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# ROTATING NIGHT SHIFT WORK AND RISK OF INVASIVE BREAST CANCER IN WOMEN OF THE NHS AND NHS II COHORTS: 24 YEARS OF FOLLOW-UP

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## Abstract

**Objective—**To evaluate associations between duration of rotating night shift work and invasive breast cancer in female nurses participating in two large longitudinal cohort studies.

**Background—**The International Agency for Research on Cancer (IARC) declared shift work that involves circadian disruption to be probably carcinogenic to humans (Group 2A) in 2007, citing earlier results from these cohorts. This analysis updates these findings with twice the follow-up time.

**Methods—**We conducted an analysis among women in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II) with baseline (1988 for NHS: n=78,516 women ages 42-67; and 1989 for NHS II: n=114,559 women ages 24-42) as well as updated (NHS II only) lifetime rotating night shift work history. Follow-up for incident invasive breast cancer continued for 24 years (NHS: 1988–2012, NHS II: 1989–2013). We used multivariable-adjusted Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI).

**Results—**During 24 years of follow-up, we documented 9,541 invasive breast cancer cases (NHS: 5,971; NHS II: 3,570). Compared to women who never worked rotating night shifts,

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**DECLARATION OF INTEREST**

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

women in NHS with 30+ years of rotating night shift work at baseline did not experience an increased risk of breast cancer ($HR_{30+\ yrs\ vs\ 0\ yrs}$=0.95, 95%CI 0.77-1.17; $p_{trend}$=0.63), However, in NHS II, breast cancer risk of women with 20+ years of rotating night shift work at baseline was significantly increased ($HR_{20+\ yrs\ vs\ 0\ yrs}$=2.16, 95%CI 1.24-3.76; $p_{trend}$=0.23). Cumulative rotating night shift work (using updated exposure information) was associated with a marginally significant increased risk of breast cancer (NHS II only; $HR_{20+\ yrs\ vs\ 0\ yrs}$=1.41, 95%CI 1.00-1.97; $p_{trend}$=0.73). The associations with breast cancer risk did not differ significantly by menopausal status at cancer diagnosis or estrogen and progesterone receptor status of tumors.

**Conclusions—**Results from our updated analyses of rotating night shift work and breast cancer risk are consistent with long-term rotating night shift work being associated with an increased risk of breast cancer. The addition of follow-up time in NHS, which occurred primarily post retirement, eliminated a previously observed increase in risk in these women and suggests that their heightened risk may wane with time.

### Keywords

breast cancer; night shift work; work schedule; circadian disruption; hormone receptor

## INTRODUCTION

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 with exposure to light during the environmental nighttime hours as with occupational night shift work schedules has been hypothesized to influence carcinogenesis through suppression of melatonin, modulation of sex hormones, or altered expression of peripheral clock genes.[3,4,5,6] 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, five systematic reviews and meta-analyses have been published in an effort to summarize the growing literature on the association between night shift work and breast cancer risk, with varying approaches and conclusions. He et al, Wang et al, and Jia et al found moderate increased risk of breast cancer with night shift work overall, in the range of 1.19-1.20.[8,9,10] The overall estimate from Kamdar et al was similar in magnitude but did not reach statistical significance.[11] Ijaz et al reported a 5% increased risk of breast cancer for every 5 years of shift work.[12] Each of the meta-analyses cited significant heterogeneity among 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.

Among the three cohort studies published since the IARC decision, two found significant positive associations[13,14] and one found no evidence of an association[15]. However, they were limited by their small sample sizes (Knutsson et al n=4036, Akerstedt et al n=13,656) or short follow-up time (Pronk et al less than 5 yrs for self-reported shift work exposure).

The Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II) were among the few cohort study analyses with prospectively collected shift work exposure that informed the 2007 IARC decision.[16,17] With double the follow-up time and twice as many breast cancer cases, the NHS cohorts remain among the most powerful cohort studies worldwide to further evaluate the association of rotating night shift work and breast cancer. With the additional cases accrued, we are now also able to investigate the timing of risk and as well as some breast cancer tumor markers.

## METHODS

The Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II) provided longitudinal data for these analyses. The NHS was established in 1976 when 121,701 female registered nurses, ages 30-55, returned a mailed questionnaire with detailed information about their lifestyles, occupational and environmental exposures, medication use, and medical conditions. The NHS II was established in 1989 when 116,430 female registered nurses, ages 24-42, returned a similar questionnaire. Participants in both cohorts have provided updated information biennially thereafter, and follow-up in the cohorts is >90%. Both studies are currently ongoing. Medical outcomes and death are determined through active reporting by the nurses or next-of-kin on the questionnaires and through passive follow-up from the National Death Index. The Institutional Review Board of Brigham & Women's Hospital (Boston, MA) approved both studies, and all participants provided informed consent through the return of the initial questionnaire.

### Study population for analysis

For this analysis, baseline was considered to be the first year that the shift work history question was asked: 1988 for NHS, twelve years after the start of the cohort, and 1989 for NHS II, the initial year of the cohort. At baseline, 103,415 participants were active in NHS and 116,430 participants were active in NHS II. Of these, participants with prior cancers except non-melanoma skin cancer (NHS: 7957 (8%); NHS II: 1050 (1%)) and those who did not answer the initial shift work history question (NHS: 16,942 (16%); NHS II: 581 (<1%)) were excluded. The remaining datasets for analysis comprised 78,516 women, ages 42-67, in NHS and 114,559 women, ages 24-42, in NHS II.

### 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)?" This question was asked of all participants in the NHS in 1988 using the following response categories: Never, 1-2, 3-5, 6-9, 10-14, 15-19, 20-29 and 30 years or more. For our analyses, these exposure categories were collapsed into never, 1-14 yrs, 15-29 yrs and 30+ yrs.

In NHS II, two measures were used to capture different aspects of shift work exposure. Baseline rotating night shift work history in NHS II was asked in 1989 when the cohort was aged 24-42 and reflected early-career exposure. This exposure measure was determined using the same rotating night shift work question as was asked in NHS (see above). A

cumulative shift work measure was determined by summing baseline history and subsequently updated duration information, collected in 1991, 1993, 1997, 2001, 2005 and for a subset or women with email addresses who were sent an online questionnaire in 2007 (N=35,418, 34% of participants active in 2007). Therefore, the cumulative shift work measure reflected more career-long exposure. Both exposure measures for NHS II were categorized as never, 1-9 yrs, 10-19 yrs and 20+ yrs of rotating night shift work.

Each question that followed a gap in exposure assessment was asked in such a way as to allow for determination of months of shift work accumulated in each prior two-year cycle. In addition, the 2001 questionnaire asked about shift work in the period 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 to fill in gaps was comparable to real-time collected information. If no shift work information was available for a given cycle, the value from the previous cycle was used to fill in the missing information. If the information was also missing in the previous cycle, participants were excluded from analyses for that cycle and subsequent cycles until or if 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 when shift work was not assessed, zero shift work was assumed rather than carrying forward previous information.

## Outcome assessment

NHS and NHS II participants are continuously followed for incident breast cancer. For these analyses, follow-up cutoffs were chosen as June 2012 for NHS and June 2013 for NHS II, yielding 24 years of follow-up (NHS: 1988–2012; NHS II: 1989–2013). Participants directly reported breast cancers in the biennial questionnaires, and were then individually contacted for confirmation and to gain access to medical records for more information. An additional small percentage of breast cancers were identified through National Death Index reports for which the primary cause of death was stated as breast cancer. Invasive breast cancers (i.e. excluding breast cancer in situ) that were confirmed either by follow-up contact with the nurse participant, medical record review or death certificate were used in these analyses.

For secondary analyses of breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status, hormone markers were determined by immunohistochemical staining of tumor tissue. The breast cancer tissue collection, tissue microarray (TMA) construction, and staining and reading for tumor markers has been described in detail elsewhere.[18] When TMA results were unavailable, medical record documentation of ER and PR status was used instead. ER and PR status was not available for 14% of the cancers in NHS and 7% of the cancers in NHS II.

## Covariate assessment

The following covariates were collected by questionnaire and were considered for inclusion in all multivariable-adjusted models as potential confounders or breast cancer risk factors in both cohorts, unless otherwise noted: height, body mass index (BMI), BMI at age 18, childhood body size (average of age 5 and age 10 diagrams), adolescent body size (average

of age 10 and age 20 diagrams), age at menarche, oral contraceptive use, age at first birth, parity, breastfeeding duration, menopausal status, type of menopause (natural or surgical), age at menopause, menopausal hormone therapy (MHT) use and duration of types of MHT, first degree family history of breast cancer, personal history of benign breast disease, smoking status and frequency, alcohol consumption, nurse's highest education level (NHS only), husband's highest education level, and mammography use.

As several covariates have common reference categories, combination variables were created to allow for multiple to be used in the same model. Specifically, age at first birth and parity were combined and categorized as nulliparous, age <25 yrs and 1-2 kids, age <25 yrs and 3+ kids, age 25-29 and 1-2 kids, age 25-29 and 3+ kids, age 30+ and 1-2 kids, and age 30+ and 3+ kids in NHS. In NHS II, a younger cohort at baseline, broader categories were needed: nulliparous, parous and age <25 yrs, parous and age 25-29, and parous and age 30+. In both cohorts, menopausal status, type of menopause and age at menopause were combined and categorized as premenopausal, natural menopause age <45 yrs, natural menopause age 45+ yrs, surgical menopause age <45 yrs, surgical menopause age 45+ yrs. See Table 2 footnotes for specific categorizations of other covariates.

All variables except for height and duration of MHT by type were included in multivariable models as categorical variables with missing indicators. Less than 1% of participants were missing information on height and were excluded. Those with missing type of were given the value of 0 months of MHT. BMI was carried forward for one cycle to fill in some missing BMI due to underreporting of weight (NHS: 9% missing reduced to 3% after carrying forward; NHS II: 14% reduced to 7%).[19]

## Statistical analyses

Cox proportional hazards models were used to calculate hazard ratios (HR) and 95% confidence intervals (CI) over the entire follow-up period. As exposure assessment differed by cohort (i.e. not updated in NHS; updated in NHS II), models were run separately in each study's dataset. All models were simultaneously adjusted for age in months and time period in two-year intervals. Participants were censored at time of breast cancer diagnosis, diagnosis of other cancer (except non-melanoma skin cancer) or death, whichever came first.

Multivariable models were adjusted for breast cancer risk factors and possible confounders of the shift work and breast cancer association. Each covariate was added into the age-adjusted model individually to see if the exposure-outcome associations changed appreciably. All covariates were included in the final multivariable-adjusted model because they either changed the estimate (i.e. they were confounders) or were associated with the outcome and thereby improved precision. Childhood body size and adolescent body size were highly correlated, so only adolescent body size was used as it was more strongly related to the outcome. See Table 2 footnotes for the complete list of covariates included in the multivariable models.

Statistical significance in the main analyses was determined by Wald chi-square tests. Tests for trend were performed with continuous exposure measures using the midpoint of shift work duration categories and truncating the highest category. All p-values are two-sided and

values less than 0.05 were considered statistically significant. SAS software, version 9 (SAS Institute, Cary, North Carolina, United States) was used for all statistical analyses.

### Secondary analyses

As similar main analyses with approximately half the follow-up time were previously published,[16,17] we ran models stratified by follow-up time period in both cohorts to separate early vs. late effects (i.e. ≤10 and >10 years of follow-up). To investigate the relationship of breast cancer risk with recency of night shift work exposure, we also ran models using an exposure variable separating never, current and past shift work, with categories for different times since stopping shift work, in the full dataset as well as a reduced dataset restricted to ever shift workers. Since updated shift work information was needed, this analysis was only possible in NHS II. Women were deemed to have stopped shift work at the last cycle with reported shift work information, regardless of whether there were prior cycles with no reported shift work.

We also ran models stratified by menopausal status and breast cancer hormonal receptor status of tumors (ER+PR+, ER+PR−, ER-PR−), as these attributes of breast cancer cases may inform etiologic interpretation of results. ER-PR+ tumor status was considered to be an artifact of reading[20] and was not included as a subtype. Cases of other subtypes and those missing ERPR subtype were treated as censored events in this competing risks analysis. Wald tests for interaction were used for analyses stratified by follow-up and menopausal status. The Likelihood Ratio Test was used to test for heterogeneity among the results by ER and PR status.

In NHS II, updated exposure information allowed us to separate shift work duration by time accrued pre- and postmenopausally. We ran models to assess the relationship of premenopausal shift work and postmenopausal shift work and breast cancer, excluding 2731 (2%) participants who were postmenopausal at baseline as we were unable to attribute reported shift work duration to either the pre- or postmenopausal period. Both measures of shift work were treated as continuous variables and included in the models together to determine the associations independent of the other measure.

All multivariable models were adjusted for mammogram in the past 2 years (yes, no), as it predicts breast cancer diagnosis. To further account for possible bias due to mammography screening (i.e. shift workers may be less likely to seek screening and therefore be less likely to have a breast cancer diagnosed), we also performed a secondary analysis using inverse probability weighting by predicted mammography use.[21]

## RESULTS

The participants in the NHS and NHS II cohorts included in our analyses showed several general patterns in distribution of baseline characteristics between cohorts and across categories of shift work (see Table 1). Participants in the NHS sample were roughly 20 years older than those in NHS II, 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, in both cohorts, women at baseline with the highest level of shift work (30+ years in NHS, 20+

years in NHS II) were heavier, more likely to have had menarche before age 12, more likely to be current smokers with more pack-years of smoking, but with lower consumption of alcohol, compared with never shift workers. They also had a lower percentage with benign breast disease, although this could be due to their lower mammography use.

Women were much more likely to be nulliparous in NHS II (28-42%), compared with NHS (5-6%). There was no substantial difference in nulliparous women across shift work categories in NHS, but women with the longest shift work history were more likely to be nulliparous in NHS II, although their age at first birth was lower than it was for the comparable group in NHS. Ever oral contraceptive and current menopausal hormone therapy was higher in NHS II compared with NHS.

In NHS, the women with the highest duration of shift work were less likely to have attained education levels above bachelor's degrees and less likely to have had husbands with education level above college. In NHS II, we did not have a measure of SES until spousal education attainment was collected in 1999 (10 years post baseline). Using this measure, the highest shift work group in NHS II at baseline had the highest spousal education attainment. However, it should be noted that by the approximate midpoint of follow-up in 1999, the highest shift work group had lower spousal education attainment, similar to NHS at baseline (data not shown).

During 24 years of follow-up, we documented 9541 total invasive breast cancers (5971 in NHS and 3570 in NHS II), with a median time to breast cancer event of 13 years in NHS and 14 years in NHS II. NHS II cumulative shift work analyses included 3188 breast cancers, due to skipping of cycles with missing updated shift work information as previously described.

In NHS, we observed no association between baseline duration of rotating night shift work and breast cancer risk in age-adjusted models, with never shift workers as the reference group ($HR_{1–14\ yrs\ vs\ 0\ yrs}$ =1.03, 95% CI 0.98–1.09; $HR_{15–29\ yrs\ vs\ 0\ yrs}$ =1.02, 95% CI 0.91–1.14; $HR_{30+\ yrs\ vs\ 0\ yrs}$ =0.92, 95% CI 0.75–1.13; $p_{trend}$=0.89). Adjustment for possible confounders and breast cancer risk factors resulted in minimal change to these null results (MV-$HR_{1\text{-}14yrs}$=1.01, 95% CI 0.96-1.07; MV-$HR_{15\text{-}29\ yrs\ vs\ 0\ yrs}$ =1.06, 95% CI 0.94-1.19; MV-$HR_{30+\ yrs\ vs\ 0\ yrs}$ =0.95, 95% CI 0.77-1.17; $p_{trend}$=0.63). (See Table 2)

By contrast, in NHS II, 20+ years of rotating night shift work at baseline was associated with a significantly increased risk of breast cancer, compared with baseline never shift work, in both the age-adjusted model ($HR_{base20+\ yrs\ vs\ 0\ yrs}$ =1.83, 95% CI 1.05-3.17) and the multivariable-adjusted model (MV-$HR_{base20+\ yrs\ vs\ 0\ yrs}$ =2.16, 95% CI 1.24-3.76, $p_{trend}$=0.23). We observed no association between shorter durations of shift work at baseline and breast cancer risk. Women with cumulative rotating night shift work exposure of 20+ years had a marginally significant increased risk of breast cancer, compared to women who never worked rotating night shifts (age-adjusted model $HR_{cum20+\ yrs\ vs\ 0\ yrs}$ =1.29, 95% CI 0.92-1.81; MV-adjusted model $HR_{cum20+\ yrs\ vs\ 0\ yrs}$ =1.41, 95% CI 1.00-1.97, $p_{trend}$=0.73). Results were null for the other durations of shift work. (See Table 2)

Stratification by follow-up period in both cohorts and both measures of shift work in NHS II showed a general pattern of increased risk with the highest level of shift work duration during the first 10 years of follow-up, which was not apparent in the remainder of the full follow-up. In NHS, the trend across categories in the first 10 years was statistically significant ($p_{trend}$=0.04), and the HR for 30+ years of shift work was non-significantly elevated (MV-$HR_{30+\ yrs\ vs\ 0\ yrs}$=1.26, 95% CI 0.97-1.64). In the last 14 years of follow-up, the HR was inverse (MV-$HR_{30+yrs}$=0.68, 95% CI 0.49-0.95), with $p_{interaction}$=0.03. In NHS II, the HRs for baseline 20+ yrs as well as cumulative 20+ years were significantly positive in the first 10 years of follow-up (MV-$HR_{base\ 20+\ yrs\ vs\ 0\ yrs}$=2.35, 95% CI 1.04-5.31 and MV-$HR_{cum\ 20+\ yrs\ vs\ 0\ yrs}$=2.12, 95% CI 1.18-3.80, respectively), and non-significantly positive with lower estimates in the last 14 years of follow-up (MV-$HR_{base\ 20+\ yrs\ vs\ 0\ yrs}$ =1.97, 95% CI 0.93-4.20 and MV-$HR_{cum\ 20+\ yrs\ vs\ 0\ yrs}$=1.20, 95% CI 0.79-1.82, respectively). Interactions with follow-up period were not significant in NHS II. (See Table 3)

No significant associations were found between a rotating night shift work exposure measure of never, current and past shift work with different times since stopping shift work and breast cancer risk. When restricted to ever shift workers, we noted a marginally significant trend for increasing breast cancer risk with greater time since stopping shift work ($p_{trend}$=0.05). (See Table 4)

Using the same categories of rotating night shift work as in the main analyses, we were only able to stratify by menopausal status in NHS II because of the small number of premenopausal cases in the highest level of shift work exposure in NHS. Baseline 20+ years of shift work was significantly associated with postmenopausal breast cancer (MV-$HR_{20+\ yrs\ vs\ 0\ yrs,\ postmeno}$=3.28, 95% CI 1.70-6.32), although this level of shift work had few cases (n=10), and the interaction between shift work and menopausal status was not significant ($p_{interaction}$=0.17). The cumulative shift work and breast cancer results were null and did not differ by menopausal status (p=0.22). In addition, neither measure of shift work duration accrued pre/postmenopausally was associated with breast cancer in multivariable-models, adjusting for the other measure (MV-$HR_{preSW}$=1.00, 95% CI 0.99-1.01; MV-$HR_{postSW}$=0.97, 95% CI 0.90-1.06).

The associations of shift work and breast cancer did not differ by ER and PR status of the breast cancer in both cohorts across the full follow-up period (NHS $p_{heterogeneity}$=0.17; NHS II baseline $p_{heterogeneity}$=0.49; NHS II cumulative $p_{heterogeneity}$=0.71), although small sample sizes in the highest shift work categories limit interpretability (See Table 5). Restricting to ER+PR+ tumors only, the association of cumulative rotating shift work and breast cancer in NHS II was strengthened (MV-$HR_{cum\ 20+\ yrs\ vs\ 0\ yrs}$=1.63, 95% CI 1.08-2.46), when compared with the main result in Table 2. Combining the highest two categories of shift work for both cohorts to better balance number of women in each exposure category showed null results and no significant heterogeneity across ER and PR status (data not shown).

The results from secondary analyses using inverse probability weighting for mammographic screening were not substantially different from the main results using traditional model adjustment for current mammography use. Reduced sample sizes were available for the IPW

models because no weights could be determined if mammography use information was missing, so comparisons were made between models using traditional adjustment and IPW weighting utilizing the same smaller dataset. In both cohorts, the multivariable-adjusted hazard ratios were similar to our unweighted results (NHS unweighted $HR_{30+\ yrs\ vs\ 0\ yrs}$ =0.97 vs. weighted $HR_{30+\ yrs\ vs\ 0\ yrs}$ =1.00; NHS II unweighted $HR_{base20+\ yrs\ vs\ 0\ yrs}$ =2.64 vs. weighted $HR_{base20+\ yrs\ vs\ 0\ yrs}$ =2.60 and unweighted $HR_{cum20+\ yrs\ vs\ 0\ yrs}$ =1.42 vs. weighted $HR_{cum20+\ yrs\ vs\ 0\ yrs}$ =1.51), indicating minimal bias due to differential screening practices among shift workers.

## DISCUSSION

In NHS, we saw no association between rotating night shift work and breast cancer incidence over the full 24 years of follow-up. The women included in this analysis were 42-67 years old at baseline in 1988, when shift work history was recorded. Current rotating night shift work (yes/no) was asked of the cohort 8 years later in 1996, and only 3% were still working rotating night shifts at that time. We seem to have captured primarily post-retirement time with the expansion of follow-up and not much additional shift work was likely accumulated. This may in part explain the lack of an association we observed in NHS with the additional 14 years of follow-up.

In NHS II, the younger age of the cohort as well as 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 of rotating night shift work early in their careers, in their 20’s and 30’s. Those participants also contributed to the 20+ year shift work category in the cumulative measure, but were mixed with women who had different patterns of shift work accumulation after baseline. The cumulative measure of shift work was also consistent with a marginally significant increased risk of breast cancer over 24 years of follow-up.

We explored the associations separately for the first 10 years of follow-up and the remaining 14 years of follow-up, 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 NHS II, we saw that breast cancer risk associated with night shift work was higher in the early part of follow-up than in the remainder. The estimates were higher in NHS II, where the shift work performance was likely closer in proximity to breast cancer risk than in NHS. We investigated the unexpected inverse finding in the latter part of follow-up for 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 therefore believe it to be due to chance.

We investigated time since stopping shift work and breast cancer risk and saw no significant associations with never shift work as the comparison group. When we restricted to ever shift workers, we saw the suggestion of a trend with longer time since stopping shift work being associated with greater breast cancer risk. Here, greater time since stopping shift work may be a marker for shift work performed at earlier, young adult ages. In 2009, the NHS II women were asked about their primary work schedule during the age ranges of 20-25,

26-35, 36-45 and 46+. For the person-time attributed to the >16 years of time since stopping shift work category, 94% reported being rotating night shift workers before age 35 (compared with 67% for current, 82% for <=8 years since stopping, and 89% for 9-16 years since stopping shift work).

To our knowledge, no other studies have specifically explored timing or proximity of shift work with breast cancer risk. However, duration of shift work may serve as a proxy for recency of exposure. Data from the Current Population Survey in the US[22] suggests that a large proportion of people who work night shifts do so to accommodate schooling and childcare needs, presumably at young ages. Other work from our group[23] suggests that most nurses in our cohorts who engage in shift work do so before age 25, possibly during training programs. Longer durations of shift work in this population likely include shift work that occurred during training and then continued on, closer to breast cancer diagnosis. In other populations, studies that have found a significant association with duration of shift work, have done so with durations of at least 15 years.[24,25,26]

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 20+ years on rotating night shifts early in their careers as young adults. The early-career time in these nurses may 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 therefore vulnerable to cancer risk factors. In a recent Spanish study, Papantoniou et al saw a slightly higher risk of breast cancer among women exposed to night shift work prior to first full-term pregnancy compared to those exposed after first full-term pregnancy.[27] Additional analyses in datasets that allow for separation of shift work exposure with respect to such early-career events are warranted.

In two recent Swedish cohort analyses, hazard ratios strengthened when the analyses were restricted to those aged less than 60 years.[13,14] To further understand timing with respect to an important change in breast tissue later in life in our data, we stratified by menopausal status and also ran separate models with an exposure definition of shift work that accrued pre- and post-menopausally. We saw no significant interaction, although we were limited by sample size in the highest shift work category. Shift work performed pre- and post-menopausally was not associated with breast cancer risk, once each was adjusted for the other along with breast cancer risk factors.

In addition, as circulating estradiol levels have been shown to be higher in night shift workers compared to day shift workers,[28] we evaluated the shift work and breast cancer association by presence of estrogen and progesterone receptors in the tumor tissue. Small numbers in the highest categories of shift work duration limited determination of statistically significant heterogeneity. However, NHS II results indicated a potentially stronger association with ER+PR+, supporting the hypothesized hormonal pathway for shift work to affect breast cancer risk.

Finally, as night shift workers are less likely to adhere to breast cancer screening guidelines[29] and we noted lower proportion of mammography use with increasing shift work

duration in our data (see Table 1), we ran models using inverse probability weights for likelihood of mammography based on factors that have been shown to predict screening behavior.[21] 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 NHS II cohorts provide rich data for examining the association of rotating night shift work and breast cancer, but also have several notable limitations. Rotating night shift work for a given month was defined as 3 or more night shifts along with other day/evening shifts in that month. This may not capture the intensity or pattern of night shift work that is most disruptive, and may have limited our ability to identify a dose-response relationship. Still, the NHS and NHS II 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 separation of effects for subtypes of the breast cancer.

The updated long-term findings in the NHS and NHS II cohorts have important implications for future IARC evaluations of the night shift work and breast cancer association. Our results may serve to put the literature into the context of short-term vs long-term effects, and suggest that there may be a period of increased risk, that wanes with time.

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**Table 1**

Age-adjusted baseline characteristics by categories of rotating night shift work duration (NHS: 1988, N=78,516; NHS II: 1989, N=114,559)

| | NHS | | | | NHS II | | | |
|---|---|---|---|---|---|---|---|---|
| **Characteristic** | **Never n=31,746** | **1–14 years n=40,966** | **15–29 years n=4,424** | **>30 years n=1,380** | **Never n=43,529** | **1–9 years n=65,783** | **10–19 years n=5,085** | **>20 years n=162** |
| Age | 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, kg/m$^2$ | 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 at age 18, kg/m$^2$ | 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[a] | 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[a] | 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 | 22 | 23 | 24 | 30 | 24 | 25 | 29 | 35 |
| Ever oral contraceptive use | 49 | 49 | 46 | 44 | 83 | 83 | 83 | 57 |
| Nulliparous | 5 | 6 | 6 | 6 | 28 | 32 | 36 | 42 |
| Number of children[b] | 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[b] | 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[b] | 47 | 49 | 47 | 43 | 48 | 46 | 39 | 32 |
| Postmenopausal | 67 | 68 | 70 | 86 | 2 | 2 | 3 | 4 |
| Age at menopause[c] | 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) |
| Menopause due to surgery[c] | 41 | 42 | 44 | 40 | 93 | 92 | 96 | 88 |
| Current menopausal hormone therapy use[c] | 24 | 24 | 21 | 25 | 83 | 79 | 84 | 82 |
| First-degree family history of breast cancer | 11 | 11 | 11 | 12 | 6 | 6 | 5 | 2 |

| Characteristic | NHS | | | | NHS II | | | |
|---|---|---|---|---|---|---|---|---|
| | Never n=31,746 | 1–14 years n=40,966 | 15–29 years n=4,424 | >30 years n=1,380 | Never n=43,529 | 1–9 years n=65,783 | 10–19 years n=5,085 | >20 years n=162 |
| 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 smoked[d] | 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, grams/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 education level bachelor's or higher[e] | 31 | 30 | 24 | 22 | – | – | – | – |
| Husband's education level college or higher[f] | 55 | 56 | 42 | 49 | 80 | 83 | 80 | 90 |
| Ever had mammogram | 77 | 76 | 70 | 72 | 38 | 37 | 34 | 29 |

Values are means (SD) or percentages and are standardized to the age distribution of the study population.

Values of polytomous variables may not sum to 100% due to rounding.

[a] Body size recalled using pictures of body outlines, numbered 1-9, leanest to fattest (NHS: 1988, NHS II: 1989)

[b] Among parous women only.

[c] Among postmenopausal women only.

[d] Among smokers only.

[e] Nurse's own education level. (NHS only: 1992)

[f] Among married or widowed women only. (NHS: 1992; NHS II: 1999)

## Table 2

Associations of duration of rotating night shift work and invasive breast cancer during 24 years of follow-up (NHS: 1988–2012; NHS II: 1989–2013)

| | No. of cases | Person-years | Age-adjusted (HR95%CI) | Multivariable-adjusted HR (95% CI)[b] |
|---|---|---|---|---|
| **NHS rotating night shift work history** | | | | |
| Never | 2382 | 640,594 | Ref | Ref |
| 1–14 yrs | 3162 | 817,778 | 1.03 (0.98–1.09) | 1.01 (0.96–1.07) |
| 15–29 yrs | 331 | 84,887 | 1.02 (0.91–1.14) | 1.06 (0.94–1.19) |
| 30+ yrs | 96 | 25,178 | 0.92 (0.75–1.13) | 0.95 (0.77–1.17) |
| | 5971 | 1,568,438 | $p_{trend}$ = 0.89 | $p_{trend}$ = 0.63 |
| **NHS II 1989 baseline rotating night shift work history (early career)** | | | | |
| Never | 1318 | 978,847 | Ref | Ref |
| 1–9 yrs | 2071 | 1,475,921 | 1.06 (0.99–1.13) | 1.05 (0.98–1.13) |
| 10–19 yrs | 168 | 112,752 | 0.94 (0.80–1.10) | 1.00 (0.85–1.17) |
| 20+ yrs | 13 | 3,335 | 1.83 (1.05–3.17) | 2.16 (1.24–3.76) |
| | 3570 | 2,570,855 | $p_{trend}$ = 0.58 | $p_{trend}$ = 0.23 |
| **NHS II cumulative rotating night shift work (updated)[a]** | | | | |
| Never | 950 | 675,209 | Ref | Ref |
| 1–9 yrs | 2002 | 1,384,743 | 1.03 (0.96–1.12) | 1.04 (0.96–1.12) |
| 10–19 yrs | 201 | 140,868 | 0.90 (0.77–1.05) | 0.94 (0.81–1.10) |
| 20+ yrs | 35 | 13,705 | 1.29 (0.92–1.81) | 1.41 (1.00–1.97) |
| | 3188 | 2,214,524 | $p_{trend}$ = 0.73 | $p_{trend}$ = 0.73 |

[a]For NHS II, analyses using updated duration of shift work excluded participants during the cycles in which they were missing shift work exposure information, resulting in fewer cases and person-years, compared to analyses using history of shift work reported at baseline in 1989.

[b]Multivariable-adjusted models include the following covariates: age (months), height (continuous in inches), BMI (<18.5, 18.5-24.9, 25.0-29.9, 30+ kg/m2), BMI at age 18 (<18.5, 18.5-24.9, 25.0-29.9, 30+ kg/m2), adolescent body size (average of age 10 and age 20 diagrams: 1, 1.5-2, 2.5-3, 3.5-4, 4.5+), age at menarche (<12 yrs, 12-13 yrs, 14+ yrs), age at first birth and parity combined (NHS: nulliparous, age <25 yrs 1-2 kids, age <25 yrs 3+ kids, age 25-29 yrs 1-2 kids, age 25-29 yrs 3+ kids, age 30+ yrs 1-2 kids, age 30+ yrs 3+ kids; NHS II: nulliparous, parous age <25 yrs, parous age 25-29 yrs, parous age 30+ yrs), breastfeeding (NHS: none, 1–11 months, 12+ months; NHS II: none, 1–12 months, >12 months), type of menopause and age at menopause combined (premenopausal, post natural age <45, post natural age 45+, post surgery age <45, post surgery age 45+), menopausal hormone therapy (never, past, current), duration of estrogen alone MHT (continuous in months), duration of estrogen and progesterone MHT (continuous in months), first-degree family history of breast cancer (yes, no), history of benign breast disease (yes, no), alcohol consumption (0, 0.1–14, 14.1–28, >28g/day), physical activity (<=8, 8.1–16, 16.1–24, >24 MET-hrs/week), and current mammography use (yes, no).

**Table 3**

Associations of duration of rotating night shift work and invasive breast cancer, stratified by follow-up period, during 24 years of follow-up (NHS: 1988–2012; NHS II: 1989–2013)

| | Follow-up <=10 years | | | | Follow-up >10 years | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. of cases | Person-years | Age-adjusted HR (95%CI) | Multivariable-adjusted HR (95% CI)[b] | No. of cases | Person-years | Age-adjusted HR (95%CI) | Multivariable-adjusted HR (95% CI)[b] | MV $p_{interaction}$ |
| **NHS rotating night shift work history** | | | | | | | | | |
| Never | 977 | 298,701 | Ref | Ref | 1405 | 336,729 | Ref | Ref | |
| 1–14 yrs | 1415 | 383,622 | 1.11 (1.02–1.21) | 1.09 (1.00–1.18) | 1747 | 427,392 | 0.97 (0.91–1.05) | 0.96 (0.89–1.03) | |
| 15–29 yrs | 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+ yrs | 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) | |
| | 2598 | 735,599 | $p_{trend}$ = 0.08 | $p_{trend}$ = 0.04 | 3373 | 819,920 | $p_{trend}$ = 0.15 | $p_{trend}$ = 0.25 | $p_{int}$ = 0.03 |
| **NHS II 1989 baseline rotating night shift work history (early career)** | | | | | | | | | |
| Never | 416 | 412,724 | Ref | Ref | 902 | 553,730 | Ref | Ref | |
| 1–9 yrs | 637 | 622,782 | 1.03 (0.91–1.17) | 1.02 (0.90–1.15) | 1434 | 833,620 | 1.07 (0.98–1.16) | 1.07 (0.98–1.16) | |
| 10–19 yrs | 57 | 47,867 | 0.94 (0.71–1.24) | 0.97 (0.73–1.28) | 111 | 63,327 | 0.94 (0.77–1.14) | 1.01 (0.83–1.23) | |
| 20+ yrs | 6 | 1,491 | 2.13 (0.95–4.80) | 2.35 (1.04–5.31) | 7 | 1,801 | 1.63 (0.77–3.45) | 1.97 (0.93–4.20) | |
| | 1116 | 1,084,864 | $p_{trend}$ = 0.76 | $p_{trend}$ = 0.70 | 2454 | 1,452,478 | $p_{trend}$ = 0.65 | $p_{trend}$ = 0.25 | $p_{int}$ = 0.86 |
| **NHS II cumulative rotating night shift work (updated)[a]** | | | | | | | | | |
| Never | 341 | 321,600 | Ref | Ref | 609 | 346,804 | Ref | Ref | |
| 1–9 yrs | 621 | 602,095 | 0.98 (0.86–1.12) | 0.97 (0.85–1.11) | 1381 | 767,303 | 1.06 (0.96–1.16) | 1.07 (0.97–1.18) | |
| 10–19 yrs | 60 | 50,481 | 0.92 (0.70–1.21) | 0.94 (0.71–1.24) | 141 | 88,801 | 0.90 (0.74–1.07) | 0.95 (0.79–1.14) | |
| 20+ yrs | 12 | 2,956 | 1.99 (1.11–3.56) | 2.12 (1.18–3.80) | 23 | 10,637 | 1.10 (0.72–1.66) | 1.20 (0.79–1.82) | |
| | 1034 | 977,132 | $p_{trend}$ = 0.83 | $p_{trend}$ = 0.74 | 2154 | 1,213,546 | $p_{trend}$ = 0.58 | $p_{trend}$ = 0.88 | $p_{int}$ = 0.73 |

[a]For NHS II, analyses using updated duration of shift work excluded participants during the cycles in which they were missing shift work exposure information, resulting in fewer cases and person-years, compared to analyses using history of shift work reported at baseline in 1989.

[b] Multivariable-adjusted models. See Table 2 footnotes for list of covariates.

## Table 4

Associations of time since stopping rotating night shift work and invasive breast cancer during 24 years of follow-up in NHS II only (1989–2013)

| | No. of cases | Person-years | Age-adjusted HR (95%CI) | Multivariable-adjusted HR (95% CI)[a] |
|---|---|---|---|---|
| **NHS II time since stopping rotating night shift work among all** | | | | |
| Never shift work | 1060 | 786,772 | Ref | Ref |
| Current shift work | 478 | 467,992 | 0.97 (0.87–1.09) | 0.96 (0.84–1.09) |
| Past, <=8 years since stopping shift work | 798 | 606,237 | 1.01 (0.92–1.11) | 1.02 (0.91–1.13) |
| Past, 9–16 years since stopping shift work | 907 | 476,794 | 1.08 (0.98–1.19) | 1.10 (0.99–1.22) |
| Past, >16 years since stopping shift work | 327 | 233,060 | 1.09 (0.94–1.27) | 1.10 (0.95–1.28) |
| | 3570 | 2,570,855 | | |
| **NHS II time since stopping rotating night shift work, restricted to ever rotating night shift workers only** | | | | |
| Current shift work (i.e. 0 years since stopping) | 478 | 467,992 | Ref | Ref |
| Past, <=8 years since stopping shift work | 798 | 606,237 | 1.03 (0.92–1.17) | 1.05 (0.93–1.19) |
| Past, 9–16 years since stopping shift work | 907 | 476,794 | 1.11 (0.97–1.27) | 1.14 (0.99–1.31) |
| Past, >16 years since stopping shift work | 327 | 233,060 | 1.17 (0.96–1.43) | 1.19 (0.96–1.46) |
| | 2510 | 1,784,083 | $P_{trend}$=0.06 | $P_{trend}$=0.05 |

[a]Multivariable-adjusted models are adjusted for the covariates listed in Table 2 footnotes, and are additionally adjusted for duration of rotating night shift work (continuous in months).

**Table 5**

Associations of duration of rotating night shift work and estrogen receptor (ER) and progesterone receptor (PR) status of invasive breast cancer tumors during 24 years of follow-up (NHS: 1988–2012; NHS II: 1989–2013)

| | ER+PR+ | | | ER+PR− | | | ER-PR− | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. of cases | Age-adjusted HR (95%CI) | Multivariable-adjusted HR (95% CI)[b] | No. of cases | Age-adjusted HR (95%CI) | Multivariable-adjusted HR (95% CI)[b] | No. of cases | Age-adjusted HR (95%CI) | Multivariable-adjusted HR (95% CI)[b] | MV $P_{heterogeneity}$ |
| **NHS rotating night shift work history** | | | | | | | | | | |
| Never | 1390 | Ref | Ref | 319 | Ref | Ref | 327 | Ref | Ref | |
| 1–14 yrs | 1879 | 1.05 (0.98–1.13) | 1.03 (0.96–1.10) | 414 | 1.00 (0.86–1.16) | 0.98 (0.85–1.14) | 398 | 0.95 (0.82–1.10) | 0.94 (0.81–1.09) | |
| 15–29 yrs | 199 | 1.05 (0.90–1.22) | 1.11 (0.95–1.29) | 34 | 0.76 (0.53–1.08) | 0.82 (0.57–1.17) | 45 | 1.01 (0.74–1.38) | 1.06 (0.77–1.45) | |
| 30+ yrs | 54 | 0.92 (0.70–1.21) | 0.96 (0.73–1.27) | 11 | 0.74 (0.40–1.35) | 0.77 (0.42–1.40) | 8 | 0.59 (0.29–1.20) | 0.63 (0.31–1.27) | |
| | 3522 | $p_{trend}$ = 0.56 | $p_{trend}$ = 0.33 | 778 | $p_{trend}$ = 0.12 | $p_{trend}$ = 0.21 | 778 | $p_{trend}$ = 0.34 | $p_{trend}$ = 0.47 | $p_{het}$= 0.17 |
| **NHS II 1989 baseline rotating night shift work history (early career)** | | | | | | | | | | |
| Never | 708 | Ref | Ref | 112 | Ref | Ref | 200 | Ref | Ref | |
| 1–9 yrs | 1166 | 1.11 (1.01–1.22) | 1.11 (1.01–1.22) | 201 | 1.21 (0.96–1.52) | 1.20 (0.95–1.52) | 268 | 0.90 (0.75–1.08) | 0.92 (0.76–1.11) | |
| 10–19 yrs | 87 | 0.90 (0.72–1.13) | 0.97 (0.77–1.21) | 16 | 1.03 (0.61–1.74) | 1.13 (0.66–1.92) | 23 | 0.88 (0.57–1.35) | 0.95 (0.61–1.46) | |
| 20+ yrs | 5 | 1.33 (0.55–3.22) | 1.59 (0.65–3.86) | 1 | 1.29 (0.18–9.35) | 1.61 (0.22–11.91) | 2 | 2.08 (0.51–8.47) | 2.14 (0.52–8.86) | |
| | 1966 | $p_{trend}$ = 0.67 | $p_{trend}$ = 0.32 | 330 | $p_{trend}$ = 041 | $p_{trend}$ = 026 | 493 | $p_{trend}$ = 0.44 | $p_{trend}$ = 0.70 | $p_{het}$= 0.49 |
| **NHS II cumulative rotating night shift work (updated)[a]** | | | | | | | | | | |
| Never | 539 | Ref | Ref | 81 | Ref | Ref | 146 | Ref | Ref | |
| 1–9 yrs | 1152 | 1.04 (0.94–1.15) | 1.05 (0.94–1.16) | 204 | 1.24 (0.96–1.61) | 1.25 (0.96–1.62) | 269 | 0.90 (0.73–1.10) | 0.92 (0.75–1.12) | |
| 10–19 yrs | 105 | 0.81 (0.66–1.00) | 0.85 (0.69–1.05) | 20 | 1.09 (0.67–1.78) | 1.20 (0.73–1.96) | 42 | 1.22 (0.86–1.72) | 1.29 (0.91–1.82) | |
| 20+ yrs | 24 | 1.50 (1.00–2.27) | 1.63 (1.08–2.46) | 2 | 0.79 (0.19–3.24) | 0.88 (0.21–3.60) | 2 | 0.50 (0.12–2.02) | 0.53 (0.13–2.14) | |
| | 1820 | $p_{trend}$ = 0. 53 | $p_{trend}$ = 090 | 307 | $p_{trend}$ = 060 | $p_{trend}$ = 0.37 | 459 | $p_{trend}$ = 0.74 | $p_{trend}$ = 0.54 | $p_{het}$= 0.71 |

[a] For NHS II, analyses using updated duration of shift work excluded participants during the cycles in which they were missing shift work exposure information, resulting in fewer cases and person-years, compared to analyses using history of shift work reported at baseline in 1989.

[b] Multivariable-adjusted models. See Table 2 footnotes for list of covariates.