, we observed a statistically significant increased risk in both NHS cohorts with approximately 10–12 years of follow-up (16, 17). The analyses presented in this paper extend these findings with 24 years of follow-up and further explore these relationships by timing of shift work performance and hormone receptor status of tumors.

We saw no association between rotating night-shift work and breast cancer incidence over the full 24 years of follow-up in the NHS cohort. Because of the older age range of the women in the NHS, we may have captured primarily post-retirement time with the expansion of follow-up (only 3% were still working rotating night shifts in 1996) and likely very little additional shift work was accumulated. This may in part explain the lack of an association we observed in the NHS with the additional 14 years of follow-up.

In the NHS2, the younger age of the cohort and the updated exposure information throughout follow-up allowed us to assess breast cancer risk with more recent shift-work exposure. We found a strong positive association with breast cancer among the women who had accumulated 20 years or more of rotating night-shift work early in their careers, in their 20s and 30s. Those participants also contributed to the category of 20 years or more shift work in the cumulative shift-work measure, but they were mixed with women who had different patterns of shift work accumulation after baseline, which likely attenuated this association. Nonetheless, the cumulative measure of shift work was consistent with a marginally significant higher risk of breast cancer. The statistically significant results in the NHS2 cohort were limited to women in the highest exposure category (≥20 years duration), with no evidence of an association among women with shorter periods of exposure.

We explored the associations separately for the first 10 years of follow-up and the remaining 14 years of follow-up in order to understand the long-term findings in the context of our previously published shorter-term associations (16, 17). In both cohorts and for both measures of shift work in the NHS2, we saw a higher risk of breast cancer associated with night-shift work in the earlier portion of follow-up than in the later portion. The estimates were higher in the NHS2, in which the shift work performance was likely closer in proximity to breast cancer risk than in the NHS. We investigated the inverse finding in the latter part of follow-up for the NHS as possibly reflecting a healthy worker effect but did not see any evidence of differential dropping out of the analysis by shift-work category, and we therefore believe it to be due to chance. In the NHS2, we were able to explore current and past shift work with varying time since quitting shift work, and we saw no significant differences in breast cancer risk among shift workers compared with those who never did shift work.

In addition, the duration of shift work may serve as a proxy for recency of exposure. Data from the Current Population Survey in the United States (21) suggests that a large proportion of people who work night shifts do so to accommodate schooling and childcare needs, presumably at young ages. Results from other work (22) suggest that most nurses in our cohorts who engaged in shift work did so before the age of 25 years, possibly during training programs. Longer durations of shift work in this population likely included shift work that occurred during training and then continued on, closer to breast cancer diagnosis. In other populations, researchers who have found a significant association with duration of shift work have done so with durations of at least 15 years (23–25).

Further, timing of shift work with respect to breast tissue development may be critical. In our analyses, the strongest associations with breast cancer risk were for those women who worked rotating night shifts for 20 years or more early in their careers as young adults. Similarly, in a lagged analysis, Lie et al. (23) found that when the 20 years closest to breast cancer diagnosed were disregarded, women who had accumulated 15 years or more of shift work before that had a suggestive higher risk of breast cancer (odds ratio = 1.55; 95% CI: 0.87, 2.78). The early-career time in these nurses might be within a window of major breast tissue change—the period between onset of puberty and breast involution due to childbirth (postlactational) or aging (lobular)—and might therefore be a period during which they are vulnerable to cancer risk factors (26).

In 2 recent studies, when comparing women who had done shift work with those who had not, researchers found that women exposed to night-shift work before their first full-term pregnancies had higher risks of breast cancer than did those exposed after first full-term pregnancies (27, 28). We further explored shift work before and after first pregnancy and its relationship with breast cancer risk in the NHS2, but results were null. This may in part have been due to exclusion of women who were parous at baseline (70%) because reported shift work at baseline could not be attributed to either the pre- or postpregnancy period. Thus, we may have missed the relevant time window in this secondary analysis. Additional analyses in data sets that allow for separation of shift-work exposure with respect to such early-career events are warranted.

In addition, because circulating estradiol levels have been reported to be higher in night-shift workers than in day-shift

workers (29), we evaluated the association between shift work and breast cancer by presence of ERs and PRs in the tumor tissue. Small numbers in the highest categories of shift-work duration limited determination of statistically significant heterogeneity. However, NHS2 results indicated a potentially stronger association with ER+/PR+ tumors, which supports the hypothesized hormonal pathway for shift work to affect breast cancer risk.

Finally, because night-shift workers are less likely to adhere to screening guidelines for breast cancer (28) and we noted lower proportion of mammography use with increasing shift work duration in our data, we ran models using inverse probability weights for likelihood of mammography based on factors that have been shown to predict screening behavior (30). We saw little evidence of bias in our main results due to differential screening practices, and it is unlikely that such bias may have distorted an association.

The NHS and NHS2 cohorts provide rich data that allow us to examine the association of rotating night-shift work and breast cancer, but they also have several notable limitations. In the NHS, shift-work exposure was assessed once as the lifetime duration of shift work near the end of the nurses' working careers. However, the NHS2 captured shift-work duration at an earlier age and then updated it throughout follow-up. Rotating night-shift work for a given month was defined as 3 or more night shifts on a rotating schedule in addition to other day/evening shifts in that month; in other words, a nurse with 20 years of night shifts who was not on a rotating shift schedule may have answered "none" to this question. Also, although night-shift workers may get more exposure to electric light at night than day-shift workers, almost all persons in the modern world are exposed to light at night, at least in the evening. It has been shown in controlled studies in the laboratory that such lighting can delay melatonin onset and duration, depending on intensity and wavelength (31). Thus, our exposure definition itself might not have captured the intensity or pattern of night-shift work that is most disruptive and may have limited our ability to identify a dose-response relationship.

In addition, although we captured 5,078 breast cancer cases in the NHS and 2,789 breast cancer cases in the NHS2 with information on ER and PR status, power was still limited in the highest exposure categories. We were also unable to evaluate breast cancer risk by histologic type because the number of lobular breast cancers was low.

Still, the NHS and NHS2 are among the largest prospective cohort studies available for quantifying the relationship between rotating night-shift work and breast cancer. They are unique in their ability to prospectively measure night-shift work, as well as most of the lifestyle and reproductive factors that are important for breast cancer development. The studies also include long follow-up and a large number of breast cancer cases to allow exploration of risk patterns over time, as well as some analyses by subtypes of breast cancer.

The updated long-term findings in the NHS and NHS2 cohorts have important implications for future IARC evaluations of the association between shift work and breast cancer. Our results may serve to put the literature into the context of short-term versus long-term associations and suggest that there may be a period of increased risk of developing breast cancer that may wane with time. Our results also suggest that performance of shift work during younger adulthood may be particularly relevant. In future studies, investigators should explore the role of age at shift-work performance in the association with breast cancer risk.

ACKNOWLEDGMENTS

Author affiliations: Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Lani R. Wegrzyn, Rulla M. Tamimi, Bernard A. Rosner, A. Heather Eliassen, Francine Laden, Walter C. Willett, Susan E. Hankinson, Eva S. Schernhammer); Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Lani R. Wegrzyn, Rulla M. Tamimi, A. Heather Eliassen, Francine Laden, Walter C. Willett, Eva S. Schernhammer); Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Bernard A. Rosner); Division of Biostatistics and Epidemiology, University of Massachusetts, Amherst, Massachusetts (Susan B. Brown, Susan E. Hankinson); Department of Community Medicine, University of Connecticut Health Center, Farmington, Connecticut (Richard G. Stevens); Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Francine Laden); Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Walter C. Willett); Department of Epidemiology, Medical University of Vienna, Vienna, Austria (Eva S. Schernhammer); and Applied Cancer Research-Institution for Translational Research Vienna (ACR-ITR VIEnna), Vienna, Austria (Eva S. Schernhammer).

This work was supported by Centers for Disease Control and Prevention/The National Institute for Occupational Safety and Health grant R01OH009803 (principal investigator, E.S.S.). The Nurses' Health Study and Nurses' Health Study 2 cohorts are supported by The National Institutes of Health grants UM1CA186107 (principal investigator, Meir Stampfer) and UM1CA176726 (principal investigator, W.C.W.). L.R.W. was supported in part by the National Institutes of Health training grant R25CA098566.

The authors would like to thank the cancer registries of the following states for their help: Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Delaware, Florida, Georgia, Idaho, Illinois, Indiana, Iowa, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Michigan, Nebraska, New Hampshire, New Jersey, New York, North Carolina, North Dakota, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Carolina, Tennessee, Texas, Virginia, Washington, Wyoming.

The authors assume full responsibility for analyses and interpretation of these data.

Conflict of interest: none declared.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, et al. Estimating the world cancer burden: Globocan 2000. *Int J Cancer*. 2001;94(2):153–156.
2. Stevens RG, Brainard GC, Blask DE, et al. Breast cancer and circadian disruption from electric lighting in the modern world. *CA Cancer J Clin*. 2014;64(3):207–218.

3. Hill SM, Belancio VP, Dauchy RT, et al. Melatonin: an inhibitor of breast cancer. *Endocr Relat Cancer*. 2015; 22(3): R183–R204.
4. Schernhammer ES, Rosner B, Willett WC, et al. Epidemiology of urinary melatonin in women and its relation to other hormones and night work. *Cancer Epidemiol Biomarkers Prev*. 2004;13(6):936–943.
5. Navara KJ, Nelson RJ. The dark side of light at night: physiological, epidemiological, and ecological consequences. *J Pineal Res*. 2007;43(3):215–224.
6. Haus E, Smolensky M. Biological clocks and shift work: circadian dysregulation and potential long-term effects. *Cancer Causes Control*. 2006;17(4):489–500.
7. Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol*. 2007;8(12): 1065–1066.
8. He C, Anand ST, Ebell MH, et al. Circadian disrupting exposures and breast cancer risk: a meta-analysis. *Int Arch Occup Environ Health*. 2014;88(5):533–547.
9. Wang F, Yeung KL, Chan WC, et al. A meta-analysis on dose-response relationship between night shift work and the risk of breast cancer. *Ann Oncol*. 2013;24(11):2724–2732.
10. Jia Y, Lu Y, Wu K, et al. Does night work increase the risk of breast cancer? A systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiol*. 2013;37(3): 197–206.
11. Kamdar BB, Tergas AI, Mateen FJ, et al. Night-shift work and risk of breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat*. 2013;138(1):291–301.
12. Ijaz S, Verbeek J, Seidler A, et al. Night-shift work and breast cancer—a systematic review and meta-analysis. *Scand J Work Environ Health*. 2013;39(5):431–447.
13. Knutsson A, Alfredsson L, Karlsson B, et al. Breast cancer among shift workers: results of the WOLF longitudinal cohort study. *Scand J Work Environ Health*. 2013;39(2): 170–177.
14. Åkerstedt T, Knutsson A, Narusyte J, et al. Night work and breast cancer in women: a Swedish cohort study. *BMJ open*. 2015;5(4):e008127.
15. Pronk A, Ji BT, Shu XO, et al. Night-shift work and breast cancer risk in a cohort of Chinese women. *Am J Epidemiol*. 2010;171(9):953–959.
16. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst*. 2001;93(20): 1563–1568.
17. Schernhammer ES, Kroenke CH, Laden F, et al. Night work and risk of breast cancer. *Epidemiology*. 2006;17(1):108–111.
18. Tamimi RM, Baer HJ, Marotti J, et al. Comparison of molecular phenotypes of ductal carcinoma in situ and invasive breast cancer. *Breast Cancer Res*. 2008;10(4):R67.
19. Hefti MM, Hu R, Knoblauch NW, et al. Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. *Breast Cancer Res*. 2013;15(4):R68.
20. Cook NR, Rosner BA, Hankinson SE, et al. Mammographic screening and risk factors for breast cancer. *Am J Epidemiol*. 2009;170(11):1422–1432.
21. McMenamin TM. Time to work: recent trends in shift work and flexible schedules. *Monthly Lab Rev*. 2007;130:3–15.
22. Ramin C, Devore EE, Wang W, et al. Night shift work at specific age ranges and chronic disease risk factors. *Occup Environ Med*. 2015;72(2):100–107.
23. Lie JA, Roessink J, Kjærheim K. Breast cancer and night work among Norwegian nurses. *Cancer Causes Control*. 2006; 17(1):39–44.
24. Hansen J, Lassen CF. Nested case-control study of night shift work and breast cancer risk among women in the Danish military. *Occup Environ Med*. 2012;69(8):551–556.
25. Hansen J, Stevens RG. Case-control study of shift-work and breast cancer risk in Danish nurses: impact of shift systems. *Eur J Cancer*. 2012;48(11):1722–1729.
26. Trichopoulos D, Adami HO, Ekbom A, et al. Early life events and conditions and breast cancer risk: from epidemiology to etiology. *Int J Cancer*. 2008;122(3):481–485.
27. Papantoniou K, Castaño-Vinyals G, Espinosa A, et al. Breast cancer risk and night shift work in a case-control study in a Spanish population. *Eur J Epidemiol*. 2015:31(9):1–12.
28. Menegaux F, Truong T, Anger A, et al. Night work and breast cancer: A population-based case–control study in France (the CECILE study). *Int J Cancer*. 2013;132(4):924–931.
29. Bracci M, Manzella N, Copertaro A, et al. Rotating-shift nurses after a day off: peripheral clock gene expression, urinary melatonin, and serum 17-β-estradiol levels. *Scand J Work Environ Health*. 2014;40(3):295–304.
30. Tsai RJ, Luckhaupt SE, Sweeney MH, et al. Shift work and cancer screening: do females who work alternative shifts undergo recommended cancer screening? *Am J Ind Med*. 2014; 57(3):265–275.
31. Gooley JJ, Chamberlain K, Smith KA, et al. Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. *J Clin Endocrinol Metab*. 2011; 96(3):E463–E472.